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Frank A. Manning, MD, *Guest Editor*

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Preface

The advances in care of the unborn patient, the fetus, have been nothing short of incredible in the past few years, and the field shows every evidence of a further acceleration of knowledge acquisition in the foreseeable future. We have moved in a few short years from the inability to examine the fetus to a breakthrough in the production of, by today's standards, what seems crude and indistinct static B-mode ultrasound, to the present, when fetal imagery is of very high resolution and, as importantly, is presented in real-time sequence. Quite suddenly, it has become possible to observe fetal activities in the normal state from immaturity to maturity, to examine fetal responses to endogenous stimuli such as asphyxia and to exogenous stimuli such as vibroacoustic stimulation. From these observations flow very specific methods for differentiation of the normal from the compromised fetus, an advance that now permits timely select intervention, with a resultant fall in the incidence of perinatal death and damage. In concert we have learned to apply Doppler ultrasound to monitor fetal heart rate and to catalogue fetal heart rate responses in the normal and compromised fetuses. Even more recently we have begun to examine the relationship between fetal arterial blood flow velocities and fetal health, a Doppler ultrasound method that holds enormous potential. As dramatic and certainly as important from the clinical viewpoint, we are learning to use ultrasound to guide diagnostic probing of the fetus and its environment and to direct life-saving fetal therapies such as fetal transfusion. Quite suddenly the sacrosanct fetal niche is opened to our examining senses and minds, resulting in a growth of clinical knowledge base quite unparalelled in obstetrics. In this edition of the *Clinics in Perinatology*, experts from Canada, the United States, and England present a series of essays describing these advances. It has been a delight to be associated with such gifted researchers. It is a further delight to realize that although each contribution in isolation provides a "state of the art" update of a given topic, the cumulative result of the

works presented here is to give the reader a comprehensive overview of a fascinating and evolving clinical arena—the care of the fetus.

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Observations of Biophysical Activities in the Normal Fetus

*Alan D. Bocking, MD, FRCSC**

FETAL BREATHING MOVEMENTS

The presence of respiratory-like activity or fetal breathing movements (FBM) were thought to be present in the human fetus from as early as 1905, when Ahlfeld[2] made permanent recordings of what was subsequently shown to be FBM using pressure sensors applied to the abdomen of pregnant women. It was not, however, until the development of methods of recording intrathoracic pressure in chronically catheterized pregnant sheep that the existence of FBM *in utero* in the undisturbed fetus was widely accepted.[18] These early studies in pregnant sheep led investigators to confirm (using A-scan ultrasound techniques) that FBM do indeed exist in healthy human fetuses.[10] This work was then followed by the introduction of real-time B-scan ultrasound with which clinicians and investigators were able for the first time to visualize directly the human fetus *in utero*, and, in particular, movement of the fetal chest and abdominal walls.[58]

FBM occur episodically and are present approximately 30 per cent of the time during the last 10 weeks of pregnancy.[50] Episodes of FBM last approximately 20 to 60 minutes, alternating with periods of apnea, with the longest period of absent FBM seen in healthy human fetuses at 38 weeks studied continuously over 24 hours being 120 minutes.[49]

Diurnal Rhythm

It has been clearly shown in carefully conducted studies of healthy pregnant women in the last 10 weeks of pregnancy that there is a diurnal rhythm of FBM with an increased incidence between 0400 and 0700 hours.[50,59] A similar diurnal rhythm in FBM in fetal sheep has been observed when temperature as well as the provision of food and water are carefully controlled, although the peak incidence in FBM was seen at

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2000 hours.[19] The diurnal rhythm in FBM in human pregnancy is not present in women who are chronically ingesting exogenous glucocorticoids for medical indications.[58] This suggests that the diurnal rhythm in FBM during the last 10 weeks of pregnancy is related in some way to the diurnal rhythm in maternal circulating cortisol concentrations normally seen in pregnant women.[55]

Meals

The incidence of FBM is closely linked to meals in the human fetus near term. Patrick et al.[50,58] observed a significant increase in the per cent of time that fetuses spend making FBM during the second and third hours following standardized 800 kcal meals during the last 10 weeks of pregnancy. In those studies, peak maternal plasma glucose concentrations were observed at 1 hour after each meal. Natale et al.[41] subsequently demonstrated that the incidence of FBM in fetuses at 32 to 34 weeks' gestation is greatest at 105 minutes following the oral ingestion of 50 gm of glucose, and this is 1 hour after the peak in the maternal plasma glucose concentrations. A similar increase in the incidence of FBM is seen in the human fetus following the intravenous administration of 25 gm of glucose at both 32 to 34 and 38 to 40 weeks' gestation, with the maximal FBM activity occurring at 45 minutes.[8,30,42] In addition to the increase in incidence of FBM following the maternal intravenous injection of glucose, there is a twofold increase in the amplitude of FBM as measured using an ultrasonic tracking device.[1]

An increase in the incidence of FBM also occurs following the maternal ingestion of tryptophan, a serotonoin precursor, although the time course for the peak in incidence of FBM is slightly longer than that for glucose.[21] Tryptophan alone does not give rise to any change in the rate of FBM in contrast to that that occurs with maternal glucose ingestion.

Premature Fetus

Natale et al.[39] recently have documented the patterns of FBM in human fetuses between 24 and 28 weeks' gestation over 24-hour periods. The premature fetus < 30 weeks' gestation spends approximately 14 per cent of the time making FBM, as seen with real-time ultrasound. Fetuses at this gestational age do not, however, demonstrate an increase in FBM following maternal meals, as observed during these 24-hour studies nor in healthy fetuses studied longitudinally for 2 hours from 24 to 32 weeks' gestation.[40] Nijhuis et al.[46] observed a stimulation of FBM at 24 to 28 weeks with the oral ingestion of 50 gm of glucose by the mother, suggesting that the preterm fetus is capable of responding to an exogenous glucose challenge.

There is an increase in the incidence of FBM between 2300 and 0800 hours even at 24 to 28 weeks' gestation,[39] although the time course in the maximal incidence of FBM appears to be shifted to earlier in the night than the older fetus.[50] FBM have been visualized consistently with real-time ultrasound from as early as 10 weeks in human pregnancies when they occupy 2 per cent of observation time, increasing in incidence to 6 per cent at 19 weeks' gestation.[22]

Alcohol

Maternal ingestion of alcohol is known to have a profound inhibitory effect on FBM in the human[26,36] and in sheep,[60] with the ingestion of the equivalent of 2 oz of alcohol by healthy pregnant women at term virtually abolishing all FBM for 3 hours.[36] In sheep, the inhibition of FBM is associated with a decrease in the incidence of eye movements and alterations in brain-wave activity.[60] The inhibition of FBM in the human fetus with alcohol is not reversed by maternal glucose administration.[35]

Physical Stimulation

Vigorous shaking of the maternal abdomen in healthy pregnant women has been carefully studied by two groups of investigators and has been found not to affect the incidence of FBM.[63,74]

Smoking

The effects of maternal smoking on FBM in healthy human fetuses remains controversial. Manning et al.[33] observed a reduction in the incidence of FBM following the smoking of two cigarettes in both normal and abnormal pregnancies that was similar to the effect seen by Gennser et al.[28] Thaler et al.,[71] however, observed an increase in the *rate* but no change in the *incidence* of FBM following maternal smoking. It is of interest that the women in this latter study were pretreated with glucose, as were the women who participated in another subsequent study by Eriksen et al.,[25] in which maternal smoking resulted also in an increase in the rate but not incidence of FBM. The chewing of nicotine-containing gum with associated increases in maternal nicotine concentrations leads to a decrease in the incidence of FBM,[28,33] whereas maternal smoking of herbal cigarettes that do not contain nicotine has no effect on FBM.[33] The effect of smoking on FBM is probably mediated therefore by nicotine either through an effect on the uterine vasculature with resultant mild fetal hypoxemia or by a direct effect on fetal respiratory drive.

Drugs

There have been few reports with adequate numbers of subjects in the literature regarding the effects of maternal drug administration on FBM. Most information pertains to narcotic analgesics and anesthetic agents.

Maternal meperidine administration has been reported to cause both a decrease or no change in the incidence of FBM.[31] The explanation again for these differing results may relate to whether the mothers were pretreated with glucose prior to the administration of the drug. FBM, are decreased in women who are known narcotic analgesic abusers and enrolled in methadone maintenance programs,[65] indicating that narcotics can have a direct depressant effect on the fetal respiratory center as in the adult. Arduini et al.[3] recently have reported that the intravenous administration of naloxone, an opiate antagonist, to healthy pregnant women leads to an increase in the incidence of FBM. Large doses of diazepam (20 mg) administered to pregnant women cause a reduction in FBM, whereas smaller doses (2 mg) have no effect.[31]

Carbon Dioxide

Maternal administration of 5 per cent CO_2 to healthy pregnant women results in a marked increase in the incidence of FBM,[66] with its effect being both dose dependent[15] and gestational-age dependent. The FBM response to maternal CO_2 administration is markedly reduced in women who are chronic methadone users.[65]

Hyperoxia

The administration of increased concentrations of oxygen to healthy pregnant women near term does not result in any alterations in the incidence, rate, or breath interval variability of FBM.[20,67,73] This is in contrast to the growth-restricted human fetus, which demonstrates a marked increase in FBM when exposed to maternal hyperoxia.[23,67] The explanation for this differential effect of maternal hyperoxia on FBM between the normal and growth-restricted human fetus remains unclear.

Labor

Braxton-Hicks or prelabor contractions in normal human pregnancies are associated with an initial fall in the rate of FBM, followed by a further increase in rate after the peak in uterine activity.[37,75] There is no change, however, in the overall incidence of FBM during Braxton-Hicks contractions when compared to time between contractions.

The incidence of FBM is diminished in healthy pregnant women during the last 3 days prior to the onset of spontaneous labor[13] and during the latent phase of electively induced labor at term.[64] A similar decrease in the incidence of FBM has been observed in chronically catheterized fetal sheep prior to the onset of spontaneous labor at term.[6] There is also a significant negative relationship between fetal plasma prostaglandin E_2 concentrations and the decrease in incidence of FBM observed in sheep undergoing ACTH-induced labor.[57] It is tempting to speculate, therefore, that prostaglandin E_2 also may be important in regulating FBM in human pregnancies before and during labor. FBM are virtually abolished during the active phase of labor[11,64] and are unresponsive to maternal glucose administration during labor.[11]

GROSS BODY MOVEMENTS

Like FBM, *gross body movements* (GBM), defined as rolling and stretching movements that can be visualized with real-time ultrasound in the near-term human fetus occur episodically alternating with times of nonmovement. During the last 10 weeks of pregnancy, GBM are present approximately 10 per cent of the time.[52]

Body movements are an important variable in determining behavioral states[62] that have been described in healthy human fetuses at term by Nijhuis et al.[47] The clear identification of different states is possible only from 36 weeks' gestation onwards.[4] The ability to identify behavioral states in the human fetus also depends on being able to visualize eye movements[12] using high-resolution real-time ultrasound.

Diurnal Rhythm

Like FBM, there is a diurnal rhythm in GBM, with an increase in both the number of movements as well as the per cent of time spent moving occurring in the evening between 2100 and 0100 hours.[52,68] Evening is a time at which the maternal perception of fetal movements also is increased[29,76] and therefore should be considered when counseling women regarding fetal movement counts during the antepartum period. The longest episode of absent movement occurring in 24-hour observations of healthy human fetuses during the last 10 weeks of pregnancy was 75 minutes. Only 1 per cent of consecutive 5-minute intervals with absent movement, however, were longer than 45 minutes.[52] This information regarding the movement patterns of healthy term fetuses is of great importance when formulating clinical management plans using fetal movements for the assessment of fetal health.

Meals

In contrast to FBM, there is no association between maternal meals and GBM.[52] In healthy human pregnancies during the last 10 weeks of pregnancy, acute elevations in maternal plasma glucose concentrations through the intravenous injection of 25 gm of glucose does not lead to any significant change in the incidence of GBM.[8,43] Similarly, maternal oral ingestion of 50 gm of glucose does not result in any change in GBM.[32,43] Recently, it has been reported that sustained maternal hyperglycemia of 2 hours' duration in term fetuses leads to a reduction in the number of movements. However, these studies were carried out using a tocodynamometer to assess fetal movement[24] and have yet to be confirmed using direct visual observation of the fetus during prolonged hyperglycemia.

Premature Fetus

GBM occur approximately 13 per cent of the time at 24 to 28 weeks' gestation,[45] which is slightly greater than that which is observed during the last 10 weeks of pregnancy.[52] Younger fetuses also move significantly more often than when at a later gestational age, although the movements are of a more sporadic nature and shorter duration.[45] This is in keeping with the maturation of sleep states with advancing gestational age, which is known to occur in both the human fetus[4,47] and in fetal sheep.[14]

In healthy human fetuses studied longitudinally, the number of movements observed in a 2-hour period decreased from 107 movements at 24 to 26 weeks to 69 movements at 30 to 32 weeks with an associated small decrease in per cent time spent moving.[40] It is of clinical interest that in human fetuses between 24 and 28 weeks' gestation, studied over 24-hour periods, the longest period of absent movement was 24 minutes, and 99 per cent of intervals less than 6 minutes contained movement.[45] As with the older fetus, there is no relationship between GBM and maternal meals at 24 to 28 weeks' gestation.[45] There is, however, a diurnal variation in the number of movements per hour at 24 to 28 weeks' gestation, with the greatest amount of movement occurring between 2300 and 0800 hours.[45] The explanation for the shift in time course of

the diurnal variation in GBM from that of the older fetus[52] remains unclear.

Earlier in gestation (<20 weeks), patterns of fetal movements have been documented using ultrasound visualization, and "general movements" occur approximately 2 per cent of the time at 8 weeks, increasing in incidence to 12.5 per cent of the time at 10 weeks' gestation, with no further change seen in their absolute incidence.[22]

Alcohol and Drugs

In contrast to FBM, acute maternal alcohol ingestion, in social quantities, has no effect on the amount of movement made by healthy human fetuses near term.[36] The intravenous administration of naloxone to healthy pregnant women near term has, however, been shown to increase the number of fetal movements, suggesting that this drug has quite pronounced effects on the fetal central nervous system.[3]

Physical Stimulation

Vigorous shaking of the maternal abdomen in healthy pregnant women near term has no effect on the per cent of time that fetuses spend making GBM, indicating that there is no physiologic basis for this action in assessing fetal health clinically.[63,74]

Smoking

The maternal perception of fetal movements has been reported to be decreased following smoking of two cigarettes.[71] With direct visualization of GBM using ultrasound, however, the incidence of fetal movements following smoking is unchanged,[25] with an apparent change in the pattern of movement in keeping with a change in behavioral state.

Hypercapnia and Hyperoxia

Maternal administration of 5 per cent CO_2 to healthy pregnant women has no effect on fetal GBM in contrast to the well-established effect of CO_2 on FBM.[15,48,65,66] The administration of 50 per cent O_2 to healthy pregnant women near term also has no discernible effect on GBM.[20,73]

Labor

There is no overall difference in the incidence of GBM during Braxton-Hicks contractions when compared to times between uterine activity.[37] There is, however, an identifiable clustering of GBM toward the beginning of Braxton-Hicks contractions, with a subsequent decline in GBM during the latter half of the measurable increase in uterine pressure with a tocotransducer. This suggests that uterine activity may play a role in modulating fetal behavior in the human, as has been observed in the sheep fetus.[44]

There is no change in the incidence of GBM in healthy pregnant women prior to the onset of spontaneous labor at term[13] nor during the latent phase of electively induced labor at term.[64] There is, however, a significant decrease in the amount of time that healthy fetuses spend making GBM during the active phase of labor.[64]

FETAL HEART RATE

The presence or absence of accelerations in fetal heart rate (FHR) is commonly used in assessing fetal health antepartum through the use of the Nonstress Test[69] or as one component of the Biophysical Profile.[34] A clear understanding, therefore, of the patterns of heart rate accelerations in the normal human fetus is of great importance in developing diagnostic strategies. Like FBM and GBM, accelerations in FHR of healthy human fetuses near term occur in episodes, in keeping with the presence of behavioral states.

In women studied over 24-hour periods, 99 per cent of intervals from the end of one acceleration to the beginning of the next were less than 8 minutes, yet the longest interval between consecutive accelerations was 37 minutes,[53] with accelerations being identified as increases in FHR of greater than 10 bpm lasting for longer than 6 seconds. When accelerations were defined as increases in FHR of greater than 15 bpm lasting for longer than 15 seconds, 95 per cent of intervals between consecutive accelerations remained less than 8 minutes, but the longest interval was 70 minutes.[54] Since clinicians generally accept the latter criteria as the definition of accelerations in nonstress testing, it is apparent that to account for the normal rest–activity cycles of healthy fetuses at term, one must be prepared to extend the observation time for at least 70 minutes.

Diurnal Rhythm

There is a significant daily variation in mean FHR of healthy human fetuses at term, with a trough being present between 0200 and 0600 hours, following closely the decrease in maternal heart rate which occurs between midnight and 0700 hours.[51] A diurnal rhythm in FHR of sheep also has been observed during the latter stages of gestation.[17] In the human, mean FHR is strongly correlated with mean maternal heart rate both on an hourly and a daily basis.[51] Mean FHR is of importance in considering the pattern of accelerations because there is a significant negative correlation between the mean daily amplitude of FHR accelerations and the mean daily FHR in healthy pregnant women studied over 24 hours near term.[53]

It is of interest that, in the late evening, there is an increase in the duration of FHR accelerations with no change in their number. This is at a time when both the number and incidence of GBM are increased and has led Patrick et al.[53] to suggest that the late evening may be a time at which the human fetus is aroused or in a state of wakefulness.

The diurnal variation in fetal heart rate variability and body movements present at 35 weeks' gestation is abolished by the pretreatment of women with glucocorticoids,[5] indicating that an intact functioning maternal or fetal adrenal gland are important in regulating this aspect of fetal behavior as with FBM.[56]

Meals

There is no association between maternal meals and the number, amplitude, or duration of FHR accelerations in healthy pregnant women

near term.[53] Acute elevations in maternal glucose concentrations through the intravenous injection of 25 gm of glucose have no effect on the number or characteristics of FHR accelerations at term.[7] There is, however, a small increase of approximately 5 bpm in both maternal and fetal heart rate following maternal intravenous glucose injections in healthy pregnant women at 38 to 40 weeks' gestation.

Relationship with Movement

Observations of healthy pregnant women near term have demonstrated a very close relationship between FHR accelerations and GBM as visualized with real-time ultrasound.[53,61] Similar observations of this association have been made by other investigators using a tocodynanometer to assess fetal movement.[72] The explanation for this close relationship between fetal movements and FHR accelerations, however, is uncertain. In fetal sheep, when all skeletal muscle activity is abolished, there is a 36 per cent reduction in the number of FHR accelerations, which like the human fetus, are often associated with fetal movements as measured by electromyogram activity.[9] It is likely therefore, that at least in the sheep fetus and possibly the human, a significant number of FHR accelerations occur together with fetal movements as a consequence of central neuronal output affecting both the cardioaccelerator fibers and motor fibers simultaneously.

Premature Fetus

The close relationship between FHR accelerations and GBM in the term fetus is not as apparent in healthy preterm fetuses, with this association becoming stronger with advancing gestational age.[38,70] In younger fetuses, most FHR accelerations which are associated with movement are less than 15 bpm in amplitude and therefore would not be considered indicative of a "reactive nonstress test." There is, in normal fetuses, a progressive decrease in the mean FHR with advancing gestational age with an associated increase in the amplitude of accelerations.[27,38]

SUMMARY

Biophysical activities such as FBM, GBM, and accelerations in the healthy human fetus near term occur episodically in keeping with the development of behavioral states *in utero*. It is therefore important to allow for the normal rest–activity cycles of healthy fetuses when designing clinical strategies for the surveillance of fetal health during the antepartum period. Diurnal rhythms are present in the incidence of FBM and GBM, as well as in mean FHR. These appear to be related to intact maternal or fetal adrenal gland function. The incidence and amplitude of FBM are strongly influenced by maternal meals, and therefore by plasma glucose concentrations, whereas maternal meals have no effect on GBM or FHR accelerations.

The association of FHR accelerations with GBM becomes stronger with advancing gestational age such that near term close to 90 per cent of accelerations occur with movement. Younger fetuses move overall ap-

proximately the same amount of time as term fetuses, although the movements are more frequent and of a shorter duration. Maternal smoking, and alcohol and drug ingestion all affect FBM, GBM, and FHR to various extents, underlining the importance of documenting the prior maternal use of these substances when using biophysical activities to assess fetal health in the antepartum period.

REFERENCES

1. Adamson SL, Bocking A, Cousin AJ et al: Ultrasonic measurement of rate and depth of human fetal breathing: Effect of glucose. Am J Obstet Gynecol 147:288–295, 1983
2. Ahlfeld F: Die intrauterine Tatiqkeit der Thorax and Zwerchfell muskulatur: Intrauterine Atmung. Monatsschr Geburtshilfe Gynaekol 21:143, 1905
3. Arduini D, Rizzo G, Dell'Acqua S, et al: Effect of naloxone on fetal behavior near term. Am J Obstet Gynecol 156:474–478, 1987
4. Arduini D, Rizzo G, Giorlandino C, et al: The development of fetal behavioral states: A longitudinal study. Prenatal Diagnosis 6:117–124, 1986
5. Arduini D, Rizzo G, Parlati E, et al: Modifications of ultradian and circadian rhythms of fetal heart rate after fetal-maternal adrenal gland suppression: A double blind study. Prenatal Diagnosis 6:409–417, 1986
6. Berger PJ, Walker AM, Horne R, et al: Phasic respiratory activity in the fetal lamb during late gestation and labor. Respir Physiol 65:55–68, 1986
7. Bocking A, Adamson L, Carmichael L, et al: Effect of intravenous glucose injection on human maternal and fetal heart rate at term. Am J Obstet Gynecol 148:414–420, 1984
8. Bocking A, Adamson L, Cousin A, et al: Effects of intravenous glucose injections on human fetal breathing movements and gross fetal body movements at 38–40 weeks' gestational age. Am J Obstet Gynecol 142:606–611, 1982
9. Bocking AD, Harding R, Wickham PJD: Relationship between accelerations and decelerations in heart rate and skeletal muscle activity in fetal sheep. J Develop Physiol 7:47–54, 1985
10. Boddy K, Robinson JS: External method for the detection of fetal breathing in utero. Lancet 2:1231, 1971
11. Boylon P, Lewis PJ: Fetal breathing in labor. Obstet Gynecol 56:35–38, 1980
12. Bots RSGM, Nijhuis JG, Martin CB, et al: Human fetal eye movements: Detection in utero by ultrasonagraphy. Early Hum Develop 5:87–94, 1981
13. Carmichael L, Campbell K, Patrick J: Fetal breathing, gross fetal body movements and maternal and fetal heart rates before spontaneous labour at term. Am J Obstet Gynecol 148:675–679, 1984
14. Clewlow F, Dawes GS, Johnston BM, et al: Changes in breathing, electrocortical and muscle activity in unanaesthetized fetal lambs with age. J Physiol 341:463–476, 1983
15. Connors G, Hunse C, Carmichael L, et al: The role of carbon dioxide in the generation of human fetal breathing movements. Am J Obstet Gynecol 158:322–327, 1988
16. Connors G, Hunse C, Carmichael L, et al: The control of fetal breathing in the human fetus between 24 and 34 weeks' gestation. Am J Obstet Gynecol 160:932–938, 1989
17. Dalton KJ, Dawes GS, Patrick JE: Diurnal, respiratory and other rhythms of fetal heart rate in lambs. Am J Obstet Gynecol 127:414–424, 1977
18. Dawes GS, Fox HE, Leduc BM, et al: Respiratory movements and rapid eye movement sleep in the fetal lamb. J Physiol 220:119–143, 1972
19. Dawes GS, Robinson JS: Rhythmic phenomena in prenatal life. Prog Brain Res 45:383–389, 1976
20. Devoe LD, Abduljabbar H, Carmichael L, et al: The effects of maternal hyperoxia on fetal breathing movements in third-trimester pregnancies. Am J Obstet Gynecol 148:790–794, 1984
21. Devoe LD, Castillo RA, Searle NS, et al: Maternal dietary substrates and human fetal biophysical activity: I. The effects of tryptophan and glucose on fetal breathing movements. Am J Obstet Gynecol 155:135–139, 1986

22. De Vries JIP, Visser GHA, Prechtl HFR: The emergence of fetal behavior: II. Quantitative aspects. Early Hum Develop 12:99–120, 1985
23. Dornon RC, Ritchie JWK: Fetal breathing movements and maternal hyperoxia in the growth retarded fetus. Br J Obstet Gynecol 90:210–213, 1983
24. Edelberg SC, Dierker L, Kalhan S, et al: Decreased fetal movements with sustained maternal hyperglycemia using the glucose clamp technique. Am J Obstet Gynecol 156:1101–1105, 1987
25. Eriksen PS, Gennser G, Lofgren O, et al: Acute effects of maternal smoking on fetal breathing and movements. Obstet Gynecol 61:367–372, 1983
26. Fox HE, Steinbrecher M, Pessel D, et al: Maternal ethanol ingestion and the occurrence of human fetal breathing movements. Am J Obstet Gynecol 132:354–358, 1978
27. Gagnon R, Campbell K, Hunse C, et al: Patterns of human fetal heart rate accelerations from 26 weeks to term. Am J Obstet Gynecol 157:743–748, 1987
28. Gennser G, Marsal K, Brantmark B: Maternal smoking and fetal breathing movements. Am J Obstet Gynecol 123:861–867, 1975
29. Goodlin RC, Lowe EW: Multiphasic fetal monitoring: A preliminary evaluation. Am J Obstet Gynecol 119:341–357, 1974
30. Goodman JDS. The effect of intravenous glucose on human fetal breathing measured by Doppler ultrasound. Br J Obstet Gynecol 87:1080–1083, 1980
31. Lewis P, Boylon P: Fetal breathing: A review. Am J Obstet Gynecol 134:587–598, 1979
32. Lewis PJ, Trudinger BJ, Mangez J: Effect of maternal glucose ingestion on fetal breathing and body movements in late pregnancy. Br J Obstet Gynecol 85:86–89, 1978
33. Manning FA, Feyerabend C: Cigarette smoking and fetal breathing movements. Br J Obstet Gynecol 83:262–270, 1976
34. Manning FA, Platt LD, Sipos L: Antepartum fetal evaluation: Development of a fetal biophysical profile. Am J Obstet Gynecol 136:787–795, 1980
35. McLeod W, Brien J, Carmichael L, et al: Maternal glucose injections do not alter the suppression of fetal breathing following ethanol administration. Am J Obstet Gynecol 148:634–639, 1984
36. McLeod W, Brien J, Loomis C, et al: Effect of maternal ethanol ingestion on fetal breathing movements, gross body movements and heart rate at 37 to 40 weeks' gestational age. Am J Obstet Gynecol 145:251–257, 1983
37. Mulder EJH, Visser GHA: Braxton Hicks' contractions and motor behavior in the near-term human fetus. Am J Obstet Gynecol 156:543–549, 1987
38. Natale R, Nasello C, Turliuk R: The relationship between movements and accelerations in fetal heart rate at twenty-four to thirty-two weeks' gestation. Am J Obstet Gynecol 148:591–595, 1984
39. Natale R, Nasello-Paterson C, Connors G: Patterns of fetal breathing activity in the human fetus at 24 to 28 weeks of gestation. Am J Obstet Gynecol 158:317–321, 1988
40. Natale R, Nasello-Paterson C, Turliuk R: Longitudinal measurements of fetal breathing, body movements, heart rate and heart rate accelerations and decelerations at 24 to 32 weeks of gestation. Am J Obstet Gynecol 151:256–263, 1985
41. Natale R, Patrick J, Richardson B: Effects of human maternal venous plasma glucose concentrations on fetal breathing movements. Am J Obstet Gynecol 132:36–41, 1978
42. Natale R, Richardson B, Patrick J: Effect of intravenous glucose infusion on human fetal breathing activity. Obstet Gynecol 59:320–324, 1981
43. Natale R, Richardson B, Patrick J: The effect of maternal hyperglycemia on gross body movements in human fetuses at 32–34 weeks gestation. Early Hum Develop 8:13–20, 1983
44. Nathanielz PW, Bailey A, Poore ER, et al: The relationship between myometrial activity and sleep state and breathing in fetal sheep throughout the last third of gestation. Am J Obstet Gynecol 138:653–659, 1980
45. Nasello-Paterson C, Natale R, Connors G: Ultrasonic evaluation of fetal body movements over twenty-four hours in the human fetus at twenty-four to twenty-eight weeks' gestation. Am J Obstet Gynecol 158:312–316, 1988
46. Nijhuis JG, Jongsma HW, Crijns IJMJ et al: Effects of maternal glucose ingestion on human fetal breathing movements at weeks 24 and 28 of gestation. Early Hum Develop 13:183–188, 1986

47. Nijhuis JG, Prechtl HFR, Martin CB, et al: Are there behavioral states in the human fetus? Early Hum Develop 6:177–195, 1982
48. O'Grady JP, Richardson B, Hohimer AR, et al: The effect of induced maternal hypercapnia on gross fetal body movements. Am J Obstet Gynecol 146:52–56, 1983
49. Patrick J, Campbell K, Carmichael L, et al: A definition of human fetal apnea and the distribution of fetal apneic intervals during the last ten weeks of pregnancy. Am J Obstet Gynecol 136:471–477, 1980
50. Patrick J, Campbell K, Carmichael L et al: Patterns of human fetal breathing during the last 10 weeks of pregnancy. Obstet Gynecol 56:24–30, 1980
51. Patrick J, Campbell K, Carmichael L, et al: Influence of maternal heart rate and gross fetal body movements on the daily pattern of fetal heart rate near term. Am J Obstet Gynecol 144:533–538, 1982
52. Patrick J, Campbell K, Carmichael L, et al: Patterns of gross fetal body movements over 24-hour observation intervals during the last 10 weeks of pregnancy. Am J Obstet Gynecol 142:363–371, 1982
53. Patrick J, Carmichael L, Chess L, et al: Accelerations of the human fetal heart rate at 38 to 40 weeks' gestational age. Am J Obstet Gynecol 148:35–41, 1984
54. Patrick J, Carmichael L, Chess L, et al: The distribution of accelerations of the human fetal heart rate at 38 to 40 weeks' gestational age. Am J Obstet Gynecol 151:283–287, 1985
55. Patrick J, Challis J, Campbell K, et al: Circadian rhythms in maternal plasma cortisol and oestriol concentrations at 30 to 31, 34 to 35 and 38 to 39 weeks gestational age. Am J Obstet Gynecol 136:325–334, 1980
56. Patrick J, Challis J, Campbell K, et al: Effects of synthetic glucocorticoid administration on human fetal breathing movements at 34 to 35 weeks' gestational age. Am J Obstet Gynecol 139:324–328, 1981
57. Patrick J, Challis JRG, Cross J, et al: The relationship between fetal breathing movements and prostaglandin E_2 during ACTH-induced labor in sheep. J Develop Physiol 9:287–294, 1987
58. Patrick J, Fetherston W, Vick H, et al: Human fetal breathing movements and gross body movements at weeks 34–35 of gestation. Am J Obstet Gynecol 130:693–699, 1978
59. Patrick J, Natale R, Richardson B: Patterns of human fetal breathing activity at 34 to 35 weeks' gestational age. Am J Obstet Gynecol 132:507–513, 1978
60. Patrick J, Richardson B, Hasen G, et al: Effects of maternal ethanol infusion on fetal cardiovascular and brain activity in lambs. Am J Obstet Gynecol 151:859–867, 1985
61. Rabinowitz R, Persitz E, Sadovsky E: The relation between fetal heart rate accelerations and fetal movements. Obstet Gynecol 61:16–18, 1983
62. Prechtl HFR: The behavioral states of the newborn infant (a review). Brain Res 76:185–212, 1974
63. Richardson B, Campbell K, Carmichael L, et al: Effects of external physical stimulation on fetuses near term. Am J Obstet Gynecol 139:344–352, 1981
64. Richardson B, Natale R, Patrick J: Human fetal breathing activity during electively induced labor at term. Am J Obstet Gynecol 133:247–255, 1979
65. Richardson BS, O'Grady JP, Olsen GD: Fetal breathing movements and the response to carbon dioxide in patients on methadone maintenance. Am J Obstet Gynecol 150:400–405, 1984
66. Ritchie JWK, Lakhani K: Fetal breathing movements in response to maternal inhalation of 5 per cent carbon dioxide. Am J Obstet Gynecol 136:386–388, 1980
67. Ritchie JWK, Lakhani K: Fetal breathing movements and maternal hyperoxia. Br J Obstet Gynecol 87:1084–1086, 1980
68. Roberts AB, Little D, Cooper D, et al: Normal patterns of fetal activity in the third trimester. Br J Obstet Gynecol 86:4–9, 1979
69. Rochard F, Schifrin BS, Goupil F, et al: Nonstressed fetal heart rate monitoring in the antepartum period. Am J Obstet Gynecol 126:699–706, 1976
70. Sorokin Y, Bottoms SF, Dierker LJ, et al: The clustering of fetal heart rate changes and fetal movements in pregnancies between 20 and 30 weeks of gestation. Am J Obstet Gynecol 143:952–957, 1982
71. Thaler I, Goodman JDS, Dawes GS: Effects of maternal cigarette smoking on fetal breathing and fetal movements. Am J Obstet Gynecol 138:282–287, 1980
72. Timor-Tritsch IE, Dierker LJ, Zador I, et al: Fetal movements associated with fetal

heart rate accelerations and decelerations. Am J Obstet Gynecol 131:276–280, 1978
73. Van Vliet MAT, Creemers HMH, Van Heyst AFJ, et al: The effect of maternal hyperoxia on breathing movements, body movements and rest–activity cycles of low-risk human fetuses. Europ J Obstet Gynecol Reprod Biol 20:221–228, 1985
74. Visser GHA, Zeelenberg HJ, DeVries JIP, et al: External physical stimulation of the human fetus during episodes of low heart rate variation. Am J Obstet Gynecol 145:579–584, 1983
75. Wilkinson C, Robinson J: Braxton-Hicks contractions and fetal breathing movements. Aust NZ J Obstet Gynecol 22:212–214, 1982
76. Wood C, Walters WAW, Trigg P: Methods of recording fetal movement. Br J Obstet Gynecol 84:561–567, 1977

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Fetal Adaptive Responses to Asphyxia

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The fetus lives and grows in a relatively "hypoxic" environment and yet normally exists with a surplus of oxygen to meet its metabolic needs. With a background in fetal metabolism and respiratory physiology, this article discusses adaptive mechanisms, both protective and potentially pathologic, whereby the fetus responds to an impairment in its exchange of oxygen. Most of this information is based on experimental data using unanesthetized fetal sheep with chronic catheterization; however, improved clinical investigative techniques including ultrasound scanning have supported the relevance of this experimental data to the human situation.

FETAL METABOLISM AND RESPIRATORY PHYSIOLOGY

Reviews of fetal metabolism and respiratory physiology exist[17,38,57,66] to which the reader is referred for more detailed information as it is beyond the scope of this article to present but a brief outline highlighting those aspects pertinent to the discussion of fetal asphyxia.

Substrate consumption has been well studied in the unanesthetized fetal sheep using Fick methodology with measurements of umbilical or cotyledonary blood flow and the venoarterial substrate difference across the placenta. Oxygen consumption rates measured by this means approximate 8 ml $\times$ min^{-1} $\times$ kg^{-1} body weight, although developmental aspects have been little studied with most measurements in near-term animals.[7] Measurements of fetal oxygen consumption in other species including humans indicate similar oxygen uptakes per kilogram body weight despite wide variations in species size, although the data are scantier and varying methodologies have been used.[7,12] Glucose would appear to be the major metabolic fuel of the ovine fetus, capable of sustaining 50 to 70 per cent of oxidative metabolism and representing 20 per cent of the total caloric requirement with substantial uptake also of lactate and amino acids.[7] Studies in the human fetus at the time of elec-

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tive cesarean section again suggest glucose to be the major metabolic fuel with a slightly higher uptake relative to oxygen than in the ovine fetus.[40,51]

This substrate consumption by the fetus serves two basic requirements: 1) the provision of fuel for energy production through the maintenance of oxidative metabolism, and 2) the provision of building materials for tissue growth. As reviewed by Battaglia and Meschia[7] one can make a quantitative comparison of these two aspects of fetal metabolism by expressing both in calories per unit time with the total caloric requirements of the fetus equal to the sum of the caloric equivalent of oxygen consumption plus the caloric equivalent of tissue growth. For the 120-day-old fetal lamb the caloric requirement of oxidative metabolism is approximately 56 kcal $\times$ day^{-1} $\times$ kg^{-1}, whereas that of tissue growth is approximately 32 kcal $\times$ day^{-1} $\times$ kg^{-1}, giving a total caloric requirement of approximately 88 kcal $\times$ day^{-1} $\times$ kg^{-1}. Although oxidative metabolism is clearly the major component of the total substrate requirements of the ovine fetus near term, tissue growth requirements are not insignificant. Furthermore, an unknown fraction of the energy produced from oxidative metabolism must fuel tissue growth. A variable "savings" in both ATP energy requirements and substrate building needs might

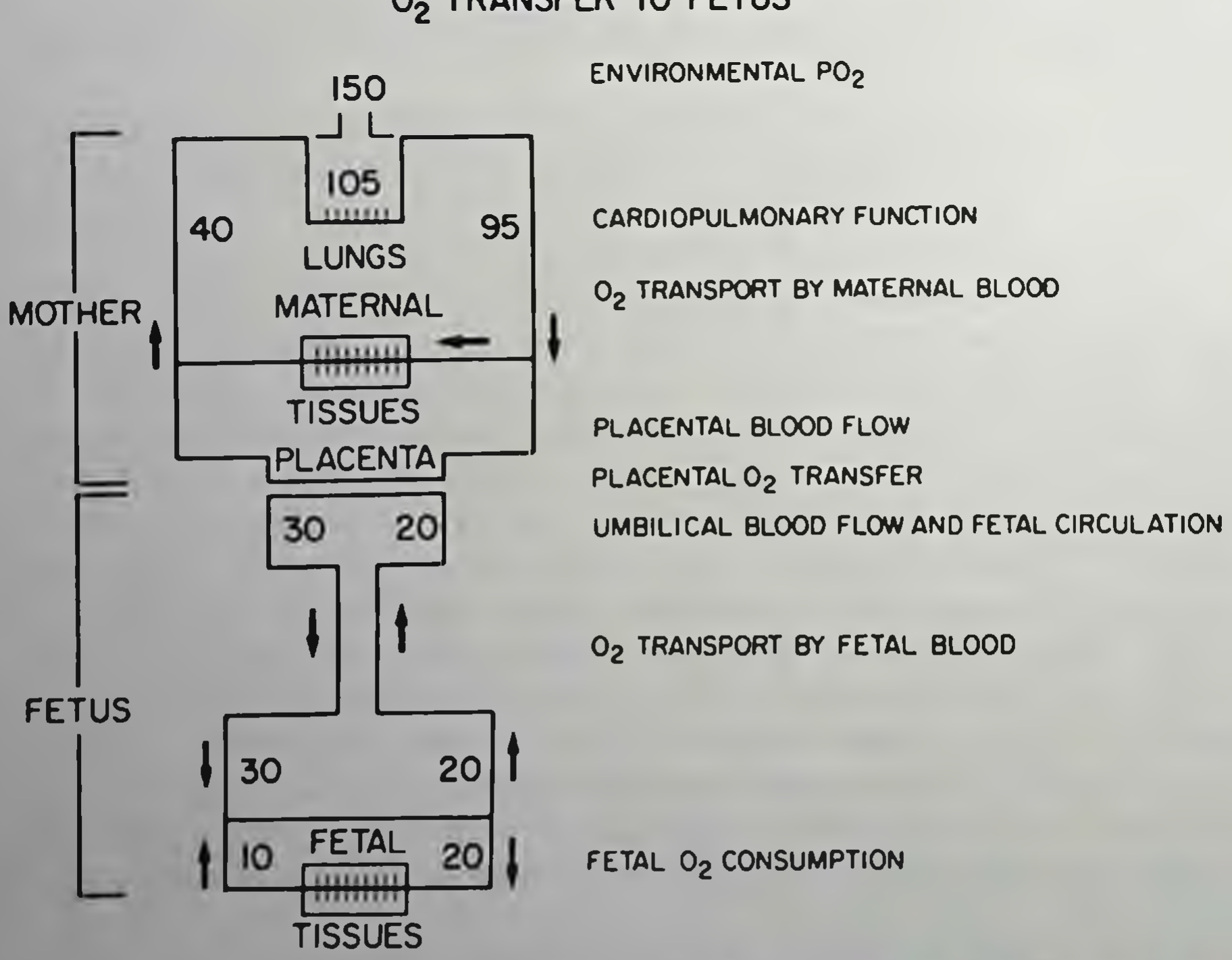

Figure 1. Maternal and fetal circulations. Numbers refer to Po_2 of each compartment (i.e., inspired air, alveolar air, maternal arterial and venous blood, umbilical venous and arterial blood, and fetal venous blood). *(Modified from* Towel M: Fetal respiratory physiology. In Goodwin JW, Godden JO, Chance GW (eds): Perinatal Medicine. Toronto, Longman–Canada Ltd, 1976, pp 171–186; with permission.)

therefore be realized with a falloff in tissue growth when substrate availability to the fetus becomes limited.

The transport of oxygen from the atmosphere to the fetal tissues requires a series of steps alternating bulk transport with transport by diffusion (Fig. 1). The normally low fetal arterial Po_2 of approximately 20 mm Hg can largely be attributed to two aspects of this transport process: 1) the venous equilibration of placental gas exchange, and 2) the admixture of umbilical venous and inferior vena caval blood within the fetus. In the ovine fetus the placenta appears to function as a venous equilibration system with concurrent gas exchange whereby both the maternal and fetal vascular streams run in the same direction.[38,69] With such a system the venous Po_2 of the umbilical circulation depends on, and cannot be higher than, the venous Po_2 of the uterine circulation. As reviewed by Meschia,[38] evidence also favors the use of this model in explaining the respiratory function of the human placenta. As shown in Figure 1, the transfer of oxygen from the uterine to the umbilical circulation does not in fact attain the maximal level of performance of a concurrent system with umbilical venous Po_2 approximately 10 mm Hg less than uterine venous Po_2 due to the consumption of oxygen, shunting of blood, and uneven perfusion within the placenta. The admixture of umbilical venous blood ($Po_2 \sim 30$ mm Hg) with blood from the fetal trunk and lower extremities ($Po_2 \sim 10$ mm Hg) further reduces the Po_2 of the resultant arterial blood supplying the fetal tissues ($Po_2 \sim 20$ mm Hg), although that supplying the upper body and head region has a slightly higher Po_2 due to preferential streaming of umbilical venous blood across the foramen ovale.[57]

In spite of the normally low arterial Po_2, the transport of oxygen to fetal tissues appears more than adequate with no evidence for anaerobic

Table 1. *Factors Decreasing O_2 Transfer to Fetus*

Environmental Po_2
High altitude
Maternal Cardiopulmonary Function
Cyanotic heart disease
O_2 Transport by Maternal Blood
Anemia
Cigarette smoking
Placental Blood Flow
Hypertension
Diabetes
Abruptio placenta
Uterine contractions
Placental O_2 Transfer
Abruptio placenta
Placental infarcts
Umbilical Blood Flow and Fetal Circulation
Umbilical cord occlusion
Heart disease
O_2 Transport by Fetal Blood
Anemia
Hemorrhage

Table 2. *Fetal Responses to Asphyxia*

Fetal Metabolism
"Oxygen margin of safety"
Substrate alterations
↓ Growth
Behavioral state alterations
↓ Fetal movements
Fetal O_2 Transport
↑ Blood O_2 capacity
Blood flow redistribution

glycolysis as a terminal source for energy production.[7] This is due in part to the increased oxygen-carrying capacity of fetal blood in turn due to the higher hemoglobin concentration which increases throughout gestation[66] and to the higher oxygen affinity, which permits the saturation of fetal blood with oxygen at a lower oxygen partial pressure. A second means whereby the oxygenation of fetal tissues is maintained is the relative overperfusion of fetal organs in comparison to their oxygen requirements; the cerebral blood flow O_2 consumption ratio is ~2.5 times higher in the fetal lamb than in the adult.[38] The result is an oxygen concentration in fetal blood only slightly less than that in maternal blood and oxygen delivery to some organs actually in access of their adult counterparts.

Interference with the transport of oxygen (and possibly of carbon dioxide) to (and from) the fetus can occur at any one of the transport steps as indicated in Table 1, thus leading to impairment of gas exchange and fetal asphyxia. It is important to note, however, that the extent to which gas exchange is impaired covers a spectrum and may lead to mild hypoxemia with little in the way of hypercapnia and acidemia or to severe hypoxemia with hypercapnia and progressive metabolic acidemia. Likewise, the time course over which the impairment in gas exchange occurs and whether there is continued deterioration of such may operate acutely over minutes or hours, subacutely over days, or chronically over weeks. Both the extent to which gas exchange is impaired and the duration of this impairment will come to bear on the fetal adaptive response. These are outlined in Table 2 and will be discussed under those metabolic and O_2 transport areas already reviewed.

FETAL RESPONSES TO ASPHYXIA

The Oxygen Margin of Safety

As previously reviewed, fetal oxygen consumption ($\dot{V}_{um}O_2$) is equal to the product of umbilical blood flow (Q_{um}) and venoarterial oxygen content difference ($v - a_{um}O_2$) across the umbilical circulation. This equation can be rearranged to $\dot{V}_{um}O_2 = Q_{um} . vO_2$ this being the umbilical oxygen delivery x

$$\frac{v - a_{um}O_2}{v_{um}O_2},$$

this being the fractional oxygen extraction (i.e., the oxygen consumed as a fraction of that delivered). Factors leading to an impairment in fetal blood gas exchange ultimately give rise to either a lowered umbilical venous oxygen concentration, as seen with a decrease in placental blood flow or O_2 transfer, or a lowered umbilical blood flow as seen with umbilical cord occlusion. Experiments in the ovine fetus with acutely induced decreases in umbilical vein oxygen content by decreasing maternal inspired oxygen concentration[18] or uterine blood flow[69] show umbilical blood flow to be little changed. Likewise, acute restrictions in umbilical blood flow appear to have little effect on umbilical vein O_2 concentration.[28] Thus acute reductions in either umbilical vein oxygen content or in umbilical blood flow will result in a corresponding reduction in umbilical oxygen delivery to the fetus. With a decrease in oxygen delivery however, the fetus is capable of a compensatory increase in fractional oxygen extraction, thus maintaining oxygen consumption. As oxygen extraction is a function of diffusion, any increase must involve an increase in the Po_2 difference across the umbilical circulation, ultimately resulting in a drop in the Po_2 of fetal arterial blood and thus fetal hypoxemia. Fetal hypoxemia, however, must be differentiated from fetal hypoxia, in which tissue oxygen supplies are inadequate to meet oxygen demands. It is in fact the degree to which fractional O_2 extraction can increase and fetal arterial Po_2 can fall before tissue oxygen supplies are inadequate which is the "oxygen margin of safety" as an indication of the oxygen reserve available to the fetus when oxygen delivery is decreased.

As reviewed by Edelstone,[23] the quantity of oxygen delivered to the fetus rather than the specific factor adversely affecting oxygen delivery appears to more important in determining the adequacy of fetal oxygenation. Studies in the ovine fetus with acute reductions in fetal oxygen delivery, including reduced maternal inspired oxygen concentration,[61] reduced uterine blood flow,[69] maternal anemia,[47] and umbilical cord restriction[28] all show fetal oxygen consumption to be well maintained by increases in O_2 extraction until oxygen delivery is reduced by approximately 50 per cent. At this time the fall in Po_2 within some fetal tissues presumably become rate limiting for oxygen consumption, which is normally ADP and not oxygen dependent. The difference between the normal fetal oxygen delivery of ~ 24 ml $\times$ $min^{-1} \times kg^{-1}$ and the lowest oxygen delivery associated with the maintenance of metabolic rate of ~ 12 ml $\times$ $min^{-1} \times kg^{-1}$ is the "oxygen margin of safety" or O_2 reserve to the ovine fetus. Of note, fractional O_2 extractions of ~ 50 per cent have been reported at the time of elective cesarean section for the human fetus,[51,60] which is somewhat higher than that of the fetal sheep in utero at ~ 33 per cent and may indicate a decreased "oxygen margin of safety."

Recently, we have studied the effect of acute but sustained hypoxemia of several hours' duration induced by decreasing maternal inspired oxygen concentration and sufficient to produce a progressive fetal metabolic acidosis.[61] Again, oxygen consumption by the ovine fetus was initially well maintained despite the drop in Po_2 of the descending aorta from 18 to 10 mm Hg, as fractional oxygen extraction increased with the fall in oxygen delivery (Fig. 2). However, acid–base balance became progressively compromised despite the maintenance of global oxygen

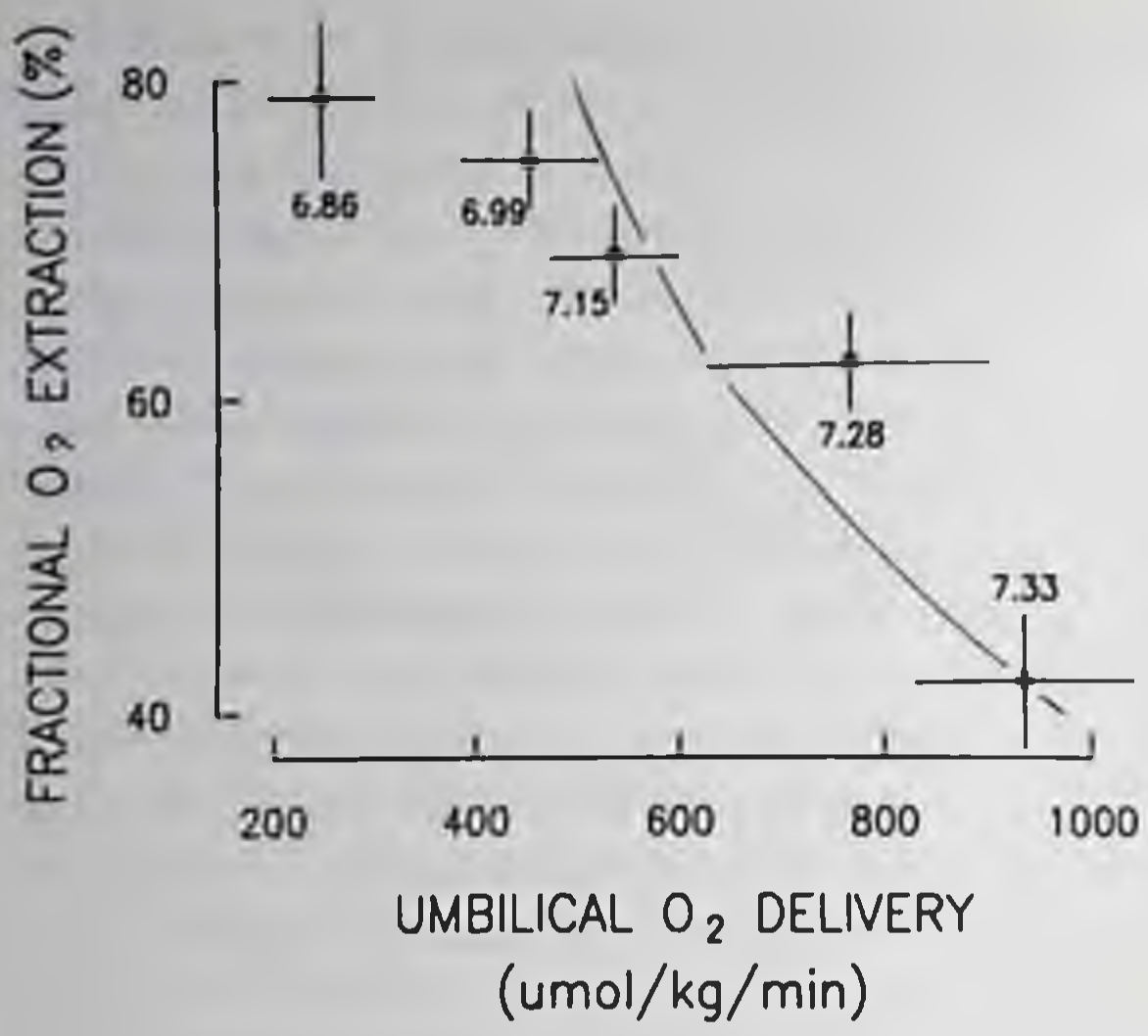

Figure 2. Relationship between umbilical O_2 delivery and fractional O_2 extraction before and during induced hypoxemia for the arterial pH changes indicated. The curvilinear line represents an iso-oxygen consumption line equal to that of the control value at pH_a 7.33 (i.e., the change in fractional O_2 extraction required with a given chance in umbilical O_2 delivery to maintain fetal O_2 consumption constant).

consumption as the degree of hypoxemia was sufficient to result in lactic acid accumulation. With the progressive metabolic acidemia, umbilical venous oxygen content continued to fall owing to the rightward shift in the oxyhemoglobin dissociation curve, resulting in a continued fall in fetal oxygen delivery. With fetal arterial pH much below 7.0, oxygen delivery fell to less than 50 per cent of control values, resulting in a terminal fall in oxygen consumption (see Fig. 2). Thus although the "oxygen margin of safety" provides the fetus with a given oxygen reserve and a degree of protection, with sustained hypoxemia sufficient to produce lactic acid accumulation this becomes limited by severe metabolic acidemia.

Anderson et al.[5] have studied the effect of prolonged reductions in fetal oxygen delivery over several days induced by decreasing distal aortic flow within the fetus to ~60 per cent of control values using inflatable occluders. Although fetal pH was little changed, oxygen consumption was a linear function of umbilical blood flow and thus oxygen delivery with no evidence for an oxygen margin of safety as seen with acute reductions in fetal oxygen delivery. This indicates that the fetus responds differently to long-term reductions in oxygenation and thus hypoxemia (or other substrate deficiencies) and with time has the ability to "turn off" oxygen-consuming processes such as growth and perhaps certain aspects of behavioral activity. The extent to which this rearrangement of metabolic priorities is protective or pathologic remains to be determined.

Substrate Alterations

Although oxidative metabolism has been studied extensively during asphyxia in the ovine fetus, there is much less information on the metabolic fate of other substrates. With acute short-term reductions in oxygenation, fetal glucose consumption may fall, and, coupled with increased glycogen mobilization, serve to ensure placental glucose

supply.[25] As fetal lactate concentrations rise this also may become an important source of substrate to sustain the placenta. During prolonged but mild hypoxemia with induced intrauterine growth restriction, Clapp et al.[17] have reported the umbilical uptake of glucose and lactate to be little changed relative to the uptake of oxygen, although both were decreased on an absolute and per kilogram fetal weight basis. Conversely in the human IUGR fetus at the time of elective cesarean section lactate production is evident, which is inversely correlated to umbilical artery oxygen content.[37,70]

Intrauterine Growth Restriction

Growth is known to account for a consequential fraction of the total substrate consumption of fetal sheep near term, as previously reviewed. In the ovine fetus with acutely induced hypoxemia of several hours' duration, protein synthesis is decreased, with a corresponding decrease in the energy requirements for growth equivalent to ~10 per cent of total oxygen consumption.[39] In the study of Anderson et al.[5] with prolonged reductions in fetal oxygen delivery over several days, total oxygen consumption was reduced 18 per cent, undoubtedly again reflecting in part a decreased rate of growth. With induced intrauterine growth restriction the ovine fetus demonstrates remarkable metabolic normality, with hypoxemia but no evidence of metabolic acidosis or anaerobic metabolism, suggesting a rapid adaptation to a limitation in substrate delivery with a decrease in growth rate and thereby substrate requirements.[17] In the study of Clapp et al.[17] with microsphere embolization of the placenta and thus a "late onsetting" IUGR, total fetal oxygen consumption was again decreased ~20 per cent. This decrease in oxidative metabolism will represent the energy "savings" from decreased tissue growth but also may reflect in part changes in behavioral activity and associated energy requirements.

The human fetus is obviously also capable of intrauterine growth restriction, and recent technical advances with intrauterine cordocentesis would suggest variable degrees of hypoxemia or decreases in umbilical venous oxygen saturation.[19,45,64] However, the human fetus grows considerably more slowly than the ovine fetus and must maintain itself metabolically over a longer period. As such the percentage of total caloric requirements represented by energy production would be especially large in comparison to that represented by tissue growth. It follows that the degree to which the human fetus can decrease its growth to provide continued substrate for needed energy production will be less than that of the ovine fetus although presumably this metabolic rearrangement of substrate use could be carried out for a longer period. Again, the extent to which this mechanism is protective by decreasing substrate requirements for energy and growth or gives rise to pathologic development of certain organ systems with time is not known.

Behavioral State Alterations

Behavioral states are evident in both the human[44] and ovine[22] fetus near term, with similarities to that of the human infant[49] in which metabolic rate differences also have been reported with oxygen consumption

higher during the active or rapid eye movement (REM) sleep state when compared to the quiet of non–rapid eye movement (NREM) sleep state.[65] The decreased incidence of the low-voltage electrocortical state or REM state seen in the ovine fetus with acute short-term hypoxemia,[11] acute sustained hypoxemia,[46] and with graded prolonged hypoxemia[52] has therefore led to speculation that this might reflect a change to a metabolic state with lower oxidative needs. Van Vliet et al.[67] have reported the appearance of well-defined behavior states to be delayed in the IUGR human fetus and the 4F or active awake state to be less evident than in the low-risk fetus, possibly again reflecting a metabolic compensatory response to mild hypoxemia. However, this speculation must be tempered by the findings of Walker et al.[68] in the ovine fetus, in which oxygen consumption fell only 6 per cent with a change from the low-voltage or REM state to the high-voltage or NREM state and only at higher prevailing levels of oxygen consumption.

Decreased Fetal Movements

Although the savings in energy expenditure with changes in fetal behavioral or activity states is questionable, at least for the fetal lamb, that with alterations in state-related biophysical parameters appears more definite. Rurak and Gruber[59] have shown neuromuscular blockade in the ovine fetus to result in a 17 per cent decrease in oxygen consumption, presumably owing in part to a decrease in breathing activity and other gross body movements. Conversely, fetal oxygen consumption has been shown to increase some 30 per cent during periods of fetal breathing activity when compared to apneic periods.[58] In the ovine fetus, body movements have been shown to decrease with acute short-term hypoxemia,[43] whereas breathing movements have been shown to decrease with both short-term[11] and prolonged hypoxemia.[52,72] Bekedam et al.[8] also have reported the number and duration of general movements to be decreased in the IUGR human fetus. Associated decreased in energy expenditure and thus oxygen requirements would be anticipated depending on the extent to which neuromuscular activity is decreased.

Increased Blood O_2 Capacity

Acute fetal hypoxemia results in an increase in hematocrit and thus blood O_2 capacity with associated increased in serum protein concentration suggesting a shift of water from the vascular to the extravascular space.[3,13] A decrease in fetal blood volume in response to induced hypoxemia has been confirmed by Brace[14] and shown to be rapid in onset and sustained, with intravascular volume returning to normal only slowly after correction of fetal blood gases. The hematocrit of human fetal blood obtained from the fetal scalp during labor and from the umbilical cord at delivery also is reportedly increased in the presence of fetal hypoxemia and acidosis.[66]

Fetal hematocrit is likewise increased in both the ovine[31,72] and human[19,64] IUGR fetus with stimulated erythropoiesis and increased red blood cell production presumably in response to chronic hypoxemia as shown in the fetal lamb.[35]

Blood Flow Redistribution

Hypoxemia results in well-described changes within the fetal circulation, both centrally and peripherally, thus enhancing the delivery of oxygen to so-called vital organs. Acute hypoxic stress in the ovine fetus increases umbilical venous return through the ductus venosus, facilitating the delivery of the most highly oxygenated blood directly to the heart, without prior passage through the hepatic circulation.[56,57] An increase in the preferential streaming of this blood through the foramen ovale into the left atrium and ventricle further enhances the delivery of available oxygen to the upper body and thus to the heart and brain.[56,57]

Peripherally, acutely induced hypoxemia results in a redistribution of cardiac output such that umbilical–placental flow is maintained, that to the heart, brain, and adrenals is increased, and that to other fetal tissues variously maintained or decreased depending on the means by which hypoxemia is induced and the severity of the insult.[18,29,48] In the ovine fetus this redistribution of cardiac output results in a hyperbolic increase in that directed to the heart and brain in inverse relation to arterial O_2 content such that oxygen delivery to these tissues is well maintained.[62] Bocking et al.[10] have shown this protective redistribution of cardiac output to be maintained for up to 48 hours with acutely induced hypoxemia (Pao_2 from 23 to 17 mm Hg, and the IUGR studies of Creasy et al.[20] with placental microsphere embolization indicate a similar blood flow pattern in response to chronic hypoxemia. Noninvasive studies in the human fetus with Doppler ultrasound imaging suggest a similar redistribution of blood flow to the brain with intrauterine growth restriction.[71] The mechanisms whereby these circulatory changes occur have been well reviewed by Rudolph et al.[56,57] and variously reflect an innerplay between local direct effects with changes in blood gases and pH, reflex effects initiated by baro- or chemoreceptors and mediated through the automatic nervous system, and hormonal influences including catecholamines, the renin–angiotensin system, vasopressin, ACTH, and cortisol.

Factors thus limiting fetal oxygenation initially will result in "hypoxemia" without acidemia, although oxygen delivery to the carcass may be decreased with a corresponding decrease in tissue Po_2. With further decreases in fetal oxygenation, the supply of O_2 to parts of the body other than the heart and brain becomes decreased such that lactic acid begins to accumulate with a resulting metabolic acidosis. This will reflect in part the onset of anaerobic metabolism in these tissues as the supply of oxygen falls below that required for aerobic energy production. However, lactate accumulation at this time also may reflect a corresponding increase in pyruvate levels triggered by relative tissue hypoxia but without relationship to actual oxygen deficiency.[27] With pronounced decreases in fetal oxygenation, oxygen supply to the heart and brain also begins to fall as the perfusion rate of these organs becomes maximal. In the ovine fetus this limit is reached at an O_2 content of ~ 1 mmol per liter in the supraductal arteries.[48,62] In the human fetus this limit may be reached at a somewhat higher level as the brain is ~ 6 to 7 times heavier per kilogram body weight and presumably receives a greater fraction of cardiac output at a given level of oxygenation.

With the venous equilibration of placental gas exchange, umbilical venous Pco_2 is also dependent on uterine venous Pco_2 although with a somewhat smaller difference ~3 mm Hg for the ovine fetus.[69] Thus factors impairing oxygen transfer to the fetus also may affect carbon dioxide transfer from the fetus, leading to CO_2 retention and fetal hypercapnia. With acute reductions in uterine blood flow and resultant increases in uterine venous Pco_2 there is a corresponding increase in fetal umbilical venous Pco_2.[69] However, the fetal Pco_2 increase is relatively small, approximating 5 mm Hg with 50 per cent reductions in uterine[69] or umbilical[28] blood flows and only 1 to 2 mm Hg with chronically induced IUGR.[17,72] Although this Pco_2 change may enhance blood flow redistribution, for example to the brain, and will contribute to fetal acidemia, the fetal response to reductions in oxygen delivery remains qualitatively the same.

FETAL CEREBRAL RESPONSES TO ASPHYXIA

Measurements of cerebral metabolism in the unanesthetized fetus of species that are more neurophysiologically mature at birth are again largely limited to sheep. Studies near term in this species, using the radioactive labeled microsphere technique for blood flow determination and Fick methodology, show cerebral oxidative metabolism to average 160 μmol $\times$ 100 gm^{-1} $\times$ min^{-1} and glucose to be the only substrate taken up in appreciable amount averaging 25 μmol $\times$ 100 gm^{-1} $\times$ min^{-1}.[33] This substrate consumption again provides for the energy requirements of tissue maintenance, functional activity and growth and for the provision of building materials for tissue growth. As reviewed by Abrams and Hutchinson[2] energy requirements for tissue maintenance are probably lower in the developing brain owing to less branching of cell processes and lower surface-to-volume ratios, whereas that owing to tissue growth is presumably increased. The response to asphyxia can again be considered under metabolic and O_2 transport headings as outlined in Table 3 and as previously reviewed for the whole fetus.

The Oxygen Margin of Safety

Cerebral oxygen consumption is equal to the product of cerebral blood flow and arterial–venous oxygen content difference across the cerebral circulation, and on rearrangement to the product of cerebral oxygen delivery and fractional O_2 extraction. In response to fetal hypox-

Table 3. *Fetal Cerebral Responses to Asphyxia*

Fetal Cerebral Metabolism
"Oxygen margin of safety"
Substrate alterations
↓ Growth
Behavioral state alterations
Fetal Cerebral O_2 Transport
Cerebral blood flow redistribution

emia, cerebral blood flow can increase to maintain oxygen delivery and thus consumption or fractional O_2 extraction can increase to maintain consumption. In the ovine fetus, acutely induced hypoxemia in fact results in a hyperbolic increase in cerebral blood flow in inverse relation to arterial O_2 content such that oxygen delivery and thus consumption is well maintained.[32] The resultant decrease in arterial–venous O_2 difference across the brain has the added advantage of minimizing decreases in capillary Po_2 and thus protects against the critical Po_2 at which oxygen availability becomes rate limiting for consumption. The minimizing of changes in capillary Po_2 and thus tissue Po_2 also may have homeostatic importance, for example, limiting any adverse effect on brain growth. Further enhancing the oxygen margin of safety for the fetal brain is the fact that relative to the amount of oxygen consumed, cerebral oxygen delivery exceeds that in the lamb and adult by some 70 per cent over a fourfold range of arterial O_2 content.[34] This can be ascribed to the higher fetal Pco_2 levels and the leftward shifted oxyhemoglobin dissociation curve, which act independently to increase cerebral blood flow at any given arterial oxygen content.[54,55]

In the studies of Jones et al.[32] with short-term fetal hypoxemia of an hour or less induced by acutely decreasing maternal inspired oxygen concentration, cerebral oxygen consumption was little changed despite reductions in fetal arterial Po_2 to 14 mm Hg or oxygen content to 1 mmol per liter with a resultant sagittal venous $Po_2 \sim 9$ mm Hg. This would indicate that cerebral oxidative metabolism is not Po_2 dependent and thus limited by oxygen availability until capillary Po_2 falls at least below this level.

In our study of acute but sustained fetal hypoxemia with progressive metabolic acidosis, cerebral oxidative metabolism was marginally decreased over the first few hours, which we speculate may be biologically significant and reflect a protective mechanism whereby nonessential metabolic activity is decreased, thus lowering oxidative needs.[53] This initial small fall in cerebral oxidative metabolism with fetal arterial pH between 7.30 and 7.15 was related to a similar fall in oxygen delivery and is consistent with the tight coupling of oxygen delivery to consumption within the brain (Fig. 3).[63] As arterial pH approached 7.00, blood pressure began to fall and a passive flow/pressure relationship became apparent for the cerebral circulation resulting in an ~50 per cent fall in cerebral oxygen delivery. However, a substantial increase in fractional O_2 extraction was now noted, thus maintaining O_2 consumption little changed from the initial decrease (see Fig. 3). With sustained hypoxemia and profound metabolic acidemia, arterial pH below 7.00, cerebral oxygen delivery fell further, with fractional O_2 extraction now also falling, resulting in a terminal fall in cerebral oxidative metabolism to less than 50 per cent of control values. Of note, sagittal vein Po_2 remained above 9 mm Hg and terminally even rose slightly. These values are within the range shown by Jones et al.[32] to be without a limiting effect on cerebral oxygen consumption supporting an intrinsic pathologic cause for the terminal fall in oxygen consumption rather than as a direct effect of limited oxygen availability.

Although the extent to which this study reflects the response of the human fetus is not known, the range in pH change induced is similar to

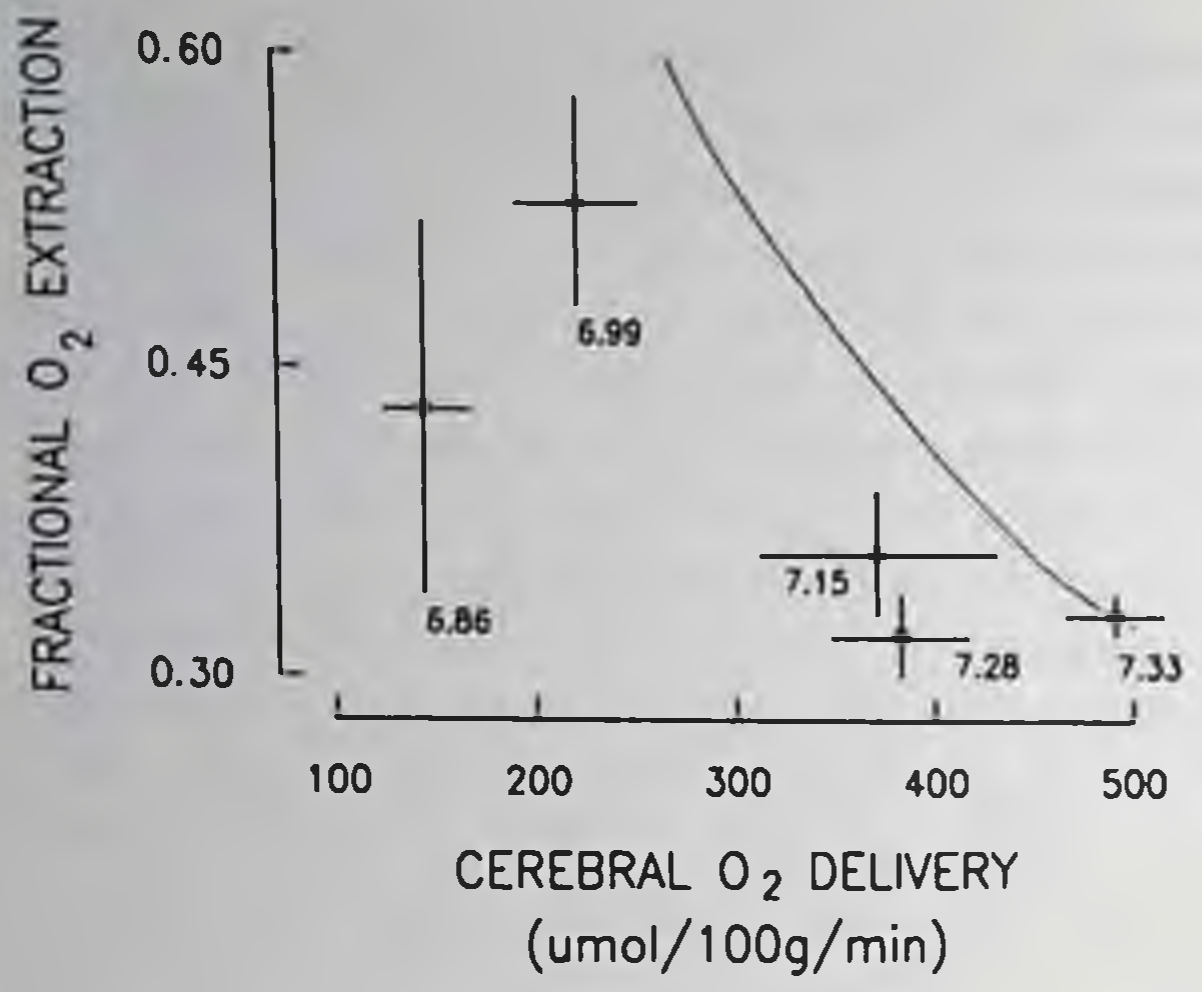

Figure 3. Relationship between cerebral O_2 delivery and fractional O_2 extraction before and during induced hypoxemia for the arterial pH changes indicated. The curvilinear line represents an iso-oxygen consumption line equal to that of the control value at pH$_a$ 7.33, i.e., the change in fractional O_2 extraction required with a given change in cerebral O_2 delivery to maintain cerebral O_2 consumption constant.

that reported by Low et al.[38] in human fetuses at birth with biochemical evidence of intrapartum fetal hypoxia. Of interest, in their study Low and colleagues found that an episode of hypoxia in excess of 1 hour resulting in a metabolic acidosis with a buffer base in the order of 25 mmol per liter would be followed by motor and cognitive deficits in approximately 50 per cent of these children. This same whole blood buffer base was reached in the ovine fetus after 5.6 hours of induced hypoxemia, at which time fetal arterial pH measured 6.99. A substantial oxygen margin of safety would thus appear to exist for the fetal brain when faced with a hypoxemic insult, with first an increase in blood flow to maintain delivery and, when this becomes limited as flow becomes pressure/passive, an increase in fractional O_2 extraction to maintain oxygen consumption. However, with progressive metabolic acidemia and a fall in O_2 delivery much below 50 per cent, cerebral O_2 consumption begins to fall abruptly and pathologic change seems likely.

Substrate Alterations

Although the cerebral uptake of other substrates has been little studied with induced fetal hypoxemia, a change in carbohydrate metabolism is suggested. In our study of acute but sustained hypoxemia, glucose uptake was increased from 26 μmol $\times$ 100 $gm^{-1} \times$ min^{-1} to a maximal value of 42 μmol $\times$ 100 $gm^{-1} \times min^{-1}$ when measured at arterial pH 7.15, with a decrease thereafter, although remaining above control values even terminally. Chao et al.[16] reported fetal cerebral glucose uptake to be increased relative to oxygen uptake, with acute decreases in oxygen delivery induced by the inflation of an occluder around the brachiocephalic artery. They also measured significant lactate excretion from the brain at this time, presumably reflecting glucose uptake in excess of aerobic glucose needs. Although this increase in glucose metabolism may provide for anaerobic ATP production as oxygen availability is decreased, an associated lactate accumulation within the fetal brain may be an important factor in subsequent brain injury.[42]

Decreased Growth

Pregnant rats made hypoxic over the latter half of gestation demonstrate a dose–response relation between the severity of hypoxia sustained and the magnitude of subsequent fetal growth restriction and reduction in brain weight.[24] Brown and Vannucci[15] have likewise shown fetal brain weight to be reduced in the IUGR rat fetus, but with no change in the level of cerebral oxidative metabolites. Studies in the fetal lamb with induced IUGR and associated hypoxemia also result in variable reductions in brain growth,[20,26] presumably dependent on the timing and severity of the inflicted insult. Although some sparing of the brain relative to other organs is usually evident, probably reflecting the increased cerebral blood flow in response to fetal hypoxemia, it is clear that with pronounced IUGR brain growth will be reduced. This same pattern is well described in the human fetus if intrinsic fetal disease or anomalies are excluded.[21] Although nutritional deprivation in other substrates cannot be excluded, oxygen availability would appear to be the primary factor determining brain growth with IUGR, possibly involving an alteration in neurotransmitter function in response to hypoxia.[15]

In the adult brain, energy-using processes are seen to be more sensitive to hypoxia than are energy-producing processes, since impairments in function may accompany hypoxia without measurable change in the store of high-energy compounds.[9] These functional impairments may be seen as protective in so far as they are reversible and maintain the levels of high-energy compounds and thus tissue integrity. In the fetus, brain growth and development may contribute significantly to energy utilization and as such be sensitive to relative hypoxia, as seen in the IUGR fetus. A decrease in brain growth may thus provide a protective mechanism whereby the level of cerebral oxidative metabolites is maintained, as noted in the study by Brown and Vannucci.[15] However, if prolonged it is conceivable that abnormalities in brain growth and development may contribute to the minimal cerebral dysfunction noted in followup studies of IUGR human infants.[4]

Behavioral State Alterations

Although the relationship between overall fetal metabolic rate and behavioral state remains unclear, evidence for such a relationship for the brain appears more certain. We have reported in the fetal lamb near term, a significant increase in cerebral oxygen consumption during the low-voltage electrocortical state or REM state.[50] Abrams et al.[2] have noted a similar increase in cerebral metabolic rate using the 2-deoxyglucose technique. Doppler flow velocity studies in the human fetus suggest a similar relationship given the tight flow-metabolism coupling reported for the brain.[71] This increased metabolic rate of the brain during the low-voltage electrocortical state may variously reflect increased neuronal activity or synthetic processes and suggests an important role for the increased incidence of this state during the accelerated growth and development of the brain through the perinatal period.[50]

As previously outlined, alterations in behavioral state are evident for both the ovine and human fetus in response to induced short-term hy-

poxemia[11] or presumed hypoxemia with IUGR.[67] With sustained fetal hypoxemia of several hours' duration, we have reported a decrease in both the low-voltage ECOG state and cerebral oxidative metabolism,[46,53] which, although possibly providing a short-term protective mechanism whereby oxidative needs are decreased, if prolonged may delay brain growth and development. Our recent studies with prolonged and graded hypoxemia over several days also resulted in a marginal but significant decrease in the incidence of the low-voltage ECOG state.[52] It is thus possible that alterations in behavioral states with associated changes in cerebral metabolism during the critical perinatal period may provide a mechanism whereby chronic hypoxemia, as seen with IUGR, gives rise to abnormal brain growth and development.

Cerebral Blood Flow Redistribution

Blood flow to the fetal brain not only increases in response to hypoxemia but a redistribution is evident with an apparent favoring of brain stem areas. In our study with sustained fetal hypoxemia, initial regional blood flow increases were such that oxygen delivery was increased to the pons and medulla, maintained to subcortical areas, and decreased to the cerebellum and cerebral cortex.[53] This hierarchy of regional blood flow change also has been noted by other groups[6,30] and has been proposed as a mechanism whereby critical brain stem structures remain little damaged during severe partial asphyxia.[41] Conversely, the relatively smaller increase in blood flow to the cerebral cortex with a resulting decrease in oxygen delivery suggests a mechanism whereby the cerebral cortex is more susceptible to asphyxial damage. However, whether these regional blood flow changes represent some protective differential effect of oxygen on cerebral vascular resistance or rather simply reflect regional changes in cerebral oxidative metabolism in response to hypoxia is not known. It is possible that nonessential metabolic activity is decreased in the cerebral cortex in response to relative hypoxia, with a resultant savings in energy expenditure, whereas that of vegetative brain stem areas may necessarily be increased. If the latter is in fact true, then mechanisms other than circulatory must be found to account for the pattern of brain damage observed with severe partial asphyxia.

SUMMARY

The fetal environment is thus well suited for normal growth and development with oxygen availability exceeding oxidative needs. With impairments in blood gas exchange this excess oxygen acts as a "margin of safety," providing for the maintenance of oxidative metabolism through increases in fractional O_2 extraction, although with resultant fetal hypoxemia. Increases in blood O_2 capacity and redistribution of cardiac output in response to this hypoxemia further protect fetal oxygenation. Additional adaptive mechanisms involve a decrease in energy-consuming processes, including growth restriction, decreasing fetal movements, and behavioral state alterations. Although protective in so

far as essential metabolic functions are maintained, pathologic change may occur as the "oxygen margin of safety" becomes limited or energy-conserving measures give rise to abnormal growth and development.

REFERENCES

1. Abrams RM, Hutchinson AA: Energy metabolism of developing brain. J Reprod Med 30:318–323, 1985
2. Abrams RM, Hutchinson AA, Jay TM, et al: Local cerebral glucose utilization nonselectively elevated in rapid eye movement sleep of the fetus. Dev Brain Res 40:65–70, 1988
3. Adamson TM, Boyd RDH, Hill JR, et al: Effect of asphyxia due to umbilical cord occlusion in the foetal lamb on leakage of liquid from the circulation and on permeability of lung capillaries to albumin. J Physiol 207:493–505, 1970
4. Allen MC: Developmental outcome and followup of the small for gestational age infant. Sem Perinat 8:123–156, 1984
5. Anderson DF, Parks CM, Faber JJ: Fetal O_2 consumption in sheep during controlled long-term reductions in umbilical blood flow. Am J Physiol 250:H1037–H1042, 1986
6. Ashwal S, Majcher JS, Longo L: Patterns of fetal lamb regional cerebral blood flow during and after prolonged hypoxia: Studies during the posthypoxic recovery period. Am J Obstet Gynecol 139:365–372, 1981
7. Battaglia FC, Meschia G: Principal substrates of fetal metabolism. Physiol Rev 58:499–527, 1978
8. Bekedam DJ, Visser GHA, de Vries JJ, et al: Motor behaviour in the growth retarded fetus. Early Hum Dev 12:155–165, 1985
9. Blass JP, Gibson GE: Consequences of mild, graded hypoxia. Adv Neurol 26:229–253, 1979
10. Bocking AD, Gagnon R, White SE, et al: Circulatory responses to prolonged hypoxemia in fetal sheep. Am J Obstet Gynecol 159:1418–1424, 1988
11. Boddy K, Dawes GS, Fisher R, et al: Foetal respiratory movements, electrocortical and cardiovascular responses to hypoxemia and hypercapnia in sheep. J Physiol 243:599–618, 1974
12. Bonds DR, Crosby LO, Cheek TG, et al: Estimation of human fetal–placental unit metabolic rate by application of the Bohr principle. J Dev Physiol 8:49–54, 1986
13. Born GVR, Dawes GS, Mott JC: Oxygen lack and autonomic nervous control of the foetal circulation in the lamb. J Physiol 134:149–166, 1956
14. Brace RA: Fetal blood volume responses to acute fetal hypoxia. Am J Obstet Gynecol 155:889–893, 1986
15. Brown JD, Vannucci RC: Cerebral oxidative metabolism during intrauterine growth retardation. Biol Neonate 34:170–173, 1978
16. Chao CR, Hohimer AR, Bissonnette JM: Cerebral carbohydrate metabolism during severe ischemia in fetal sheep. J Cereb Blood Flow Metab 9:53–57, 1989
17. Clapp JF, Szeot HH, Larrow R, et al: Fetal metabolic response to experimental placental vascular damage. Am J Obstet Gynecol 140:446–451, 1981
18. Cohn HE, Sacks EJ, Heyman MA, et al: Cardiovascular responses to hypoxemia and acidemia in fetal lambs. Am J Obstet Gynecol 120:817–824, 1974
19. Cox WL, Daffos F, Forestier F, et al: Physiology and management of intrauterine growth retardation: A biologic approach with fetal blood sampling. Am J Obstet Gynecol 159:36–41, 1988
20. Creasy RK, De Swiet M, Kahanpaa KV, et al: Pathophysiological changes in the foetal lamb with growth retardation. In KS Comline, KW Cross, GS Dawes, et al (eds): Foetal and Neonatal Physiology. Cambridge, Cambridge University Press, 1973, pp 398–402
21. Creasy RK, Resnik R: Intrauterine growth retardation. In Creasy RK, Resnik R (eds): Maternal–Fetal Medicine: Principles and Practice, Philadelphia, WB Saunders, 1984, pp 491–510

22. Dawes GS, Fox HE, Leduc BM, et al: Respiratory movements and rapid eye movement sleep in the foetal lamb. J Physiol 220:119–143, 1972
23. Edelstone DI: Fetal compensatory responses to reduced oxygen delivery. Semin Perinatol 8:184–191, 1984
24. de Grauw TJ, Myers RE, Scott WJ: Fetal growth retardation in rats from different levels of hypoxia. Biol Neonate 49:85–89, 1986
25. Gu W, Jones CT, Parer JT: Metabolic and cardiovascular effects on fetal sheep of sustained reduction of uterine blood flow. J Physiol 368:109–129, 1985
26. Harding JE, Jones CT, Robinson JS: Studies on experimental growth retardation in sheep: The effects of a small placenta in restricting transport to and growth of the fetus. J Dev Physiol 7:427–442, 1985
27. Huckabee WE: Relationships of pyruvate and lactate during anaerobic metabolism. III. Effect of breathing low-oxygen gases. J Clin Invest 37:264–271, 1958
28. Itskovitz J, La Gamma EF, Rudolph AM: The effect of reducing umbilical blood flow on fetal oxygenation. Am J Obstet Gynecol 145:813–818, 1983
29. Itskovitz J, La Gamma EF, Rudolph AM: Effects of cord compression on fetal blood flow distribution and O_2 delivery. Am J Physiol 252:H100–H109, 1987
30. Johnson GH, Palahniuk RJ, Tweed WA, et al: Regional cerebral blood flow changes during severe fetal asphyxia produced by slow partial umbilical cord compression. Am J Obstet Gynecol 135:48–52, 1979
31. Jones MD, Burd LI, Makowski EL, et al: Cerebral metabolism in sheep: a comparative study of the adult, the lamb, and the fetus. Am J Physiol 229:235–239, 1975
32. Jones MD, Sheldon RE, Peeters LL, et al: Fetal cerebral oxygen consumption at different levels of oxygenation. J Appl Physiol 43(6):1080–1084, 1977
33. Jones MD: Energy metabolism in the developing brain. Sem Perinat 3:121–129, 1979
34. Jones MD, Rosenberg AA, Simmons MA, et al: Oxygen delivery to the brain before and after birth. Science 216:324–325, 1982
35. Kitanaka T, Gilbert RD, Longo LD: Fetal responses to long-term hypoxemia (abstr 7). Society for Gynecologic Investigation 1987
36. Low JA, Galbraith RS, Muir DW, et al: Factors associated with motor and cognitive deficits in children after intrapartum fetal hypoxia. Am J Obstet Gynecol 148:533–539, 1984
37. Marconi AM, Cetin I, Ferrari MM, et al: Umbilical venous-arterial lactate concentration differences in normal and growth retarded human fetuses (abstr 18). Society for Gynecologic Investigation 1988
38. Meschia G: Placental respiratory gas exchange and fetal oxygenation. In Creasy RK, Resnik R (eds): Maternal–Fetal Medicine: Principles and Practice. Philadelphia, WB Saunders, 1984, pp 274–285
39. Milley JR: Protein synthesis during hypoxia in fetal lambs. Am J Physiol 252:E519–E524, 1987
40. Morriss FH, Makowski EL, Meschia G, et al: The glucose/oxygen quotient of the term human fetus. Biol Neonate 25:44–52, 1975
41. Myers RE: Two patterns of perinatal brain damage and their conditions of occurrence. Am J Obstet Gynecol 112:246–276, 1972
42. Myers RE, de Courten-Myers GM, Wagner KR: Effect of hypoxia on fetal brain. In Beard RW, Nathanielsz PW (ed): Fetal Physiology and Medicine: The Basis of Perinatology. New York, Marcel Dekker, 1984, pp 419–458
43. Natale R, Clewlow F, Dawes GS: Measurement of fetal forelimb movements in the lamb in utero. Am J Obstet Gynecol 140:545–551, 1981
44. Nijhuis JG, Prechtl HFR, Martin CB, et al: Are there behavioural states in the human fetus? Early Hum Dev 6:177–195, 1982
45. Pardi G, Buscaglia M, Ferrazzi E, et al: Cord sampling for the evaluation of oxygenation and acid–base balance in growth retarded human fetuses. Am J Obstet Gynecol 157:1221–1228, 1987
46. Patrick J, Richardson B, Rurak D, et al: Biophysical variables during sustained hypoxemia in fetal sheep (abstr 8). Society for Gynecologic Investigation 1987
47. Paulone ME, Edelstone DI, Shedd A: Effects of maternal anemia on uteroplacental and fetal oxidative metabolism in sheep. Am J Obstet Gynecol 156:230–236, 1987
48. Peeters LLH, Sheldon RE, Jones MD, et al: Blood flow to fetal organs as a function of arterial oxygen content. Am J Obstet Gynecol 135:637–646, 1979
49. Prechtl HFR: the behavioural states of the newborn infant. Brain Res 76:185–212, 1974

50. Richardson BS, Patrick JE, Abduljabbar H: Cerebral oxidative metabolism in the fetal lamb: Relationship to electrocortical state. Am J Obstet Gynecol 153:426–431, 1985
51. Richardson BS, Callahan W, Burnett A: Umbilical metabolites of the human fetus at term. Society of Perinatal Obstetricians, Abstr 154, 1987
52. Richardson B, Carmichael L, Homan J, et al: Electrocortical activity, electroocular activity and breathing movements in fetal sheep with prolonged, graded hypoxemia (abstr 233). Society for Gynecologic Investigation 1988
53. Richardson BS, Rurak D, Patrick JE, et al. Cerebral oxidative metabolism during sustained hypoxemia in fetal sheep. J Dev Physiol (in press)
54. Rosenberg AA, Jones MD, Traystman RJ, et al: Response of cerebral blood flow to changes in PCO_2 in fetal, newborn, and adult sheep. Am J Physiol 242:H862–H866, 1982
55. Rosenberg AA, Harris AP, Koehler RC, et al: Role of O_2 hemoglobin affinity in the regulation of cerebral blood flow in fetal sheep. Am J Physiol 251:H56–H62, 1986
56. Rudolph AM, Itskovitz J, Iwamoto H, et al: Fetal cardiovascular responses to stress. Semin Perinatol 5:109–121, 1981
57. Rudolph AM: The fetal circulation and its response to stress. J Dev Physiol 6:11–19, 1984
58. Rurak DW, Gruber NC: Increased oxygen consumption associated with breathing activity in fetal lambs. J Appl Physiol 54(3):701–707, 1983
59. Rurak DW, Gruber NC: The effect of neuromuscular blockade on oxygen consumption and blood gases in the fetal lamb. Am J Obstet Gynecol 145:258–262, 1983
60. Rurak DW, Selke P, Fisher M, et al: Fetal oxygen extraction: Comparison of the human and sheep. Am J Obstet Gynecol 156:360–366, 1987
61. Rurak DW, Richardson BS, Patrick JE, et al: Oxygen consumption in the fetal lamb during sustained hypoxemia with progressive acidemia. Am J Physiol (in press)
62. Sheldon RE, Peeters LLH, Jones MD, et al: Redistribution of cardiac output and oxygen delivery in the hypoxemia fetal lamb. Am J Obstet Gynecol 135:1071–1078, 1979
63. Sokoloff L: Relationships among local functional activity, energy metabolism and blood flow in the cerebral nervous system. Fed Proc 40:2311–2316, 1981
64. Soothill PW, Nicolaides KH, Campbell S: Prenatal asphyxia, hyperlacticaemia, hypoglycaemia, and erythroblastosis in growth retarded fetuses. Br Med J 294:1051–1053, 1987
65. Stothers JK, Warner RM: Oxygen consumption and neonatal sleep states. J Physiol 278:435–440, 1978
66. Towell ME: Fetal respiratory physiology. In Goodwin JW, Godden JO, Chance GW (eds): Perinatal Medicine. Toronto, Longman Canada Ltd, 1976, pp 171–186
67. van Vliet MAT, Martin CB, Nijhuis JG, et al: Behavioural states in growth-retarded human fetuses. Early Hum Dev 12:183–197, 1985
68. Walker AM, Fleming J, Smolich R, et al: Fetal oxygen consumption, umbilical circulation and electrocortical activity transitions in fetal lambs. J Dev Physiol 6:267–274, 1984
69. Wilkening RB, Meschia G: Fetal oxygen uptake, oxygenation, and acid-base balance as a function of uterine blood flow. Am J Physiol 244:H749–H755, 1983
70. Willett J, Richardson BS, Hunse C: Umbilical metabolites of the human fetus with intrauterine growth restriction or premature delivery (abstr 87). Society of Obstetricians and Gynaecologists of Canada 1988
71. Wladimiroff JW, van Bel F: Fetal and neonatal cerebral blood flow. Semin Perinatol 11:335–346, 1987
72. Worthington D, Piercy WN, Smith BT: Effects of reduction of placental size in sheep. Obstet Gynecol 58:215–221, 1981

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Fetal Movement Monitoring: Clinical Application

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It is 100 years since Playfair recommended that induction of labor should be carried out for decreased fetal movement.[36] However, it is only in the past 15 to 20 years that systematic assessment of fetal movement has been advocated. Over the same period, there has been increasing application of sophisticated technology to evaluate fetal health and, with the development of fetal heart rate monitors and ultrasound, biophysical methods have superseded biochemical tests. Assessment of fetal movement is the simplest of all the biophysical tests and can be done by the mother alone. Maternal counting of fetal movements is emerging as a useful component of fetal assessment—usually as a screening tool to guide more detailed investigation. We will outline the evaluation of fetal body movements as a clinical method of antepartum fetal assessment, its role in high-risk pregnancy and potential use as a universal screening technique in low-risk pregnancy.

PHYSIOLOGIC ASPECTS OF FETAL BODY MOVEMENTS

The motor function of the neonate develops *in utero* and requires complex neuromuscular control. Thus, the study of fetal movement patterns may give an indirect assessment of the integrity of the fetal central nervous system. Real-time ultrasound studies of fetal body movements from early pregnancy show a progressive development in the complexity of fetal movements throughout the first trimester.[3,17] By the early second trimester, the fetus performs the same range of movements as it does at term. Indeed, fetal movements have been correlated with outcome following first-trimester bleeding by Reinold[44] and Birnholz et al.[3] In cases of threatened abortion with the fetal heart present, the chances of subse-

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quent complete abortion was increased if fetal movement was absent. Studies on normal women in the third trimester show that fetal body movements occur 10 to 18 per cent of the time[45,46,48]

FACTORS INFLUENCING FETAL BODY MOVEMENTS

Gestational Age

Using real-time ultrasound, Roberts et al. found the percentage incidence of fetal trunk movements to be the same from 28 weeks to term.[48] Up to 33 weeks' gestation, however, the number of individual movements was greater, suggesting that the duration of individual movements was shorter in the early third trimester. This was supported by the 24-hour ultrasonic observations of fetal body movements between 24 and 28 weeks' gestation by Nasello-Paterson et al.[26] This showed that fetuses at 24 to 26 weeks' gestation averaged 53.4 movements per hour, significantly different from 46.2 movements per hour at 26 to 28 weeks. The total time spent moving was no different, however: 13.1 per cent at 24 to 26 weeks and 12.4 per cent at 26 to 28 weeks. Studies of maternally perceived fetal activity throughout the third trimester show maximal activity between 28 to 32 weeks' gestation and a gradual reduction toward term.[33,41] This may be related to a change in the fetus/amniotic fluid volume ratio and the maturing fetus with longer sleep cycles. This reduction in fetal activity in the late third trimester is slight and not enough to influence the normal range of fetal movement counting techniques. Connors et al. found that the number of maternally perceived fetal movements was constant from 24 weeks' gestation to term.[6]

Diurnal Rhythm

Using ultrasound observation over 24-hour periods, both Roberts et al.[47] and Patrick's group[32] found that the highest incidence of fetal movement was in the late evening.

Fetal Behavioral State

The function and activity of the fetal central nervous system exhibits a cyclical rhythmicity and this influences fetal movement and other biophysical activities. During quiet sleep, fetal movement is absent or diminished, whereas during active (rapid eye movement) periods the fetus is most active. It has been shown that fetal movement activity has a short term (20–40 minutes) cyclicity in addition to the longer diurnal rhythm.[31,55] Periods of fetal inactivity longer than 90 minutes are very unlikely to be due to these physiologic sleep periods. Fetal and maternal sleep cycles are independent of each other.

Hypoxia

The fetus responds to chronic hypoxia by attempting to reduce oxygen consumption and conserve energy. This may include a reduction or cessation of body movements. Goodlin and Lowe[11] observed that fetal movement and fetal heart rate accelerations were blunted in the pres-

ence of supine hypotension, suggesting that these activities may be lost early during asphyxia.

Drugs

Depressant drugs such as barbiturates, benzodiazepines, narcotics, and alcohol all cross the placenta and can reduce fetal movement temporarily. In therapeutic doses, most drugs do not reduce fetal movement.[59]

Smoking

Maternal cigarette smoking can reduce fetal movements temporarily.[12] This may be due to raised maternal carboxyhemoglobin levels or a direct effect of nicotine on the fetal central nervous system.[59] A recent review has shown that nicotine reduces fetal blood flow.[19]

Maternal Blood Glucose

Miller et al.[23] found an increase in fetal movements during the 30 minutes following maternal ingestion of 100 gm glucose, although there was no direct relationship between fetal movements and maternal blood glucose levels. However, Zimmer et al.[60] found no change in fetal body movements after intravenous administration of 50 gm dextrose in term and post-term fetuses, although fetal breathing movements were increased. Ritchie[46] found no correlation between the time of the last meal or plasma glucose levels and fetal body movements. In addition, fetal movement has not been found to be altered by a recent meal.[5,32]

Physical Stimulation

It is commonly believed that vigorous palpation will waken the fetus from a physiologic rest period and stimulate movement. This is not always so, and indeed Richardson et al.[45] found no significant change in fetal body movements following vigorous shaking of 17 normal, term fetuses. Fetal movements are often stimulated by amniocentesis.[16,49]

Light

A source of intense light applied to the maternal abdomen may stimulate fetal activity, but this has not been pursued as a clinical tool.[37]

Fetal Malformation

The fetus with a major malformation is more likely to have reduced fetal activity. In 822 high-risk pregnancies, Sadovsky and his colleagues recorded a 16.5 per cent fetal anomaly rate in those with reduced fetal activity compared to 1.0 per cent in those with normal movement patterns.[53] Rayburn and Barr[42] found that 28 per cent of abnormal fetuses had reduced fetal movements compared to 4 per cent of structurally normal fetuses. The main anomalies were detectable by ultrasound and included hydrocephaly, gastroschisis, musculoskeletal deformities, and nonimmune hydrops. This is a similar finding to the increased incidence of abnormal antepartum fetal heart rate testing in fetal anomalies[39] and confirms the observation that in fetal biophysical assessment: "abnormal fetuses do abnormal things."

Ultrasound

In 1975, David et al, reported that exposure of the fetus to ultrasound increased fetal movements.[7] This was refuted by subsequent reports,[15,38] including the prospective, randomized, double-blind study of Murrills et al.[25] It seems likely that the apparent increase in fetal activity during monitoring is due to greater maternal awareness and concentration. This is supported by the observation that women feel more fetal movements when connected to a cardiotocograph irrespective of whether the ultrasound is on or off.[56]

Sound

It has been reported that external sound stimulation will cause increased fetal movements in the third trimester that may be analogous to the neonatal "startle reflex."[4,10] Gagnon et al. found that a 5-second vibroacoustic stimulus from an electronic artificial larynx produced increased fetal movements over the next hour.[9] They postulated that this stimulus may alter the fetal behavioral state. This observation has been incorporated into some fetal assessment protocols.

FACTORS INFLUENCING MATERNAL PERCEPTION OF FETAL BODY MOVEMENTS

In general, maternal perception of fetal movements correlates well with objective ultrasound observation. The mother usually reports about 90 per cent of fetal movements detected by machine (range 64–100 per cent),[54] although she may not feel smaller movements.[14]

Rayburn noted that the small number of women who have difficulty in perceiving fetal body movements often improve when shown their fetus moving with real-time ultrasound.[43] We have made the same observation in our antepartum assessment unit.

Women perceive most fetal movements when lying down, fewer when sitting, and fewest while standing.[15] This is quite likely related to variation of maternal concentration in the different positions. Parity and fetal sex do not alter fetal activity or its perception by the mother.[59] The presence of an anterior placenta may reduce the mother's perception of fetal movements before but not after 28 weeks' gestation.[28] Mild exercise in normal pregnant women does not seem to alter the frequency of fetal body movements.[35]

Although several investigators have reported on the value of formal recording by the mother of perceived fetal movement with respect to fetal outcome, few have explored the effect of movement counting on the mother. The fear that daily movement counting may promote stress and anxiety as suggested by McIlwaine et al.[22] may have discouraged the more widespread acceptance of this technique of fetal evaluation. Draper et al. reported on postpartum observations made by 132 women asked to complete a fetal movement chart at some time during their pregnancy.[8] Although 55 per cent were "reassured," 23 per cent claimed they were "worried," and 17 per cent were neutral. Of 45

women making further comment, 21 made negative remarks about keeping a movement chart. These observations were made either in late pregnancy, or 6 weeks postpartum. In addition, the comments were subjective in that the women were directly solicited for their views. We have investigated maternal anxiety associated with fetal movement recording by applying the Spielberger State/Trait Anxiety Inventory, a standard psychometric instrument, to 200 healthy primigravidas at 28 weeks' gestation before randomizing them to keep fetal movement charts, record sleep patterns, or to do nothing (Liston RM, Bloom K, Zimmer P: unpublished data, 1988). The inventory was repeated at 37 weeks prior to the influence of the events of labor and delivery. There was no significant difference in state or trait anxiety between the groups, and no demonstrable deleterious effect from fetal movement counting with respect to state or trait anxiety.

METHODS OF ASSESSING FETAL MOVEMENT

Electromechanical Instruments

These devices rely on the fact that fetal movements alter the shape of the uterine and abdominal walls and that this is converted to an electrical signal. Such instruments may be electromagnetic or based on a strain gauge system and have been mainly used for investigation.[52,58]

Real-time Ultrasound

This is the most accurate method of assessing fetal movement and can be set up to video record movements for 24-hour studies. In most clinical assessment units, fetal movement is observed for shorter periods (up to 30 minutes) as part of a profile of fetal biophysical evaluation.[1,21]

Maternal Counting

Several different counting protocols have been proposed to record maternal perception of fetal movement. They all involve either: 1) counting for a fixed time period and recording the number of movements, or 2) recording the time taken to count a fixed number of movements. Initially, long, fixed periods (up to 12 hours) were tried but found to be impractical. In most studies, the mother is asked to rest quietly and count fetal movements for set periods—usually 30 to 60 minutes—once or more during the day.[13,18,27,30,40,51] Pearson and Weaver[33] developed the Cardiff "count-to-ten chart," which involves the mother counting until a specified number of movements are felt. The acceptable limits were determined by a study of daily fetal movement counts after 32 weeks' gestation in healthy women with a normal pregnancy outcome. Over the 12-hour counting period, 2.5 per cent of all counts fell below ten movements, and this was adopted as the lower limit of normal. This method has the advantage of allowing women to count while carrying on their daily activities and stop counting for the day when ten fetal movements have been noted. One disadvantage with this method is that by waiting the full 12 hours, abnormal results are reported in the evening when further fetal evaluation is difficult to arrange.

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Name:_____ Gestation:_____ Date Started:_____

Sample:

A.M.	M	T	W	T	F	S	S
8:00							
8:30							
9:00							
9:30				■			■
10:00		■			■		
10:30	■		■			■	
11:00							
11:30							
12:00							

Instructions:

This is a simple method by which the mother plays a role in checking the health of her own baby.

Start at 8:00 A.M. each day and count the number of times your baby moves until you have recorded ten movements. Block out the time the tenth movement occured, as shown in the sample.

If the baby has moved less than ten times by noon (ie. four hours), fill in the exact number of times the baby moved and notify your doctor or the nursing staff in the Antepartum Assessment Unit.

A.M.	M	T	W	T	F	S	S	M	T	W	T	F	S	S	M	T	W	T	F	S	S	M	T	W	T	F	S	S	M	T	W	T	F	S	S
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A.M.	M	T	W	T	F	S	S	M	T	W	T	F	S	S	M	T	W	T	F	S	S	M	T	W	T	F	S	S	M	T	W	T	F	S	S
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Figure 1. Fetal movement record (Grace Maternity Hospital, Halifax, Nova Scotia).

Table 1. *Fetal Movement Counting*•

TIME (HOURS)	WOMEN (%)	DAILY COUNTS (%)
<3	419 (54.4)	3717 (83.3)
3–6	251 (32.6)	582 (13.0)
6–12	97 (12.6)	162 (3.6)
>12	3 (0.4)	3 (0.1)
Total	770	4464

• Time taken to reach 10 movements.

In a study of 770 high-risk pregnancies admitted to the antenatal ward of the Grace Maternity Hospital in Halifax beyond 30 weeks' gestation, 4464 daily observations of fetal movement were made on the Cardiff count-to-ten chart (Liston RM, Baskett TF: unpublished data). In 96 per cent of the days, ten movements were perceived within 6 hours (Table 1). Thus, we have modified the Cardiff chart using a fixed counting time frame from waking to noon (Fig. 1). This facilitates further fetal assessment on the same day by biophysical profile or nonstress test for the small number of patients who do not perceive ten movements by noon.

APPLICATION TO HIGH-RISK PREGNANCY

Several authors have reported on the association of reduced fetal activity with fetal compromise. Sadovsky and others,[50] after examining daily fetal movement counts in women with chronic disease, described "a movement alarm signal" based on a substantial decrease or total absence of movements. Leader and co-workers[18] asked women to record fetal movements for $4 \times \frac{1}{2}$ hour periods daily, "abnormal movement" was defined as a day of absent movement, or 2 successive days in which there were fewer than 10 movements in the total counting period. They found a significant association between abnormal fetal movements and both stillbirth and poor neonatal condition. Pearson and Weaver[33] in a study of 61 "at-risk" women, found a normal daily fetal movement count was associated with a good outcome, whereas low movement counts were associated with fetal asphyxia and death. When stillbirth occurred, movements diminished rapidly and stopped 12 to 24 hours prior to documented fetal death.

Since these initial reports, several authors have incorporated movement counting protocols for fetal surveillance in high-risk pregnancy.[13,20,30,43] They have employed different counting protocols using different "movement alarm signals" and different outcome measures against which to evaluate movement counting. Most authors have commented on the value of reduced movement as a predictor of intrauterine fetal death. Because in these descriptive series the results of movement counting were usually available to the clinician, however, pregnancy intervention may have resulted from reduced fetal movement alone or as a result of further fetal evaluation. Thus, in all series, in addition to considering perinatal death, abnormal antepartum and intrapartum

heart rate tracings and indices of neonatal morbidity have been used as measures of outcome.

Liston and co-workers, using a count-to-ten chart, found that fetal compromise, defined as intrauterine fetal death, fetal distress in labor and, in the absence of labor, a positive contraction stress test, was significantly more common in women who perceived reduced movement. Reduced fetal activity was reported in 8 per cent and fetal compromise occurred in three quarters of these. The positive predictive value for fetal compromise in this series was 63 per cent. Rayburn and others[43] asked women to record fetal movement counting for at least 1 hour each day. A movement count of three or less being considered abnormal. Women were also subject to routine antepartum heart rate monitoring. They compared the predictive value of movement counting with that of the antepartum heart rate monitoring and, not surprisingly, found that an active fetus was as reliable a predictor of a good outcome as a reactive nonstress test. More important, the predictive value for an unfavorable perinatal outcome with reduced fetal activity was similar to that of a nonreactive nonstress test.

Rayburn later reported the use of fetal movement counting in over 1000 high-risk pregnancies,[41] using a similar counting protocol. Reduced activity was reported in 5 per cent of women, and 35 per cent of these experienced stillbirths. The stillbirth rate among women reporting good fetal activity was 0.6 per cent. Using a combined morbidity/mortality index, incorporating abnormal fetal heart rate patterns and low Apgar scores as well as intrauterine fetal death, 54 per cent of pregnancies with reduced movement were so compromised as compared to 9 per cent with good movement. The high numbers of stillbirths in this series suggest that this counting protocol is too strict as fetal hypoxia may be well established by the time movements fall to this low level.

Harper et al.[13] compared fetal movement recording with nonstress testing, using counting over 3 × 1 hour periods in a day and absence of movement over the day as the alarm signal. Reduced movement was predictive of an abnormal nonstress test. However, O'Leary and Andrinopoulous[30] did not find such an association using three 30-minute counting periods in a day, with five movements or fewer in each period constituting an abnormal count. The difference in these two studies is probably related to the strictness of the movement alarm signal.

In relating the individual components of a biophysical profile to perinatal death, we found that, of all the variables, fetal movement had the best predictive value.[2] This lends support to the use of fetal movement counting as a screening test for fetal asphyxia. It is probable that maternal perception of fetal movement will be reduced earlier than ultrasound observation and thus may represent an earlier warning of asphyxia.

Thus, the association between reduced movement and fetal compromise seems clear. Its simplicity and ease of use commends its application as an adjunct to conventional monitoring for fetal surveillance in high-risk pregnancy. The reported false-negative result rates for the various methods are low. The false-positive rates, up to 70 per cent considering morbidity and 80 per cent considering mortality, need to be appreciated.[54] Because the proportion of women reporting reduced

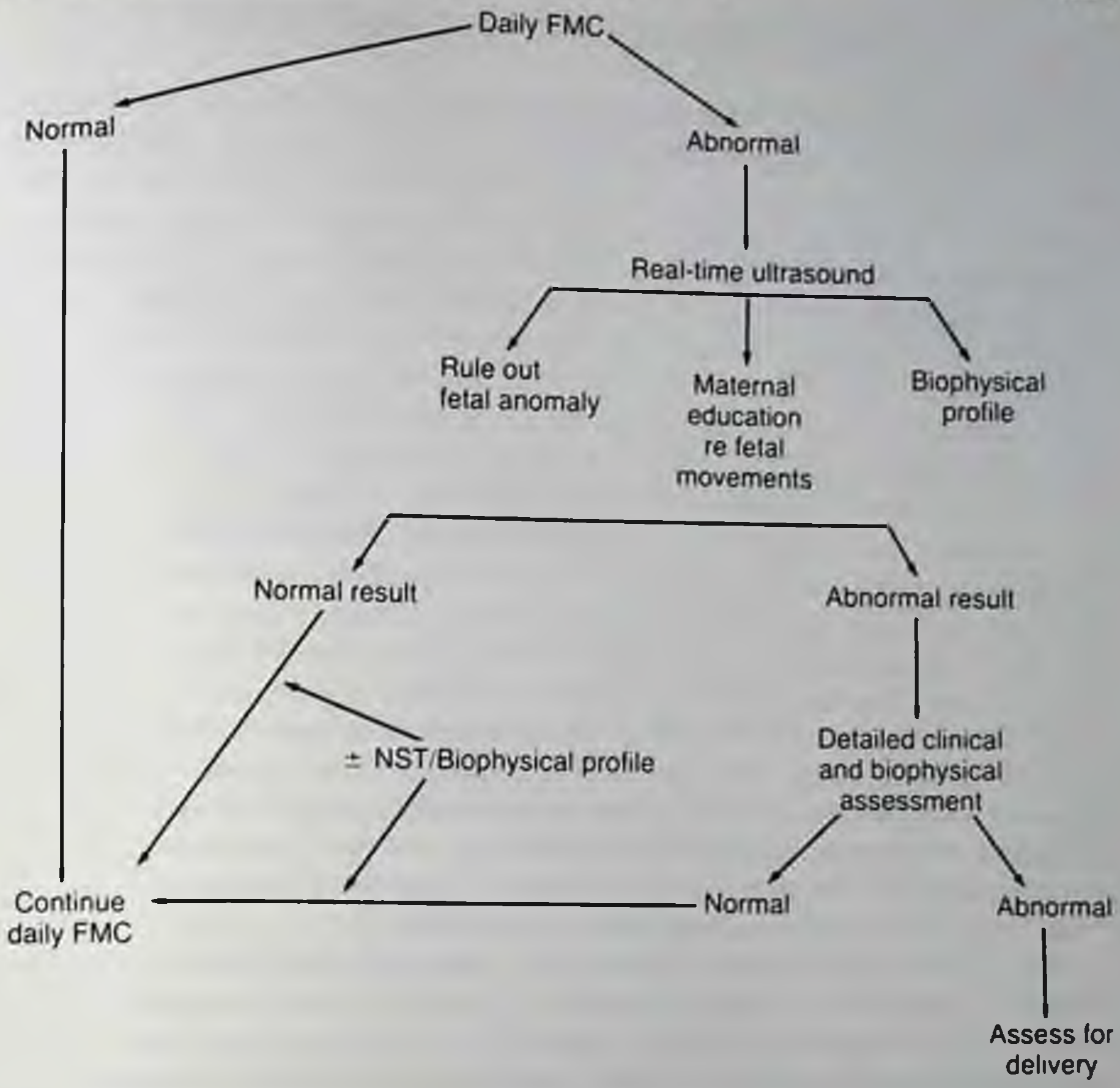

Figure 2. Fetal movement counting. Protocol for high-risk pregnancy.

movement is low, however, these high false-positive results are manageable. Nevertheless, as Rayburn has stressed,[40] a decision to intervene should not be based solely on fetal activity patterns.

The patient recording diminished fetal movements should have a careful clinical review and fetal assessment by ultrasound. During real-time ultrasound evaluation, fetal death and gross fetal anomalies should be excluded. Fetal biophysical activities can be assessed and the mother educated as she observes the fetus moving on the ultrasound screen. If this assessment shows the fetus to be active and normal, the mother can continue with fetal movement counting—often more aware for this visual demonstration. If not, a more detailed clinical and fetal biophysical assessment is indicated. This may include a full biophysical profile, amniocentesis, nonstress test, and contraction stress test to evaluate the fetus and guide subsequent management further (Fig. 2).

The choice of counting protocol should be guided by its acceptance and ease of application in the pregnant population. In addition, the level of the alarm signal should be high enough to detect early asphyxia, but low enough to keep the false-positive rate to a manageable level. We believe that the modified Cardiff count-to-ten chart fulfills these criteria.

APPLICATION TO LOW-RISK PREGNANCY

The experience of fetal movement counting in high-risk pregnancy has prompted the suggestion that movement counting be applied as a means of fetal assessment to the general pregnant population. In this regard, fetal movement counting is attractive in that it is cheap, requiring no sophisticated equipment or personnel, may be carried out on a daily basis in the home, and is noninvasive. Westgate and Jamieson[57] compared stillbirth and perinatal death rates in a hospital clinic population in Australia prior to and after the introduction of fetal movement record cards. There was a significant reduction in both death rates, but unfortunately information as to which patients received movement record cards and how they were completed is not available. It is not possible, therefore, to relate the changes in perinatal mortality directly to the introduction of such cards. Piacquadio and Moore[34] reported a significant drop in the fetal mortality rate at one hospital in San Diego, after the introduction of a fetal movement counting protocol. The warning sign was taken as fewer than 10 perceived movements in 2 hours. Again, no indication of compliance is given and details of other policy changes that could have affected the stillbirth rate are not mentioned. Even more important, there is no mention of overall perinatal mortality, and therefore it is not possible to ascertain the perinatal implications of the "threefold increase in intervention for inadequate fetal activity" and the 13 per cent increase in the requirement for antepartum monitoring.

Neldam[27] used a protocol in which women counted movements for 1 hour, 2 hours after a meal, three times weekly after 30 weeks' gestation. Counts below three were repeated for a second hour, and women were instructed to report if the count remained at fewer than three per hour. On the basis of their record numbers, 2250 women were assigned to counting protocols, or not to count. When a reduction in movement was perceived, further fetal evaluation, using ultrasound and antepartum heart rate monitoring, was instituted and delivery expedited if fetal movement remained reduced. Neldam reported a significant difference in the number of stillbirths (> 1500 gm, without lethal anomaly): eight in the noncounting group and zero in the counting group. However, allocation was not random, could have been biased, and no demographic details for the two groups are available. There was a high attrition rate (almost 30 per cent) and the control group—although not formally counting—were asked about reduced fetal movement during their antenatal visits. Whether the intervention for reduced fetal movement itself led to perinatal morbidity or mortality is not detailed. Nevertheless, the results point toward a potential benefit for fetal movement counting in low-risk pregnancy and, of note, only nine of those counting fetal movements reported a diminution, with intervention occurring in seven—certainly a low false-positive rate. Acceptability by the women appears to have been a problem with a high rate of attrition. Patient motivation in a problem pregnancy may be high, focused by concern, but in low-risk pregnancy, testing of any kind may be seen as "unnecessary intervention." On the other hand, the high attrition may simply be a reflection of the rather complicated and prolonged counting protocol employed.

Further information is available in a second report from Neldam of an extended study[29] in which demographic data on the two groups suggest no major differences. Again, there was a significant difference in the number of stillbirths between the control group (12 stillbirths), and the experimental group (3 stillbirths).

In our population, experience with the modified Cardiff chart in low-risk pregnancy suggests high patient acceptability and a low false-positive result rate. Of 178 women recording fetal movements, only 1 perceived diminished movement and was subjected to further assessment. This demonstrated an active fetus with a reactive nonstress test and thereafter fetal movement counts were plentiful. The overall attrition rate (8 per cent) was the same whether women were assigned to record fetal movement, or sleep patterns (Liston RM, Bloom K, and Zimmer P: Unpublished data, 1988).

SUMMARY

Although many factors influence fetal movements, maternal perception of gross fetal movement appears to be an accurate reflection of fetal activity. Observation in humans and studies in animals indicate that the compromised fetus reduces its oxygen requirements by reducing activity. This fact has enabled perceived fetal movement to become a useful adjunctive test of fetal asphyxia in high-risk pregnancy.

Its application to low-risk pregnancy has many attractions, particularly as approximately 50 per cent of stillbirths occur without obvious cause in normal pregnancies. Although studies suggest that such application would be beneficial, questions about acceptability, the burden of further testing precipitated by reports of diminished movement, and the perinatal implications of unwarranted early intervention need to be clarified before the universal application of fetal movement counting protocols can be recommended.

REFERENCES

1. Baskett TF, Gray JH, Prewett SJ, et al: Antepartum fetal assessment using a fetal biophysical profile score. Am J Obstet Gynecol 148:630, 1984
2. Baskett TF, Allen AC, Gray JH, et al: Fetal biophysical profile and perinatal death. Obstet Gynecol 70:357, 1987
3. Birnholz JC, Stephens JC, Faria M: Fetal movement patterns: A possible means of developing neurologic developmental milestones in utero. Am J Roentgenol 130:537, 1978
4. Birnholz JC, Benacerrof BR: The development of human fetal hearing. Science 222:516, 1983
5. Birkenfeld A, Laufer N, Sadovsky E: Diurnal variation of fetal activity. Obstet Gynecol 55:417, 1981
6. Connors G, Natale R, Nasello-Paterson C: Maternally perceived fetal activity from twenty-four weeks' gestation to term in normal and at risk pregnancies. Am J Obstet Gynecol 158:294, 1988
7. David H, Weaver JB, Pearson JF: Doppler ultrasound and fetal activity. Br Med J 2:62, 1975

8. Draper J, Field S, Thomas H: Women's views on keeping fetal movement charts. Br J Obstet Gynaecol 93:334, 1986
9. Gagnon R, Hunse C, Carmichael L, et al: Effects of vibratory acoustic stimulation on human fetal breathing and gross body movements near term. Am J Obstet Gynecol 155:1227, 1986
10. Gelman SR, Wood S, Spellacy WN, et al: Fetal movements in response to sound stimulation. Am J Obstet Gynecol 143:484, 1982
11. Goodlin RC Lowe EW: Multiphasic fetal monitoring. Am J Obstet Gynecol 119: 341, 1974
12. Goodman JDS, Visser FGA, Dawes GS: Effects of maternal cigarette smoking on fetal trunk movements, fetal breathing movements and the fetal heart rate. Br J Obstet Gynaecol 91:657, 1984
13. Harper RG, Greenberg M, Farahani G, et al: Fetal movement, biochemical and biophysical parameters and the outcome of pregnancy. Am J Obstet Gynecol 141:39, 1981
14. Hertogs K, Roberts AB, Cooper D, et al: Maternal perception of fetal motor activity. Br Med J 2:1183, 1979
15. Hertz RH, Timor-Tritsch I, Dierker LJ, et al: Continuous ultrasound and fetal movement. Am J Obstet Gynecol 135:152, 1979
16. Hill LM, Platt LD, Manning FA: Immediate effect of amniocentesis on fetal breathing and gross body movements. Am J Obstet Gynecol 135:689, 1979
17. Ianniruberto A, Tajani E: Ultrasonographic study of fetal movements. Semin Perinatol 5:175, 1981
18. Leader LR, Baillie P, Van Scholkwyk DJ: Fetal movements and fetal outcome: A prospective study. Obstet Gynecol 57:431, 1981
19. Lindblad A, Marsal K, Andersson K: Effect of nicotine on human fetal blood flow. Obstet Gynecol 72:371, 1988
20. Liston RM, Cohen AW, Mennuti MT, et al: Antepartum fetal evaluation by maternal perception of fetal movement. Obstet Gynecol 60:424, 1982
21. Manning FA, Platt LD, Sipos L: Antepartum fetal evaluation: Development of a fetal biophysical profile. Am J Obstet Gynecol 136:787, 1980
22. McIlwaine GM, Howat RCL, Dunn FM, et al: Perinatal practice and compensation for handicap. Br Med J 281:1067, 1980
23. Miller FC, Skiba H, Klapholz H: The effect of maternal blood sugar levels on fetal activity. Obstet Gynecol 52:662, 1978
24. Minors D, Waterhouse J: The effect of maternal posture, meals and time of day on fetal movements. Br J Obstet Gynaecol 86:717, 1979
25. Murrills AJ, Barrington P, Harris PD, et al: Influence of Doppler ultrasound on fetal activity. Br Med J 286:1009, 1983
26. Nasello-Paterson C, Natale R, Connors G: Ultrasonic evaluation of fetal body movements over twenty-four hours in the human fetus at twenty-four to twenty-eight weeks' gestation. Am J Obstet Gynecol 158:312, 1988
27. Neldam S: Fetal movements as an indicator of fetal well-being. Lancet 7:1222, 1980
28. Neldam S: Fetal movements: A comparison between maternal assessment and registration by means of dynamic ultrasound. Dan Med Bull 29:196, 1982
29. Neldam S: Fetal movements as an indicator of fetal well-being. Dan Med Bull 30:274, 1983
30. O'Leary JA, Andrinopoulos GC: Correlation of daily fetal movements and the nonstress test as tools for assessment of fetal welfare. Am J Obstet Gynecol 139:107, 1981
31. Patrick J, Fetherson W, Vick H, et al: Human fetal breathing and gross body movements at 34-35 weeks gestation. Am J Obstet Gynecol 130:693, 1978
32. Patrick J, Campbell K, Carmichael L, et al: Patterns of gross fetal body movements over 24-hour observation intervals over the last 10 weeks of pregnancy. Am J Obstet Gynecol 142:363, 1982
33. Pearson JF, Weaver JB: Fetal activity and fetal wellbeing: An evaluation. Br Med J 1:1305, 1976
34. Piacquadio K, Moore TR: Prospective evaluation of fetal movement screening to reduce the incidence of antepartum fetal death (abstr). Proceedings of the American College of Obstetricians and Gynecologists, Boston, 1988

35. Platt LD, Artal R, Semel J, et al: Exercise in pregnancy: II Fetal responses. Am J Obstet Gynecol 147:487, 1983
36. Playfair WS: A Treatise on the Science and Practice of Midwifery. London, Smith Elder, 1884:153
37. Polishuk WZ, Laufer N, Sadovsky E: Fetal response to external light stimulus. Harefuah 89:395, 1975
38. Powell Phillips WD, Towell ME: Doppler ultrasound and subjective assessment of fetal activity. Br Med J 2:101, 1979
39. Powell Phillips WD, Towell ME: Abnormal fetal heart rate associated with congenital abnormalities. Br J Obstet Gynaecol 87:270, 1980
40. Rayburn WF, Zuspan FP, Motley ME: An alternative to antepartum fetal heart rate testing. Am J Obstet Gynecol 138:223, 1980
41. Rayburn WF: Clinical implications from monitoring fetal activity. Am J Obstet Gynecol 144:967, 1982
42. Rayburn WF, Barr M: Activity patterns in malformed fetuses. Am J Obstet Gynecol 142:1045, 1982
43. Rayburn WF: Antepartum fetal assessment: Monitoring fetal activity. Clin Perinatol 9:232, 1982
44. Reinhold E: Clinical value of fetal spontaneous movements in early pregnancy. J Perinat Med 1:65, 1973
45. Richardson B, Campbell K, Carmichael L, et al: Effect of external physical stimulation on fetuses near term. Am J Obstet Gynaecol 139:344, 1981
46. Ritchie JWK: Fetal breathing and generalized fetal movements in normal antenatal patients. Br J Obstet Gynaecol 86:612, 1979
47. Roberts AB, Little D, Cooper D, et al: Normal patterns of fetal activity in the third trimester. Br J Obstet Gynaecol 86:4, 1979
48. Roberts AB, Griffin D, Mooney R, et al: Fetal activity in 100 normal third trimester pregnancies. Br J Obstet Gynaecol 139:344, 1981
49. Ron M, Yaffe H, Sadovsky E: Fetal heart response to amniocentesis in cases of decreased fetal movements. Obstet Gynaecol 48:456, 1976
50. Sadovsky E, Yaffe H, Polishuk WZ: Fetal movement monitoring in normal and pathologic pregnancy. Int J Gynaecol Obstet 12:75, 1974
51. Sadovsky E, Polishuk WZ: Fetal movements in utero. Obstet Gynaecol 50:49, 1977
52. Sadovsky E, Polishuk WZ, Yaffe, et al: Fetal movements recorder, use and indications. Int J Gynaecol Obstet 15:20, 1977
53. Sadovsky E, Rabinowitz R, Yaffe H: Decreased fetal movements and fetal malformations. J Fetal Med 1:62, 1981
54. Thacker SB, Berkelman RL: Assessing the diagnostic accuracy and efficacy of selected antepartum fetal surveillance techniques. Obstet Gynaecol Surv 4:121, 1986
55. Timor-Tritsch IE, Dierker LJ, Hertz RH et al: Studies of antepartum behavioral state in the human fetus at term. Am J Obstet Gynaecol 132:524, 1978
56. Weinstein D, Navot D, Sadovsky E: Antepartum ultrasound fetal heart rate monitoring and fetal movements. J Obstet Gynaecol 2:85, 1981
57. Westgate J, Jamieson M: Stillbirths and fetal movements. NZ Med J 99:114, 1986
58. Wood C, Walters WAW, Trigg P: Methods of recording fetal movement. Br J Obstet Gynaecol 84:561, 1977
59. Wood C, Gilbert M, O'Connor A, et al: Subjective recording of fetal movement. Br J Obstet Gynaecol 86:836, 1979
60. Zimmer EZ, Divonm MY, Goldstein, et al: Intrauterine fetal activity in at term and prolonged pregnancy. J Perinat Med 13:201, 1985

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Antepartum Fetal Heart Rate Monitoring

State of the Art

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Antepartum fetal heart rate testing (AFHRT) as a tool to evaluate the fetus prior to the onset of labor was a natural development of the techniques of continuous intrapartum fetal heart monitoring. Although specifically developed for use in labor, indirect methods of fetal monitoring appropriately are applied to the nonlaboring patient.

Early proponents of AFHRT used the concept of transient and controllable fetal stress to evaluate the potential for tolerance of labor. Maternal hypoxemia and exercise were used in an attempt to decrease uterine blood flow and thus demonstrate this effect via characteristics of the fetal heart rate.[10,36] The logical outcome of this line of thinking was to use the "natural" stress of uterine contractions to determine whether the fetus could indeed withstand repetitive decreases in intervillous blood flow.[69] The oxytocin challenge test (OCT) became the standard antepartum fetal evaluation modality. Because contractions were not always oxytocin induced, the term *contraction stress test* (CST) has been widely used. Late decelerations, previously described as being indicative of uteroplacental insufficiency in labor, were shown to have the same predictive value in the antepartum period for subsequent labor events and perinatal outcome.[26,29]

It was noted that accelerations of the fetal heart rate, incidentally detected during the performance of stress testing, were associated with a decreased incidence of abnormal CSTs.[46,86] It also had been demonstrated that certain characteristics of the fetal heart rate in response to fetal movement were predictive of fetal condition.[34,44] Subjective assessment of fetal movement by a pregnant patient long has been used as a test of fetal health. This has been quantitatively evaluated and been correlated with abnormal fetal heart rate monitoring and perinatal outcome.[73]

In combining maternal perception of fetal movement with recorded fetal heart rate accelerations, the concept of nonstress testing (NST) was

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proposed. The relationship between fetal heart rate accelerations and subsequent excellent perinatal outcome was demonstrated in numerous studies.[22,46,62,64,71] The advantage of the NST was the ease of performance, ease of interpretation, lack of requirement to use oxytocin, and decrease in the time required to perform the test. These important characteristics, as well as the predictive reliability of the test, made the NST the primary modality of fetal evaluation.[1,23,62]

The NST became accepted widely as a primary test with the CST used as a secondary modality in the setting of an abnormal NST. There is still some controversy concerning the ideal sequence of testing. This has remained the basic scheme of antepartum testing, although there is a school of thought in which the primary surveillance technique is the CST.[27,28] It has, however, been demonstrated that perinatal outcome is improved whichever sequence of testing is used.[27,76]

The primary goal of AFHRT is to prevent fetal death, and both NST and CST have low false-negative result rates.[22,64] Newer techniques, such as the biophysical profile (BPP), were developed to decrease the relatively high false-positive result rate (false-abnormal rate) and to thus lower the incidence of unnecessary delivery.[50,51] By extrapolation, therefore, AFHRT should have predictive reliability for total perinatal outcome.

It should be clearly stated that the purpose of this discussion will not be to determine which is the "best" antepartum fetal heart rate test. The goal is to examine currently used systems of AFHRT and evaluate their strengths, weaknesses, and clinical usefulness. The BPP only will be mentioned in the context of its integration into AFHRT schemes. A complete discussion of the BPP is outside the purpose and scope of this article.

PHYSIOLOGIC CONSIDERATIONS

The autonomic nervous system and related cardiac innervation is the controlling mechanism for variations in fetal heart rate. A dynamic balance between the parasympathetic and sympathetic components of the autonomic nervous system contributes to the appearance of "beat-to-beat" variability. Vagal tone with cardiodecelerator activity has a more rapid effect on the heart than does cardioaccelerator sympathetic activity.[88]

The well-known relationship between fetal movement and fetal heart rate accelerations depends on the integration of peripheral receptors, spinal cord, brain, autonomic nervous system, and intact myocardium.[85] The many factors that can influence this well-coordinated cascade of events range from physiologic to pathologic. Lack of accelerations may merely be due to fetal rest–activity cycles or may be secondary to medication, hypoxia, or acidosis.[40,85] The human fetus is known to exhibit highly organized and integrated behavioral states.[52,57] Fetal heart activity thus may be influenced by a bewildering array of stimuli. Chronic hypoxia, the sine qua non of fetal compromise, may modify the parasympathetic response (vagus) prior to sympathetic activation.[53] Acute hypoxemia leads to redistribution of cardiac output sec-

ondary to baroreceptor activation and changes in peripheral vascular resistance.[9,61]

Uteroplacental insufficiency, with transient fetal hypoxia, may be clinically detected by the presence of late decelerations in response to uterine contractions. The decrease in intervillous blood flow during contractions is well tolerated by the healthy fetus with a normally functioning fetoplacental unit. Inadequate placental reserve may manifest clinically as late decelerations.[7,55]

INDICATIONS FOR ANTEPARTUM FETAL HEART RATE TESTING

Indications for the NST include diabetes mellitus, post-term pregnancy, hypertensive disorders of pregnancy, intrauterine growth retardation, history of previous stillbirth, anemia, hemoglobinopathies, decreased fetal movement, cyanotic heart disease, collagen vascular disease, premature labor and premature rupture of the membranes, and other disorders associated with increased perinatal loss.

In general, the decision of when to start AFHRT should be based on the risk of intrauterine death and at a point in gestation at which therapy or intervention by delivery give the infant a reasonable chance of survival.

There are no contraindications to the use of the NST. It is relatively simple to perform and has the advantage over the contraction stress test of more rapid testing sequence, no contraindications, and no intravenous oxytocin infusion.

PERFORMANCE OF THE NST

The NST is performed with the patient in the semi-Fowler's position, using an external system to monitor fetal movement, uterine contractions, and FHR. Uterine activity is obtained with a tocodynamometer strapped to the abdomen in conjunction with manual palpation of the uterus by the examiner. This method will register the frequency and relative duration but not the actual strength of the contractions. The patient is given an "event marker" with which she can register perceived fetal movements on the strip chart; thus, the patient and the examiner may both record fetal movements.

The FHR can be derived from ultrasonic, phonocardiogram, or abdominal wall electrocardiogram signals. Ultrasound will provide an adequate FHR tracing in up to 95 per cent of the cases, whereas the success rate of the other two methods has been reported in 40 to 60 per cent of cases.

INTERPRETATION OF THE NST

At our institution, we use the NST as our primary screening test with the CST and/or BPP performed in cases of abnormal NST. Our testing protocol is illustrated in Figure 1.

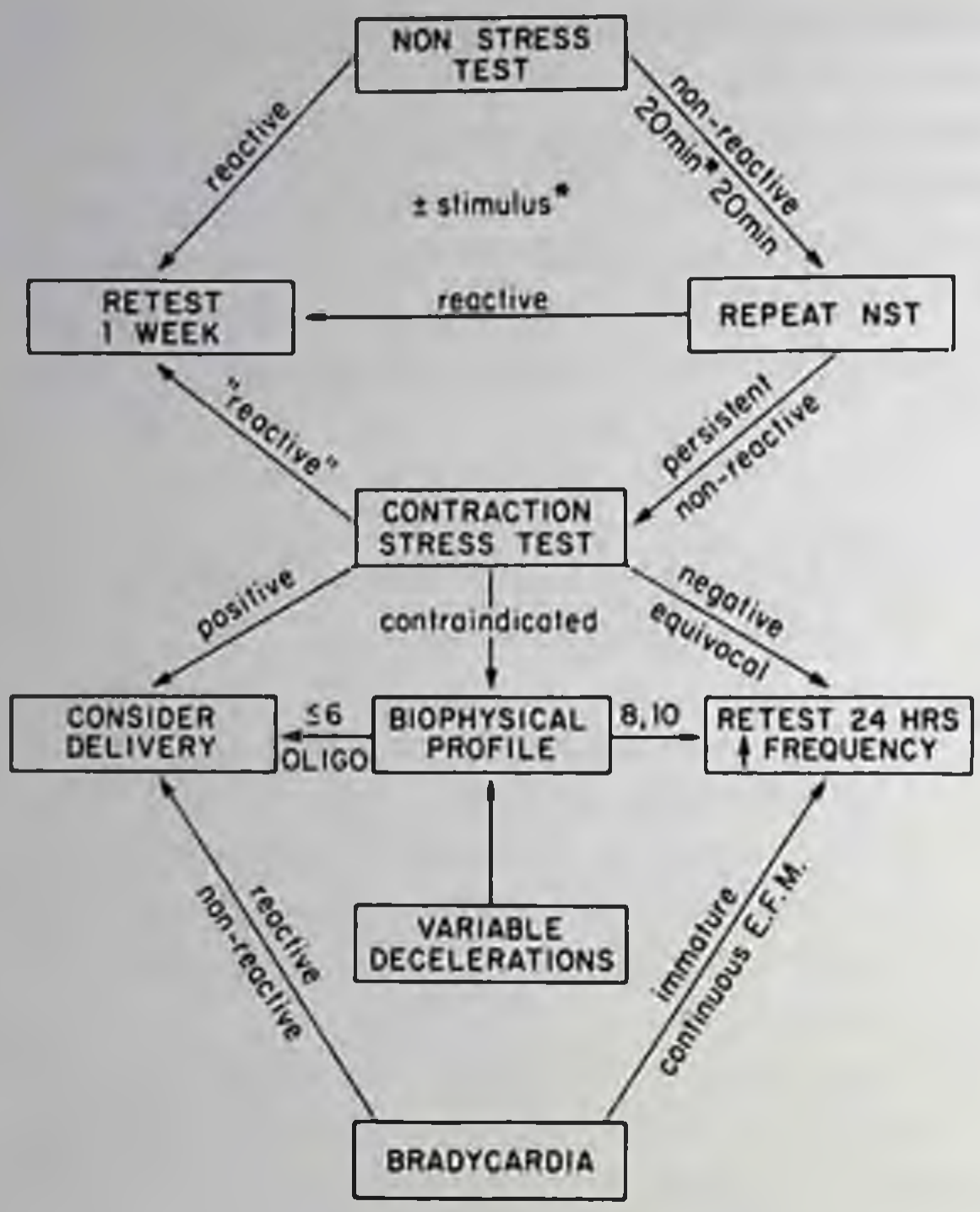

Figure 1. Antepartum testing protocol (AFHRT) at New York Hospital.

The NST is an observational test in which the FHR response to fetal movement is noted. An NST is considered reactive (normal) if there are two accelerations of the FHR, equal to or greater than 15 beats per minute above the baseline, lasting at least 15 seconds, associated with fetal movement in a 20-minute period. Accelerations without perceived fetal movement are acceptable. If these criteria are not met in two successive 20-minute periods, a CST is performed unless medically contraindicated. Accelerations meeting the criteria for a reactive NST which occur during the performance of the CST qualify the test as reactive.

A reactive NST usually is repeated in 7 days, although more frequent testing may be indicated in conditions in which sudden deterioration of the fetoplacental unit may occur (e.g., diabetes and growth retardation). Initially, both a reactive NST (normal) and a nonreactive NST (abnormal) followed by a negative CST (normal) were repeated in seven days, whereas a nonreactive NST (abnormal) with positive CST (abnormal) led to consideration for delivery. This protocol was amended in 1979 following reevaluation of the nonreactive NST with negative CST. It was found that this combination was associated with a higher antepartum death rate than a reactive NST.[17] The nonreactive NST with negative CST is now considered equivocal and is repeated in 24 hours rather than 7 days.

An NST result is considered abnormal, whether it is reactive or nonreactive, in the presence of fetal bradycardia. This deceleration is defined as a decrease from the baseline of at least 40 beats per minute or an absolute heart rate of 90 beats per minute or less, lasting 60 seconds or longer.[16] In such cases, delivery is considered unless fetal lung immaturity is documented, in which case continuous FHR monitoring for 12 to 24

hours and repeat testing is indicated daily for 3 days then decreased frequency if testing remains normal.

Testing interval varies with the clinical situation, which may require more frequent testing. If frequent nonperiodic variable decelerations occur during the NST, an evaluation of amniotic fluid volume is performed and testing should be done two to three times a week, depending on the clinical situation. Variable decelerations are indicative of umbilical cord compression and often are associated with decreased amniotic fluid volume. Any deterioration in the clinical situation, irrespective of the diagnosis, should be an indication for more frequent testing.

PERFORMANCE OF THE CST

The CST is performed while the patient is in the semi-Fowler's position to avoid the supine-hypotensive syndrome. A baseline period of 10 to 15 minutes is used to assess FHR characteristics and the possibility of periodic changes. Blood pressure should be monitored every 10 minutes to identify supine hypotension that might provoke an abnormal CST. Uterine activity is evaluated for spontaneous contractions. If recurrent late decelerations occur with spontaneous contractions, the test result is interpreted as positive irrespective of the frequency of uterine contractions. In patients having fewer than three spontaneous contractions in 10 minutes in which no decelerations are noted, stimulation of the nipple by the patient is used to obviate the need for intravenous oxytocin. This procedure has resulted in a qualifying CST in over 70 per cent of cases.

The CST is contraindicated in the presence of premature labor, premature multiple gestation, incompetent cervix, previous vertical uterine incision, placenta previa, premature rupture of the amniotic membranes, polyhydramnios, and third-trimester bleeding.

INTERPRETATION OF THE CST

There are two schemes of interpretation of the CST as described by Garite and Freeman[31] and Schifrin.[75,77] The scheme proposed by Garite and Freeman is as follows.

1. *Negative:* A test is interpreted as negative if no late decelerations appear any time in the test period, including the observation period and the period after the completion of the test. There must be a minimum of three contractions lasting longer than 40 seconds in a 10-minute period to qualify as a CST.

2. *Equivocal:* The test demonstrates late decelerations that do not persist throughout the tracing.

3. *Positive:* A test result is positive when it demonstrates persistent or consistent late decelerations associated with more than half of the uterine contractions, provided there is no evidence of uterine hyperstimulation. A test result also may be interpreted as positive if repetitive late decelerations occur with less uterine activity than required in the definition of the negative CST. Thus, a test result showing repetitive late decelerations with uterine activity, either sponta-

neous or induced, of fewer than three contractions in 10 minutes may be interpreted as positive, and further uterine stimulation should not be undertaken.

4. *Hyperstimulation:* This defines FHR decelerations occurring with excessive uterine activity as defined by contractions lasting more than 90 seconds or occurring more frequently than every 2 minutes. When FHR decelerations are present, the test is considered inconclusive. In the absence of periodic changes of the FHR, in spite of uterine hyperstimulation, the test result is interpreted as negative.

5. *Unsatisfactory:* In certain cases, adequate duration or frequency of the uterine contractions is not achieved, or the FHR tracing is not of a quality to be adequately interpreted.

An alternative interpretation of the CST, based on the "10-minute" window, has been proposed by Schifrin.[75,77] When the test is interpreted an attempt is made to identify a 10-minute segment of the tracing that satisfies the criteria for a positive or a negative test, which requires three uterine contractions in the 10-minute segment. Using this scheme he describes the following:

1. *Negative:* A negative test result shows a stable FHR without evidence of periodic heart rate decelerations.

2. *Equivocal:* In this test, neither a positive nor a negative window can be identified. This is considered inconclusive.

3. *Positive:* This test shows repeated late decelerations. In cases showing both a positive and a negative window, the test is considered positive. Using this scheme, positive tests may be found in 3 to 10 per cent of cases.

4. *Unsatisfactory:* Those tests in which either the FHR cannot be monitored satisfactorily or adequate uterine activity cannot be elicited within 2 hours of the beginning of the test.

According to this scheme of interpretation, occasional decelerations are disregarded in the presence of a negative window.

It should be noted that the above schemata for NST and CST happen to be widely used and accepted. However, various other criteria have been used in many centers, and a careful evaluation of the data reveals similar perinatal outcome, irrespective of the criteria used. The number of accelerations required for the NST varies from one acceleration for 10 beats per minute[54] through two accelerations,[39,76] three accelerations,[46] four accelerations,[58] and five accelerations.[38,89] In view of this widely differing interpretation of data, each clinician should choose a practical, well-documented scheme that he or she feels is pertinent to his or her patients and use this approach consistently.

RECENT DEVELOPMENTS IN ANTEPARTUM FETAL HEART RATE TESTING

Fetal State

It has become obvious that arbitrary times used in AFHRT are artificial and do not take fetal physiologic variation into account. The standard 10-, 20-, and 40-minute rules are for convenience and are often necessary in a practical sense to allow the optimal number of patients to be evaluated. It has been shown that periods of fetal inactivity can be pro-

longed for more than 1 hour.[60] The same investigators showed that observation periods of up to 80 minutes may be necessary to observe fetal accelerations.[6] Sleep–wake cycles may vary from 20 minutes up to 3 hours.[37] When total NST time was extended to 90 minutes, marked improvement in the false-positive rate (false nonreactive rate) was observed.[12] This was a classic demonstration of fetal state being a most important variable in the assessment of fetal health.

Baseline Heart Rate and Beat-to-Beat Variability

The normal fetal heart rate baseline is 110 to 160 beats per minute. Many factors can influence baseline heart rate. Factors causing an increase in baseline fetal heart rate include maternal fever, thyrotoxicosis, and chronic hypoxia. A decrease in heart rate may be due to acute hypoxia, local anesthetics and congenital heart block.[53] In the human fetus, it has been demonstrated that in the second half of gestation baseline fetal heart rate declines, but at no time from 20 to 40 weeks are baseline heart rate levels outside the normal range.[19] A deviation from baseline should be further investigated.

Beat-to-beat variability is the term used to describe beat-to-beat variation of the fetal heart rate, mediated by the autonomic nervous system. This is the difference between each successive R–R interval of the fetal ECG, expressed as a rate. The presence of variability is thought to reflect an intact pathway from cerebral cortex, through the midbrain and to the vagus and conducting system of the heart itself. By extension, cerebral tissue oxygenation is thus normal with normal fetal heart rate variability, and this is important clinically.[74] In the antepartum period, using mainly ultrasound-derived fetal heart rate, the appearance of beat-to-beat variability is often artifactual. If *absent* beat-to-beat variability is noted on indirect methods of monitoring, there is often true decreased beat-to-beat variability, and a search for the cause of this must be undertaken. Disappearance of beat-to-beat variability may be ominous.[21,71,87] However, fetal beat-to-beat variability may be decreased in response to barbiturates, narcotics, and prematurity. Fetal sleep is probably the most common single cause of decreased beat-to-beat variability.[53]

In summary, fetal heart rate characteristics such as baseline fetal heart rate and beat-to-beat variability are helpful if *abnormal* (i.e., fetal tachycardia or bradycardia), and decreased beat-to-beat variability.

Fetal Heart Rate Decelerations During AFHRT

The presence or absence of accelerations of the fetal heart rate is the basic information required for interpretation of the NST. However, other characteristics of the fetal heart rate are extremely helpful in further evaluating the fetus. Nonperiodic decelerations of the fetal heart, whether spontaneous or related to fetal movement, have been shown to be important during AFHRT. The presence of variable type decelerations—15 beats per minute for 15 seconds—has been correlated with a greater likelihood of poor perinatal outcome.[65,66] This is true regardless of whether the NST is reactive or not.[79]

Of even more ominous import is the occurrence of fetal bradycardia during AFHRT. This pattern originally was correlated with an increased

incidence of fetal distress in labor when delivery was instituted within 24 hours.[16] Two subsequent studies in which delivery was *not* instituted based on the appearance of bradycardia confirmed the markedly increased risk of fetal death.[2,11] The importance of this pattern in predicting perinatal morbidity has recently been confirmed in a large series of cases (Druzin ML: Fetal bradycardia during antepartum testing: Further observations. J Reprod Med [in press]). In most cases in these four series, pregnancies greater than 32 weeks' gestation were evaluated. A study is ongoing to determine the significance of fetal bradycardia in the preterm gestation. In a specific group of patients, namely systemic lupus erythematosus with antiphospholipid antibodies, bradycardia is a predictor of intrauterine growth retardation and fetal death in the preterm fetus.[20] Elective preterm delivery may be indicated in these cases.

Gestational Age

Gestational age has been shown to be correlated with fetal reactivity.[45,84] The general consensus is that the preterm fetus is more likely to be nonreactive (lack of accelerations) than the fetus at term.[15,82] In these cases, the criteria for reactivity used were identical for term and preterm gestations. Rates of reactivity became similar after 30 to 32 weeks.[56] Thus, the fetus at gestational ages of 30 weeks or less may be nonreactive based on gestational age alone. It is tempting, and it has been suggested that criteria for reactivity be altered to reflect gestational age. However, this is likely to be confusing to the clinician, as this author has enough trouble teaching his housestaff one simple, consistent set of criteria!

In the study of gestational age and the NST,[15] those fetuses who were reactive at an early gestational age, even as early as 20 to 24 weeks, remained so until term with normal outcome. The CST has been shown to be predictive at early gestational ages, less than 34 weeks. Thus, an abnormal screening NST (which may be so because of prematurity) can be followed reliably with a CST.[30] The BPP is being used more frequently in these cases because the CST is often contraindicated in preterm pregnancies. Many preterm pregnancies are being tested for premature rupture of the membranes, preterm labor, multiple gestation, and placenta previa, which are all relative contraindications to the CST. Therefore, management decisions can be made with some degree of confidence in terms of impending fetal compromise. Most obstetric services would perform a cesarean section for fetal distress in labor in a gestation estimated to be >28 weeks in duration or at an estimated fetal weight of >1000 gm.[3] Continuous intrapartum electronic fetal monitoring has been shown to be reliable in the fetus who weighs 1500 gm or less.[4] It would be inconsistent, therefore, not to act on antepartum indicators of fetal compromise.

The definition of fetal "viability" in terms of birth weight and gestational age is controversial. Although a fetal weight $>$ equal to 800 gm is considered by most neonatal intensive care units to be compatible with survival and will lead to maximal efforts by the neonatologists, the management of the 600- to 800-gm group is still under much discussion.[5,35,41] The importance of correlating birthweight and gestational age cannot be overemphasized. A small-for-gestational age fetus who weighs 750 gm at 28 weeks' gestation because of severe intrauterine growth retardation

will have a different prognosis than that of an adequate-for-gestational age 750 gm fetus at 26 weeks' gestation.

Application of the NST to gestational ages < 28 weeks awaits further study. Use of the biophysical profile and other parameters of testing may be of use in ascertaining those fetuses who are at risk prior to 28 weeks' gestation.[51] In some conditions, such as collagen-vascular disease and severe hypertensive diseases, there are fetuses who may be compromised prior to 28 weeks (birthweight approximately 1000 gm), or prior to 26 weeks (birthweight approximately 800 gm). Identification of a group such as this would lead to optimal use of fetal surveillance techniques at later gestational ages and consideration of elective premature delivery.[20]

The use of identical criteria for reactivity at all gestational ages has recently been questioned.[84] Further large-scale studies with clinical application of different criteria are necessary. Use of the same criteria for all gestational ages may be less confusing and more clinically applicable until further information is available.

External Influences on the NST

Various external stimuli have been shown to impact on the NST, but misconceptions abound as to the usefulness of these methods. It has been demonstrated that narcotics such as phenobarbital[40] and cigarette smoking[33] are associated with an increased incidence of nonreactive NSTs.

It has become common practice to suggest that glucose-containing drinks will shorten time to reactivity, thus increasing the percentage of reactive NSTs. Our experience suggests that glucose ingestion by the mother compared with ingestion of an identical volume of tap water has no effect on time to reactivity or the incidence of reactive NSTs.[14]

As to the effect of manual manipulation of the fetus on the NST, our data suggest that simple manual manipulation of the fetus neither decreases the time required for performance of a NST nor changes the reactive NST to nonreactive NST ratio.[18]

The only external stimulus that has proved to be consistently reliable in altering fetal reactivity has been vibroacoustic stimulation (VAS). An earlier study showing improved rates of reactivity[70] was followed by numerous attempts to integrate this into clinical practice.[59,75]

A retrospective analysis of the adjunctive use of VAS demonstrated a 50 per cent reduction in the number of nonreactive NSTs.[80] Consequently, a prospective randomized clinical trial was undertaken to compare the standard NST with the fetal VAS test. Those patients randomized to the VAS test underwent transabdominal acoustic stimulation with a Model 5C electronic artificial larynx. The incidence of nonreactive tests was 14 per cent in the control group and 9 per cent in the study group ($P = 0.004$). A significant reduction in testing time also was observed.[83]

In another study, Smith et al.[81] further assessed the usefulness of transabdominal VAS of the fetus and demonstrated an approximately 50 per cent reduction in the number of nonreactive tests and a shorter testing time. No change in the predictive reliability of a reactive test was observed. With regard to the intrapartum and neonatal outcome in women delivering within 7 days of a reactive test, no difference between

the incidence of meconium stained amniotic fluid, depressed 1- or 5-minute Apgar scores or operative intervention for fetal distress could be identified. A reactive test evoked by VAS is as reliable as the NST.

VAS offers distinct advantages to the traditional NST. Fewer nonreactive tests reduce patient anxiety, shorten overall testing time, and allow perinatal resources to be more efficiently used. Although definitive advantages to VAS exist, its routine implementation should await further investigation of its safety and predictive reliability.[72]

Amniotic Fluid Assessment

Amniotic fluid is now recognized as one variable that is important to assess in an antepartum evaluation scheme. The original BPP proposed by Manning[51] gave equal weight to all parameters, irrespective of the mechanism. It is now recognized that fetal movement, fetal breathing, fetal tone, and the NST are likely to be mediated by the central nervous system while amniotic fluid volume (AFV) is an index of fetal renal or placental function.

Qualitative AFV assessment was used to predict oligohydramnios and intrauterine growth retardation. A single amniotic fluid pocket of 1 cm or less was found to be highly correlated with intrauterine growth retardation.[49] This measurement also was used as the criterion of AFV in the BPP.[51] Phelan et al.[67] found that there were patients with >1 cm pockets of amniotic fluid who gave an overall impression of decreased AFV to the trained observer. In the postdate patients, perinatal morbidity and mortality were high in this specific group.[67]

Chamberlain et al.[8] subsequently reported on the 2-cm rule. The next step was the development of the amniotic fluid index (AFI) by Phelan et al.[68] This technique divides the abdomen into four quadrants using the umbilicus as the horizontal line and the linea negra as the vertical line. The vertical diameter of the largest pocket in each quadrant is measured, and the summation of numbers represents the AFI in centimeters. An AFI of 5 cm or less was correlated with increased perinatal morbidity in spite of reactive NST and no fetal heart rate decelerations.[66] The AFI is used as the AFV evaluation in the BPP. A scheme of NST with VAS and AFI has been proposed as the primary form of fetal surveillance.[63]

Scoring Systems

Some investigators have proposed "scoring systems" to better quantify changes and predictive reliability in AFHRT schemes.[13,43,48] Although this has been demonstrated to be reliable, it requires a further set of criteria to be memorized. This also leads to reliance on a set of "numbers" without taking into consideration the clinical implications of that number. It is more clinically applicable to report observations that allow the clinician to form a composite picture of fetal condition.

Congenital Anomalies

There is an increased incidence of abnormal AFHRT in the fetus with major congenital anomalies. Repetitive abnormal AFHRT should prompt evaluation for anomalies.[32]

Multiple Gestation

Multiple gestations have increased perinatal morbidity and mortality secondary to increased rates of prematurity and placental insufficiency. The NST has been used reliably in determining the fetus at risk in multiple gestations. Abnormal results often were associated with intrauterine growth retardation.[42,47] With the increased use of techniques to enhance fertility, multiple gestations are presenting more frequently to the practicing obstetrician.

CONDITION-SPECIFIC ANTEPARTUM FETAL HEART RATE TESTING

Our suggested guidelines follow:

1. Diabetes Mellitus

   Diet controlled with no complications
   26–32 weeks: once a week
   32 weeks–term: twice a week

   Insulin-dependent in good control
   26–32 weeks: once a week
   32–34 weeks: twice a week
   34 weeks–term: three times a week

   Diet control with previous stillbirth or added medical problem and insulin-dependent in poor control, or previous stillbirth, or added medical problem
   26–32 weeks: once a week
   32–34 weeks: twice a week
   34–36 weeks: three times a week
   36 weeks–term: daily

Good control is defined as pregestational diabetic in good control before 12 weeks or gestational diabetic in good control before 32 weeks.

2. Post dates/poor dates using earliest EDC:

   40–41 weeks: once a week
   41–42 weeks: twice a week
   >42 weeks: —biophysical profile
   —NST three times a week
   Delivery is often advocated at this time but if the delivery option is not chosen then observe above protocol.
   Normal NST, CST, BPP with low or very low AFI—consider delivery in the term fetus

All postdate patients undergo CST with nipple stimulation at each test and evaluation of amniotic fluid volume at 42 weeks and weekly thereafter. The necessity of CST in the face of a normal NST is being currently evaluated.

3. Multiple mild variables (>3 in 5 minutes) or any variables lasting >30 seconds:

   Biophysical profile, then NST three times a week irrespective of gestational age

4. Minimum testing starting at 26 weeks or at onset of problem:
   a. Abnormal FHR by auscultation or office doptone: once a week
   b. Asthma: once a week
   c. Cardiac disease: once a week
   d. Chronic hypertension: twice a week
   e. Collagen-vascular disease: once a week (if in remission)
   f. Congenital anomalies: once a week
   g. Decreased fetal movement: once a week
   h. Intrauterine growth retardation: twice a week
   i. Multiple gestation: once a week
   j. Oligohydramnios: once a week
   k. Polyhydramnios: once a week
   l. Poor ob history: once a week
   m. Preeclampsia: twice a week
   n. Premature labor: once a week
   o. Placenta previa: once a week if no bleeding
   p. PROM: twice a week
   q. Renal disease: once a week
   r. Rh disease: once a week
   s. Sickle cell disease: once a week (daily during crisis)
   t. Previous stillbirth: once a week if cause unknown; if cause known, follow guidelines for specific diagnosis
   u. Substance abuse: once a week
   v. Third trimester bleeding: once a week
   w. Thyroid disease: once a week
5. Nonreactive NST at 26–32 weeks:
   Attempt CST with nipple stimulation
   If CST is negative: NST twice a week
   If CST is unsuccessful: BPP (If BPP score is 6 or 8: NST twice a week)
6. Postamniocentesis for diagnostic studies, greater than 26 weeks (whether or not amniocentesis is successful): Frequency of testing will vary depending on the clinical situation.
7. The BPP:
   a. If the NST is nonreactive and the CST is either unobtainable or contraindicated
   b. PROM: once a week
   c. Multiple variable decelerations (> 3 in 5 minutes or any lasting > 30 seconds): once a week
   d. Any isolated late decelerations and/or atypical decelerations on NST even if the CST is negative
   e. 42 weeks postdates and once a week thereafter

SUMMARY

1. AFHRT remains one of the most widely used methods of assessing fetal condition.
2. The actual types of tests used as primary surveillance tests are unimportant. Both the NST and CST have been successfully used.
3. The clinician should adopt a scheme in which they have all the data necessary to determine whether this will fit in with their practice.
4. Characteristics other than reactivity or nonreactivity are important.
   a. Abnormal baseline fetal heart rate or beat-to-beat variability
   b. Fetal heart rate decelerations

5. Amniotic fluid volume assessment is important particularly in cases of postdates and intrauterine growth retardation.
6. Condition-specific AFHRT (i.e., modifications of schemes to fit clinical circumstances) is an important concept.
7. Testing at gestational ages of 26 to 28 weeks may be appropriate in certain situations. After 28 weeks, AFHRT can be used reliably.
8. The integration of an AFHRT scheme into the total clinical picture is the key to success.

REFERENCES

1. Barrett JM, Salyer SL, Boehm FH: The nonstress test: An evaluation of 1,000 patients. Am J Obstet Gynecol 141:153, 1981
2. Bourgeois FJ, Thiagarajah S, Harbert G Jr: The significance of fetal heart rate decelerations during nonstress testing. Am J Obstet Gynecol 150:213, 1984
3. Bowes WA Jr: Delivery of the very low birth weight infant. Clin Perinatol 8:183, 1981
4. Bowes WA Jr, Gabbe SG, Bowes C: Fetal heart rate monitoring in premature infants weighing 1,500 grams or less. Am J Obstet Gynecol 137:791, 1980
5. Bowes WA Jr, Halgrimson M, Simmons MA: Results of the intensive perinatal management of very low birth weight infants 501–1500 gm. J Reprod Med 23:245, 1979
6. Brown R, Patrick J: The nonstress test: How long is enough? Am J Obstet Gynecol 141:646, 1981
7. Caldeyro B, Mendez-Bauer C, Poseior JJ, et al: Control of human fetal heart rate during labor. In Cassels EE (ed): The Heart and Circulation in the Newborn and Infant. New York, Grune & Stratton, 1966, p 7
8. Chamberlain PF, Manning FA, Morrison E, et al: Ultrasound evaluation of amniotic fluid volume: I. The relationship of marginal decreased amniotic fluid volume to perinatal outcome. Am J Obstet Gynecol 150:245, 1984
9. Cohn HE, Sacks EJ, Heymann MA, et al: Cardiovascular responses to hypoxemia and acidemia in fetal lambs. Am J Obstet Gynecol 120:817, 1974
10. Copher DE, Hurber CP: Heart rate response of the human fetus to induced maternal hypoxia. Am J Obstet Gynecol 98:320, 1967
11. Dashow EE, Read JA: Significant fetal bradycardia during antepartum heart rate testing. Am J Obstet Gynecol 148:187, 1984
12. Devoe LD, McKenzie J, Searle NS, et al: Clinical sequelae of the extended nonstress test. Am J Obstet Gynecol 151:1074, 1985
13. Devoe LD, Yankowitch G, Azor H: The application of multiparameter scoring to antepartum fetal heart rate testing. J Reprod Med 26:250, 1981
14. Druzin ML, Foodim J: Effect of maternal glucose ingestion compared with maternal water ingestion on the nonstress test. Obstet Gynecol 67:425, 1986
15. Druzin ML, Fox A, Kogut E, et al: The relationship of the nonstress test to gestational age. Am J Obstet Gynecol 153:383, 1985
16. Druzin ML, Gratacos J, Keegan KA, et al: Antepartum fetal heart rate testing: VII. The significance of fetal bradycardia. Am J Obstet Gynecol 139:194, 1981
17. Druzin ML, Gratacos J, Paul RH: Antepartum fetal heart rate testing: VI. Predictive reliability of "normal" tests in the prevention of antepartum death. Am J Obstet Gynecol 137:746, 1980
18. Druzin ML, Gratacos J, Paul RH, et al: Antepartum fetal heart rate testing: XII. The effect of manual manipulation of the fetus on the nonstress test. Am J Obstet Gynecol 151:61, 1985
19. Druzin ML, Hutson JM, Edersheim T: Relationship of baseline fetal heart rate to gestational age and fetal sex. Am J Obstet Gynecol 154:1102, 1986
20. Druzin ML, Lockshin M, Edersheim TG, et al: Second trimester fetal monitoring and preterm delivery in pregnancies with systemic lupus erythematosus and/or circulating anticoagulant. Am J Obstet Gynecol 157:1503, 1987
21. Emmen L, Huisjes HJ, Aarnoudse JG, et al: Antepartum diagnosis of the "terminal" fetal state by cardiotocography. Br J Obstet Gynaecol 82:353, 1975

22. Evertson LR, Paul RH: Antepartum fetal heart rate testing: The nonstress test. Am J Obstet Gynecol 132:895, 1978
23. Evertson LR, Gauthier RJ, Schifrin BS, et al: Antepartum fetal heart rate testing: I. Evolution of the nonstress test. Am J Obstet Gynecol 133:29, 1979
24. Evertson LR, Paul RH: Antepartum fetal heart rate testing: The nonstress test. Am J Obstet Gynecol 132:895, 1978
25. Fliegner JR, Eggers TR: The relationship between gestational age and birth weight in twin pregnancy. Aust NZ J Obstet Gynecol 24:192, 1984
26. Freeman RK: Clinical value of antepartum fetal heart rate monitoring. In Gluck L (ed): Modern Perinatal Medicine. Chicago, Year Book Medical, 1974, p 163
27. Freeman RK, Anderson G, Dorchester W: A prospective multi-institutional study of antepartum fetal heart rate monitoring: I. Risk of perinatal mortality and morbidity according to antepartum fetal heart rate test results. Am J Obstet Gynecol 143:771, 1982
28. Freeman RK, Anderson G, Dorchester W: A prospective multi-institutional study of antepartum fetal heart rate monitoring: II. Contraction stress test versus nonstress test for primary surveillance. Am J Obstet Gynecol 143:778, 1982
29. Freeman RK, James J: Clinical experience with the oxytocin challenge test: II. An ominous atypical pattern. Obstet Gynecol 46:255, 1977
30. Gabbe SG, Greeman RK, Goebelsmann U: Evaluation of contraction stress test before 33 weeks gestation. Obstet Gynecol 52:649, 1978
31. Garite TJ, Freeman RK: Antepartum stress test monitoring. In Quilligan EJ (ed): Clinics in Obstetrics and Gynecology. Philadelphia, WB Saunders, 1979, p 295
32. Garite TJ, Linzey EM, Freeman RK, et al: Fetal heart rate patterns and fetal distress in fetuses with congenital anomalies. Obstet Gynecol 53:716, 1979
33. Goodman LDS, Visser FGA, Dawes GS: Effects of maternal cigarette smoking on fetal trunk movements, fetal breathing movements and the fetal heart rate. Br J Obstet Gynaecol 91:657, 1984
34. Hammacher K: The clinical significance of cardiotocography. In Huntington PM, Huter KA, Saline E (eds): Perinatal Medicine. Stuttgart, George Thieme Verlagg, 1969, p 80
35. Hirata T, Epcar JR, Walsh A, et al: Survival and outcome of infants 501 to 750 gm: A six-year experience. J Pediatr 102:741, 1983
36. Hon EH, Wohlgemuth R: The electronic evaluation of fetal heart rate: IV. The effect of maternal exercise. Am J Obstet Gynecol 81:361, 1961
37. Hoppenbrouwers T, Combs D, Ugartechea JC, et al: Fetal heart rates during maternal wakefulness and sleep. Obstet Gynecol 57:301, 1981
38. Ingardia CJ, Cetrulo CL, Knuppel RA, et al: Prognostic components of the non-reactive non-stress test. Obstet Gynecol 56:305, 1980
39. Keane MWD, Horger EO, Vice L: Comparative study of stressed and non-stressed antepartum fetal heart rate testing. Obstet Gynecol 57:320, 1981
40. Keegan KA, Paul RH, Broussar PM, et al: Antepartum fetal heart rate testing: III. The effect of phenobarbital on the nonstress test. Am J Obstet Gynecol 133:579, 1979
41. Kitchen W, Ford G, Orgill A, et al: Outcome in infants with birth weight 500 to 900 gm: A regional study of 1979 and 1980 births. J Pediatr 104:921, 1984
42. Knuppel RA, Pawan KR, Scerbo JC, et al: Intrauterine fetal death in twins after 32 weeks of gestation. Obstet Gynecol 65:172, 1985
43. Krebs HB, Petres RE: Clinical application of a scoring system for evaluation of antenatal fetal heart rate monitoring. Am J Obstet Gynecol 130:765, 1978
44. Kubli FW, Kaeser O, Kinselman M: Diagnostic management of chronic placental insufficiency. In Pecile A, Finzi C (eds): The Foeto-Placental Unit. Amsterdam, Excerpta Medica Foundation, 1969, p 323
45. Lavin JP Jr, Miodovnik M, Barden TP: The relationship of nonstress test reactivity and gestational age. Obstet Gynecol 63:338, 1984
46. Lee CY, DiLoreto PC, Logrand B: Fetal activity acceleration determination for the evaluation of fetal reserve. Obstet Gynecol 48:19, 1976
47. Lenstrup C: Predictive value of antepartum nonstress test in multiple pregnancies. Acta Obstet Gynecol Scand 63:597, 1984
48. Lyons ER, Bylsma HM, Sham S, et al: A scoring system for nonstressed antepartum fetal heart rate monitoring. Am J Obstet Gynecol 133:242, 1979
49. Manning FA, Hill LM, Platt LD: Qualitative amniotic fluid volume determination by ultrasound. Am J Obstet Gynecol 139:254, 1981

50. Manning FA, Morrison I, Lange IR, et al: Fetal assessment based on fetal biophysical profile scoring: Experience in 12,620 referred high-risk pregnancies: I. Perinatal mortality by frequency and etiology. Am J Obstet Gynecol 151:343, 1985
51. Manning FA, Platt LD, Sipos L: Antepartum fetal evaluation development of a fetal biophysical profile. Am J Obstet Gynecol 136:787, 1980
52. Martin CB Jr: Behavioural states in the human fetus. J Reprod Med 26:425, 1981
53. Martin CB Jr: Regulation of the fetal heart rate and genesis of FHR patterns. Semin Perinatol 2:131, 1978
54. Mendenhall KW, O'Leary JA, Phillips KO: The non-stress test—the value of a single acceleration in evaluating the fetus at risk. Am J Obstet Gynecol 136:87, 1980
55. Myers RE, Mueller-Heubach E, Adamsons K: Predictability of the state of fetal oxygenation from a quantitative analysis of the components of late deceleration. Am J Obstet Gynecol 115:1083, 1973
56. Natale R, Nasello C, Turliuk R: The relationship between movements and accelerations in fetal heart rate at twenty-four to thirty-two weeks gestation. Am J Obstet Gynecol 148:591, 1984
57. Nijhuis JG, Prechtl HFR, Martin CB Jr, et al: Are there behavioural states in the human fetus? Early Hum Dev 6:177, 1982
58. Nochimson DJ, Turbeville JS, Terry JE, et al: The non-stress test. Obstet Gynecol 51:419, 1978
59. Ohel G, Birkenfeld A, Rabinowitz R, et al: Fetal response to vibratory acoustic stimulation in periods of low heart rate activity. Am J Obstet Gynecol 154:619, 1986
60. Patrick J, Campbell K, Carmichael L, et al: Patterns of gross fetal body movements over 24 hour observation intervals. Am J Obstet Gynecol 142:363, 1982
61. Peeters LLH, Sheldon RE, Jones MD Jr, et al: Blood flow to fetal organs as a function of arterial oxygen content. Am J Obstet Gynecol 135:637, 1979
62. Phelan JP: The nonstress test: A review of 3000 tests. Am J Obstet Gynecol 139:7, 1981
63. Phelan JP: Antepartum fetal assessment: New techniques. Sem Perinatol 12:57, 1988
64. Phelan JP, Cromartie AP, Smith CV: The nonstress test: The false negative test. Am J Obstet Gynecol 142:293, 1982
65. Phelan JP, Lewis PE: Fetal heart rate decelerations during a nonstress test. Obstet Gynecol 57:288, 1981
66. Phelan JP, Platt LD, Yeh SY, et al: Continuing role of the nonstress test in the management of the postdates pregnancy. Obstet Gynecol 64:624, 1984
67. Phelan JP, Platt LD, Yeh SY, et al: The role of ultrasound assessment of amniotic fluid volume in the management of the post date pregnancy. Am J Obstet Gynecol 151:304, 1984
68. Phelan JP, Smith CV, Broussard P, et al: Amniotic fluid volume assessment using the four quadrant technique in the pregnancy between 36 and 42 weeks gestation. J Reprod Med 32:540, 1987
69. Pose SV, Castillo JB, Mora-Rojas EO, et al: Test of fetal tolerance to induced uterine contractions for the diagnosis of chronic distress. In Perinatal Factors Affecting Human Development. Pan Am Health Organization Scientific Publication 1969, No. 185
70. Read JA, Miller FC: Fetal heart rate acceleration in response to acoustic stimulation as a measure of fetal well-being. Am J Obstet Gynecol 129:512, 1977
71. Rochard F, Schifrin BS, Goupil F, et al: Nonstressed fetal heart rate monitoring in the antepartum period. Am J Obstet Gynecol 126:699, 1976
72. Romero R, Mazor M, Hobbins JC: A critical appraisal of fetal acoustic stimulation as an antenatal test for fetal well-being. Obstet Gynecol 71:781, 1988
73. Sadowsky E, Yaffe H: Daily fetal movement recording and fetal prognosis. Obstet Gynecol 41:6, 1973
74. Schifrin BS: The rationale for antepartum fetal heart rate monitoring. J Reprod Med 23:213, 1979
75. Schifrin BS: Antepartum fetal heart rate monitoring. In Gluck L (ed): Intrauterine Asphyxia and the Developing Fetal Brain. Chicago, Year Book Medical, 1977, p 205
76. Schifrin BS, Foye G, Amato J, et al: Routine fetal heart rate monitoring in the antepartum period. Obstet Gynecol 54:21, 1979
77. Schifrin BS, Lapidus M, Doctor G: Contraction stress test for antepartum fetal evaluation. Obstet Gynecol 45:433, 1975

78. Serafini P, Lindsay MB, Nagey DA, et al: Antepartum fetal heart rate response to sound stimulation: The acoustic stimulation test. Am J Obstet Gynecol 148:41, 1984
79. Small ML, Phelan JP, Smith CV, et al: The impact of an active management approach to the postdate fetus with a reactive nonstress test and FHR decelerations. Obstet Gynecol 70:636, 1987
80. Smith CV, Phelan JP, Broussard PM, et al: Fetal acoustic stimulation testing: A retrospective analysis of the fetal acoustic stimulation test. Am J Obstet Gynecol 153:567, 1985
81. Smith CV, Phelan JP, Broussard P, et al: Fetal acoustic stimulation testing: III. Predictive value of a reactive test. J Reprod Med 33:217, 1988
82. Smith CV, Phelan JP, Paul RH: A prospective analysis of the influence of gestational age on the baseline fetal heart rate and reactivity in a low-risk population. Am J Obstet Gynecol 153:780, 1985
83. Smith CV, Phelan JP, Platt LD, et al: Fetal acoustic stimulation testing: II. A randomized clinical comparison with the nonstress test. Am J Obstet Gynecol 155:131, 1986
84. Sorokin Y, Dierker LJ, Pillay SK, et al: The association between fetal heart rate patterns and fetal movements in pregnancies between 20 and 30 weeks' gestation. Am J Obstet Gynecol 143:243, 1982
85. Timor-Tritsch IE, Dieker LJ, Hertz RH, et al: Studies of antepartum behavioral state in the human fetus at term. Am J Obstet Gynecol 132:524, 1978
86. Trierweiler MW, Freeman RK, James J: Baseline fetal heart rate characteristics as an indicator of fetal status during the antepartum period. Am J Obstet Gynecol 125:618, 1976
87. Visser GHA, Huisjes HJ: Diagnostic value of the unstressed antepartum cardiotocogram. Br J Obstet Gynaecol 84:321, 1977
88. Warner HR, Cox A: A mathematical model of heart rate control by sympathetic and vagus efferent information. J Appl Physiol 17:349, 1962
89. Weingold AB, Yonekura ML, O'Kieffe J: Non-stress testing. Am J Obstet Gynecol 138:195, 1980
90. Young BK, Suidan J, Antoine C, et al: Differences in twins: The importance of birth order. Am J Obstet Gynecol 151:915, 1985

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Acoustic Stimulation: Effect on Heart Rate and Other Biophysical Variables

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The relationship between the presence of fetal heart rate (FHR) accelerations and fetal health is now well accepted.[30] Although absence of FHR accelerations and fetal movements may be a useful test of fetal compromise, prolonged episodes of fetal rest are characteristic of healthy human fetuses.[40] A problem with antepartum FHR testing is the difficulty in separating healthy fetuses at rest from sick fetuses who are not moving because of hypoxemia or asphyxia.[2] Antepartum FHR testing also has been criticized because of a low positive predictive value,[8] the potential effect of gestational age on FHR reactivity,[14] and the intraobserver and interobserver variability in the visual assessment of nonstress testing.[15] To improve the predictive value and to decrease the length of nonstress testing, there has been a widespread introduction of different fetal acoustic stimulation tests combined with nonstress testing in the assessment of fetal health.

The purpose of this article is to review briefly FHR patterns in healthy human fetuses and to describe fetal responses to acoustic stimulation. The underlying objective is to summarize the clinical implications of combined acoustic stimulation and nonstress testing in the evaluation of fetal health.

PATTERNS OF FHR ACCELERATIONS IN HEALTHY FETUSES

Until recently, accurate recording of FHR tracings obtained with Doppler ultrasound was associated with an extremely high signal loss, approaching 60 per cent at 26 to 28 weeks' gestational age.[5] With the advent of second-generation FHR monitors using autocorrelation tech-

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nique, signal loss has been markedly reduced in early gestation. Using a microprocessor, it is now possible to fit on-line a baseline to the heart record and to recognize automatically FHR accelerations of a predefined amplitude and duration.[6,7,14] This technique allows a more objective and reproducible assessment of FHR tracings. Using computerized analysis of FHR, we continuously recorded FHR during 60 minutes in a group of 83 healthy fetuses between 26 and 40 weeks' gestation.[14] We described important maturational changes in FHR patterns occurring during a critical and narrow period between 28 and 30 weeks' gestation characterized by 1) a decrease in baseline FHR of 5 bpm, 2) an increase in FHR accelerations' amplitude of 4 bpm, and 3) an increase in long-term FHR variability. We measured the intervals necessary to detect ≥ 2 FHR accelerations of ≥ 15 bpm for ≥ 15 sec, this definition being commonly used for a reactive nonstress test. Figure 1 represents the percentage of time intervals during which fewer than two FHR accelerations occurred (nonreactive FHR pattern), plotted in 10-min increments. From 30 to 40 weeks, 57.5 per cent of tracings were nonreactive (< 2 FHR accelerations) at 10 minutes and 2.7 per cent at 60 minutes. In contrast, at 26 to 28 weeks, 95.3 per cent of recordings were nonreactive at 10 minutes, 67.0 per cent at 40 minutes, and 65.0 per cent at 60 minutes (Fig. 1). This

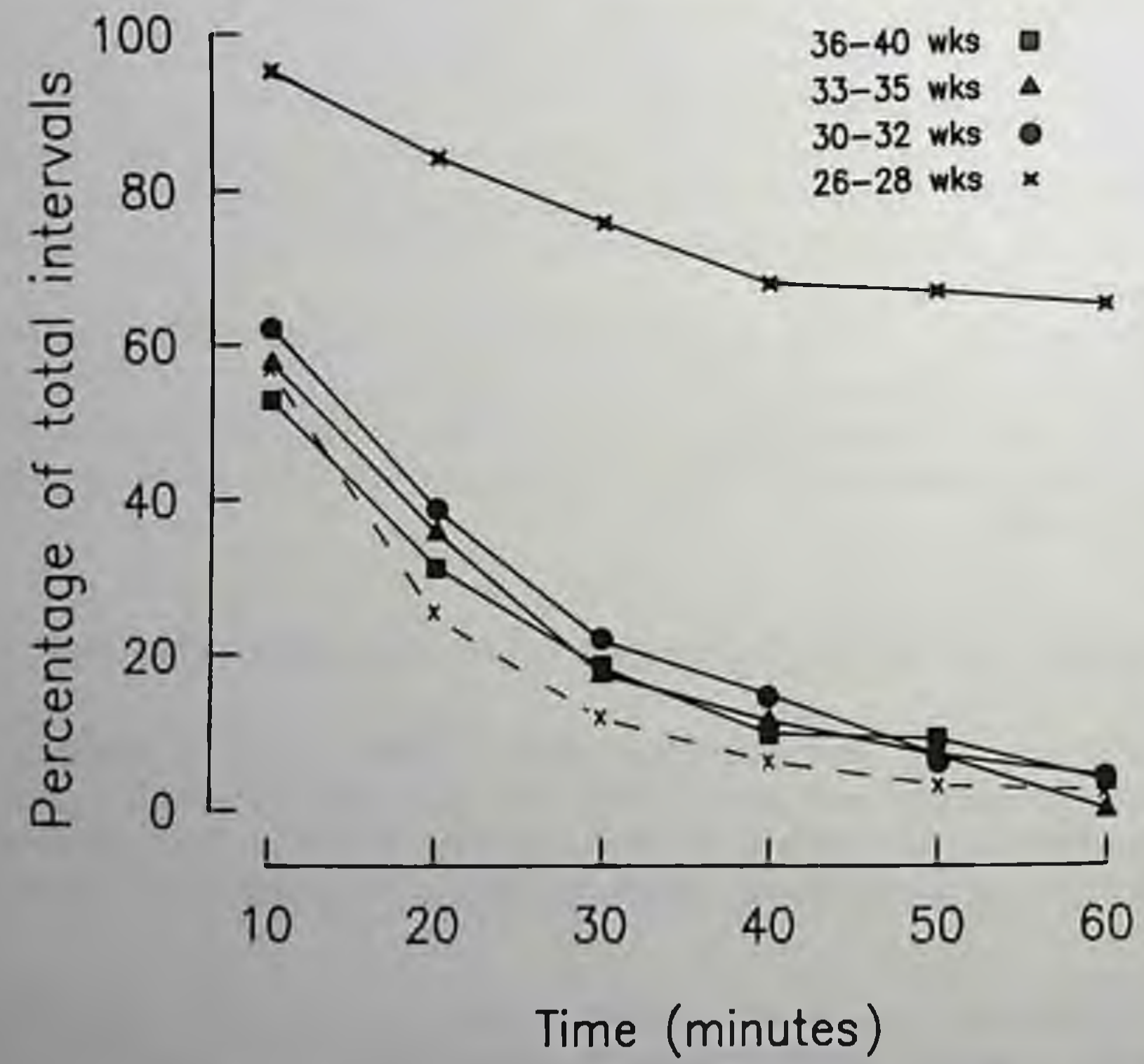

Figure 1. The percentage of time intervals during which fewer than two FHR accelerations of ≥ 15 beats per min for ≥ 15 seconds occurred was plotted for all fetuses from 26 weeks to term (solid line). The percentage of time intervals during which fewer than two FHR accelerations of ≥ 10 beats per min for ≥ 15 seconds was also plotted for fetuses from 26 to 28 weeks on the same time scale (dashed line). (*From* Gagnon R, Campbell K, Hunse C, et al: Patterns of human fetal heart rate accelerations from 26 weeks to term. Am J Obstet Gynecol 157:745, 1987; with permission.)

indicates that most of the FHR accelerations in the young gestational age group (26–28 weeks) were <15 bpm and cannot be detected with an increase in the observation time. Using a minimal amplitude of 10 bpm for ≥ 15 sec above the baseline to define an acceleration at 26 to 28 weeks, however, the length of time from the beginning of recordings until 2 FHR accelerations occurred was similar to that at 30 to 40 weeks. (see Fig. 1).

A negative correlation between the amplitude of spontaneous FHR accelerations and the baseline FHR is seen between 30 and 40 weeks in healthy human fetuses (Fig. 2). It can be seen that using a minimal acceleration amplitude of ≥ 15 bpm for ≥ 15 sec, it is possible to detect more than 97.5 per cent of FHR accelerations, only if the basal FHR is ≤ 128 bpm. Moreover, when the baseline FHR is ≥ 150 bpm, more than 50 per cent of healthy human fetuses will experience FHR accelerations of < 15 bpm and therefore could be classified as "nonreactive" and possibly "compromised" using current criteria for nonstress testing (see Fig. 2). We believe that individual fetuses after 30 weeks' gestation have a "set gain" for FHR accelerations that is related to the basal heart rate, and this "set gain" reflects maturation of the autonomic control of the fetal heart.

DEVELOPMENT OF THE FETAL AUDITORY SYSTEM

The embryonic ear forms from an ectodermal thickening, the auditory placode.[1] In the 4- to 5-week embryo, the otocyst divides into two

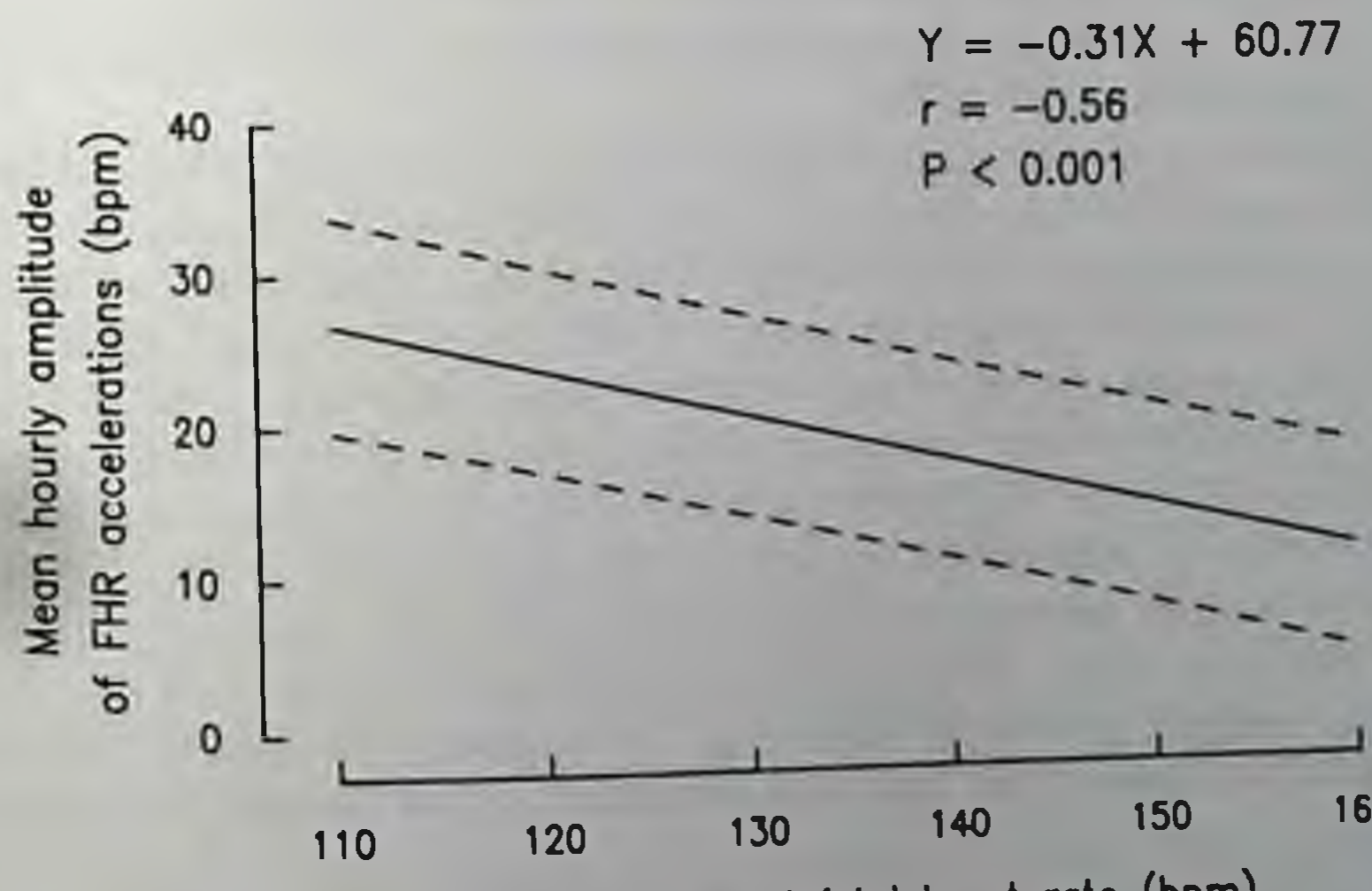

Figure 2. Regression line (solid line) of the mean hourly amplitude of FHR accelerations was plotted in relationship to the mean hourly basal heart rate in all fetuses from 30 to 40 weeks with the 95 per cent confidence interval (dashed line). A definition of ≥ 15 beats per min for ≥ 15 seconds will detect more than 97.5 per cent of all FHR accelerations only if the basal FHR is ≤ 128 beats per min. (*From* Gagnon R, Campbell K, Hunse C, et al: Patterns of human fetal heart rate accelerations from 26 weeks to term. Am J Obstet Gynecol 157:747, 1987; with permission.)

lobes; one lobe becomes the cochlea and the other the labyrinth.[39] At 6 months, both the organ of Corti (containing auditory receptors) and the tunnel of Corti are present in all turns of the cochlea.

At the onset of cochlear functioning, auditory competencies, which are well characterized in animal studies,[48,49] are poor. Electrophysiologic responses can be recorded only for medium frequencies (1000–2000 Hz, depending on the species). Auditory thresholds are high (100 dB). There is no frequency discrimination and no temporal coding. During maturation, auditory thresholds decrease, temporal coding begins, frequency sensitivity widens, first in the low-frequency range and finally in the high frequencies. The last event in the functional maturation of the cochlea is sharpening of unit frequency selectivity.[49] Electrophysiologic studies relative to the maturation of the sleep states,[57] brain metabolism,[3] and behavioral responses[50] in human neonates suggest that cortical functioning, and therefore processing of sensory information, may begin at about 30 weeks' gestation.

INTRAUTERINE SOUND STIMULATION AVAILABLE TO THE FETUS

It is not clear yet to which sound intensity the human fetus is exposed. Estimations of the average intrauterine noise range from 28 dB to 95 dB sound pressure levels (SPL), depending on the recording devices and methods.[43,61] The intrauterine background noise in human pregnancy is believed to come from pulsations in the mother's cardiovascular system.[61] Vince et al.[59,60] implanted hydrophone into the amniotic cavity of pregnant ewe and reported average intrauterine background noise of 60 dB, with maximal attenuation of sound across the abdominal wall of 25 dB at frequencies of 5000 Hz.

Vibratory acoustic stimulation, using an electronic artificial larynx (EAL; Western Electric, Model 5C, New York, New York), is now widely used in the assessment of fetal health. The device produces a broad-band noise with multiple harmonics up to 10,000 Hz.[16] Maximal sound pressure level as measured in air at 1 cm from the surface is 110 dB at 10,000 Hz.[16] The surface of the instrument also vibrates at all frequencies between 10 and 20,000 Hz, with maximal vibration occurring at 450 Hz.[16] Gerhardt et al.[25] implanted a hydrophone inside the uterine cavity of pregnant ewe and measured the intrauterine SPL produced during stimulation with the EAL. They reported an overall SPL of 135 dB during stimulus, suggesting that fetuses can be exposed to higher SPL than previously believed.[16] No data are available yet in human pregnancy.

FETAL RESPONSES TO ACOUSTIC STIMULATION

Fetal Heart Rate Response

Originally, the fetal heart rate response to acoustic stimulation was used by otolaryngologists in an attempt to detect deafness during the antenatal period.[10,29] However, this has been proved unsuccessful and

Table 1. *Fetal Heart Rate Responses to Acoustic Stimulation*

	FREQUENCY (HZ)	SOUND PRESSURE LEVEL (DB)	DURATION OF STIMULUS (SEC)	GA (WKS)	EFFECT ON FHR
Johannson (29)	3000	110	1	Last 2–7 wks	↑ 10–15 bpm
Dwornicka (10)	1000	100	5	Last 4 wks	↑ 7 bpm
	2000	100	5		↑ 11 bpm
Grimwade (26)	500–1000	80	20	≥ 38 wks	↑ 27 bpm × 3 min
Read and Miller (45)	2000	105, 115, 120	5	NA	↑ >15 bpm 75% of the time
Luz (36) (Labor Study)	1500	125	2–10	NA	↑ 29 bpm
Serafini (52)	1220	126	4	NA	↑ ≥ 15 bpm 83% of time
Jensen (28)	2000	70–80	5	32–39 wks	↑ 10–17 bpm
Davey (4)	98–6000 Multiple harmonics of 98 Hz	74	10	32–36 wks	↑ ≥ 15 bpm 66% of the time
Querleu (44)	White noise >1000 Hz	110 dB	5	>28 wks	↑ ≥ 15 bpm 83% of the time
Ohel (37)	EAL	110 dB	5*	Term	↑ 15 bpm number‡
Gagnon (16–19)	EAL	110 dB	5†	>30 wks	↑ Amplitude‡ Duration‡ Number‡ Prolonged Tachycardia

* Stimulus applied during low FHR variability.
† Stimulus applied irrespective of FHR variability (low + high).
‡ of FHR accelerations.
GA, gestational age; FHR, fetal heart rate; EAL, electronic artificial larynx. Reference number in parenthesis. NA: not available.

was abandoned. With the advent of antepartum FHR monitoring, Read and Miller[45] suggested the use of FHR response (usually a FHR acceleration) to a pure tone external sound stimulation to assess fetal health. Table 1 summarizes the FHR responses described following different sources of external sound. It is obvious that the usual FHR response to acoustic stimulation is a FHR acceleration rather than a FHR deceleration.

Studies were conducted in our laboratories to determine the effect of a 5-second vibroacoustic stimulation with the EAL on human fetal heart rate. Eighty-three highly selected healthy pregnant women between 26 and 40 weeks' gestational age were included. Computerized FHR analysis was used to fit a baseline to the heart rate record and to detect automatically FHR accelerations above the baseline.[6,17] Examples of the FHR response after vibroacoustic stimulation at 27 and 38 weeks are shown in Figure 3. We demonstrated a significant increase in the basal FHR in healthy fetuses after 30 weeks' gestation.[19] This fetal tachycardia can be prolonged up to 1 hour following the 5-second stimulus in healthy term fetuses.[17] Maternal heart rate and blood pressure are not affected by vibroacoustic stimulation.[17-19] Before 30 weeks, FHR response to EAL is usually characterized by a single, long-duration acceleration (see Fig. 3). After 33 weeks, there is a delayed increase in the number of FHR accelerations between 10 and 20 minutes following

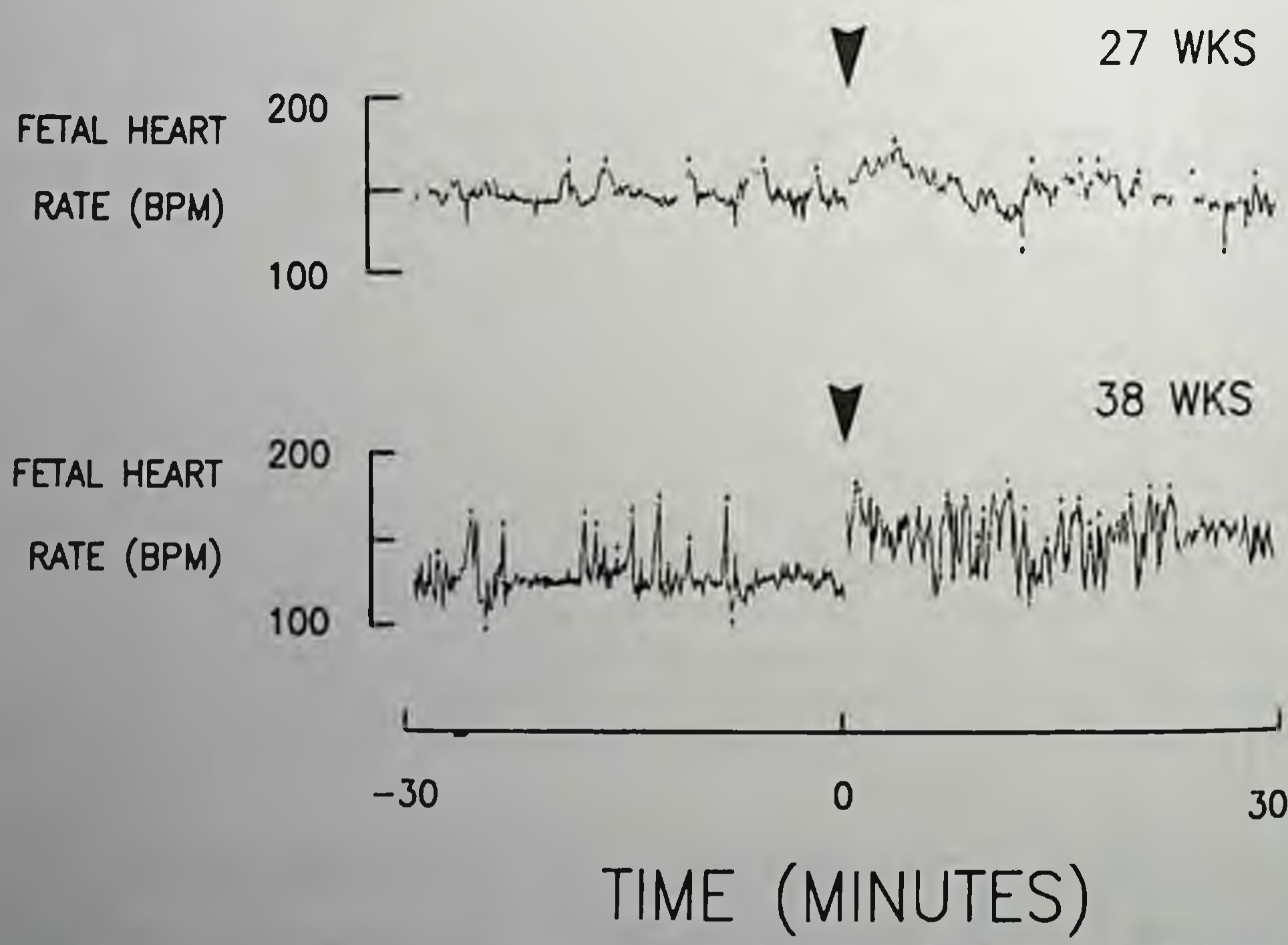

Figure 3. Examples of an increase in FHR after a 5-second vibratory acoustic stimulus with the electronic artificial larynx in a 27-week fetus and in a 38-week fetus. (*From* Gagnon R, Hunse C, Carmichael L, et al: Human fetal responses to vibratory acoustic stimulation from 26 weeks to term. Am J Obstet Gynecol 157:1377, 1987; with permission.)

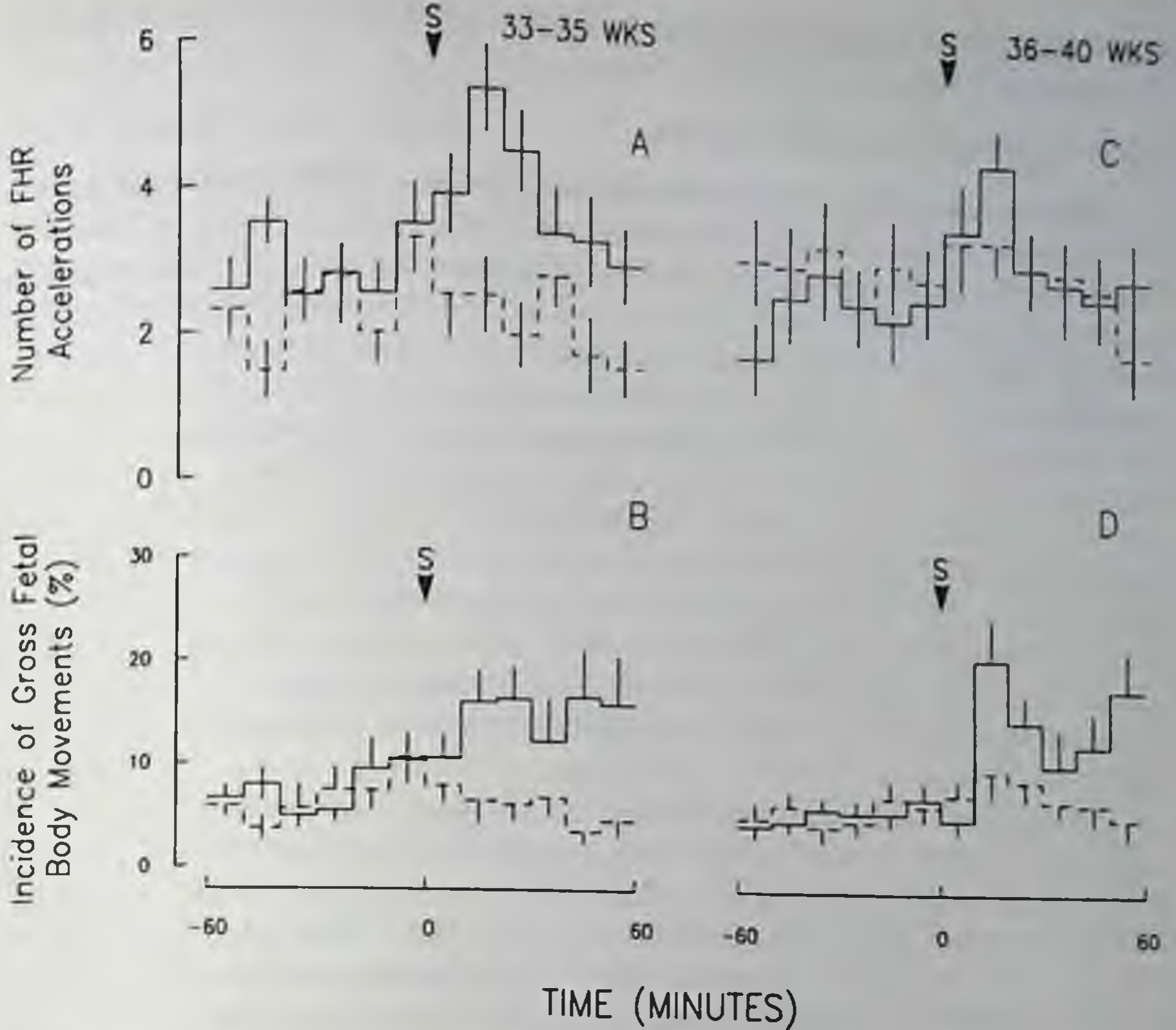

Figure 4. The mean number of FHR accelerations was plotted in 10-minute intervals from 33 to 40 weeks before and after control (dashed line) or stimulus (solid line). The mean incidence of gross fetal body movements was also plotted on the same time scale. There was a delayed increase in both the number of FHR accelerations and the incidence of gross fetal body movements after vibratory acoustic stimulation. (*From* Gagnon R, Hunse C, Carmichael L, et al: Human fetal responses to vibratory acoustic stimulation from 26 weeks to term. Am J Obstet Gynecol 157:1379, 1987; with permission.)

stimulus (see Fig. 4). In a group of 13 healthy fetuses between 26 and 28 weeks, absent FHR response to EAL was seen in 2 of these fetuses.[19]

A negative correlation between the maximal amplitude of the first FHR acceleration following vibroacoustic stimulation and prestimulation basal FHR is seen between 30 and 40 weeks in healthy human fetuses.[20] In the presence of fetal tachycardia (>160 bpm), more than 50 per cent of healthy fetuses will experience FHR accelerations of <15 bpm amplitude following stimulation with the EAL. Therefore, vibroacoustic stimulation is probably of limited value in the presence of fetal tachycardia. Computer-derived indices of long-term FHR variability are not significantly altered following vibroacoustic stimulation.[17–19]

Abnormal FHR response to EAL characterized by a FHR deceleration or bradycardia followed or preceded by a FHR acceleration has been reported in pregnancies complicated by intrauterine growth restriction and oligohydramnios,[21] nuchal cord,[53] and during labor after rupture of membranes.[46] This altered FHR response might indicate umbilical cord

compression associated with the fetal "startle reflex" usually seen during vibroacoustic stimulation.[9,33,62,31]

Effect on Fetal Body Movements

It is important to the clinician that there is a close relationship between fetal heart rate accelerations and fetal movements. In healthy term fetuses, more than 90 per cent of all gross fetal body movements are associated with fetal heart rate accelerations.[41] Quantitative observations of fetal movements using real-time ultrasound suggest they are interchangeable with fetal heart rate accelerations.[41] For these reasons, it would appear that FHR accelerations induced with external acoustic stimulation are associated with fetal movements. Gelman et al.[24] reported a significant increase in the number of fetal movements following a 2000-Hz, 100-dB acoustic stimulus applied on the maternal abdomen for 1 minute. This increase in fetal activity persisted for 30 minutes after the stimulus. However, Schmidt et al.,[51] using sound stimulation (2000 Hz, 120 dB, 5-sec duration) without touching the maternal abdomen, were not able to observe any change in patterns of fetal activity or heart rate.

The author and co-workers used real-time ultrasound and external cardiotocograph simultaneously to determine the effect of a 5-second vibratory acoustic stimulation with the EAL on fetal movements and FHR patterns. Figure 4 demonstrates a plot of the number of FHR accelerations and incidence of gross fetal body movements in 27 healthy fetuses between 33 and 40 weeks' gestational age receiving stimulation with the EAL compared with 27 healthy controls. There is a significant but delayed increase in both number of FHR accelerations and fetal movements following a 5-second vibroacoustic stimulus. This increase in fetal activity persisted up to 1 hour following the 5-second stimulus (see Fig. 4).[22] Before 32 weeks' gestation,[18,19] gross fetal body movements are not altered by the stimulus, suggesting that FHR and fetal movement responses to vibroacoustic stimulation are relatively independent. We believe that fetal motor and heart rate responses to EAL depend on functional maturation of the fetal central nervous system and reflect a state of wakefulness.[17–19,22]

Leader et al.,[33] using an electrical toothbrush as a vibroacoustic stimulation applied on the maternal abdomen, demonstrated the presence of a fetal "startle reflex" during such stimulus. This *reflex* was defined as an immediate marked fetal response involving either trunk or limb movement together or independently that occurs during vibroacoustic stimulation and for above 2.5 seconds afterward. *Habituation* is the decrease in responsiveness that occurs when an organism is stimulated repeatedly. This is widely regarded as a form of learning,[56] and there is good evidence that a normal habituation pattern reflects an intact and fully functioning central nervous system. Fetal habituation, using the "startle reflex" as a response to repeated vibroacoustic stimulation, has been demonstrated in the human fetus.[33] Fetuses with intrauterine growth restriction have habituation patterns that differ from normally grown fetuses.[34] Hypoxemic fetuses owing to a decrease in inspired maternal oxygen do not habituate to vibroacoustic stimula-

tion.[35] Whether fetal habituation is a sensitive measure of central nervous system integrity remains to be determined.

Fetal Breathing Movements

A significant decrease in fetal breathing movements has been reported, only in term (36–40 weeks) fetuses, following vibroacoustic stimulation. Fetuses were not only breathing less but also more irregularly after stimulation.[22]

It is hypothesized that the changes in fetal breathing patterns following stimulation with the electronic artificial larynx reflects a state of wakefulness and a release of fetal catecholamines.[22]

Umbilical Artery Flow Velocity Waveform

Measurements of flow velocity waveforms in both the umbilical and uterine arteries have been used in the evaluation of fetal health.[12–13] It is believed that changes in these waveforms reflect alterations in downstream vascular resistance and are independent of heart rate.[12] The most widely used index of vascular resistance is the ratio between the peak-systolic flow velocity and the end-diastolic flow velocity (S/D) ratio. Investigators have demonstrated a significant decrease in umbilical artery S/D ratio following vibroacoustic stimulation. However, these changes in flow velocity waveforms following stimulation with EAL are due to changes in FHR (usually tachycardia) rather than changes in the placental vascular resistance.[23]

CLINICAL SIGNIFICANCE OF FETAL ACCOUSTIC STIMULATION

Read and Miller[45] were the first to propose that fetal heart rate response to acoustic stimulation could be used in the evaluation of fetal health. They used pure-tone, high-frequency (2000 Hz) source of sound of 105 and 120 dB applied over the fetal head for 5 seconds. They reported that adequate FHR response to sound (FHR acceleration of $\geq$ 15 bpm) was associated with a negative contraction stress test (CST). In contrast, an inadequate FHR response to acoustic stimulation (FHR acceleration $>$ 15 bpm) was associated with 65 per cent of suspicious or positive CST.[45] The primary outcome measure was CST results, which is known to have a high incidence of false-positive results (erroneously abnormal test), and therefore could not be used to assess the predictive value of acoustic stimulation in the assessment of fetal health.

However, since this observation in 1977,[45] fetal acoustic stimulation has rapidly become a popular clinical tool in North America (14 scientific abstracts using vibroacoustic stimulation were presented at the Annual Meeting of the Society of Perinatal Obstetricians in 1987–1988). An important question remains: What is the value of acoustic stimulation in the prediction of fetal outcome?

A laboratory test usually is assessed by statistical parameters of its predictability of outcome. These measures include sensitivity (detection of abnormal outcome), specificity (prediction of normal outcome with a

Table 2. *Matrix for Perinatal Outcome and Fetal Acoustic Stimulation Tests*

	ABNORMAL OUTCOME	NORMAL OUTCOME	TOTAL
Abnormal Test	A	C	A + C
Normal Test	B	D	B + D
Total	A + B	C + D	A + B + C + D

Sensitivity = A/A + B.
Specificity = D/C + D.
Positive predictive value = A/A + C.
Negative predictive value = D/B + D.
Prevalence = A + B/A + B + C + D.

normal test), positive predictive value (probability of abnormal outcome with an abnormal test, PPV), and negative predictive value (probability of normal outcome with a normal test, NPV). The prevalence is the occurrence of an abnormal event in the entire group. When the prevalence of an abnormal event is high, the PPV of an abnormal test will increase and the NPV of a normal test will decrease, but to a lesser degree. Table 2 illustrates definitions used to predict perinatal outcome following fetal acoustic stimulation based on fetal heart rate response.

Fetal Acoustic Stimulation in Antepartum Surveillance

All reports published in the literature by October 30, 1988, regarding the use of fetal acoustic stimulation as a test of fetal health were reviewed. Articles were included in this analysis only if they met the following criteria: 1) they were population studies, not case reports; 2) fetal acoustic test results were correlated with perinatal outcome; and 3) fetal acoustic stimulation was done within 7 days before delivery.

Five original studies[4,44,45,52,58] and one review[32] reported the use of fetal heart rate response to acoustic stimulation in the assessment of antepartum fetal health. The characteristics of the stimulus used and the perinatal outcome parameters are summarized in Table 3. It can be seen that a wide variety of sound frequencies and intensities have been used for stimulation. The usual outcome parameters were intrapartum fetal distress, 5-minute Apgar score, and perinatal mortality. It is important that the criteria used for an adequate fetal heart rate response were all different and therefore cannot be matched together. There was one common denominator, however: A clinically significant FHR response to acoustic stimulation was always defined as $\geq$15 bpm amplitude. The false-positive result rate (abnormal test with a normal outcome) was above 50 per cent in one (25 per cent) out of four studies evaluating the risk of intrapartum fetal distress. Intrauterine fetal death within 7 days of a "reactive" fetus to acoustic stimulation has not been reported yet, but the number of patients studied has been too small to make any firm conclusion. Smith et al.[55] reported that external vibroacoustic stimulation with the electronic artificial larynx produces a 48 per cent reduction in nonreactive NST without a loss of reliability. The perinatal outcome was not clearly stated, however, and the predictive value for outcome could not be calculated.

Table 3. *Predictive Value of Fetal Acoustic Stimulation in Antenatal Surveillance*

STIMULUS	PERINATAL OUTCOME PARAMETER	PERCENT					
		N	*Sensitivity*	*Specificity*	*PPV*	*NPV*	*Prevalence*
2000 Hz (45) 105, 115, 120 dB	CST	36	100	90	67	100	12
1220 Hz (52) 126 dB	Intrapartum fetal distress	159	45	90	52	87	20
	5-min Apgar < 7	159	20	83	4	96	3
1000, 1500, (44)	Neonatal distress	73	53	64	31	82	23
2000 Hz, white noise >1000 Hz 110 dB							
98 Hz with multiple harmonics 74 dB (4)	Perinatal mortality	86	100	69	12	100	4
850 Hz (58)	Intrapartum fetal distress	116	64	60	14	94	10
	5-min Apgar < 8	116	78	61	14	97	8
	Perinatal mortality	116	100	59	6	100	2.6
EAL (32)	Intrapartum fetal distress	117	88	83	45	98	14
	5-min Apgar < 7	117	100	76	13	100	3.4
	pHa < 7.20	117	47	78	29	88	16
	Perinatal mortality	117	100	100	33	100	0.9

Key: PPV = positive predictive value; NPV = negative predictive value; EAL = electronic artificial larynx; CST = contraction stress test. (References in parentheses.)

With currently available data on the value of fetal acoustic stimulation during antenatal surveillance, the following conclusions can be made:

1. The risk of intrauterine fetal death within 7 days of a "reactive" fetal acoustic stimulation test cannot be determined, the number of patients studied being too small. So far, however, on small series, the negative predictive value for perinatal mortality has been 100 per cent irrespective of the type of stimulus used.

2. The positive predictive value for fetal distress during labor (based on abnormal FHR pattern) is probably 40 to 50 per cent with the highest sensitivity reported (88 per cent) using the FHR response to the EAL.

3. The definition and nomenclature of an adequate fetal heart rate response to acoustic stimulation based on physiologic studies remain to be determined. From previous studies, FHR response to acoustic stimulation can be affected by gestational age,[19] prestimulation baseline,[20] labor,[46] and rupture of membranes.[46] These factors should be taken into account when assessing predictive value for fetal outcome.

4. There is an urgent need for a large-scale multicenter clinical trial to determine the clinical efficacy and safety of antenatal FHR response to acoustic stimulation compared to nonstress testing due to the widespread utilization of this technique in clinical practice. Neurologic development assessment after delivery and during infancy should be integrated to such clinical trial.

Fetal Acoustic Stimulation in Intrapartum Surveillance

Ingemarsson et al.[27] used FHR response to vibroacoustic stimulation as a screening test in early labor to determine fetal outcome. Only patients of ≥ 34 weeks who delivered within 24 hours of the FAS test were included and the stimulus used was the EAL applied for 5 seconds over the fetal head. The FAS test result was interpreted as the immediate FHR response to sound stimulation within a 5-minute window. Four different FHR patterns were recognized: type IA, prolonged period of acceleration (s) (> 15 bpm, > 3 minutes); type IB, one acceleration lasting > 1 minute or at least two accelerations of > 15 seconds' duration; type II, a biphasic response with acceleration (s) followed by a deceleration; type III, no response or a prolonged deceleration (> 60 bpm and > 60 seconds). Fetal distress was based on abnormal FHR tracing necessitating immediate delivery or a 5-minute Apgar score < 7 at 5 minutes. Type II and III responses were considered abnormal. The risk of fetal distress for a type III response was 75 per cent if the previous FHR tracing was ominous. If the previous FHR tracing was reactive, type II and III responses were associated with fetal distress only 14.2 per cent of the time. Therefore, the overall positive predictive value for fetal distress was less than 50 per cent (Table 4).

Labor and rupture of membranes usually give access to the fetal circulation. The metabolic status can be easily assessed using fetal scalp sampling to measure fetal pH. All reports published by October 30, 1988, regarding the use of intrapartum fetal acoustic stimulation to predict fetal acidosis were reviewed. Articles were included in this analysis only if they met the following criteria: 1) they were population studies, not case reports; 2) fetal acoustic test results were correlated to perinatal outcome. Results are summarized in Table 4. Intrapartum studies evaluating the relationship between fetal heart rate response to acoustic stim-

Table 4. *Predictive Value of Intrapartum Acoustic Stimulation*

STIMULUS	PERINATAL OUTCOME PARAMETERS	*N*	PERCENT				
			Sensitivity	*Specificity*	*PPV*	*NPV*	*Prevalence*
EAL (27) 5 seconds	Fetal distress	766	32	98	30	98	3
EAL (11) 3 seconds	FSS	188	61	70	46	82	29
	pH ≤ 7.25 FSS	188	100	64	8	100	3
EAL (42)	pH ≤ 7.20 FSS	100	45	83	43	84	22
	pH ≤ 7.25 FSS	100	90	84	39	99	10
EAL (54) 3–5 sec	pH ≤ 7.20 FSS	64	100	65	53	100	28
Combined	pH ≤ 7.25	352	65	73	47	85	27
	pH ≤ 7.20	288	94	71	16	99.5	6.5

Key: FSS, fetal scalp sampling; PPV, positive predictive value; NPV, negative predictive value; and EAL, electronic artificial larynx. (References in parentheses.)

ulation and fetal scalp pH were all conducted using the electronic artificial larynx as the external source and used the same criteria for an adequate FHR response (a FHR acceleration of ≥ 15 bpm for 15 seconds above the baseline). They are therefore easier to compare than antenatal studies. Using fetal scalp pH ≤ 7.25 to define fetal acidosis, the combined false-positive rate was 53 per cent (range 53–57 per cent). Using fetal scalp pH ≤ 7.20 to define fetal acidosis, the positive predictive value was unacceptably low at 16 per cent. Therefore, absence of FHR response to EAL during labor does not necessarily indicate fetal acidosis.

Currently available data suggest that

1. More than 90 per cent of acidotic fetuses (scalp pH < 7.20), when an abnormal FHR pattern is present, could be detected using FHR response to EAL during labor.

2. Virtually 100 per cent of fetuses demonstrating FHR acceleration following vibroacoustic stimulation during labor will have scalp pH > 7.20. However, it is not known if acidotic fetuses will experience FHR acceleration following stimulus.

3. The positive predictive value to detect fetal acidosis during labor (scalp pH < 7.20) using FHR response to EAL remains low (< 50 per cent) and should be confirmed by fetal scalp sampling to confirm metabolic status of the fetus. If fetal scalp sampling cannot be done, usual criteria of fetal distress using FHR patterns should be used to decide if immediate delivery is indicated.

Advantages of Fetal Acoustic Stimulation

Although vibroacoustic stimulation with the electronic artificial larynx has produced the most consistent increase in fetal heart rate, the significance of this FHR response is not clear yet. The only practical advantages demonstrated so far, compared to nonstress testing, are a decrease in the mean test length of 4.5 minutes,[55] a decrease in the incidence of nonreactive NST by 48 per cent,[55] and a reduction in the necessity for fetal scalp sampling during labor of 50 per cent.[54] As a research tool, fetal acoustic stimulation might help to elucidate mechanisms controlling human fetal behavioral states and maybe fetal neurologic maturation.[17,19]

Limitations of Fetal Acoustic Stimulation

The Influence of Gestational Age. Before 30 weeks' gestation, FHR response to vibroacoustic stimulation is occasionally absent in healthy human fetuses[19,20] and therefore might be of limited value in this gestational age group.

The Influence of Prestimulation Basal FHR. In the presence of fetal tachycardia (> 160 bpm), FHR response can be absent in 50 per cent of healthy human fetuses after 30 weeks' gestation and is probably of limited value to predict fetal outcome.[20]

The Effect of Labor and Rupture of Membrane. The FHR response to acoustic stimulation is decreased during active phase of labor and after rupture of membranes.[36,46] Moreover, an absence of heart rate response to EAL does not necessarily indicate fetal acidosis during labor (Table 4).[11,42,54]

Safety. It is not yet possible to determine the safety of repetitive vibroacoustic stimulations on human fetuses. Gerhardt et al.[25] reported

extremely high (135 dB) intrauterine sound pressure levels during stimulation with the EAL, in the pregnant ewe. No data have been available in humans. Ohel et al.,[38] however, in a small group of 20 2-day-old neonates exposed *in utero* to stimulation with EAL, reported normal auditory acuity. No one has carefully evaluated the influence of repetitive sound stimulation on subsequent neurologic development. Finally, there is at least one case reported in which external vibroacoustic stimulation performed on a term fetus produced severe prolonged bradycardia, necessitating cesarean section delivery.[53] There was a tight nuchal cord and the Apgar scores were 7 and 10 at 1 and 5 minutes, respectively. Therefore, no firm conclusion can be made at this point about the safety of external vibroacoustic stimulation. The device should remain a research tool until clinical research evidence of negative and positive predictive value for fetal outcome are clearly documented.

Before this modality of antenatal or intrapartum testing is accepted as a standard means of assessing fetal health, it should be proved not only safe but also clinically efficacious. It is also possible that stimulation with EAL might be too strong to differentiate the healthy from sick human fetuses. The most rational approach, as recently suggested,[47] to developing an optimal method of stimulation is to perform a dose–response study. The type of stimulus (vibratory vs acoustic), frequency (low vs high frequency), and intensity necessary to change the fetal quiet sleep states should be determined experimentally. The author and co-workers would certainly not recommend external vibroacoustic stimulation in routine obstetric care until benefits and predictive value for fetal outcome are clearly established.

SUMMARY

It is clear that external vibroacoustic stimulation produces remarkable changes in fetal heart rate and fetal movement patterns which are related to changes in fetal behavior. The clinical significance of these effects on human fetuses has been addressed by many authors in series of small number of patients involved. There is an obvious lack of uniformity in the different protocols used to determine the predictive value of fetal acoustic stimulation in the assessment of fetal health. Current knowledge of the normal responses of healthy human fetuses to acoustic stimulation and the limitations of this type of testing should be taken into account to determine more accurately the negative and positive predictive value for fetal outcome.

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REFERENCES

1. Altmann E: Normal development of the ear and its mechanics. Arch Otolaryngol 52:725, 1950
2. Brown R, Patrick J: The nonstress test: How long is enough? Am J Obstet Gynecol 141:646, 1981

3. Chugani HT, Phelps ME: Maturational changes in cerebral function in infants determined by 18 FDG positron emission tomography. Science 231:840, 1986
4. Davey DA, Dommisse J, Macnab M, et al: The value of an auditory stimulatory test in antenatal fetal cardiotocography. Eur J Obstet Gynecol Reprod Biol 18:273, 1984
5. Dawes GS, Visser GHA, Goodman JDS, et al: Numerical analysis of the human fetal heart rate: The quality of ultrasound records. Am J Obstet Gynecol 141:43, 1981
6. Dawes GS, Redman CWG, Smith JH: Improvements in the registration and analysis of fetal heart rate records at the bedside. Br J Obstet Gynecol 92:317, 1985
7. Dawes GS, Houghton CRS, Redman CWG: Baseline in human fetal heart rate records. Br J Obstet Gynaecol 89:270, 1982
8. Devoe LD, Castillo RA, Sherline DM: The nonstress test as diagnostic test: A critical reappraisal. Am J Obstet Gynecol 152:1047, 1985
9. Divon MY, Platt LD, Cantrell CJ, et al: Evoked fetal startle response: A possible intrauterine neurological examination. Am J Obstet Gynecol 153:454, 1988
10. Dwornicka B, Jasienska A, Smolarz W, et al: Attempt of determining the fetal reaction to acoustic stimulation. Acta Otolaryngol 57:571, 1964
11. Edersheim TG, Hutson JM, Druzin ML, et al: Fetal heart rate response to vibratory acoustic stimulation predicts fetal pH in labor. Am J Obstet Gynecol 157:1557, 1987
12. Fleischer A, Schulman H, Farmakides G, et al: Umbilical artery velocity waveforms and intrauterine growth retardation. Am J Obstet Gynecol 151:502, 1985
13. Fleischer A, Schulman H, Farmakides G, et al: Uterine artery Doppler velocimetry in pregnant women with hypertension. Am J Obstet Gynecol 154:806, 1986
14. Gagnon R, Campbell K, Hunse C, et al: Patterns of human fetal heart rate accelerations from 26 weeks to term. Am J Obstet Gynecol 157:743, 1987
15. Gagnon R, Campbell K, Hunse C, et al: Visual interpretation of nonstress testing: Intraobserver and interobserver variability. Scientific Abstract, 44th Annual Meeting of the Society of Obstetricians and Gynaecologists of Canada, Vancouver, BC, June 22-25, 1988
16. Gagnon R, Patrick J, Foreman J, et al: Stimulation of human fetuses with sound and vibration. Am J Obstet Gynecol 155:848, 1986
17. Gagnon R, Hunse C, Carmichael L, et al: External vibratory acoustic stimulation near term: Fetal heart rate and heart rate variability responses. Am J Obstet Gynecol 156:323, 1987
18. Gagnon R, Hunse C, Carmichael L, et al: Fetal heart rate and fetal activity patterns after vibratory acoustic stimulation at thirty to thirty-two weeks' gestational age. Am J Obstet Gynecol 158:75, 1988
19. Gagnon R, Hunse C, Carmichael L, et al: Human fetal responses to vibratory acoustic stimulation from twenty-six weeks to term. Am J Obstet Gynecol 157:1375, 1987
20. Gagnon R, Hunse C, Patrick J: Fetal responses to vibratory acoustic stimulation: Influence of basal heart rate. Am J Obstet Gynecol 159:835, 1988
21. Gagnon R, Hunse C, Fellows F, et al: Fetal heart rate and activity patterns in growth-retarded fetuses: Changes after vibratory acoustic stimulation. Am J Obstet Gynecol 158:265, 1988
22. Gagnon R, Hunse C, Carmichael L, et al: Effects of vibratory acoustic stimulation on human fetal breathing and gross body movements near term. Am J Obstet Gynecol 155:1227, 1986
23. Gagnon R, Morrow R, Ritchie K, et al: Umbilical and uterine artery blood flow velocities after vibratory acoustic stimulation. Am J Obstet Gynecol 159:574, 1988
24. Gelman SR, Wood S, Spellacy WN, et al: Fetal movements in response to sound stimulation. Am J Obstet Gynecol 143:484, 1982
25. Gerhardt KJ, Abrams RM, Kovaz BM, et al: Intrauterine noise levels produced in pregnant ewes by sound applied to the abdomen. Am J Obstet Gynecol 159:228, 1988
26. Grimwade JG, Walker DW, Bartlett M, et al: Human fetal heart rate change and movement in response to sound and vibration. Am J Obstet Gynecol 109:86, 1971
27. Ingemarsson I, Arulkumaran S, Paul RH, et al: Fetal acoustic stimulation in early labor in patients screened with the admission test. Am J Obstet Gynecol 158:70, 1988
28. Jensen OH: Fetal heart rate response to controlled sound stimuli during the third trimester of normal pregnancy. Acta Obstet Gynecol Scand 63:193, 1984

29. Johannson B, Wedenberg E, Westin B.: Measurement of tone response by the human fetus. A preliminary report. Acta Otolaryngol 57:188, 1964
30. Keegan RA.: The Nonstress Test. Clin Obstet Gynecol 30:921–935, 1987
31. Kuhlman KA, Kayreen AB, Depp R, et al: Ultrasonic imaging of normal fetal response to external vibratory acoustic stimulation. Am J Obstet Gynecol 158:47, 1988
32. Kuhlman KA, Depp R: Acoustic stimulation testing. Obstet Gynecol Clin North Am 15:303, 1988
33. Leader LR, Baillie P, Martin B, et al: The assessment and significance of habituation to a repeated stimulus by the human fetus. Early Hum Devel 7:211, 1982
34. Leader LR, Baillie P, Martin B, et al: Fetal habituation in high-risk pregnancies. Br J Obstet Gynecol 89:441, 1982
35. Leader LB, Baillie P: The changes in fetal habituation patterns due to a decrease in inspired maternal oxygen. Br J Obstet Gynecol 95:664, 1988
36. Luz NP, Lima CP, Luz SH, et al: Auditory evoked responses of the human fetus. I. Behavior during progress of labor. Acta Obstet Gynecol Scand 59:395, 1980
37. Ohel G, Birkenfield A, Rabinowitz, et al: Fetal response to vibratory acoustic stimulation in periods of low heart rate reactivity and low activity. Am J Obstet Gynecol 154:619, 1986
38. Ohel G, Harawitz E, Linder N, et al: Neonatal auditory acuity following in utero vibratory acoustic stimulation. Am J Obstet Gynecol 157:440, 1987
39. Ormerod FC: The pathology of congenital deafness in the child. In Ewing A (ed): The Modern Educational Treatment of Deafness. Manchester, Manchester University Press, 1960, pp 811
40. Patrick J, Campbell K, Carmichael L et al: Patterns of gross fetal body movements over 24-hour observation intervals during the last 10 weeks of pregnancy. Am J Obstet Gynecol 142:363, 1982
41. Patrick J, Carmichael L, Chess L, et al: Accelerations of the human fetal heart rate at 38–40 weeks' gestational age. Am J Obstet Gynecol 148:35, 1984
42. Polzin GB, Blakemore KJ, Petrie RG, et al: Fetal vibroacoustic stimulation: Magnitude and duration of fetal heart rate accelerations as a marker of fetal health.
43. Querleu D, Renard X, Versyp F: Vie sensorielle du foetus. In Tournaire M, Levy G (eds): L'Environnement de la Naissance. Paris, Vigot, 1986, pp 15–41
44. Querleu D, Boutteville C, Renard X, et al: Evaluation diagnostique de la souffrance foetale pendant la grossesse au moyen d'un test de stimulation sonore. J Gynecol Obstet Biol Reprod 13:789, 1984
45. Read JA, Miller FC: Fetal heart rate acceleration in response to acoustic stimulation as a measure of fetal well-being. Am J Obstet Gynecol 129:512, 1977
46. Richards DS, Cefalo RC, Thorpe JM, et al: Determinants of fetal heart rate response to vibroacoustic stimulation in labor. Obstet Gynecol 71:535, 1988
47. Romero R, Mazor M, Hobbins JC: A critical appraisal of fetal acoustic stimulation as an antenatal test for fetal well-being. Obstet Gynecol 71:781, 1988
48. Rubel EW: Auditory system development. In Gottlieh G, Krasnegor (eds): Measurement of Audition and Vision in the First Year of Postnatal Life: A Methodological Overview. Ablex, Norwood, 1985, pp 53–90
49. Rubel EW, Ryals BM: Development of the place principle: Acoustical trauma. Science 219:512, 1983
50. Sammons WAH: Premature behavior and the neonatal intensive care unit environment. In: Cloherty JP, Stark AR (eds): Manual of Neonatal Care. Boston, Little Brown, 1980, pp 359–360
51. Schmidt W, Boos R, Gnirs J, et al: Fetal behavioral states and controlled sound stimulation. Early Hum Devel 12:145, 1985
52. Serafini P, Lindsay MBJ, Nagey DA, et al: Antepartum fetal heart rate response to sound stimulation: The acoustic stimulation test. Am J Obstet Gynecol 148:41, 1984
53. Sherer DM, Menashe M, Sadovsky E: Severe fetal bradycardia caused by external vibratory acoustic stimulation. Am J Obstet Gynecol 159:334, 1988
54. Smith CV., Nguyen HN, Phelan JP, et al: Intrapartum assessment of fetal well-being: A comparison of fetal acoustic stimulation with acid-base determinations. Am J Obstet Gynecol 155:726, 1986
55. Smith CV, Phelan JP, Platt LD, et al: Fetal acoustic stimulation testing: II. A randomized clinical comparison with the nonstress test. Am J Obstet Gynecol 155:131, 1986

56. Stevensen D, Siddle D.: Theories of habituation. In Siddle D (ed): Orienting and Habituation: Perspective in Human Research New York, John Wiley & Sons , 1983, pp 183–236
57. Torres F, Anderson C.: The normal EEG of the human newborn. J Clin Neurophysical 2:89, 1985
58. Trudinger BJ, Boylan P: Antepartum fetal heart rate monitoring: Value of sound stimulation. Obstet Gynecol 55:265, 1980
59. Vince MA, Armitage SE: Sound stimulation available to the sheep foetus. Reprod Nutr Dev 20:801, 1980
60. Vince MA, Billing AE, Baldwin BA, et al: Maternal vocalizations and other sounds in the fetal lamb's sound environment. Early Hum Devel 11:179, 1985
61. Walker DW, Grimwade JC, Wood C: Intrauterine noise: A component of the fetal environment. Am J Obstet Gynecol 109:91, 1971
62. Westgren M, Almstrom H, Nyman M, et al: Maternal perception of sound-provoked fetal movements as a measure of fetal well-being. Br J Obstet Gynaecol 94:523, 1987

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Fetal Biophysical Profile Scoring: Current Status

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The purpose of antepartum fetal surveillance in terms of biophysical and biochemical monitoring is to avoid fetal death *in utero* and perhaps some hypoxic complications of the neonate related to intrauterine asphyxia. Prior to the advent of fetal heart rate monitoring and dynamic imaging ultrasound, nonspecific markers of potential fetal disease were used, such as fundal height measurement, maternal weight and various biochemical markers (placental alkaline phosphatase, human placental lactogen, and estriols). With the introduction of electronic fetal heart rate monitoring and dynamic imaging ultrasound, a more specific and direct examination of the fetus became possible.

Since the introduction of external fetal heart rate monitoring, the nonstress test (NST) and contraction stress test (CST) have been the most commonly used tests as means of antepartum fetal surveillance. The introduction of these two tests, along with the improvement in neonatal care have resulted in a dramatic decrease in perinatal mortality to less than 12 per 1000 live births. Since the stillbirth to neonatal death ratio was changed from 1 : 2 in 1970 to 2 : 1 in 1980,[25] the focus has been in the development of tests to decrease the number of stillbirths. Nonstress test and CST predict normal outcome reasonably well; however, they are much less accurate in the prediction of poor outcome as judged by Apgar scores, fetal distress, and perinatal death rate. The nonstress test has a low false-negative result rate (1 per cent or less) and a high false-positive rate (more than 75 per cent).[11,35] Similarly, the CST has a low false-negative rate (2–2.7 per cent) and a false-positive rate ranging from 50 per cent to greater than 75 per cent.[5,12,32] The appearance of late decelera-

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tions of the fetal heart rate in response to uterine contractions suggests fetal hypoxia due to uteroplacenta insufficiency. However, this concept is clearly related to labor. During the intrapartum period, the frequency and intensity of the uterine contractions can be monitored with internal monitoring techniques, and therefore a judgment about fetal reserve could be made reasonably. CST is an attempt to mimic the events of labor in the antepartum period with induced uterine contractions (by oxytocin or nipple stimulation) and to judge the fetal reserve on the basis of the presence or absence of late decelerations. External monitoring techniques, however, like those used in the antepartum period, are not capable of measuring the intensity of the uterine contractions and therefore the strength of the stimulus to the fetus. In our view, any judgment about the fetal reserve, when the intensity of the stress factor (uterine activity) is unknown, has no scientific basis. In addition there is no known relationship between the ability of the fetus to tolerate labor and a safe prolongation of the pregnancy. An additional disadvantage of the CST is that its use is relatively contraindicated in patients with premature rupture of the membranes, multiple gestation, incompetent cervix, premature labor, or third-trimester vaginal bleeding.

SINGLE VERSUS COMBINED BIOPHYSICAL VARIABLE ASSESSMENT

There have been many methods for biophysical testing to determine fetal health based on single biophysical variable assessment such as fetal movement monitoring,[33] fetal breathing,[26,27] fetal heart rate accelerations in response to fetal movements (NST),[11] or decelerations with induced uterine contractions (CST).[32] Experience has demonstrated clearly that the predictive accuracy of each normal biophysical variable is high and approximately equal among variables; however, the false-positive rate for each single abnormal variable is greater than 50 per cent. Experience also has shown that combinations of biophysical variables are useful in lowering the false-positive result rate. For instance, when NST and fetal breathing are combined, most of the false-positive results are eliminated because the presence of fetal breathing in patients with nonreactive NST and the converse observation of reactive NST with absence of fetal breathing has the same predictive accuracy as either normal test.[24] Similarly, a combination of fetal breathing assessment to the scheme of NST–CST testing can eliminate most of the false-positive results.[23] These observations suggest that multiple biophysical variable assessment may be a more accurate method than is the single biophysical variable testing using NST, fetal breathing movements, or fetal movements as a single test. The concept of multiple variable assessment is well established in extrauterine medicine, for example, with Apgar scoring in the neonate or vital sign assessment in the adult. The application of the same concept of performing a physical examination of the fetus *in utero* became possible with the advent of dynamic ultrasound imaging. Real-time ultrasound now permits objective evaluation of multiple fetal activities—fetal movements, fetal breathing movements, and tone—as well as

assessment of the intrauterine environment (i.e., estimation of amniotic fluid volume and placental grading). The combination of these biophysical variables, which is analogous to performing a fetal physical examination, was first introduced by Manning et al. in 1980.[24] The combination of biophysical variables (fetal biophysical profile) was developed to decrease the false-positive results and to enhance the ability to identify accurately the hypoxic fetus in the antepartum period. The most important factor in the sensitivity of this testing method is the combination of acute (fetal heart rate reactivity, fetal movements, fetal breathing movements, fetal tone) and chronic (amniotic fluid volume) markers of the fetal condition. Although in itself it is not a biophysical variable, placental grade also has been included to assess the fetal environment.[37]

PHYSIOLOGY AND PATHOPHYSIOLOGY OF FETAL BIOPHYSICAL COMPONENTS

The acute markers of the fetal condition (fetal heart rate reactivity, fetal movements, fetal breathing movements, and fetal tone) are dynamic activities that are initiated and regulated by complex integrated mechanisms of the fetal central nervous system (CNS). The presence or absence of these markers reflects fetal status at the time of testing. The presence of a normal biophysical activity is indirect evidence that the portion of the CNS that controls that activity is intact and functioning and therefore nonhypoxemic. The absence of a given fetal biophysical activity, however, is difficult to interpret because it may reflect either pathologic depression or normal periodicity. Cyclic variations in the frequency of fetal biophysical activities such as fetal breathing movements and fetal body movements have been observed in normal and high-risk pregnancies. The periodicity in these biophysical activities is short-term (20–40 minutes) or long-term similar to diurnal rhythms seen in extrauterine life. Also, periodicity in fetal heart rate variability has been commonly observed in human fetuses. The presence or absence of cyclicity in fetal tone or fetal heart rate accelerations is not known. Central nervous system stimulants such as hyperglycemia and catecholamines may result in increased biophysical activities. In contrast, central nervous system depressants such as analgesics (morphine, meperidine), sedatives (barbiturates, diazepam), anesthetics (halothane), and drugs such as heroin, methadone, etc. may reduce or inhibit fetal biophysical activities.

The effects of hypoxia on the fetal biophysical profile depends on the extent, duration, chronicity, and frequency of the insult. Fetal hypoxia may be transient, without acidosis, or prolonged, with associated metabolic or respiratory acidosis, consequently affecting multiple organ systems. Acute fetal hypoxia produces a dramatic decrease of fetal heart rate reactivity (nonreactive NST) and fetal breathing movements, and when severe will result in reduced or absent fetal movements and fetal tone.[37,44]

The fetal biophysical activities (acute markers) are reflex activities that are controlled by different CNS centers (Table 1). Recent evidence suggests that there are variations in the sensitivity of these centers to

Table 1. *Fetal Central Nervous System Centers*

		Embryogenesis	Hypoxia
1. FT	Cortex (subcortical area?)	↓	↑
2. FM	Cortex-nuclei	↓	↑
3. FBM	Ventral surface of 4th ventricle	↓	↑
4. NST	Posterior hypothalamus, medulla	↓	↑

Key: FT = fetal tone; FM = fetal movements; FBM = fetal breathing movements; NST = nonstress test.

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hypoxia and acidosis.[37,44] From the standpoint of fetal neurodevelopment, a higher oxygen level is required for newly developing CNS centers and for reflex biophysical activities. The biophysical activities that become active first in fetal development are the last to disappear when asphyxia arrests all biophysical activities. For instance, the fetal tone center—which starts functioning at 7.5 to 8.5 weeks' gestation—and fetal movement center—which starts functioning at 9 weeks' gestation—are the earliest to function during intrauterine life and the last to disappear during asphyxia. The fetal breathing movement center, which starts functioning after 20 to 21 weeks' gestation, requires a higher Po_2 level to start functioning as compared to the fetal tone and the fetal movement centers. The fetal heart rate reactivity center, which starts operating by the end of the second trimester or early third trimester, requires the highest Po_2 level to start functioning *in utero* and is therefore the most sensitive to hypoxia. The fetal CNS centers that control the biophysical activities have different degrees of sensitivity to hypoxia and acidosis, the most sensitive being the fetal heart rate reactivity and fetal breathing movement centers, and the least sensitive being the fetal movement and fetal tone centers. Recent data[44] from our institution indicate that the fetal heart rate reactivity and fetal breathing centers cease when the pH is lower than 7.20; the centers controlling movement and tone begin to malfunction at pH values of 7.10 to 7.20, and are completely abolished at a pH lower than 7.10. Thus, the first manifestations of fetal hypoxia and acidosis are nonreactive NST and loss of fetal breathing; in advanced acidemia, fetal movements and tone are compromised. The presence of poor fetal tone has indeed been found in clinical studies to be associated with the highest perinatal death rate (42.8 per cent because it signifies advanced fetal hypoxia and acidosis.[37] The above concept of a different level of sensitivity to hypoxia of the CNS centers is of significant value in antepartum fetal assessment because it allows for the estimation of the level of deterioration of the fetal condition and perhaps determination of the degree of change in fetal status (gradual hypoxia concept).

Chronic sustained fetal hypoxia or acidosis may produce protective redistribution (by stimulation of aortic body chemoreceptors) of cardiac output away from nonvital fetal organs (i.e., kidney or lung) toward vital fetal organs (i.e., heart, brain, or adrenals). With prolonged asphyxia the redistribution may be so profound that the perfusion to the lung and kidneys ceases and decreased urine production and lung liquid flow, as well as oligohydramnios, develops.[6] Amniotic fluid volume, unlike the

biophysical activities, is not acutely influenced by alterations in fetal CNS function. Previous studies have shown a high correlation between decreased amniotic fluid volume and increased incidence of abnormal pregnancy outcome. The corrected perinatal mortality rate in patients with normal qualitative amniotic fluid volume (largest pocket > 2 to < 8 cm) has been reported to be 1.97 per 1000, whereas in patients with marginal (largest pocket 1 to 2 cm) and decreased amniotic fluid (largest pocket < 1 cm) 37.74 per 1000 and 109.4 per 1000, respectively.[4] Fetuses with oligohydramnios are not only chronically stressed but also at high risk for cord compression and *in utero* death. The presence of oligohydramnios at a term or near-term gestation has been considered as an indication for delivery regardless of the presence or absence of the biophysical activities. In preterm gestations with decreased amniotic fluid volume and no demonstrable fetal anomalies, the judgment should be made between early delivery to avoid cord accident or frequent antepartum testing (every 24 – 48 hours). In preterm fetuses with oligohydramnios, the use of pulsed or continuous Doppler ultrasound may be proved useful in determining the timing of delivery or frequency of testing. The presence of fetal heart rate variable decelerations during nonstress testing in the presence of oligohydramnios is an indication for delivery regardless of gestational age. In our institution, placental grading also is included in the fetal biophysical profile, although in itself it is not a biophysical variable. We have found that in patients with grade III pla-

Table 2. *Fetal Biophysical Profile Scoring According to Manning et al.*[24]

Variable	Score 2	Score 0
Fetal breathing movements	The presence of at least 30 sec of sustained FBM in 30 min of observation	< 30 sec of FBM (FBM) in 30 min
Fetal movements	Three or more gross body movements in 30 min of observation. Simultaneous limb and trunk movements are counted as a single movement	Two or fewer gross body movements in 30 min of observation
Fetal tone	At least one episode of motion of a limb from a position of flexion to extension and a rapid return to flexion	Fetus in a position of semi- or full-limb extension with no return to flexion with movement. Absence of fetal movement is counted as absent tone
Fetal reactivity	The presence of two or more fetal heart rate accelerations of at least 15 bpm and lasting at least 15 sec and associated with fetal movement in 40 min	No acceleration or less than two accelerations of the fetal heart rate in 40 min of observation
Qualitative amniotic fluid volume	A pocket of amniotic fluid that measures at least 1 cm in two perpendicular planes	Largest pocket of amniotic fluid measures < 1 cm in two perpendicular planes
Maximal score	10	0
Minimal score	—	—

From Manning FA, Platt LD, Sipos L: Am J Obstet Gynecol 136:787 – 795, 1980; with permission.

Table 3. *Criteria for Scoring Biophysical Variables According to Vintzileos et al.*[37]

Nonstress test
Score 2 (NST 2): 5 or more FHR accelerations of at least 15 bpm in amplitude and at least 15 seconds' duration associated with fetal movements in a 20-minute period
Score 1 (NST 1): 2 to 4 accelerations of at least 15 bpm in amplitude and at least 15 seconds' duration associated with fetal movements in a 20-minute period
Score 0 (NST 0): 1 or fewer accelerations in a 20-minute period
Fetal movements
Score 2 (FM 2): At least 3 gross (trunk and limbs) episodes of fetal movements within 30 minutes. Simultaneous limb and trunk movements were counted as a single movement.
Score 1 (FM 1): 1 or 2 fetal movements within 30 minutes
Score 0 (FM 0): Absence of fetal movements within 30 minutes
Fetal breathing movements
Score 2 (FBM 2): At least 1 episode of fetal breathing of at least 60 seconds' duration within a 30-minute observation period
Score 1 (FBM 1): At least 1 episode of fetal breathing lasting 30 to 60 seconds within 30 minutes
Score 0 (FBM 0): Absence of fetal breathing or breathing lasting less than 30 seconds within 30 minutes
Fetal tone
Score 2 (FT 2): At least 1 episode of extension of extremities with return to position of flexion, and also 1 episode of extension of spine with return to position of flexion
Score 1 (FT 1): At least 1 episode of extension of extremities with return to position of flexion, or 1 episode of extension of spine with return to position of flexion
Score 0 (FT 0): Extremities in extension. Fetal movements not followed by return to flexion. Open hand
Amniotic fluid volume
Score 2 (AF 2): Fluid event throughout the uterine cavity. A pocket that measures 2 cm or more in vertical diameter
Score 1 (AF 1): A pocket that measures less than 2 cm but more than 1 cm in vertical diameter
Score 0 (AF 0): Crowding of fetal small parts. Largest pocket less than 1 cm in vertical diameter
Placental grading
Score 2 (PL 2): Placental grading 0, 1, or 2
Score 1 (PL 1): Placental posterior difficult to evaluate
Score 0 (PL 0): Placental grading 3

Key: NST = nonstress test; FHR = fetal heart rate; bpm = beats per minute; FM = fetal movements; FBM = fetal breathing movements; FT = fetal tone; AF = amniotic fluid; PL = placental grading.

Maximal score 12; minimal score 0.

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centas there is an increased incidence of abnormal intrapartum fetal heart rate patterns and abruptio placentae during labor.[37] The inclusion of grade III placentas serves the purpose of alerting the clinician in the intrapartum management of these patients.

Unlike amniotic fluid volume and placental grading, the other biophysical components (biophysical activities) are influenced by changes

in fetal CNS function. Because the absence of a given biophysical activity could be explained by asphyxia or sleep–wake cycles, it is necessary to develop a test that can differentiate between these two conditions. This diagnostic dilemma could be resolved by observing multiple biophysical variables and extending the observation period beyond that of a sleep–wake cycle. This hypothesis should ideally produce an antepartum test which could be highly sensitive and specific, and also capable of identifying the fetus with major anomalies incompatible with extrauterine life, thus avoiding unnecessary surgical intervention. Indeed, the use of heart rate monitoring alone (NST or CST) for antepartum fetal surveillance has not uncommonly resulted in unnecessary surgical interventions, given the high incidence of major fetal anomalies in fetuses with abnormal fetal heart rate testing.[30] Since the early 1980s an attempt was made to score each biophysical variable to determine a "fetal biophysical profile score." There are currently two types of scoring systems: one proposed by Manning et al. (Table 2)[24] in which each variable is either normal (score = 2) or abnormal (score = 0), and the other by Vintzileos et al. (Table 3)[37] in which each variable receives a score of 0, 1, or 2. In both systems a fetal biophysical score of 8 or more is reassuring of fetal well-being; however, a biophysical score of less than 8 is nonreassuring and repeat testing or delivery is indicated. In both systems the presence of oligohydramnios constitutes an abnormal biophysical assessment regardless of the overall scoring.

THE FETAL BIOPHYSICAL PROFILE AND SCORING: CLINICAL STATUS

Because variations in the individual biophysical components—such as NST reactivity, fetal movements, amniotic fluid volume and placental grading—have been described according to gestational age, the question of whether these variations could normally change the biophysical profile and scoring of the healthy fetus throughout gestation was addressed by a retrospective analysis of 210 patients with intact membranes and normal pregnancy outcome, who had a total of 951 serial examinations from 25 to 44 weeks' gestation.[45] The frequency of the individual biophysical variables, as well as fetal biophysical scoring of 8 or more, throughout gestation are shown in Table 4. As can be seen there is a significant increase in reactive NSTs after 32 weeks; both fetal breathing and amniotic fluid volume were found to be decreased after 40 weeks, whereas the incidence of grade III placentas increased significantly after 32 weeks. The fetal movements and fetal tone were found to remain unchanged throughout gestation. These variations in the observed frequencies of the fetal biophysical components throughout gestation agree with the findings of several investigators.[13,16,31,34] Despite these variations in the frequency of the biophysical components, the frequency of reassuring biophysical scoring (8 or more) was not found to change significantly throughout gestation. It should be emphasized that the described changes in the biophysical components across gestation pertain to the biophysical profile scoring as defined per our criteria[37] for

Table 4. *Frequency of Individual Biophysical Variables and Biophysical Scoring of Eight or More in Pregnancies with Intact Membranes**

GESTATION (WEEKS) TOTAL NUMBER = 951 % OF THE TOTAL NO.	25–28 NO = 61 (6.4%)	P VALUE	29–32 no = 92 (20.1%)	P VALUE	33–36 no = 347 (36.4%)	P VALUE	37–40 no = 257 (27.0%)	P VALUE	41–44 no = 94 (9.8%)
NST-2	22(36.0%)	NS	82(42.7%)	<0.01	223(64.2%)	NS	188(73.1%)	NS	77(81.9%)
NST-1	19(31.1%)	NS	68(35.4%)	<0.01	86(24.7%)	NS	44(17.1%)	NS	9(9.5%)
NST-0	20(32.7%)	NS	42(21.8%)	<0.01	38(10.9%)	NS	25(9.7%)	NS	8(8.5%)
FBM-2	36(59.0%)	NS	143(74.4%)	NS	264(76.0%)	NS	181(70.4%)	<0.05	52(55.3%)
FBM-1	4(6.5%)	NS	15(7.8%)	NS	31(8.9%)	NS	20(7.7%)	NS	6(6.3%)
FBM-0	21(34.4%)	NS	34(17.7%)	NS	52(14.9%)	NS	56(21.7%)	<0.05	36(38.3%)
FM-2	61(100%)	NS	188(97.9%)	NS	331(95.3%)	NS	242(94.1%)	NS	86(91.4%)
FM-1	0(0.0%)	NS	4(2.0%)	NS	14(4.0%)	NS	12(4.6%)	NS	5(5.3%)
FM-0	0(0.0%)	NS	0(0.0%)	NS	2(0.5%)	NS	3(1.1%)	NS	3(3.1%)
FT-2	61(100.0%)	NS	182(94.7%)	NS	324(93.3%)	NS	232(90.2%)	NS	79(84.0%)
FT-1	0(0.0%)	NS	9(4.6%)	NS	21(6.0%)	NS	24(9.3%)	NS	12(12.7%)
FT-0	0(0.0%)	NS	1(0.5%)	NS	2(0.5%)	NS	1(0.4%)	NS	3(3.1%)
AF-2	58(95.0%)	NS	189(98.4%)	NS	331(95.3%)	NS	231(89.8%)	<0.01	70(74.4%)
AF-1	1(1.6%)	NS	3(1.5%)	NS	11(3.1%)	NS	22(8.5%)	<0.01	16(17.0%)
AF-0	2(3.2%)	NS	0(0.0%)	NS	5(1.4%)	NS	4(1.5%)	<0.01	8(8.5%)
PL-2	61(100.0%)	NS	189(98.4%)	NS	321(92.5%)	NS	212(82.4%)	<0.01	64(68.0%)
PL-1	0(0.0%)	NS	3(1.5%)	NS	12(3.4%)	NS	10(3.8%)	<0.01	13(13.8%)
PL-0	0(0.0%)	NS	0(0.0%)	<0.05	14(4.0%)	<0.01	35(13.6%)	<0.01	17(18.0%)
Total score 8 or more	61(100%)	NS	186(96.8%)	NS	341(98.2%)	NS	249(96.8%)	NS	83(88.2%)

* Scoring according to the criteria by Vintzileos et al. See Table 3.

Key: NST = Nonstress test; FBM = fetal breathing movements; FM = fetal movements; FT = fetal tone; AF = amniotic fluid volume; PL = placenta grading; NS = not significant.

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the purpose of antepartum fetal surveillance. Using the scoring criteria of Manning et al., Baskett et al. also had similar findings regarding the changes of the biophysical components of the healthy fetus throughout gestation.[1] Their study involved 5,582 singleton fetuses with normal perinatal outcome who had 11,012 biophysical profile examinations. There was a significant increase in reactive NSTs and fetal breathing movements at 34 to 41 weeks as compared to earlier gestations. A comparison of the test results at term (37–41 weeks) with those of prolonged (42–44 weeks) pregnancies showed that the NST, fetal breathing movements, fetal tone, and amniotic fluid volume were more likely to be abnormal in prolonged pregnancies. Despite these changes in the individual biophysical components throughout gestation, the frequency of normal biophysical scoring (8 or more) did not change significantly throughout gestation. The understanding of the normal changes of the different biophysical components throughout gestation is imperative for the proper clinical application of this tool especially in early gestational ages.

In their initial study of antepartum fetal surveillance, Manning et al.[24] reported on 216 patients who were primarily managed by NST testing. The results of the other biophysical variables were not disclosed and, therefore, did not influence management or outcome. There was a significant correlation between abnormal biophysical profile score and low 5-minute Apgar scores, fetal distress in labor, and perinatal death rate. The combination of the individual parameters of the profile resulted in a significant change in both the false-negative and false-positive result rates as compared to any single test. The most accurate differentiation of the normal from the compromised fetus was obtained when all biophysical variables were studied. When all variables were normal (score 10) the perinatal death rate was 0, and when all variables were abnormal (score 0) the perinatal death rate was 600 per 1000 and the fetal death rate was 400 per 1000. Based on the results of their study Manning and colleagues proposed a management protocol according to the biophysical profile scoring as outlined in Table 5. This protocol was used for management in a followup study by the same investigators, involving 1184 consecutive referred high-risk patients who had 2238 fetal biophysical scores performed.[20] The purpose of the study was to determine the effect of this management scheme on perinatal death rate

Table 5. *Management Scheme Based on Biophysical Profile Scoring*

SCORE	RECOMMENDED MANAGEMENT
8–10	Repeat in 1 week. In diabetic (insulin-dependent) and postdate patients, repeat twice weekly. No indication for active intervention
4–6	If fetal pulmonary maturity assured and cervix favorable, delivery, otherwise repeat in 24 hr. If persistent score of 4 to 6, deliver if fetal pulmonary maturity certain. Otherwise treat with steroid and deliver in 48 hr
0–2	Evaluate for immediate delivery. In cases of certain pulmonary immaturity, give steroids and deliver in 48 hr

From Manning FA et al: Am J Obstet Gynecol 140:289–294, 1981; with permission.

among referred high-risk patients. There were only six perinatal deaths in the study group (perinatal mortality 5.06 per 1000). This perinatal mortality rate of 5.06 per 1000 was significantly less than the predicted rate for a similar high-risk population (65 per 1000) or the general population (14.3 per 1000) in Manitoba. Only one fetus suffered unpredictable death (true false-negative rate 0.8 per 1000). In addition, 13 of 19 (68.4 per cent) fetuses with major congenital anomalies were detected as a result of ultrasound scanning. Of the 13 major congenital anomalies detected, 8 were lethal; in two the antepartum detection of the anomaly contributed to neonatal survival. Platt et al.[28] reported on 1112 biophysical profiles in 283 patients. Patients were managed according to the NST results and not the results of the ultrasound-monitored biophysical variables. The perinatal mortality rate for all patients delivered in their institution was 22.6 per 1000 as compared to 14 per 1000 (corrected 7 per 1000) for the study population and 7.4 per 1000 for fetuses with a reassuring score (8 or more). These authors questioned whether the predictive value of the biophysical score is better as compared to the NST alone.

A comparative trial between fetal biophysical profile scoring (375 patients) and NST testing scheme (360 patients) showed that the fetal biophysical profile scoring had a significantly higher predictive value in regard to low Apgar scores.[18] Although the sensitivity and specificity were higher with fetal biophysical profile scoring, this did not reach statistical significance when compared with the NST. The negative predictive value between the two methods were similar. All major anomalies were detected, however, during ultrasound scanning, whereas none of the anomalies were detected by heart rate testing alone. In another study, Platt et al.[29] randomized patients into two groups according to the primary test of fetal surveillance used: one managed with NST and the other managed with fetal biophysical profile score. Three hundred seventy-three patients were managed by the NST protocol and two hundred seventy-nine by a biophysical profile protocol. The corrected perinatal mortality in the biophysical profile group was 5 per 1000 and in the NST group 7 per 1000. The overall perinatal mortality rate in their hospital during the study period was 19 per 1000. Abnormal pregnancy outcomes included perinatal mortality, fetal distress in labor, low 5-minute Apgar score, and birth weight small for gestational age. The results of the study suggested that except for the negative predictive value in the sensitivities in the outcome parameters of low 5-minute Apgar scores, the diagnostic values for all outcome parameters were consistently higher in the fetal biophysical profile as opposed to the NST group. Although higher, only two of the values, positive predictive value of overall abnormal outcome and negative predictive value of small for gestational age infants, were statistically significant.

Baskett et al.[3] reported their experience with using the fetal biophysical profile score in the management of 2400 high-risk pregnancies that had a total of 5618 biophysical profiles performed. In their hospital during the study period the overall perinatal mortality was 14.5 per 1000. The perinatal mortality in the study population which was managed by the biophysical scoring was 9.2 per 1000. Excluding lethal

anomalies, fetuses with a normal biophysical profile score had a perinatal mortality of 1 per 1000, whereas fetuses with abnormal scores (0 – 4) had a perinatal mortality rate of 292 per 1000. In this study abnormal perinatal outcome was defined as fetal distress in labor, 5-minute Apgar score less than 7, intrauterine growth retardation, and perinatal death. An abnormal biophysical profile score had the best positive predictive value (79.2 per cent) for an abnormal perinatal outcome. This predictive value was significantly better than the values of the NST, fetal breathing movements, and fetal tone but did not reach statistically significance with fetal movement and amniotic fluid volume. In a further followup study Manning et al. reported on 12,620 high-risk patients who had a total number of 26,257 biophysical profiles performed.[21] The gross perinatal mortality rate was 7.37 per 1000 (93 perinatal deaths). Of these, only 24 occurred in structurally normal, nonisoimmunized fetuses (corrected perinatal mortality rate 1.9 per 1000). Eight of these structurally normal fetuses died within 1 week of a normal biophysical assessment (corrected false-negative rate of 0.634 per 1000). The gross stillbirth rate was 3.64 per 1000 and the gross neonatal death rate was 3.72 per 1000. Perinatal mortality was correlated to the biophysical score results; overall mortality ranged from as low as 0.652 per 1000 tests with a normal score (8 or more) to as high as 187 per 1000 tests with a completely abnormal score (score = 0). Sixty-two of the ninety-three perinatal deaths (66.7 per cent) were due to major congenital anomalies. The majority of the tests (97.5 per cent) were normal and only 0.76 per cent had a score of 4 or less. The same authors subsequently reported the largest antenatal experience with 19,221 high-risk pregnancies, on which a total number of 44,828 tests were performed.[19] The calculated rate of *in utero* death among structurally normal, nonisoimmunized fetuses after a last normal test was 0.726 per 1000 (14 deaths). Because four of these deaths occurred intrapartum (two of which were due to cord prolapse), under the most ideal circumstances the false-negative rate of a normal test result could have been reduced to 0.518 per 1000 (10 deaths). Because eight of the antepartum fetal deaths occurred within 3 to 7 days after the reassuring testing, it is possible that increased frequency of testing (i.e., twice a week) could have prevented some of these deaths. The ability of the biophysical profile score to predict perinatal death was also investigated by Baskett et al. in 4184 fetuses with intact membranes who had their last test within 7 days of delivery or death.[2] The biophysical profile score was more likely to predict perinatal death due to asphyxia than lethal anomalies. The overall perinatal mortality was 7.6 per 1000; the perinatal mortality rate was 1 for a normal biophysical score (score 8 – 10), 31.3 for an equivocal score (score 6), and 200 for an abnormal score (score 0 – 4). The false-negative rate for the biophysical profile score was 0.7 per 1000, which is very similar to the false-negative rate reported by Manning et al. (0.726 per 1000).

Recently, Manning et al.[22] have reported on the selective use of the NST. By omitting the NST from the initial biophysical evaluation and including only the other four remaining parameters (fetal breathing movements, fetal movements, fetal tone, and amniotic fluid volume) the authors demonstrated similar results in terms of test accuracy by study-

ing 2712 patients who had a total number of 7851 tests. The need for NST was reduced to only 2.7% of the tests. According to the authors, the selective use of NST dramatically improved the efficacy of their testing unit, shortened the duration of the patient's visit, and increased the number of tests that could be performed daily. A recent report, however, by Eden et al. questioned the wisdom of not including the NST in the initial biophysical assessment because according to their experience fetuses with normal all biophysical components but variable decelerations during NST testing have increased incidence of adverse perinatal outcome.[10]

Johnson et al. managed 307 consecutive post-term pregnancies with twice-weekly biophysical scores. Their results suggest that if the biophysical score is normal waiting for spontaneous labor results in healthy neonates and a much lower cesarean section rate (15 vs 42 per cent for induction patients).[14] The same authors also used the fetal biophysical profile scoring as the principle technique of antepartum fetal surveillance in 238 diabetic pregnancies who had a total number of 1028 tests performed.[15] There was a low incidence of abnormal biophysical scores (3.3 per cent) and in those with an abnormal score there was a high rate of intensive care nursery admissions and cesarean section rate (50 per cent). In fetuses with normal biophysical profile scoring, 57.4 per cent entered labor spontaneously, 31.3 per cent were induced, and the remaining 11.3 per cent were delivered by elective repeat or primary cesarean section. Eight fetuses had major congenital anomalies (three lethal). The authors concluded that antepartum fetal surveillance by biophysical scoring is a safe expectant management in the diabetic pregnancy. Unexplained stillbirths were prevented and 87 per cent of the patients delivered at term with minimal maternal or neonatal morbidity. In contrast, abnormal biophysical profile scoring was associated with a significantly higher rate of operative intervention and neonatal morbidity.

The efficacy of the fetal biophysical profile in twin gestations has also been reported by Lodeiro et al.[17] Forty-nine patients with twin gestations and additional risk factors such as suspected growth retardation of one or both twins, chronic hypertension, or pregnancy-induced hypertension were followed with biophysical profiles. The sensitivity, specificity, positive predictive value, and negative predictive value of the biophysical profile in predicting fetal distress was 83.3, 100, 100, and 97.7 per cent, respectively. The false-negative rate was 2.2 per cent and involved one twin pair delivered at 26 weeks' gestation, where both neonates expired because of extreme prematurity. Four twin gestations were complicated by fetal distress of only one of the twins and all eight fetuses (four pairs) had nonreactive NSTs. The biophysical profile, however, predicted accurately the distressed twin of each of the four pairs, whereas it correctly indicated well-being for its counterpart twin. The authors concluded that the biophysical profile can be safely used as followup means of nonreactive nonstress testing in twin gestations.

We have reported our initial experience with 150 high-risk pregnancies, which had a total of 342 biophysical profiles.[37] The patients were managed according to the traditional NST–CST protocol. There

was a good correlation between biophysical score and adverse outcomes such as abnormal intrapartum fetal heart rate patterns, meconium during labor, fetal distress, and perinatal mortality rate. Reassuring biophysical scores (8 or more) were associated with good pregnancy outcome in 100 per cent of cases and very abnormal scores (4 or less) were associated with very high incidence of fetal distress. The absence of fetal movements was the best predictor of abnormal heart rate patterns in labor (80 per cent), nonreactive NST was the best predictor of meconium (33.3 per cent), oligohydramnios was the best predictor of fetal distress (37.5 per cent) and poor fetal tone was the best predictor of fetal death rate (42.8 per cent). There were 11 hypoxic fetuses. All had nonreactive NSTs and none had fetal breathing present (they already had lost the two most sensitive biophysical activities). There were two fetuses with normal fetal movement and none died. Of five fetuses with movement present but compromised only one died. Of four fetuses who had absent fetal movement, three died as neonates. When the fetal tone was poor the perinatal death rate was even higher (100 per cent). These observations suggested variations in sensitivity to hypoxia of the fetal CNS centers that control the biophysical activities.

THE RELATIONSHIP BETWEEN THE FETAL BIOPHYSICAL COMPONENTS AND FETAL ACID–BASE STATUS AT THE TIME OF TESTING

To further explore the issue of variations in sensitivity to hypoxia at which the fetal biophysical activities become compromised, we studied patients undergoing cesarean section prior to the onset of labor to investigate the relationship between the fetal biophysical profile and fetal acid–base status at the time of testing.[44] The aim of the study was to avoid the inherent drawbacks of previous studies in which the last biophysical assessment within a week of delivery was used for correlation with fetal condition at birth. The long interval between performing the biophysical assessment and the birth of the infant, as well as the effects of labor and drugs on the fetus, are factors that can alter fetal condition at birth. The investigation included 124 consecutive patients with singleton pregnancies and gestational ages between 26 and 43 weeks, delivered by cesarean section because of indications such as pregnancy-induced hypertension, intrauterine growth retardation, or placenta previa. Since fetal metabolic state is more accurately reflected in cord arterial blood, fetal acidosis was defined as cord arterial pH less than 7.20. Figure 1 illustrates the relationship between the biophysical score and cord arterial pH. There were 102 fetuses with biophysical scores of 8 or more; the mean (± SD) cord arterial pH of these fetuses was 7.28 ± 0.04; two fetuses (2 per cent) were acidotic in this group. Thirteen fetuses with scores of 5 to 7 had a mean (± SD) cord arterial pH of 7.19 ± 0.06; nine fetuses (69 per cent) were acidotic in this group. Nine fetuses with scores of 4 or less had a mean (± SD) cord arterial pH of 6.99 ± 0.10, and all were acidotic. The differences in the mean cord arterial pH values of the three groups were statistically significant. Fig-

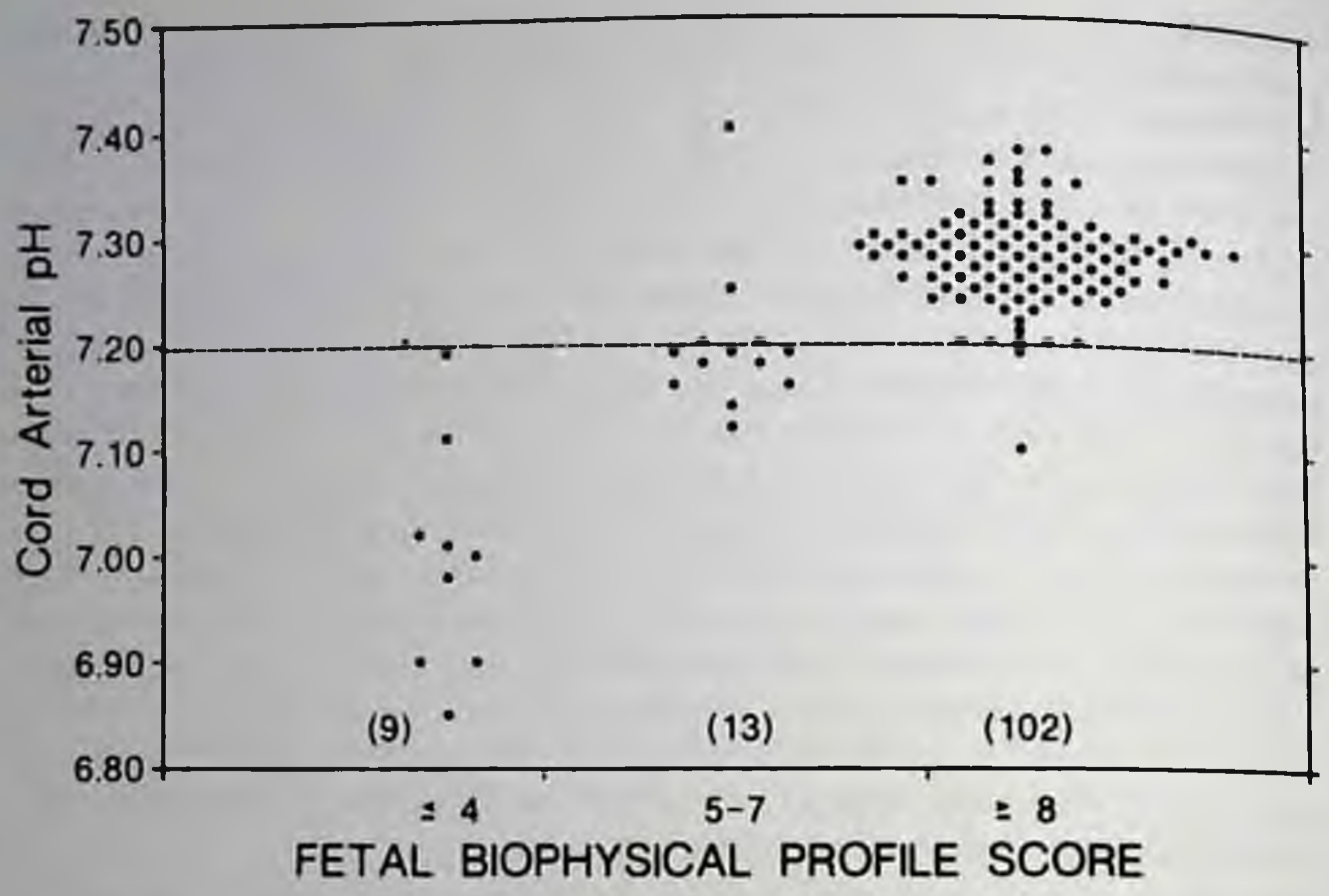

Figure 1. Relationship between the fetal biophysical profile score and cord arterial pH. Number of fetuses in parentheses. (Reprinted with permission from the American College of Obstetricians and Gynecologists. Obstet Gynecol 70:196–201, 1987.)

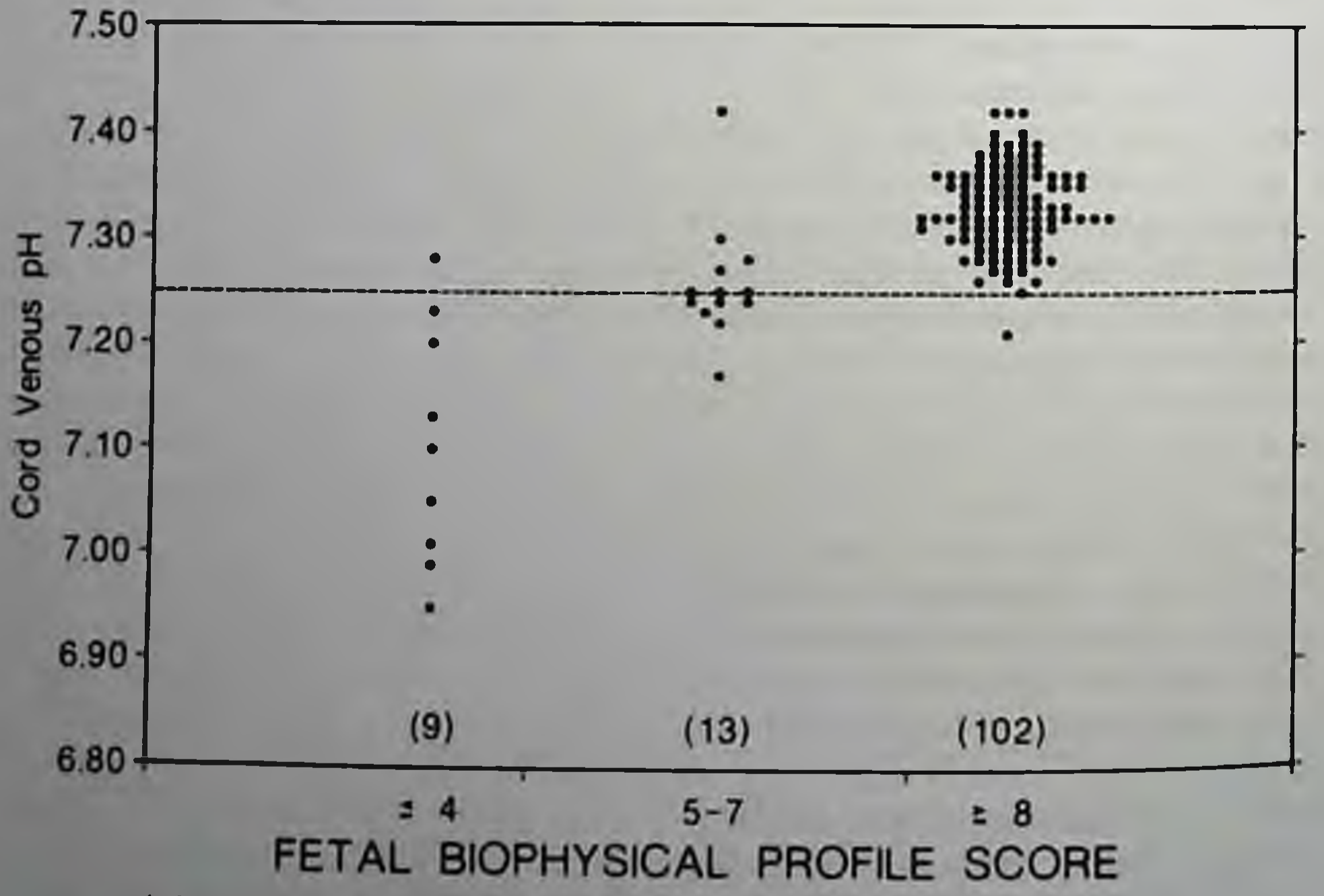

Figure 2. Relationship between the fetal biophysical profile score and cord venous pH. (Number of fetuses in parentheses.) (Reprinted with permission from the American College of Obstetricians and Gynecologists. Obstet Gynecol 70:196–201, 1987.)

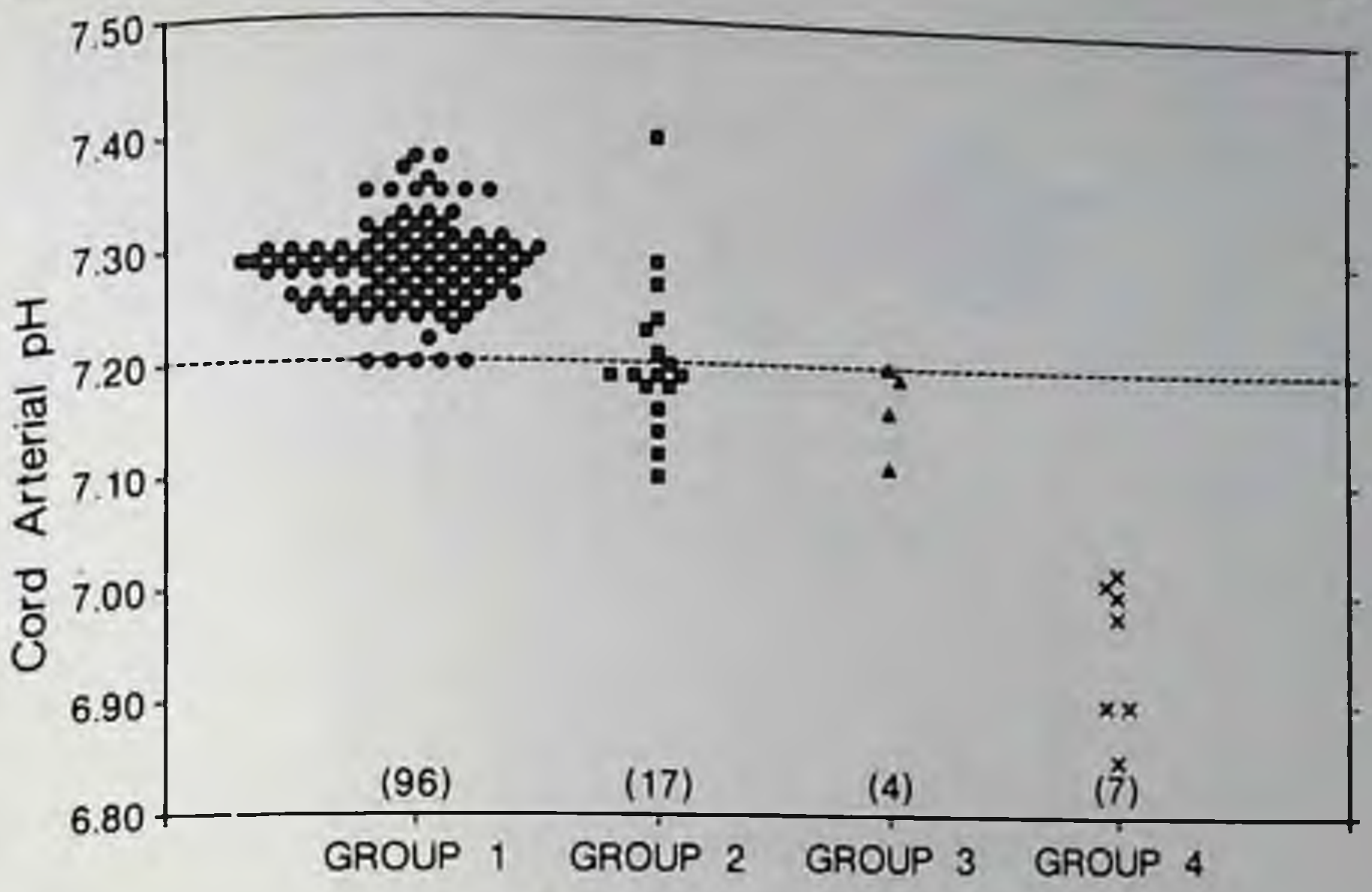

Figure 3. Relationship between the fetal biophysical activities (acute markers) and cord arterial pH. (Number of fetuses in parentheses.) (Reprinted with permission from the American College of Obstetricians and Gynecologists. Obstet Gynecol 70:196–201, 1987.)

ure 2 illustrates a similar relationship between the biophysical score and cord venous pH. Figure 3 illustrates the relationship between the biophysical activities and cord arterial pH measurements. Group 1 included 96 fetuses with a reactive NST or fetal breathing present (lasting more than 30 seconds) of whom none were acidotic. This group was further subdivided into 50 fetuses who had both a reactive NST and breathing present (mean cord arterial pH 7.28), 29 fetuses with a reactive NST and fetal breathing absent (mean cord arterial pH 7.28), and 17 fetuses with a nonreactive NST and fetal breathing present (mean cord arterial pH 7.28). The common denominator in groups 2, 3, and 4 was that all fetuses had nonreactive NST and no breathing present. However, group 2 (17 fetuses) had normal movements and tone; the mean pH of this group was 7.20 and 10 (59 per cent) were acidotic. Group 3 (4 fetuses) had compromised (present but abnormal) movements or tone; the mean cord arterial pH of this group was 7.16 and 3 (75 per cent) were acidotic. Group 4 (7 fetuses) had all biophysical activities absent and a mean cord arterial pH of 6.95; all 7 (100 per cent) fetuses were acidotic at birth. The outcomes of the 7 fetuses, who had absent all biophysical activities, were four deaths in the immediate neonatal period, two survivors with major hypoxic sequelae (seizures, intraventricular hemorrhage, etc), and one

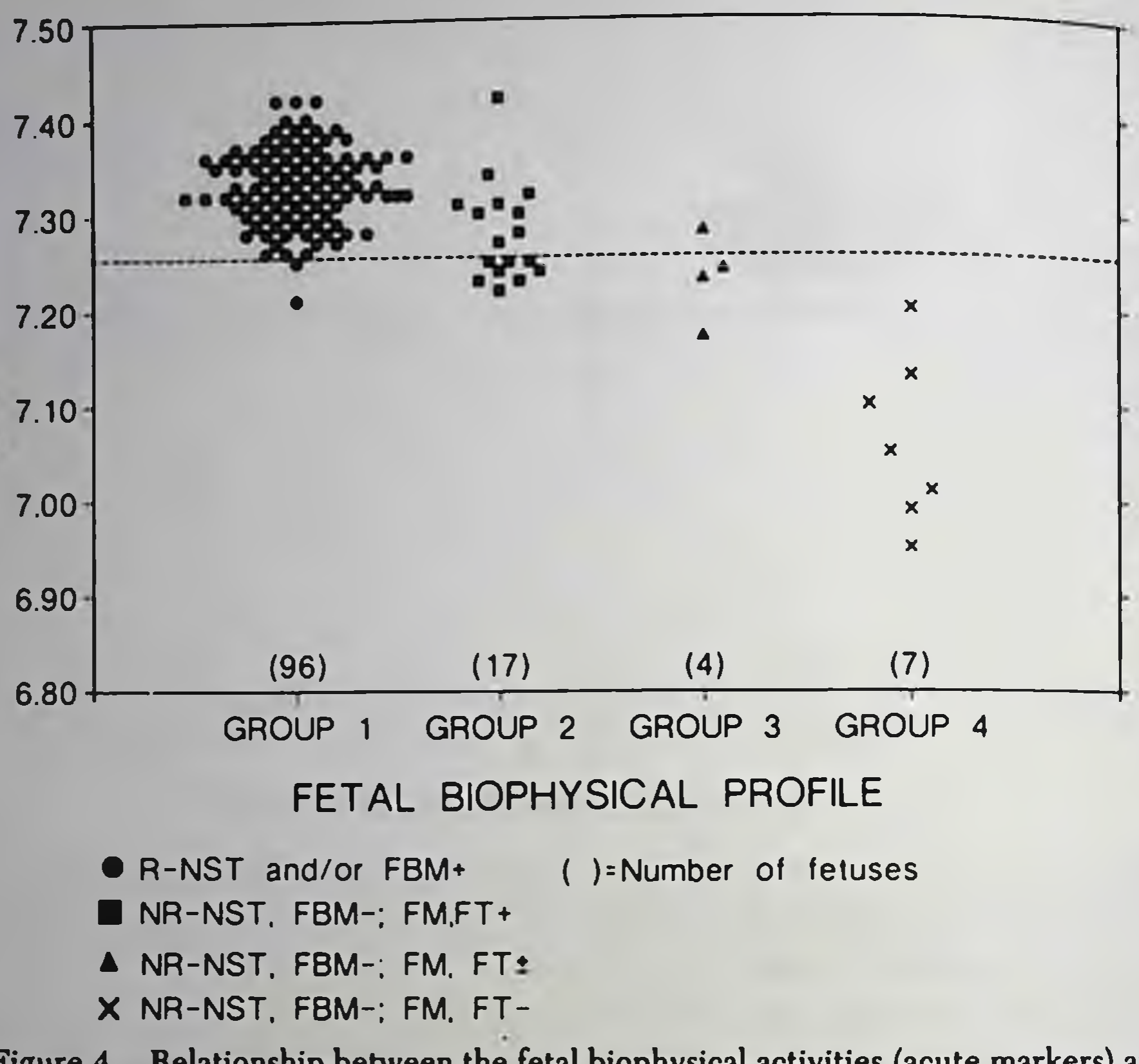

Figure 4. Relationship between the fetal biophysical activities (acute markers) and cord venous pH. (Number of fetuses in parentheses.) (Reprinted with permission from the American College of Obstetricians and Gynecologists. Obstet Gynecol 70:196–201, 1987.)

normal survivor. Similar relationship was also found between the biophysical activities (acute markers) and cord venous pH measurements (Fig. 4). This analysis of the results provides for the first time information regarding the pH level below which the fetal biophysical activities become compromised. As can be seen in Figure 3, the fetal heart rate reactivity and fetal breathing become compromised when the pH is lower than 7.20. At pH values of 7.10 to 7.20 fetal movements and tone become compromised and at pHs lower than 7.10 movements and tone are completely abolished. These observations suggest that the first manifestations of fetal acidosis are nonreactive NST and absence of fetal breathing; in advanced acidosis fetal movements and tone are lost. This concept (gradual hypoxia concept) of different levels of sensitivity to hypoxia and acidosis of the fetal CNS centers, is very important for the proper interpretation and clinical application of the biophysical profile. The efficacies of the individual biophysical components alone and in combination, as well as of the biophysical score, to predict fetal acidosis are shown in Table 6. Of the individual biophysical components, the NST and fetal breathing had the highest sensitivities and negative predictive values (both 100 per cent); their combination (nonreactive NST and fetal breathing absent as the "abnormal test") increased the specificity and positive predictive values to 92 and 71 per cent, respectively. Fetal tone

Table 6. *Efficacy of the Fetal Biophysical Variables to Predict Fetal Acidosis*

BIOPHYSICAL VARIABLE(S)	DEFINITION OF THE ABNORMAL TEST	SENSITIVITY	SPECIFICITY	POSITIVE PREDICTIVE VALUE	NEGATIVE PREDICTIVE VALUE
Biophysical score	≤7	90%(18/20)	96%(100/104)	82%(18/22)	98%(100/102)
Nonstress test, fetal breathing movements	Nonreactive NST and no breathing	100%(20/20)	92%(96/104)	71%(20/28)	100%(96/ 96)
Nonstress test	≤1 acceleration in 20 min	100%(20/20)	76%(79/104)	44%(20/45)	100%(79/ 79)
Fetal breathing movements	<30 sec	100%(20/20)	64%(67/104)	35%(20/57)	100%(67/ 67)
Fetal movements	<3	50%(10/20)	96%(100/104)	71%(10/14)	91%(100/110)
Fetal tone	Compromised or absent	45%(9/20)	100%(104/104)	100%(9/ 9)	90%(104/115)
Amniotic fluid	<1 cm	35%(7/20)	93%(97/104)	50%(7/14)	88%(97/110)
Amniotic fluid	<2 cm	45%(9/20)	86%(89/104)	38%(9/24)	89%(89/100)
Placental grading	Grade 3	5%(1/20)	94%(98/104)	14%(1/ 7)	84%(98/117)

( ) = Number of fetuses.
From Vintzileos AM, Gaffrey SE, Salingez LM, et al: Am J Obstet Gynecol 157:627–631, 1987; with permission.

had the highest positive predictive value (100 per cent) but low sensitivity (45 per cent). Of the total number of 20 acidotic fetuses, 7 (35 per cent) had amniotic fluid pockets less than 1 cm and 9 (45 per cent) had amniotic fluid pockets less than 2 cm. The frequency of oligohydramnios in the acidotic group was significantly higher (35 and 45 per cent) as compared to the nonacidotic group of fetuses (7 and 14 per cent, respectively). In comparing the ability to diagnose fetal acidosis between the biophysical profile and Apgar scores, we found that the sensitivity of the combination of "nonreactive NST and breathing absent" was significantly better than the 1- and 5-minute Apgar scores, and the sensitivity of the biophysical score was better than the 5-minute Apgar score. In terms of positive predictive value, the combination "nonreactive NST and breathing absent" was better than the 1-minute Apgar score and the biophysical score was better than the 1-minute Apgar score. No differences in specificity and negative predictive values were noted.

Considering the physiology and pathophysiology of the fetal biophysical activities, as well as the 100 per cent sensitivity for predicting the acidotic fetus using the combination of "nonreactive NST and absent fetal breathing" as the abnormal test, we have recommended an alternative antepartum fetal evaluation scheme for patients with intact membranes based on the individual biophysical components (Fig. 5). This protocol basically includes assessment of both, an acute (NST or fetal

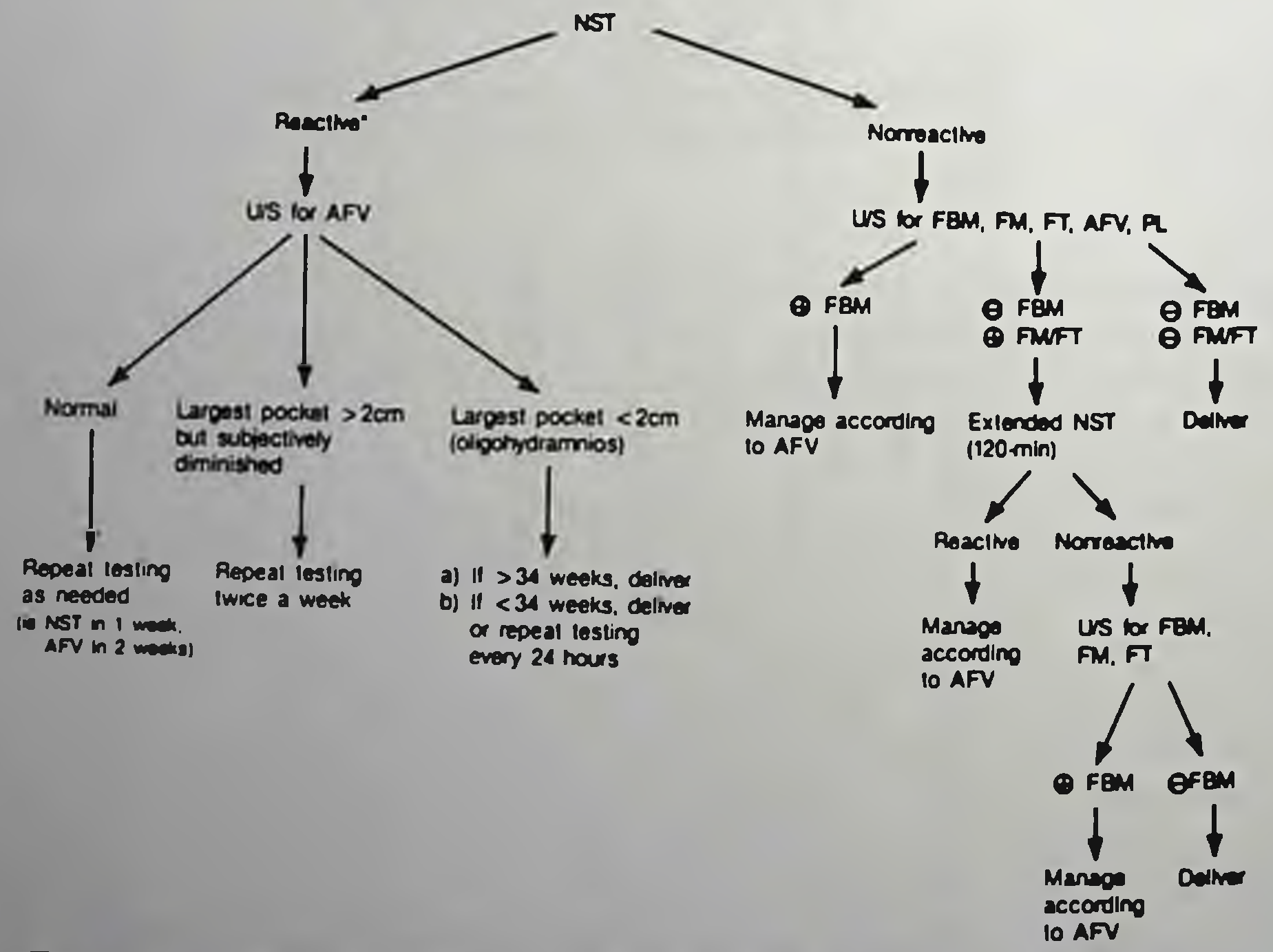

Figure 5. Protocol of antepartum fetal evaluation in pregnancies with intact membranes. * In the presence of variable decelerations and oligohydramnios, consider delivery; in the presence of variable decelerations and normal AFV, consider extended (120 minutes) or repeat NST within 24 hours. *Key.* NST = Nonstress test; U/S = ultrasound; AFV = amniotic fluid volume; FBM = fetal breathing; FM = fetal movement; FT = fetal tone; PL = placental grading, + = present/normal; − = absent/abnormal. (Reprinted with permission from Am J Obstet Gynecol 157:627–631, 1987.)

breathing) and a chronic (amniotic fluid volume) marker, and basically addresses two questions when evaluating a fetus of a high-risk pregnancy. The first question is whether the fetus is asphyxiated at the time of testing. A reactive NST or fetal breathing lasting more than 30 seconds (even in the presence of a nonreactive NST) excludes the possibility of fetal acidosis at the time of testing. In the presence of a nonreactive NST, real-time scanning is performed for a maximum of a 30-minute observation period. If fetal breathing is detected (lasting more than 30 seconds), the examination is ended and further management is based on the amniotic fluid volume assessment. If all biophysical activities (nonreactive NST, fetal breathing, fetal movements, and fetal tone) are absent or compromised after 30 minutes of continuous observation, prompt delivery is undertaken. If the fetus has a nonreactive NST and breathing absent, while movements and tone are normal, extended testing is indicated to differentiate sleeping state from asphyxia. The NST is continued until a reactive pattern is observed or until 120 minutes of continuous fetal heart rate monitoring have elapsed. At this point, if the NST is still nonreactive, the ultrasound-monitored variables are reassessed. If no fetal breathing is observed, then delivery is considered. If the fetus is not acutely asphyxiated at the time of testing, as evidenced by a reactive NST or breathing present, the second question is addressed of whether the fetus is chronically stressed and therefore a candidate for a cord accident. This judgment is based on the presence or absence of oligohydramnios or variable decelerations during nonstress testing. If there are no variable decelerations and a normal amount of amniotic fluid is present, then testing is repeated after individualizing for each case. The presence of oligohydramnios in a term or a near-term gestation with intact membranes is considered an indication for delivery regardless of the presence or absence of the other biophysical activities. (We use less than 2-cm pocket, for the definition of oligohydramnios, based on the data of Chamberlain et al.[4]) The combination of oligohydramnios and variable decelerations during the NST is also an indication for delivery in viable, structurally normal fetuses, regardless of gestational age. In very preterm gestations (< 32 weeks) in the presence of oligohydramnios and no identifiable fetal anomalies, individualization is recommended; if delivery is not undertaken, frequent testing (every 24 hours) is an alternative plan of management. In this group of fetuses we have recently used continuous or pulsed Doppler studies to decide proper management. Fetuses with subjectively diminished amniotic fluid volume, but having an amniotic fluid pocket greater than 2 cm, are tested more frequently (i.e., twice a week). We have applied this scheme of antepartum fetal evaluation to 6543 fetuses over a 4-year period, and we have never encountered a fetal death of a structurally normal fetus within a week after a reassuring biophysical assessment. This alternative protocol of antepartum fetal evaluation, without including the scoring of the biophysical variables not only increases the sensitivity of this testing method but also shortens the testing time. The understanding of the different degrees of acidosis at which the fetal biophysical activities become compromised, as well as the significance of oligohydramnios, is crucial to avoid errors that may result in unnecessary interventions or adverse

perinatal outcome. The most common errors in the interpretation and application of the fetal biophysical profile have been when management decisions are based on the biophysical score alone without considering the individual biophysical components or the overall clinical context of each case, inappropriate interval between testing, or procrastination to act promptly on the abnormal test results. The use and misuse of the fetal biophysical profile has been described in detail by our group.[43]

At this point it should be emphasized that the biophysical scoring systems we currently use are arbitrary and do not provide exact quantification of the dynamic fetal variables over a long period, nor do they account for the occasionally long intervals of fetal inactivity in normal fetuses; in addition, the biophysical activities are observed sequentially rather than concurrently. To avoid these drawbacks, an extended period of concurrent observation of the biophysical activities has been attempted by using computer-assisted systems[9] or phonographic transducers.[7] Devoe et al. recently have reported their experience by using a computerized analysis system for simultaneously acquired biophysical variables in 200 term high-risk fetuses.[8] The dynamic parameters obtained for each fetus were compared with previously established nomograms, and the results correlated with the presence or absence of perinatal mortality, fetal distress, a 5-minute Apgar score <7, and intrauterine growth retardation. A test was considered abnormal if two or more parameters fell more than 2 SD from the population mean. A decreased incidence of fetal body movements, amniotic fluid volume, and frequency of fetal heart rate accelerations were the most common individual test abnormalities. When fetuses with normal or abnormal perinatal outcomes were classified by the last biophysical test the sensitivity was 86 per cent, specificity 89 per cent, positive predictive value 75 per cent, negative predictive value 93 per cent, and overall diagnostic accuracy 86.2 per cent. This diagnostic accuracy was significantly better as compared to the standard scoring system of Manning et al. However, this comparison was not based on a randomized trial, and in addition the authors did not mention if and how their system influenced patient management.

THE FETAL BIOPHYSICAL PROFILE AND PREMATURE RUPTURE OF THE MEMBRANES (PROM)

The need for antepartum fetal surveillance frequently involves gestational ages as early as 25 to 26 weeks. The biophysical profile scoring of the healthy fetus with intact membranes already has been discussed (see Table 4). Many patients, however, may need antepartum fetal surveillance because of PROM, which can occur at any gestational age. The question, therefore, to be addressed is the effect of PROM on the fetal biophysical profile and scoring throughout gestation. This question was investigated by our group in a retrospective analysis of 1151 fetal biophysical profiles associated with good pregnancy outcome.[45] In that study normal fetal biophysical profiles and scores were determined throughout gestation from 25 to 44 weeks in patients with intact mem-

Table 7. *Frequency of Individual Biophysical Variables and Biophysical Scoring of Eight or More in Pregnancies with Ruptured Membranes**

GESTATION (WEEKS) TOTAL NUMBER = 200 % OF THE TOTAL NO.	25–28 NO = 30 (15%)	*P* VALUE	29–32 no = 72 (36%)	*P* VALUE	33–36 no = 76 (38%)	*P* VALUE	37–40 no = 20 (10%)	*P* VALUE	41–44 no = 2 (1%)
NST-2	17(56.6%)	NS	52(72.2%)	NS	56(73.6%)	NS	20(100.0%)	NS	2(100.0%)
NST-1	9(30.0%)	NS	10(13.8%)	NS	16(21.0%)	NS	0(0.0%)	NS	0(0.0%)
NST-0	4(13.3%)	NS	10(13.8%)	NS	4(5.2)	NS	0(0.0%)	NS	0(0.0%)
FBM-2	10(33.3%)	NS	38(52.7%)	NS	49(64.4%)	NS	13(65.0%)	NS	2(100.0%)
FBM-1	1(3.3%)	NS	5(6.9%)	NS	8(10.5%)	NS	4(20.0%)	NS	0(0.0%)
FBM-0	19(63.3%)	NS	29(40.2%)	NS	19(25.0%)	NS	3(15.0%)	NS	(0.0%)
FM-2	30(100%)	NS	69(95.8%)	NS	73(96.0%)	NS	20(100.0%)	NS	2(100.0%)
FM-1	0(0.0%)	NS	3(4.1%)	NS	3(3.9%)	NS	0(0.0%)	NS	0(0.0%)
FM-0	0(0.0%)	NS	0(0.0%)	NS	0(0.0%)	NS	0(0.0%)	NS	0(0.0%)
FT-2	30(100.0%)	NS	69(95.8%)	NS	74(97.3%)	NS	20(100.0%)	NS	2(100.0%)
FT-1	0(0.0%)	NS	3(4.2%)	NS	2(2.6%)	NS	0(0.0%)	NS	0(0.0%)
FT-0	0(0.0%)	NS	0(0.0%)	NS	0(0.0%)	NS	0(0.0%)	NS	0(0.0%)
AF-2	19(63.3%)	NS	46(63.8%)	<0.05	66(86.8%)	NS	16(80.0%)	NS	0(0.0%)
AF-1	5(16.6%)	NS	17(23.6%)	<0.05	7(9.2%)	NS	1(5.0%)	NS	0(0.0%)
AF-0	6(20.0%)	NS	9(12.5%)	<0.05	3(3.9%)	NS	3(15.0%)	NS	2(100.0%)
PL-2	29(96.6%)	NS	72(100.0%)	NS	71(93.4%)	NS	17(85.0%)	<0.05	0(0.0%)
PL-1	0(0.0%)	NS	0(0.0%)	NS	2(2.6%)	NS	0(0.0%)	NS	0(0.0%)
PL-0	1(3.3%)	NS	0(0.0%)	NS	3(3.9%)	NS	3(15.0%)	<0.05	2(100.0%)
Total score 8 or more	26(86.6%)	NS	70(97.2%)	NS	75(98.6%)	NS	18(90.0%)	NS	2(100.0%)

* Scoring according to the criteria by Vintzileos et al. See Table 3.

Key: NST = Nonstress test; FBM = fetal breathing movements; FM = fetal movements; FT = fetal tone; AF = amniotic fluid volume; PL = placenta grading; NS = not significant.

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branes and compared with profiles and scores of a group of patients with PROM and good pregnancy outcome. Only cases with serial biophysical profile determinations were included that had good pregnancy outcomes as defined by the absence of congenital anomalies, infection, fetal distress, perinatal mortality, and morbidity. Table 4 demonstrates the frequency of the individual biophysical components, and biophysical scoring of 8 or more, throughout gestation for patients with intact membranes. In patients with intact, as well as ruptured membranes (Table 7), the incidence of biophysical scoring of 8 or more was not found to change significantly throughout gestation. In PROM patients, there was more amniotic fluid volume after 32 weeks compared with early gestations and more grade III placentas after 40 weeks. The frequency of reactive NSTs, fetal breathing, fetal movements, and fetal tone remain unchanged throughout gestation in patients with PROM (see Table 7). The presence of PROM, as compared to intact membranes, was associated with higher incidence of reactive NST testing, absence of fetal breathing, and reduced amniotic fluid volume in most gestational ages (Figs. 6 to 8). However, it should be emphasized that the overall biophysical scoring of the healthy fetus was found not to be altered throughout gestation by the presence of ruptured membranes. An interesting finding was that the frequency of nonreactive nonstress testing at less than 32 weeks' gestation was only 13.5 per cent in the presence of ruptured membranes (see Table 7). The clinician should be very careful before he or she attributes nonreactivity to prematurity in these very preterm gestations because, as we will discuss later, nonreactive nonstress testing in the presence of PROM may be an indication of impending fetal infection.

A prospective study by our group[38] using serial fetal biophysical assessments in patients with PROM demonstrated that an abnormal biophysical profile was an early predictor of fetal infection. A total of 73

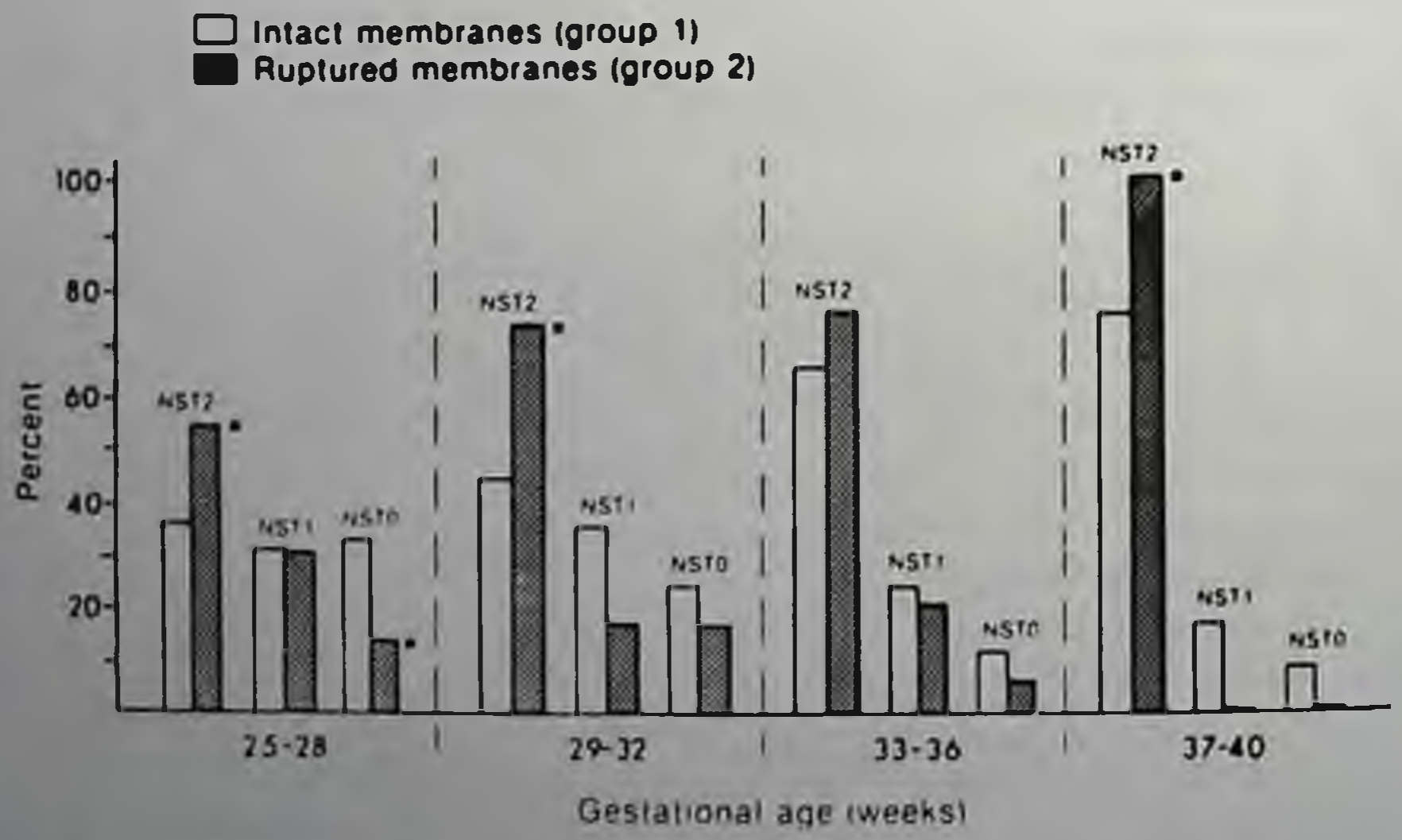

Figure 6. Incidence of nonstress tests (NST) throughout gestation for intact versus ruptured membranes groups ($P < 0.05$). (Reprinted with permission from the American College of Obstetricians and Gynecologists. Obstet Gynecol 67:818–823, 1986.)

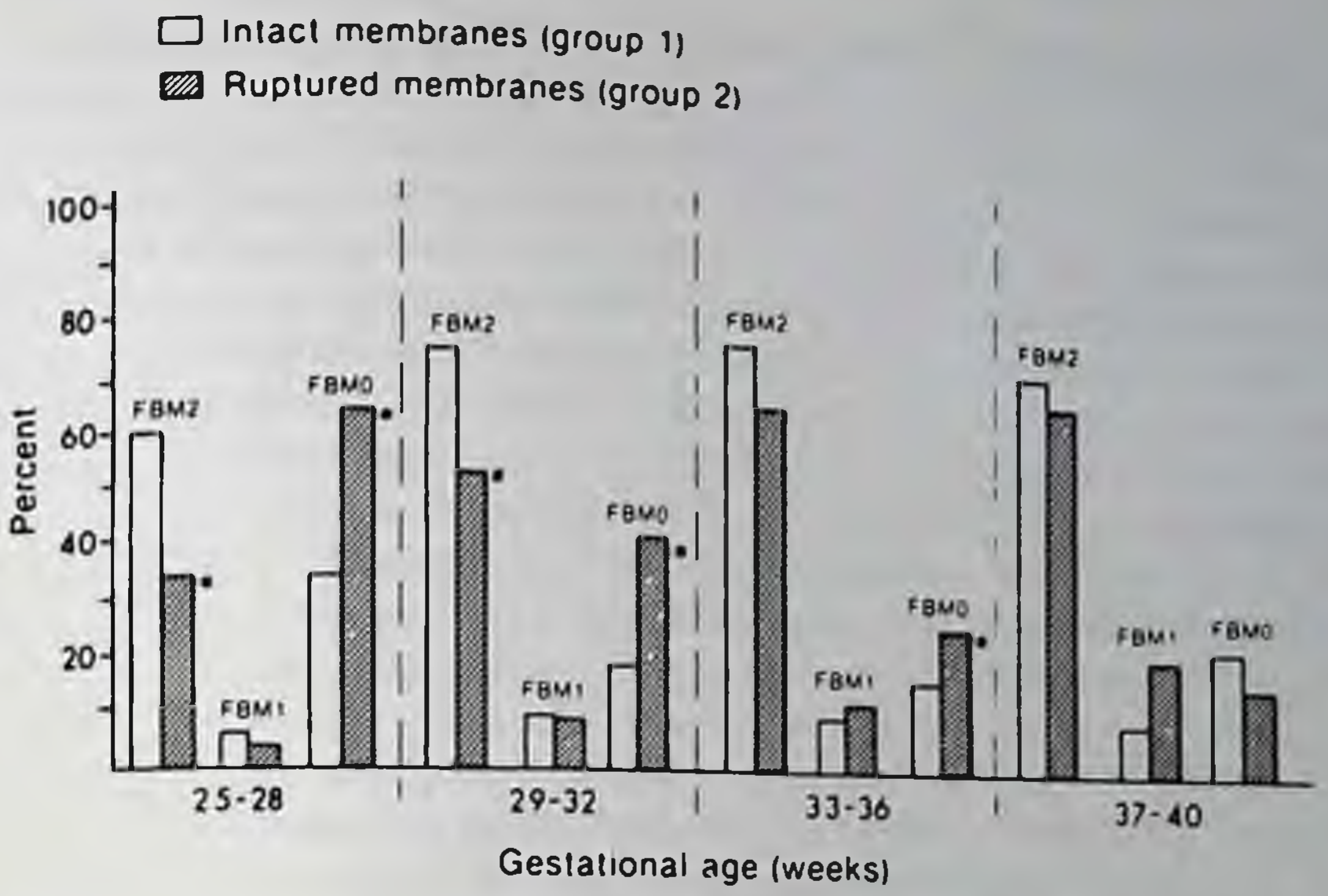

Figure 7. Incidence of fetal breathing movements (FBM) throughout gestation for intact versus ruptured membranes groups ($P < 0.05$). (Reprinted with permission from the American College of Obstetricians and Gynecologists. Obstet Gynecol 67:818–823, 1986.)

patients with no signs of labor or infection were studied. A biophysical profile assessment was performed on admission and was repeated every 24 to 48 hours if patients remained undelivered. The last biophysical assessment before delivery was compared with infection outcome as reflected by the development of clinical amnionitis, possible neonatal

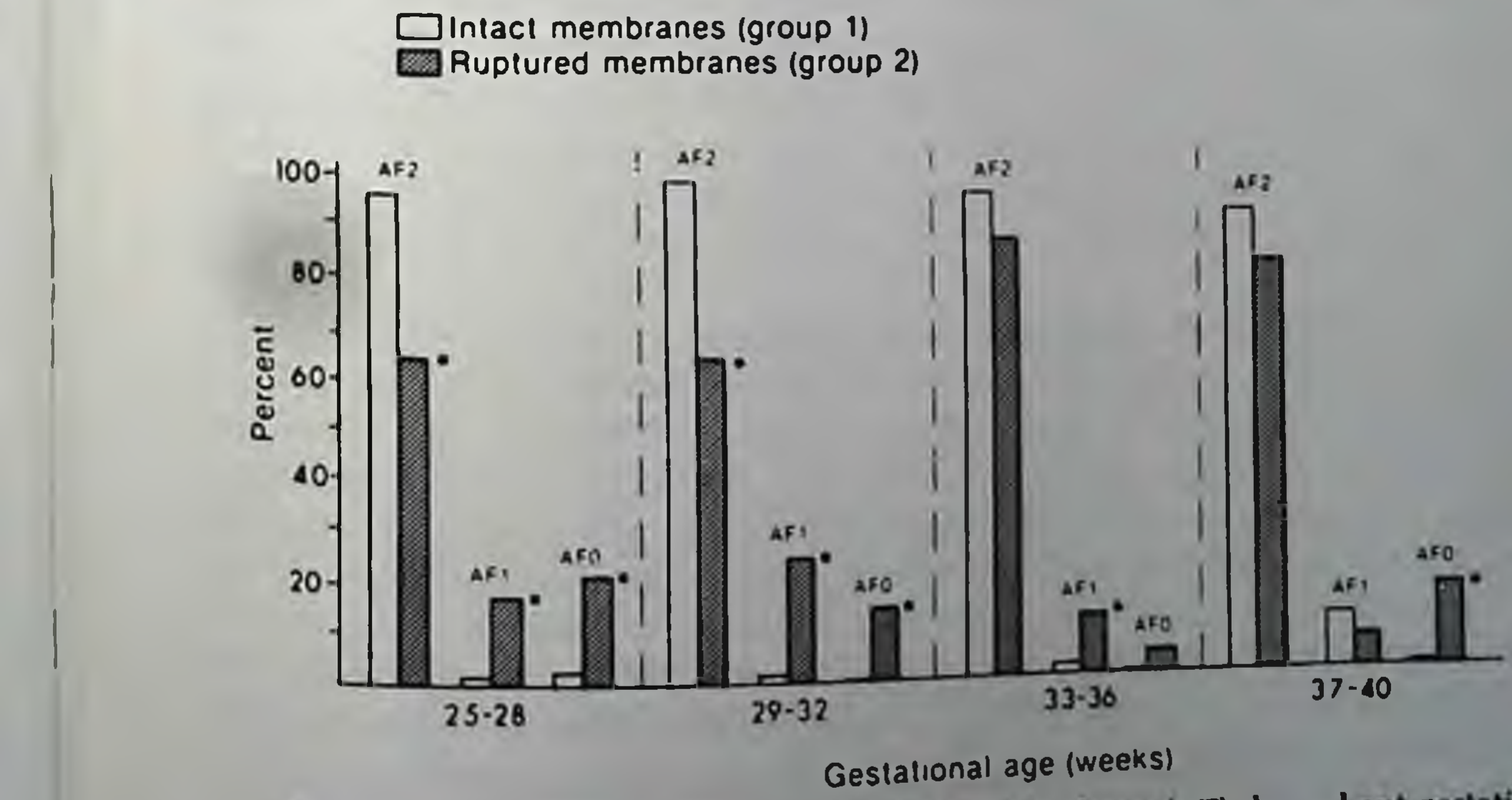

Figure 8. Incidence of qualitative amniotic fluid volume (AF) throughout gestation for intact versus ruptured membranes groups ($P < 0.05$). (Reprinted with permission from the American College of Obstetricians and Gynecologists. Obstet Gynecol 67:818–823, 1986.)

sepsis and neonatal sepsis. Possible neonatal sepsis was diagnosed in neonates with strong clinical and laboratory evidence of infection but with negative cultures. Neonatal sepsis was diagnosed only in the presence of positive cultures of blood, urine, or cerebrospinal fluid. Twenty of the seventy-three patients were delivered more than 24 hours from the last fetal biophysical assessment; in this group there was no correlation between the fetal biophysical assessment and infection outcome. There were 53 patients who delivered within 24 hours of the final examination; in this group of patients a biophysical score of 8 or more was associated with an infection rate of 2.7 per cent, and a low biophysical score (7 or less) was associated with an infection rate of 93.7 per cent. The first manifestations of impending infection were nonreactive nonstress testing and absence of fetal breathing. Loss of fetal movement and poor fetal tone were late signs of fetal infection. The best predictor of infection was found to be the biophysical score, whereas of the individual biophysical variables the NST, fetal breathing movements, fetal movement, and fetal tone were found to be important, in the above sequence. The relationship between each biophysical variable and infection outcome is illustrated in Table 8. Sixteen cases developed infection, of which fourteen were associated with fetal compromise (possible neonatal sepsis or neonatal sepsis); the fetal biophysical score was 7 or less in all these 14 cases. Because there was no difference in the mean cord pH

Table 8. *Relationship of Each Biophysical Variable to Infection Outcome*

BIOPHYSICAL VARIABLE	NUMBER OF PATIENTS	TOTAL LAST TESTS (%)	INFECTED		NONINFECTED	
			No.	*(%)*	*No.*	*(%)*
NST2	27	50.9	1/27	3.7	26/27	96.2
NST 1	8	15.0	2/8	25.0	6/8	75.0
NST 0	18	33.9	13/18	72.2	5/18	27.7
FBM 2	24	45.2	0/24	0.0	24/24	100.0
FBM 1	3	5.6	0/3	0.0	3/3	100.0
FBM 0	26	49.0	16/26	61.5	10/26	38.4
FM 2	43	81.1	8/43	18.6	35/43	81.3
FM 1	4	7.5	2/4	50.0	2/4	50.0
FM 0	6	11.3	6/6	100.0	0/6	0.0
FT 2	46	86.7	9/46	19.5	37/46	80.4
FT 1	5	9.4	5/5	100.0	0/5	0.0
FT 0	2	3.7	2/2	100.0	0/2	0.0
AF 2	27	50.9	3/27	11.1	24/27	88.8
AF 1	13	24.5	4/13	30.7	9/13	69.2
AF 0	13	24.5	9/13	69.2	4/13	30.7
PL 2	50	94.3	14/50	28.0	36/50	72.0
PL 1	1	1.8	1/1	100.0	0/1	0.0
PL 0	2	3.7	1/2	50.0	1/2	50.0
TOTAL	53		16	30.1	37	69.8

Scoring according to the criteria by Vintzileos et al. See Table 3.

Key: NST = nonstress test; FBM = fetal breathing movements; FM = fetal movements; FT = fetal tone; AF = amniotic fluid; PL = placental grading.

From Am J Obstet Gynecol 152:510–516, 1985; with permission.

between the infected and noninfected cases, the low scores of the infected group was not attributed to hypoxia, but rather to fetal infection.

Of the individual biophysical components, the degree of oligohydramnios, in patients with PROM, is well correlated to the outcome of pregnancy, as reflected by pregnancy prolongation, intrapartum fetal heart rate patterns consistent with umbilical cord compression, cesarean section rate, fetal distress, infection, and perinatal mortality rate. The relationship between the degree of oligohydramnios and infection outcome in 90 patients presented with PROM and no signs of infection or labor has been presented by our group.[39] Patients with severe oligohydramnios (largest amniotic fluid pocket less than 1 cm) had the highest incidence of amnionitis (47.3 per cent), possible neonatal sepsis (26.3 per cent), and neonatal sepsis (31.5 per cent); the incidence of amnionitis, possible neonatal sepsis, and neonatal sepsis in patients with largest amniotic fluid pocket 2 cm or more was 9.2, 3.7, and 1.8 per cent, respectively. Patients with PROM and severe oligohydramnios should be followed closely with daily fetal biophysical profile determinations to detect impending fetal infection.

The value of NST in evaluating patients with PROM also was determined by a retrospective analysis of 127 consecutive patients presented with PROM.[40] These patients had NSTs every 24 to 48 hours as part of the fetal biophysical profile assessment. The sensitivity, specificity, positive predictive value, and negative predictive value of the NST to predict infection outcome was 78.1, 86.3, 67.7, and 92.1 per cent, respectively. Analysis of the longitudinal trend of the NST results showed that patients who had a reactive NST initially, but subsequently converted to a nonreactive NST, developed infection in almost 90 per cent of the cases.

The efficacy of fetal breathing, lasting more than 30 seconds, to predict infection outcome in patients with PROM also has been investigated in 130 patients who were followed with assessments every 24 to 48 hours.[41] The sensitivity, specificity, positive predictive value, and negative predictive value of fetal breathing to predict infection outcome was 91.6, 64.8, 50, and 95.3 per cent, respectively. Of the individual biophysical components, the presence of fetal breathing has been the most reliable in ruling out fetal infection, if observed within 24 hours prior to delivery.

In our institution a comparison between daily fetal biophysical profile determinations and amniocentesis (for Gram's stain and culture) was carried out in 58 patients who presented with preterm PROM and no apparent infection or labor.[42] In addition to the usual indications for delivery, the presence of bacteria on Gram's stain or positive culture results (aerobic/anaerobic) or a persistently low biophysical score (7 or less on two examinations 2 hours apart in the presence of a nonreactive NST and absence of fetal breathing) were also considered as indications for delivery. The final biophysical profile assessment and amniocentesis results on admission were compared with infection outcome. All but one of the thirteen cases with fetal infectious compromise were associated with a low biophysical score (7 or less). There were two cases with amnionitis and no fetal infection; both cases had reassuring biophysical scores. The sensitivity, specificity, positive predictive value, and nega-

tive predictive value of the biophysical profile scoring was 80, 97.6, 92.3 and 93.3 per cent, respectively. The sensitivity, specificity, positive predictive value, and negative predictive value of the Gram's stain were 60, 81.3, 52.9, and 85.3 per cent, respectively, whereas the amniotic fluid cultures were 60, 86, 60, and 86 per cent, respectively. These observations suggest that in preterm PROM daily biophysical profiles are superior to amniocentesis on admission in selecting those patients who are candidates for fetal infection and therefore in need of prompt delivery. Fetal infectious compromise seems to be responsible for the abnormal biophysical assessment, whereas maternal infection (clinical amnionitis) without fetal infection may very well be associated with normal profiles. In our institution, the fetal biophysical profile has replaced amniocentesis because it is simple, noninvasive, and applicable to all patients. In addition, it can be repeated daily (or more frequently) and is more efficacious in predicting infection outcome especially when the fetus is compromised.

The efficacy of such a protocol using daily biophysical profiles was prospectively evaluated in our institution to see if such an approach improves pregnancy outcome in patients with PROM.[36] The study group (73 consecutive patients) were managed with daily biophysical assessment (Fig. 9). The pregnancy outcome of this group was compared with the outcomes of two historic groups: one managed conservatively (73 consecutive patients) and the other managed with amniocentesis on admission (73 consecutive patients). Infection outcomes—maternal as well as neonatal—and low 5-minute Apgar scores were significantly less in the study than in the control group. The percentage of patients who developed infection in the study group (10.9 per cent) was significantly less than in the control group (30.1 per cent). Clinical amnionitis was also reduced from 20.5 to 5.4 per cent. The incidences of possible neonatal sepsis and neonatal sepsis were also lower in the study group as compared to the control group (5.4 vs 13.6 per cent and 1.3 vs 9.5 per cent,

Figure 9. Protocol for management of premature rupture of the membranes. *Key:* BS = biophysical score, NST-0 = nonreactive nonstress test, FBM-0 = fetal breathing absent, and SOL = pontaneous onset of labor. (Reprinted with permission from Am J Obstet Gynecol 152:510–516, 1985.)

respectively). When combined possible neonatal sepsis and neonatal sepsis were considered together, the overall neonatal infection was significantly lower in the study group (6.7 vs 23.2 per cent). As compared with the amniocentesis group, the study group was found to have less neonatal sepsis (1.3 vs 12.3 per cent). The overall neonatal infection was also less in the study group (6.7 vs 24.6 per cent). These observations suggest that the use of amniocentesis may decrease the incidence of clinical amnionitis, but it does not improve the neonatal infection outcome. The neonatal infection outcome was reduced by using daily biophysical assessment, a modality that reflects fetal status rather than fetal colonization. Our approach to patients with PROM takes into consideration the condition of the fetus before deciding upon the optimal plan of management. In our view the fetus is the final arbiter and any protocol must include the condition of the fetus before deciding management. In our institution this approach has improved pregnancy outcome by reducing the incidence of maternal as well as neonatal infection.

SUMMARY

The fetal biophysical profile may assist the clinician to ascertain the fetal condition at the time of testing (acute markers), the degree of fetal compromise (gradual hypoxia concept), the presence of chronic fetal stress or possibility of *in utero* death due to cord accident (oligohydramnios), intrapartum complications such as abnormal heart rate patterns and abruptio (grade III) placenta, and impending fetal infection in patients with PROM (if performed daily). In addition it may identify major congenital anomalies which may drastically alter obstetric management. It remains to be seen if the use of computer-assisted systems for concurrent observation of the biophysical activities, or the addition of more biophysical variables, will further improve the accuracy of this testing method.

REFERENCES

1. Baskett TF: Gestational age and fetal biophysical assessment. Am J Obstet Gynecol 158:332, 1988
2. Baskett TF, Allen AC, Gray JH, et al: Fetal biophysical profile and perinatal death. Obstet Gynecol 70:357, 1987
3. Baskett TG, Gray JH, Prewett SJ, et al: Antepartum fetal assessment using a fetal biophysical profile score. Am J Obstet Gynecol 148:630, 1984
4. Chamberlain PFC, Manning FA, Morrison I, et al: Ultrasound evaluation of amniotic fluid volumes: I. The relationship of marginal and decreased amniotic fluid volumes to perinatal outcome. Am J Obstet Gynecol 150:245, 1984
5. Christie CB, Cudmore W: The oxytocin challenge test. Am J Obstet Gynecol 118:327, 1979
6. Cohn HE, Sachs ET, Heyman MA, et al: Cardiovascular responses to hypoxemia and acidemia in fetal lambs. Am J Obstet Gynecol 120:817, 1974
7. Colley N, Southall DP: Biophysical profile in the fetus from a phonographic sensor. Eur J Obstet Gynecol Reprod Biol 23:261, 1986
8. Devoe LD, Castillo RA, Searle N, et al: Prognostic components of computerized fetal biophysical testing. Am J Obstet Gynecol 158:1144, 1988

9. Devoe LD, Searle N, Phillips M, et al: Computer-assisted assessment of the fetal biophysical profile. Am J Obstet Gynecol 153:317, 1985
10. Eden RD, Seifert LS, Kodack LD, et al: A modified biophysical profile for antenatal fetal surveillance. Obstet Gynecol 71:365, 1988
11. Evertson LR, Gauthier RJ, Schifrin BS, et al: Antepartum fetal heart rate testing: I. Evolution of the nonstress test. Am J Obstet Gynecol 29:133, 1979
12. Gauthier RJ, Evertson LR, Paul RH: Antepartum fetal heart rate testing: II. Intrapartum fetal heart rate testing and neonatal outcome following a positive contraction stress test. Am J Obstet Gynecol 133:34, 1979
13. Hopper KD, Komppa GH, Bice P, et al: A reevaluation of placental grading and its clinical significance. J Ultrasound Med 3:261, 1984
14. Johnson JM, Harman CR, Lange IR, et al: Biophysical profile scoring in the management of postterm pregnancy: An analysis of 307 patients. Am J Obstet Gynecol 154:269, 1986
15. Johnson JM, Lange IR, Harman CR, et al: Biophysical profile scoring in the management of the diabetic pregnancy. Obstet Gynecol 72:841, 198
16. Lavin JP, Miodovnik M, Barden TP: Relationship of nonstress test reactivity and gestational age. Obstet Gynecol 63:338, 1984
17. Lodeiro JG, Vintzileos AM, Feinstein SJ, et al: Fetal biophysical profile in twin gestations. Obstet Gynecol 67:824, 1986
18. Manning FA, Lange IR, Morrison I, et al: Fetal biophysical profile score and the nonstress test: A comparative trial. Obstet Gynecol 64:326, 1984
19. Manning FA, Morrison I, Harman CR, et al: Fetal assessment based on fetal biophysical profile scoring: Experience in 19,221 referred high risk pregnancies: II. An analysis of false-negative fetal deaths. Am J Obstet Gynecol 157:880, 1987
20. Manning FA, Morrison I, Lange IR: Fetal biophysical profile scoring: A prospective study of 1,184 high-risk patients. Am J Obstet Gynecol 140:289, 1981
21. Manning FA, Morrison I, Lange IR, et al: Fetal assessment based on fetal biophysical profile scoring: Experience in 12,620 referred high risk pregnancies: I. Perinatal morbidity by frequency and etiology. Am J Obstet Gynecol 151:343, 1985
22. Manning FA, Morrison I, Lange IR, et al: Fetal biophysical profile scoring: Selective use of the nonstress test. Am J Obstet Gynecol 156:709, 1987
23. Manning FA and Platt LD: Fetal breathing movements and the abnormal contraction stress test. Am J Obstet Gynecol 133:590, 1979
24. Manning FA, Platt LD, Sipos L: Antepartum fetal evaluation. Development of a fetal biophysical profile score. Am J Obstet Gynecol 136:787, 1980
25. Morrison I: Perinatal mortality: Basic considerations. Semin Perinatol 9:1985
26. Patrick J and Challis J: Measurement of human fetal breathing movements in healthy pregnancies using a real-time scanner. Semin Perinatol 4:275, 1980
27. Patrick JE, Featherson W, Vick H, et al: Human fetal breathing and gross body movements at weeks 34–35 of gestation. Am J Obstet Gynecol 130:693, 1978
28. Platt LD, Eglington GS, Sipos L, et al: Further experience with the fetal biophysical profile score. Obstet Gynecol 61:480, 1983
29. Platt LD, Walla CA, Paul RH, et al: A prospective trial of fetal biophysical profile versus the nonstress test in the management of high risk pregnancies. Am J Obstet Gynecol 153:624, 1985
30. Powell-Phillips WD, Towell ME: Abnormal fetal heart rate associated with congenital anomalies. Br J Obstet Gynecol 87:270, 1980
31. Queenan JT, Thompson W, Whitfield CR, et al: Amniotic fluid volume in normal pregnancies. Am J Obstet Gynecol 114:34, 1972
32. Ray M, Freeman R, Pine S, et al: Clinical experience with the oxytocin challenge test. Am J Obstet Gynecol 114:1, 1972
33. Sadovsky E: Daily fetal movement monitoring and fetal prognosis. Obstet Gynecol 50:49, 1977
34. Sadovsky E, Laufer N, Allen JW: The incidence of different types of fetal movement during pregnancy. Br J Obstet Gynecol 86:10, 1979
35. Schifrin BS: The rationale of antepartum fetal heart rate monitoring. J Reprod Med 23:213, 1979
36. Vintzileos AM, Bors-Koefoed R, Pelegano JF, et al: The use of fetal biophysical profile improves pregnancy outcome in premature rupture of the membranes. Am J Obstet Gynecol 157:236, 1987

37. Vintzileos AM, Campbell WA, Ingardia CJ, et al: The fetal biophysical profile and its predictive value. Obstet Gynecol 62:271, 1983
38. Vintzileos AM, Campbell WA, Nochimson DJ, et al: The fetal biophysical profile in patients with premature rupture of the membranes—an early predictor of fetal infection. Am J Obstet Gynecol 152:510, 1985
39. Vintzileos AM, Campbell WA, Nochimson DJ, et al: Degree of oligohydramnios and pregnancy outcome in patients with premature rupture of the membranes. Obstet Gynecol 66:162, 1985
40. Vintzileos AM, Campbell WA, Nochimson DJ, et al: The use of the nonstress test in patients with premature rupture of the membranes. Am J Obstet Gynecol 155:149, 1986
41. Vintzileos AM, Campbell WA, Nochimson DJ, et al: Fetal breathing as a predictor of infection in premature rupture of the membranes. Obstet Gynecol 67:813, 1986
42. Vintzileos AM, Campbell WA, Nochimson DJ, et al: Fetal biophysical profile versus amniocentesis in predicting infection in preterm premature rupture of the membranes. Obstet Gynecol 68:488, 1986
43. Vintzileos AM, Campbell WA, Nochimson DJ, et al: The use and misuse of the fetal biophysical profile. Am J Obstet Gynecol 156:527, 1987
44. Vintzileos AM, Gaffney SE, Salinger LM, et al: The relationship between fetal biophysical profile and cord pH in patients undergoing cesarean section before the onset of labor. Obstet Gynecol 70:196, 1987
45. Vintzileos AM, Feinstein SJ, Lodeiro JG, et al: Fetal biophysical profile and the effect of premature rupture of the membranes. Obstet Gynecol 67:818, 1986

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Fetal Monitoring in the Alloimmunized Pregnancy

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Many opportunities occur to interrupt the process of alloimmune disease. Between initial maternal exposure to foreign red cells and the ultimate in fetal disease—early hydropic stillbirth, several points occur, at which early detection, proper management, and intrauterine therapy, will mean successful outcome to alloimmune disease managed today. This article outlines steps at which fetal information, direct or indirect, invasive or observational in nature, directs management (Fig. 1). The maternal context is integral in these processes, so that it may be artificial indeed to focus solely on the fetus.

EVENTS CAUSING FETAL-PLACENTAL DISRUPTION

Included in these are chorion villus sampling, spontaneous abortion (double exposure when dilation and curettage are required), therapeutic abortion, ectopic pregnancy, genetic amniocentesis, antepartum hemorrhage, fetal blood sampling, third-trimester amniocentesis, external version, internal version, fetal death, all operative deliveries, difficult vaginal delivery, manual removal of the placenta, and postpartum hemorrhage—practically any unusual event in pregnancy. Many are spontaneous; others are as yet unavoidable, but in many instances care can be modified specifically to avoid the initial steps. For example, choosing an approach for genetic amniocentesis that avoids the placenta, detecting transplacental hemorrhage (TPH) if it occurs, giving anti-D immune globulin prophylaxis in a dosage that accounts for the TPH will result in none of the women who had a TPH (up to 5 per cent of all amniocenteses, 15 per cent with transplacental tap) being sensitized.[1-3]

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Spontaneous event, antepartum or peripartum *or* invasive maneuvers *or* obstetric manipulation
Fetal–placental disruption
○ Fetal–maternal bleeding (transplacental hemorrhage)
● or incompletely matched transfusion
○ Maternal immune exposure
● to foreign RBC antigen
○ Competent immune processing
○ Primary immune response (IgM) "sensitization"
Second exposure
○ Competent secondary immune response (IgG)
Transplacental passage of IgG
RBC binding in fetal circulation
○ Hemolysis of fetal RBC
○ ● Fetal Anemia
○ Compensatory responses
○ ● Decompensation
○ ● Hepatic failure
Cardiac failure
Placental failure
Fetal death

Figure 1. Opportunities for intervention in the pathologic process of alloimmune disease (○ detection, ● management).

INCOMPLETELY MATCHED TRANSFUSION

Detailed cross-matching has been in place for over two decades, but a major contribution to "atypical" red cell antigen sensitization remains in this area. Kell, Duffy, Kidd, Cw, and c are all antigens that cause serious alloimmune disease, often initiated by incomplete transfusion matching. The routine question, "Any previous transfusions?" may have lost some of its lustre but none of its import in this area.[4] Obstetricians may be obliged to use "undermatched" emergency blood. We must not omit the monitoring that may be necessary in subsequent pregnancies.

MATERNAL EXPOSURE TO FOREIGN RBC ANTIGEN

Potential for maternal–fetal red cell antigen incompatibility exists in many pregnancies. Care must be taken in all women (even Rh-positive women) to reduce causes of fetal–maternal bleeding. Equally important is the second step: sensitive testing for detection of TPH. Of practical laboratory methods, the standard remains the semiquantitative Kleihauer test, which routinely detects 0.01 ml or less fetal blood in maternal circulation. Other than identifying causative events and mandating serial evaluations to discern sensitization, TPH detection is not useful in atypical antigen exposure. In anti-D incompatibility, however, a positive Kleihauer test result directs treatment with appropriate intravenous anti-D IgG (e.g., Winrho).[1] In unsensitized Rh-negative women, therefore, it is better to test in all suspicious circumstances. Maximizing prophylaxis utilization yields sensitization in <2 per 10,000 pregnant

women.[5] In addition to routine antepartum (28 weeks) and postpartum (72 hours) prophylaxis, the use of Kleihauer "monitoring" is an important component in ensuring maximum prevention.

COMPETENT IMMUNE PROCESSING

There is limited ability to influence these factors. Some women respond to minute amounts of fetal blood and rapidly progress to full immunization; others ("nonresponders," about one third of Rh-negative women) never develop an immune response despite proven exposure. Other modifiers include volume and frequency of exposure, immunogenic antigen strength, immune response of the host, and presence of other antigens modifying red cell immune processing. In ABO-incompatible, Rh-incompatible TPH, for example, moderate TPH usually will not provoke Rh sensitization. The ubiquitous ABO antibodies in maternal circulation cause RBC lysis before the "new" Rh antigen can be fully processed; no anti-Rh antibody is formed.

Anti-D prophylaxis acts here. "Immune blockade" involves anti-D IgG in maternal circulation, via prophylactic injection—Winrho (intravenous or intramuscular) or Rhogam (intramuscular). Circulating at low levels, it binds to fetal cells that may reach the maternal circulation, coating the "foreign" red blood cells, forming small rosettes, and presenting IgG Fc fragments to regional lymph node/reticuloendothelial processors. IgM Fc fragments provoke IgG development, but IgG Fc fragments stimulate suppressor T-cell function, in effect blocking antigen processing.[4]

PRIMARY IMMUNE RESPONSE (IgM): "SENSITIZATION"

Competent primary immune processing results in plasma cell lines, producing anti-D IgM. This antibody may take months to develop. It is a large molecule and does not cross the placenta. In the laboratory, IgM binds target red blood cells (detectable as hemagglutination) in almost any suspension (saline or "complete" antibody). IgG, in contrast, will form bridges, and positive hemagglutination, only when RBC are close together (in albumin suspension) an "incomplete" antibody. ("Antibody screening" tests for *any* Ig is by indirect Coombs' test; it provides an "alert" for these more definitive tests.) Once significant IgM has been provoked, only one more exposure is needed to cause development of the fully mature IgG response. No amount of IgG prophylaxis will prevent it.

SECONDARY (IgG) IMMUNE RESPONSE

This follows reexposure to the sensitizing antigen almost automatically. Response is rapid, and may be rapidly accelerating, as the small IgG molecule, the agent of disease. In Rh disease, three IgG subclasses (IgG_1,

IgG_{1-3}, IgG_3) cross the placenta readily and cause fetal hemolysis. This usually takes place on a background of IgM, although complete conversion to IgG may evolve. This impacts on maternal monitoring, of course, in explaining antibody in maternal circulation. Differentiation of passive IgG levels from superimposed, active antibody production is usually not difficult. Prophylactic IgG, so-called passive immunity, is pure IgG (albumin titer only), usually IgG_1 and IgG_3 at low concentrations (measured in ng per ml). Women becoming sensitized will have pure IgM or mixed IgM/IgG, at significant, rising levels (measured in μg per ml, saline and albumin titres).

Detectable maternal antibody levels always precede development of fetal disease. The first step in monitoring alloimmune disease, therefore, is meticulous screening of all pregnant women for detection of *any* red cell antibodies. A "positive screen" by whatever method, is followed up promptly by detailed specification and quantitation. This initial screen should be done at the first prenatal visit, ideally by 12 to 14 weeks at the latest.

Monitoring maternal antibody levels after they are detected is an important second step in predicting the likelihood of fetal disease. "Critical" IgG levels vary between tests and between laboratories. In our laboratory, dilutions of 1 : 64 (indirect Coombs test), 1 : 32 (saline) or 1 : 16 (albumin) or absolute IgG levels $> 2.0\ \mu$g per ml all signify a threshold above which serious fetal hemolytic disease is likely. These critical levels apply to anti-D sensitization only; Kell alloimmunization, for example, is notably unpredictable and may cause hydropic disease at levels of only 1 : 8. Once maternal levels have reached these stages, maternal monitoring is no longer a satisfactory means of determining fetal disease.

The next steps in alloimmune pathology are clinically invisible, although they would be documented if fetal serology were available. Transplacental passage of maternally circulating IgG is automatic via facilitated uptake, beginning at 8 to 10 weeks' gestation. Binding to fetal RBC is also automatic. The fetal Rh antigen is fully developed at an early stage. This binding may be subject to modulation: 1) maternal plasmapheresis may lower IgG concentration enough to delay accelerated disease for some time[6]; 2) maternal administration of massive doses of nonspecific IgG (IV ISG-immune serum globulin) may cause fetal reticuloendothelial saturation, making RBC binding of relatively less consequence.[5] Although we may be able to modify these steps, monitoring these reactions is not yet precise—the next practical stage for monitoring alloimmunization focuses on the fetus.

HEMOLYSIS OF FETAL BLOOD

Amniotic Fluid Bilirubin—delta OD 450

Bilirubin is the end-product of fetal red blood cell destruction. It is cleared placentally via maternal circulation, but small amounts enter the fetal enterohepatic circulation. Some is redistributed to the lungs, thence via fetal pulmonary fluid into the amniotic fluid. Fetal urine

bilirubin is negligible even in advanced disease. Passage by other routes (mucous membranes, or across membranes from cord or placental vessels) is speculative. Bilirubin is highly concentrated in ascites and other effusions—a helpful discriminator between bladder (urine is crystal clear, under pressure) and abdomen (ascites is brilliant yellow, slight pressure) on needle placement.

When fluid containing bilirubin is analyzed spectrophometrically, a classic rise in absorption occurs: the *delta OD 450* (change in optical density at 450 nm). This peak (450 nm) is unique to bilirubin. Blood pigments may produce peaks at 405 and 420 nm, which "contaminate" the reading; meconium may raise delta OD diffusely from 550 to 380, obscuring the 450 peak; oxyhemoglobin interferes at 580, 540, and 415 nm.[4] Thick meconium and intact red blood cells usually can be filtered out, posing less difficulty. On an uncomplicated sample, with a "pure" delta OD 450 peak, quantitative bilirubin measurement may be obtained mathematically.

Timing. Amniocentesis delta OD 450 is indicated by the factors in Table 1. Placental site and target access make these indicators somewhat relative. Easy access to generous fluid, without transplacental passage, favors amniocentesis; anterior placenta or small fluid pockets suggest cordocentesis. Serial amniocentesis for fetal monitoring is predicated on simultaneous evaluation of fetal structure and function by detailed ultrasound examination, described later: only cordocentesis provides monitoring suitable for hydropic disease or the ultimate decision to transfuse the nonhydropic fetus. A significant chance of the fetus being antigen-negative (false-positive delta OD 450) suggests blood typing by cordocentesis.

Flexibility is the rule in timing of first amniocentesis. Hydropic disease is exceedingly rare before 18 weeks when the earliest amniocentesis is recommended. Timing of subsequent procedures may vary from 6 days to 6 weeks, depending on interpretation. Initiation of this monitoring may be at any stage on the basis of sudden changes in maternal antibody levels; such changes in the third trimester strongly suggest fetal blood sampling.

Table 1. *Indications for Invasive Fetal Testing*

History	Hydropic stillbirth
	Fetal transfusions
	Premature delivery—fetal disease
	Neonatal exchange transfusions
Maternal Serology	"Critical" titer level*
	Sudden titer rise†
Fetal Examination	"Suspicious" indices—rising abdominal circumference.
	Impending hydrops, hydramnios, placental edema.†
	Ascites, hydrops fetalis†
Other	Positive Kleihauer†
	Rising maternal serum AFP

* Winnipeg Rh laboratory: Coombs indirect 28, saline titer 32, albumin titer 16, absolute anti-D, IgG level > 2 μg/ml.

† In almost all cases, cordocentesis required.

Performance. Amniocentesis for delta OD 450 is an ultrasound-directed procedure. If the placenta is posterior, fluid is generous and the maternal abdomen is not obese, continuous ultrasound direction may not be necessary. In cases meeting these criteria, the procedure is done in straightforward fashion, using a 20- or 22-gauge spinal needle. Decanted into a light-proof container, the fluid is immediately sent for analysis. Fluid also is sent for determination of fetal pulmonary maturity when appropriate.

At the end of the procedure, fetus and uterus are again scanned and intrauterine bleeding is excluded. Maternal bleeding from the uterine wall usually appears in a "falling leaves" pattern in amniotic fluid; fetal bleeding produces a "plume," or "streamers." Very small amounts of fetal blood, under normal intravascular pressure, will produce such turbulence. Unless the injury is a laceration, or the fetus is severely thrombocytopenic, even a direct needle puncture of the umbilical cord attains rapid hemostasis. Any blood aspirated during the procedure is sent for Kleihauer examination, and blood grouping when appropriate. Inadvertently obtaining a small amount of blood at amniocentesis is usually not critical for fetal welfare but could provide the evidence of fetal antigen negativity necessary to avoid any further invasive testing.[7]

If the amniotic fluid pocket is small, careful determination of cord location is essential. Doppler ultrasound is used to rule out multiple cord loops masquerading as amniotic fluid.[8] For anterior placentas, an approach that completely avoids even the thinnest placental edge is chosen. This often involves accepting an approach that is extremely lateral, suprapubic, or fundal. Transplacental amniocentesis may be necessary in a few situations—in general this approach is replaced by cordocentesis. If transplacental amniocentesis is elected, 25-gauge needle is used.

In either case (small pockets or anterior placenta), continuous ultrasound needle guidance is used. The transducer with a small amount of ultrasound gel, is placed in a sterile plastic bag; sterile mineral oil is used as the acoustic coupler to the maternal abdomen. Single-operator amniocentesis, one hand inserting the needle, the other hand holding the transducer, is quite straightforward. We do not, however, employ this technique for fetal blood sampling or intravascular fetal transfusion.

Interpretation. If the fluid is grossly contaminated with blood, vernix, or meconium, filtration or centrifugation is required before analysis. If the fluid is deeply stained with heme pigment, denatured blood, or other contaminants, specific methods may improve the quality of the spectrophotometry.

We continue to use standard Liley zones (Fig. 2).[9,10] (Liley obtained data down to 28 weeks' gestation only; below that, interpretation is done on an institutionalized basis.) Extrapolation of the zones backward to 22 to 24 weeks is usually accurate. Before then, most fetuses demonstrate a rounded arc in amniotic fluid bilirubin levels: levels rise from 16 weeks to 20 weeks, plateau for 2 to 4 weeks, and then decline along the more or less linear limits of the Liley zones. These values must be interpreted on a background of institutional experience. Some authors believe the relative unreliability of Liley zones at these gestations mandate cordocentesis in all cases. We do not share this absolute position; cordo-

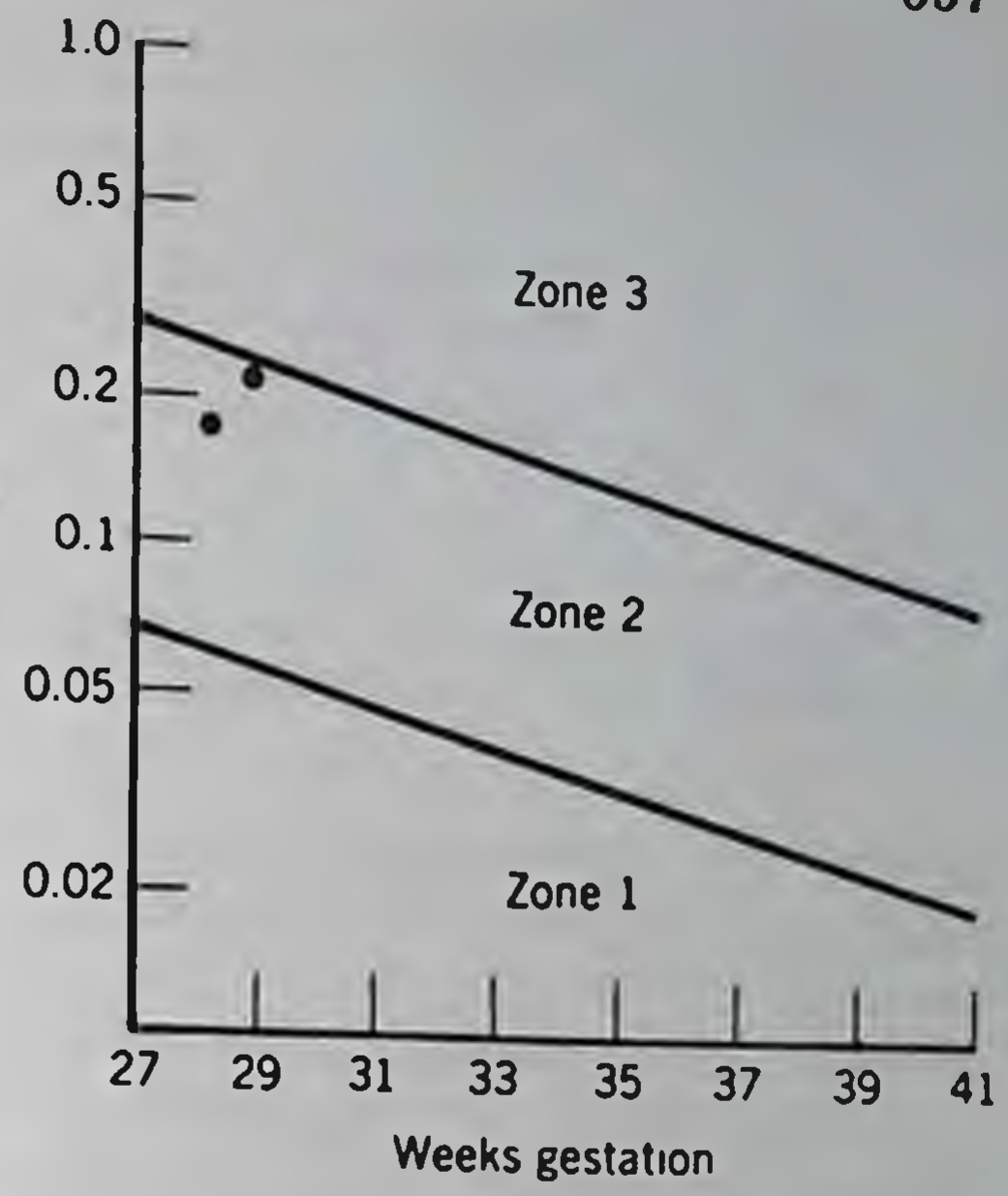

Figure 2. Interpretation of delta OD 450. Optical density rise from baseline at 450 nm is specifically due to bilirubin. This measurement, the delta OD 450, is plotted on semi-log paper, with Liley zones as shown. Example shows measurements obtained at 28 and 29 weeks' gestation, showing significant rise toward zone 3.

centesis is elected whenever delta OD 450 results are not totally reassuring.

The Liley zones were established on the basis of controlled data with untreated subjects. It is clear that such experimentation is no longer ethical. On the other hand, significant data are being accumulated demonstrating that the relationship between the Liley zones and fetal amniotic fluid levels may be substantially variable. Interpretation therefore must be with a detailed background knowledge of antibody strengths, previous history, and ultrasound examination of the current fetus.

Zone 1 amniotic fluid levels indicate low likelihood of fetal disease (either antigen-negative, or little hemolysis at all). In general, these are followed monthly. Levels in zone 2 may or may not represent a serious prospect for fetal disease, depending on the trend. Below 50 per cent zone 2, delta OD 450 is repeated every 2 to 4 weeks, depending on clinical setting. Levels that appear to be rising (relative to the downward slope of the zone lines, even an unchanging series of measurements would be interpreted as "rising"), call for more frequent testing, at 1- to 2-week intervals. Levels beyond 80 to 90 per cent zone 2 call for direct fetal testing by cordocentesis.

Numerous references to cordocentesis in this discussion might suggest it is a superior procedure in all instances. That viewpoint has merit but is by no means proved. Detailed fetal hematology may demonstrate physical evidence of red cell damage; the importance of this is as yet untested. Theoretically, fetal serum bilirubin rises before amniotic fluid bilirubin; the latter remains a safer, simpler, practical source of evidence regarding the probable range of fetal disease. (Antibody levels determine potential for disease, amniotic fluid bilirubin suggests likely range of disease, fetal examination and direct testing define extent of disease in the individual).

An important point deserves emphasis—hemolysis, and generation

Table 2. *Specific Indications for Cordocentesis*

Anterior placenta, disease likely*
Fetal blood typing necessary
All hydropic fetal disease
ΔOD 450 excessive vs. antibody level (exclude false positive)
ΔOD 450 lower than expected by antibody level (exclude false negative)
?ΔOD 450 unreliable (?18–22 weeks)

* Father homozygous for antigen; suspicious ultrasound examination; known positive fetal blood type (previous cordocentesis).

of RBC degradation products such as bilirubin, precede anemia significantly in most situations. Amniotic fluid bilirubin is cumulative. It follows that high amniotic fluid bilirubin levels may overestimate severity of fetal anemia, specifically discernible only by direct fetal testing.

About 10 per cent of amniotic fluid values may overestimate fetal hemolysis so seriously as to call for unnecessary intrauterine transfusion. Conversely, amniotic fluid bilirubin is sometimes unreliable, in *underestimating* fetal disease.[5,10] This affects 2 to 5 per cent of evaluations and may occur in two different ways.[1] Hemolysis is so sudden and so complete as to constitute a fetal hemolytic crisis, with fetal hemoglobin levels falling from 110 gm per liter to zero in as few as 9 days.[11] This may follow an acute event, such as a large TPH, which provokes a large antibody titer rise. The volume of hemolytic degradation products may take time to process: bilirubin levels may rise *after* the development of severe fetal disease.[2] In end-stage disease, there is very little hemoglobin left, and therefore very little hemolysis, and very little amniotic fluid bilirubin generated.

Amniocentesis is used to provide reassurance that direct fetal testing is not required. When any doubt exists about the evaluation of amniotic fluid delta OD 450 (Table 2), cordocentesis is indicated.

FETAL ANEMIA

Once hemolysis proceeds significantly, the fetus becomes anemic. Anemia defined by a particular fetal hemoglobin concentration may be helpful for discussion purposes but does not necessarily reflect the need for fetal compensation. At a hemoglobin level of 100 gm per liter the fetus may or may not be compelled by homeostatic regulatory forces to generate significant hematopoietic effort. At this level, some fetuses will be making considerable effort, manifested by increased circulating reticulocytes and nucleated red cells; others will be quite comfortable, with no significant hematopoiesis. At lower levels, some fetuses will exhibit severe signs of compromise, with full-blown hydrops fetalis, whereas others have only limited ascites. In end-stage disease, fetuses with identical hemoglobin levels may have the ultimate form of fetal disease (moribund fetal hydrops) or may continue to be normally active with relatively moderate physical findings.

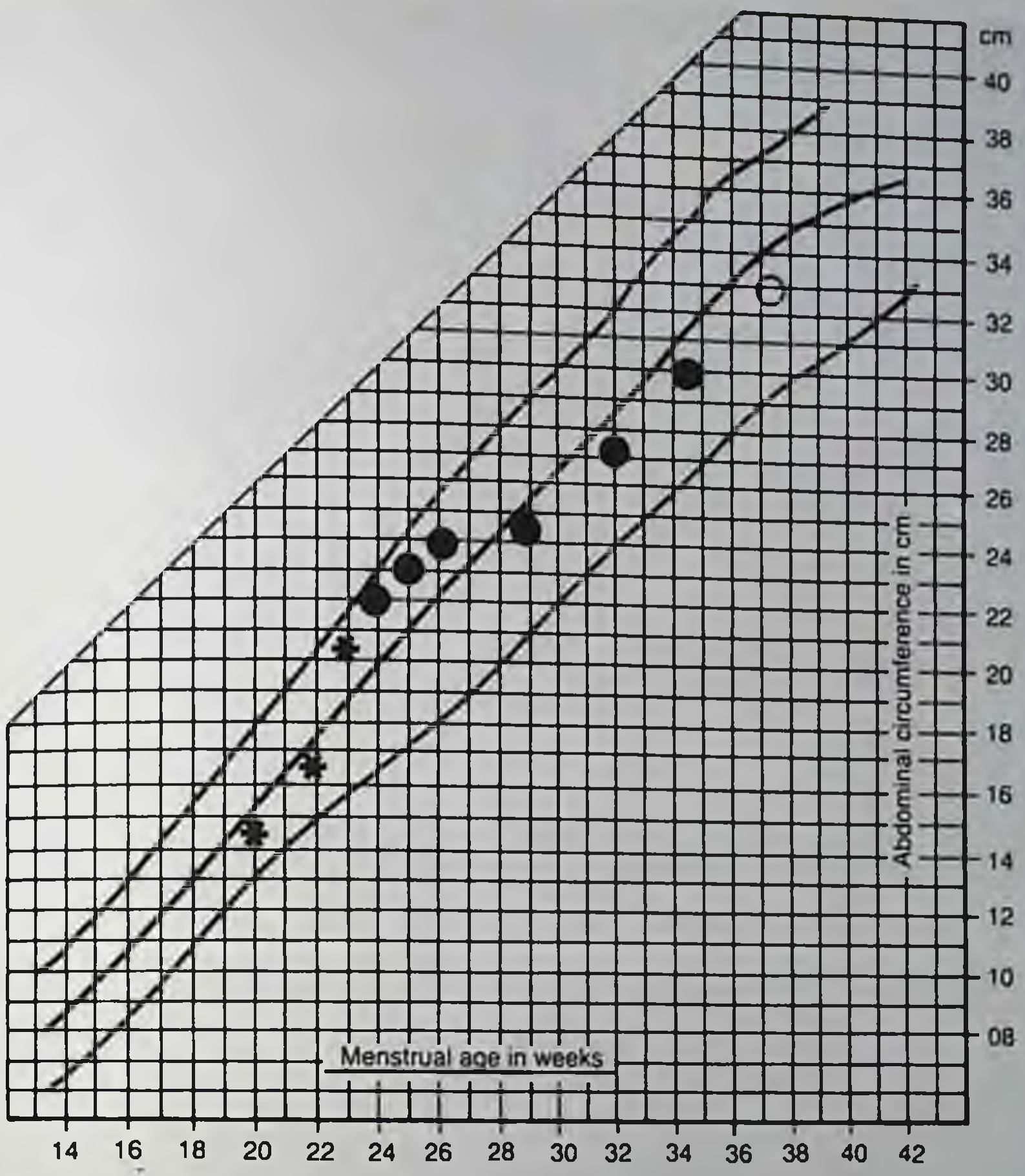

Figure 3. Growth chart. Serial abdominal circumference (AC) measurements in a fetus followed for severe alloimmunization. Abrupt AC rise from 40th to 75th centile, at 23 weeks' gestation, was associated with a sharp rise in amniotic fluid values. Intravascular transfusions were begun at 24 weeks (solid circles) lasting 10 weeks, during which time liver size, and AC, resumed previous levels. Open circle at 37.5 weeks' gestation represents the last measurement prior to delivery of a healthy male infant.

Absolute measurement of fetal hemoglobin, bilirubin, and serum proteins, have intrinsic scientific appeal. They are not necessarily more accurate in representing the level of compromise to which the fetus has been forced by his ongoing anemia. Some of the earliest signs of anemic compromise may be in subtle changes, in the fetus, placenta, and amniotic fluid.[12] Our approach is that *all* data helpful in formulating a management plan, and a prognosis, should be sought. Detailed physical examination of the fetus and cordocentesis are equal partners in the ultimate evaluation.

Fetal Examination

Nonhydropic Fetal Disease. In the absence of overt ascites, or other indices of fetal hydropic disease, several findings may be helpful in indicating the onset of compensatory efforts in response to fetal anemia.[13] Because these parameters are more or less subjective, it is important they are assessed serially by the same individual. Serial abdominal

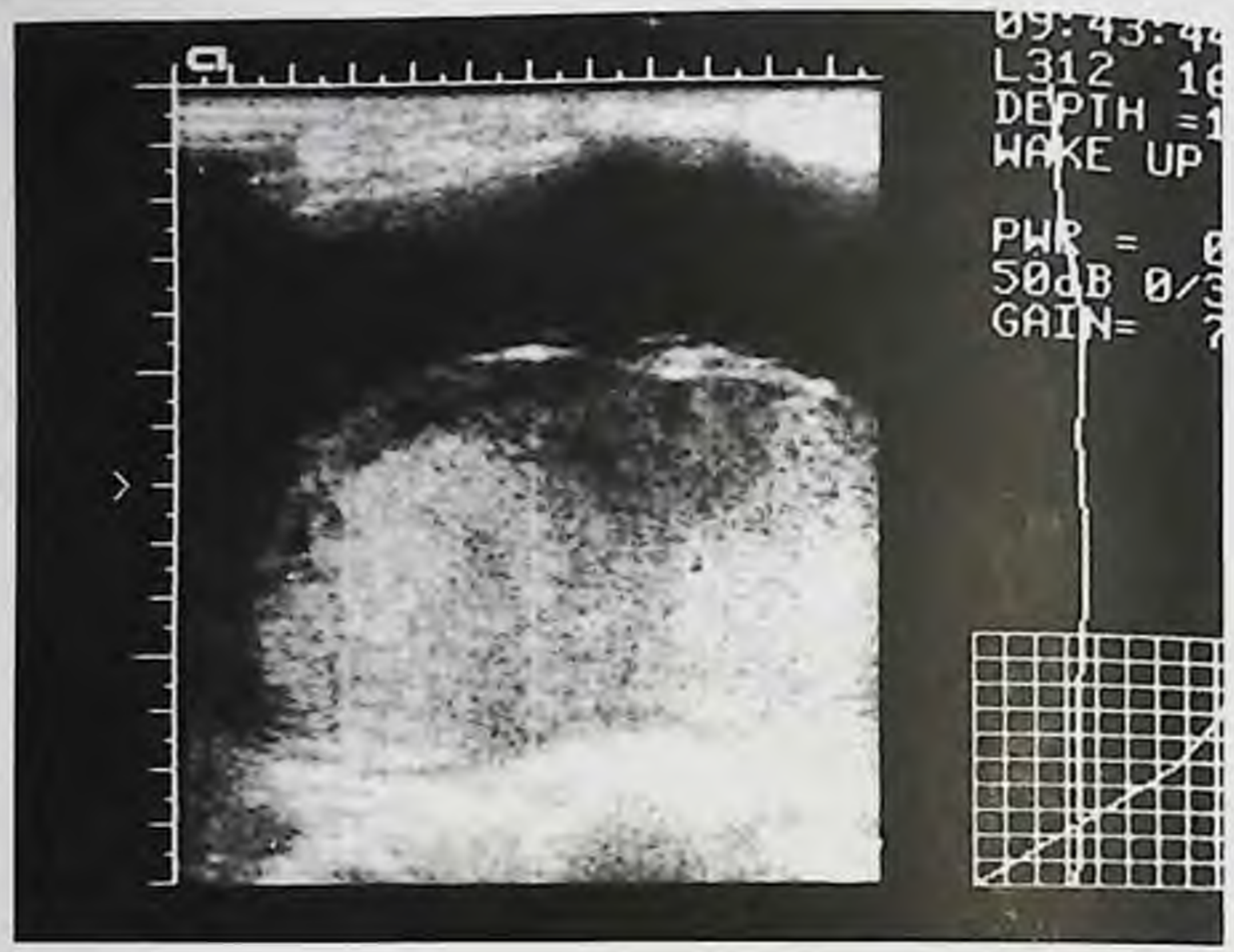

Figure 4. Rounded, tense placenta, serious anti-D disease at 24 weeks, nonhydropic. Maximal placental thickness 7.5 cm. Hydramnios is present, maximal vertical pocket depth 8.9 cm. Fetal blood sampling demonstrated serious hemolysis, hemoglobin 83 gm per liter.

circumference may show an accelerating trend before onset of hydropic disease (Fig. 3).[14] Placental thickening, loss of architecture, increased homogeneity, and assumption of a round uterine profile (compared to the normal oval), may be the first indicators of disease (Fig. 4).[12] Hydramnios has been cited as the first indicator of accelerating disease; this is a semiquantitative parameter, but many variables influence its measurement.[15] The emergence of "double outlining,"[12] or demarcation of adjacent small bowel loops,[16] suggests impending ascites (Fig. 5). Early pericardial effusion, possibly from increased cardiac work in the face of anemia, may herald serious acceleration. Detection requires M-mode ultrasound, with careful attention to echocardiographic details.[18] Finally, whereas the systolic/diastolic (S/D) velocity ratio (obtained by Doppler ultrasound blood flow velocity waveform analysis) normally falls with advancing gestation, anemic fetuses may have increasing S/D ratios (Fig. 6). There may not be a reliable way to extrapolate from single Doppler measurements to fetal hemoglobin, but serial assessments may prove valuable.[19,20]

Many parameters are *not* useful: umbilical vein diameter, placental thickness, abdominal wall thickness, intrahepatic umbilical vein diameter, or occipital scalp thickness.[21] Some authors dispute the value of amniotic fluid or abdominal circumference measurements. We find they may prove valuable, on a serial basis. Isolated estimates are less valuable.

A fetus may be severely anemic before hydrops is apparent. The lowest value obtained in a nonhydropic fetus was 52 gm per liter at 29

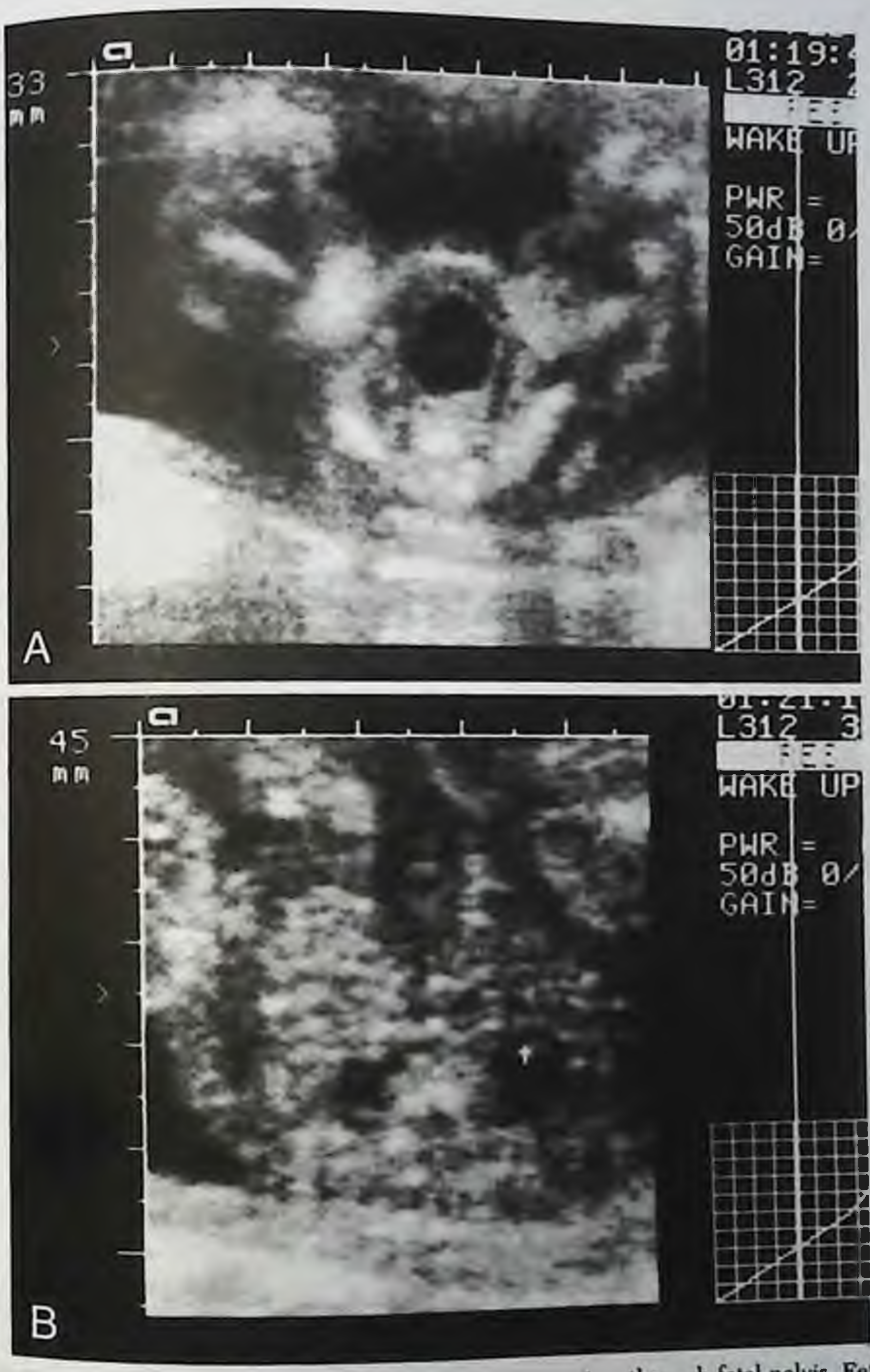

Figure 5. Signs of insipient ascites. *A*, Transverse view through fetal pelvis. Fetal bladder is clearly outlined, with a rim of ascitic fluid on the outside, and fetal urine on the inside. Fetal hemoglobin measured the same day was 66 gm per liter. The fetus was managed with serial intravascular transfusions, and did not ever become hydropic. *B*, Same fetus, demonstrating outlining of loops of small bowel *(arrow)*. This rippled effect, accentuation of the normal small bowel pattern is attributed to intraperitoneal fluid lying between adjacent bowel loops.

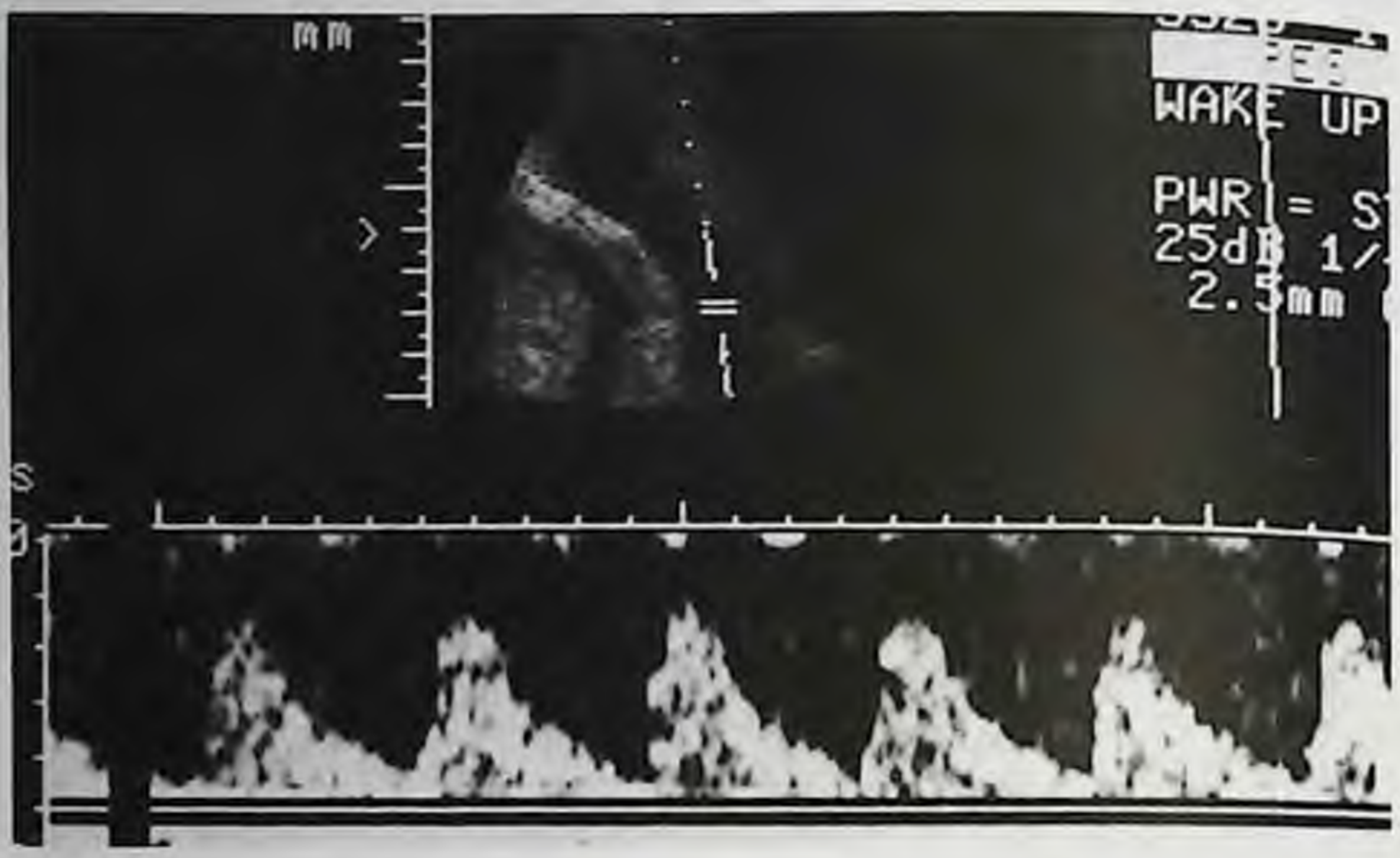

Figure 6. Doppler ultrasound pattern with severe anemia. The fetus had ascites and was moribund, with emergency delivery at 34 weeks' gestation. The fetus had a hemoglobin of 14 gm per liter and died neonatally. Doppler waveform shows elevated S/D ratio.

weeks' gestation.[22] Physical examination demonstrating no hydropic disease, therefore, must be interpreted with caution. Knowledge of the antibody, its course during the pregnancy, and the specific history help to determine the need for invasive testing despite reassuring physical findings.[23,24] In general, suspicious or suggestive ultrasound signs, coupled with rising or frankly elevated delta OD 450, call for invasive fetal testing by cordocentesis. Only cordocentesis can determine the extremity of fetal anemia, but absence of physical signs of decompensation suggests a more moderate level of compromise (and less therapeutic urgency) than obvious hydropic disease. It is important, therefore, to obtain detailed hematology by cordocentesis, before instituting dangerous therapy (intravascular or intraperitoneal fetal transfusion), when the fetus is not yet hydropic.

Cordocentesis. As noted in Table 2, this procedure has many applications—placing the description at this point in the text is somewhat arbitrary.[25-27] Cordocentesis is used *before* any suggestion of fetal disease, in circumstances in which fetal blood typing at an early stage is indicated. This includes situations with a high probability that the fetus is antigen negative (father known heterozygote) or with a relatively rare antigen and unknown paternal blood type. It is key when disease is strongly suspected, or when significant hemolysis is shown by amniocentesis, but the fetus is not yet hydropic. In these situations cordocentesis is pivotal and may be necessary on a serial basis to continue to defer intrauterine treatment. When disease is probable, cordocentesis forms the basis for proceeding with intravascular fetal therapy. When fetal disease is obvious, as in any of the classes of hydropic disease, cordocentesis is to some extent a formality and is followed sequentially by the infusion of the

Table 3. *Prerequisites to Performance of Cordocentesis*

Detailed indication
Informed consent
Experienced team
High-resolution ultrasound
Accessible target
Bed-side testing
Detailed blood typing laboratory
Transfusion blood available
Fetal monitoring capability•
Emergency obstetric services•
Tertiary-level neonatal intensive care•
Maternal/family support systems

• Usually applicable only when gestation is > 25–26 weeks.

first transfusion. The procedure clearly is not performed in isolation or according to rigid guidelines.

Preparation includes a clear indication, informed consent, and several other prerequisites (Table 3). If immediate transfusion is likely, additional personnel and detailed cross-matching of maternally compatible, densely packed donor red cells are also necessary. In nonhydropic disease, cordocentesis is usually performed as a separate procedure. Sedation is used if fetal interference or a long procedure is likely. With the anterior placenta, for simple fetal blood sampling, no sedation or light sedation of 5 mg diazepam PO, is given. If transfusion is planned, sedation is heavier, usually diazepam 5 to 10 mg PO. If the cord insertion is posterior or is quite likely to be disturbed by fetal movement during the longer transfusion procedure, the fetus and mother are heavily sedated (diazepam 10 mg PO; morphine 10 mg IM) 60 to 90 minutes before the procedure.

For simple cordocentesis, antibiotics are not used; if fetal infusion is likely, antibiotic prophylaxis is given. In over 1000 intrauterine fetal transfusions, the University of Manitoba Intrauterine Transfusion Team has had no serious fetal or maternal infection.[28,29] The short history of fetal intravascular monitoring and therapy includes several examples in the literature, of fetal demise and significant maternal morbidity, following procedure-related chorioamnionitis. Although these data do not represent a scientific study, the small risk of any untoward effect of the prophylaxis leads us to continue its use. Cloxacillin 500 mg PO, and ampicillin 500 mg PO, q.i.d., two doses prior to the procedure, and six doses afterward, are given. Such prophylaxis is employed with the rationale that we are in fact infusing something directly into the fetal circulatory system, and as such the risk of serious compromise due to infection may be maximal.

Before surgical prep, the cord insertion is identified meticulously (Fig. 7). Clinical success with this procedure is based on defining the exact location of the cord insertion at the placenta; the key to identifying the optimal target is taking enough time. An ideal target represents the umbilical vein within the cord substance just as it turns onto the surface of the placenta. Such a target is anchored in a stable fashion anywhere

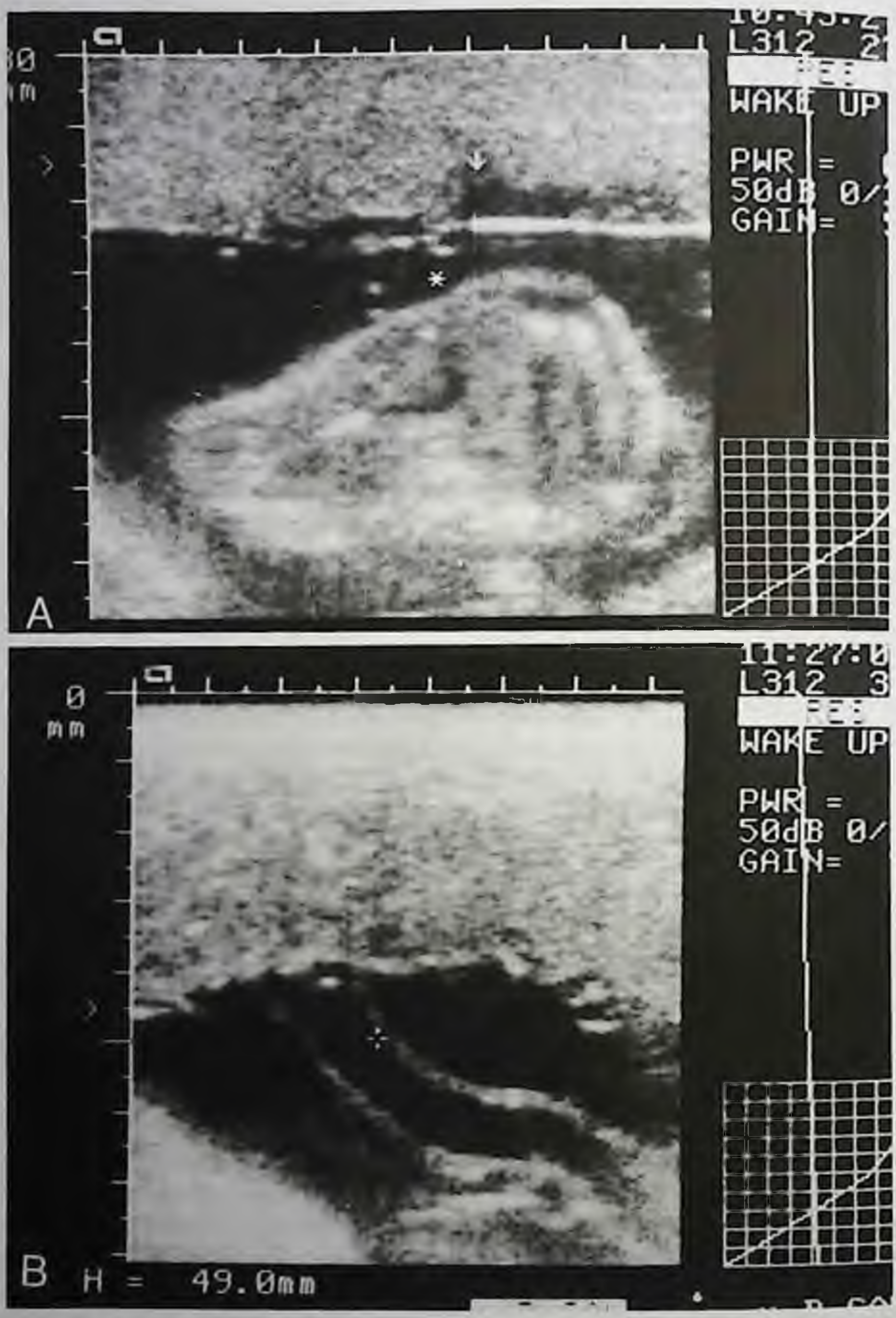

Figure 7. *A*, Anterior umbilical cord insertion, 20 weeks' gestation. The fetus required serial intravascular transfusion for hydropic anti-D disease. Needle placement in the cord insertion *(above*)* faced possible contamination from nearby maternal intervillous lakes (*below arrow.*) *B*, Anterior cord insertion, 33 weeks' gestation, at the time of the final intravascular transfusion in the series. Targets like this have probably contributed to the popularity of the procedure.

within 1 to 2 cm of the placental surface. Selection of a target slightly proximal to the placenta averts entering the maternal intervillous space usually underlying the cord insertion (see Fig. 7*A*). With difficult visualization of a posterior cord insertion, maternal repositioning to rotate the target anteriorly, may be helpful. Doppler ultrasound may play a useful role in defining the exact relation of cord vessels as they enter the insertion.

Even the centrally located anterior cord insertion may be difficult to visualize. With nuchal cord, for example, tension on the cord draws it horizontally along the surface of the placenta, attenuating the insertion and making it difficult indeed to localize. Careful attention to these details, taking the time to achieve a complete understanding of the cord location, will usually overcome such difficulties.

Many reasons suggest the vein as the target. It is larger and usually vessel entry is easier. Vein walls are more yielding than arteries, and the flattening of the vein with the pressure of the needle tip means that the target remains large, as opposed to the rolling tendency of the arteries. Turbulence radiating down the vein toward the fetus through the amniotic cavity is easily visualized, as opposed to turbulence within the umbilical arteries, which spreads along the surface of the placenta in increasingly smaller vessels, sometimes difficult to visualize (Fig. 8).

Once the insertion is identified, at an angle and distance that allow needle placement, the procedure is begun. Surgical draping usually is not employed. A small amount of maternal tilt will avert supine hypotension. The abdomen is cleansed with antiseptic, and local anesthetic is infiltrated. A complete setup of 12 heparinized tuberculin syringes, two tuberculin syringes containing normal saline, and two 10-ml syringes are prepared on the sterile tray. (This may seem like a lot of syringes, but during the course of the procedure, as specimens are handed on, and other syringes are used verifying correct needle position, this supply dwindles rapidly.)

For cordocentesis alone, fetal paralysis is not used. If transfusion is likely, and the fetus is vigorous, pancuronium (diluted to 0.4 to 0.6 mg in 1-ml tuberculin syringe) is prepared, carefully identified and segregated, not to be confused with the saline syringes. The two-person team uses caps, masks, and sterile gloves. The ultrasound operator, using sterile technique, places his or her scanning arm in a sterile plastic bag, holding the transducer. The bag (24" – 36" long), loaded with a dollop of ultrasound gel, acts as a closed sleeve, part of the sterile field with the transducer in it. The other hand is thus free to operate the ultrasound instrument. Our preference is to use a linear array, but many different transducers have been used successfully.

The 22-gauge, 12.5-cm spinal needle is introduced in the appropriate plane and guided to the cord insertion in increments of 1 cm or more when the target is distant, and in increments of 1 to 2 mm as the target is approached. The "zoom" feature of current ultrasound instruments is useful for the last steps. At the insertion, a significant push of the needle is usually required to overcome tissue resistance and enter the vessel. Here, the operator's "touch" is important to gain efficient vessel entry. Up to this point, however, guidance for the procedure rests entirely with the ultrasound operator. Description of this two-person procedure sug-

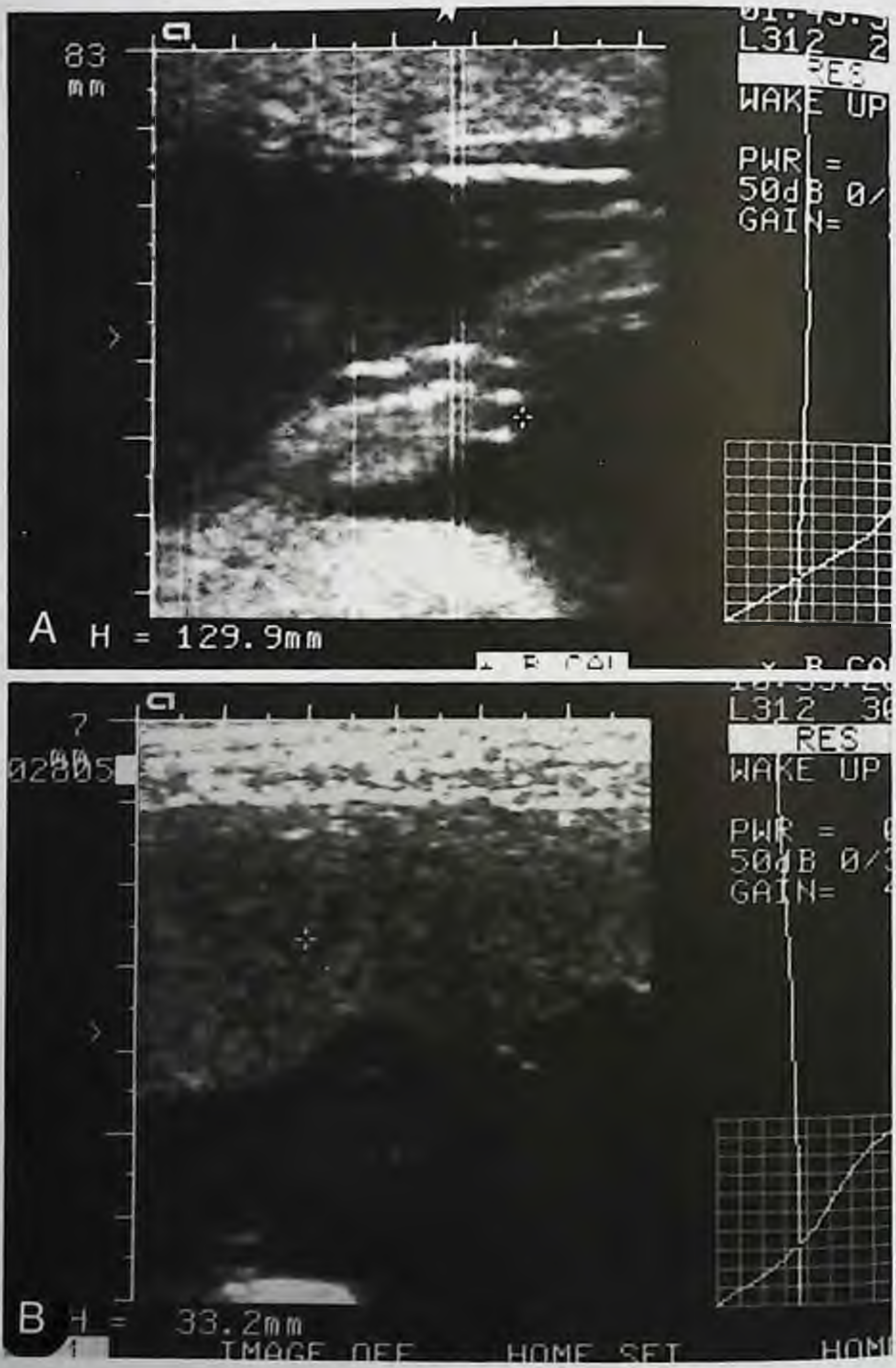

Figure 8. Saline injection to identify vessel sampled. *A*, 0.5 ml of saline given as a push, "lights up" the umbilical vein *(star)*. *B*, Shows an anterior cord insertion, no injection. *Illustration continued on opposite page*

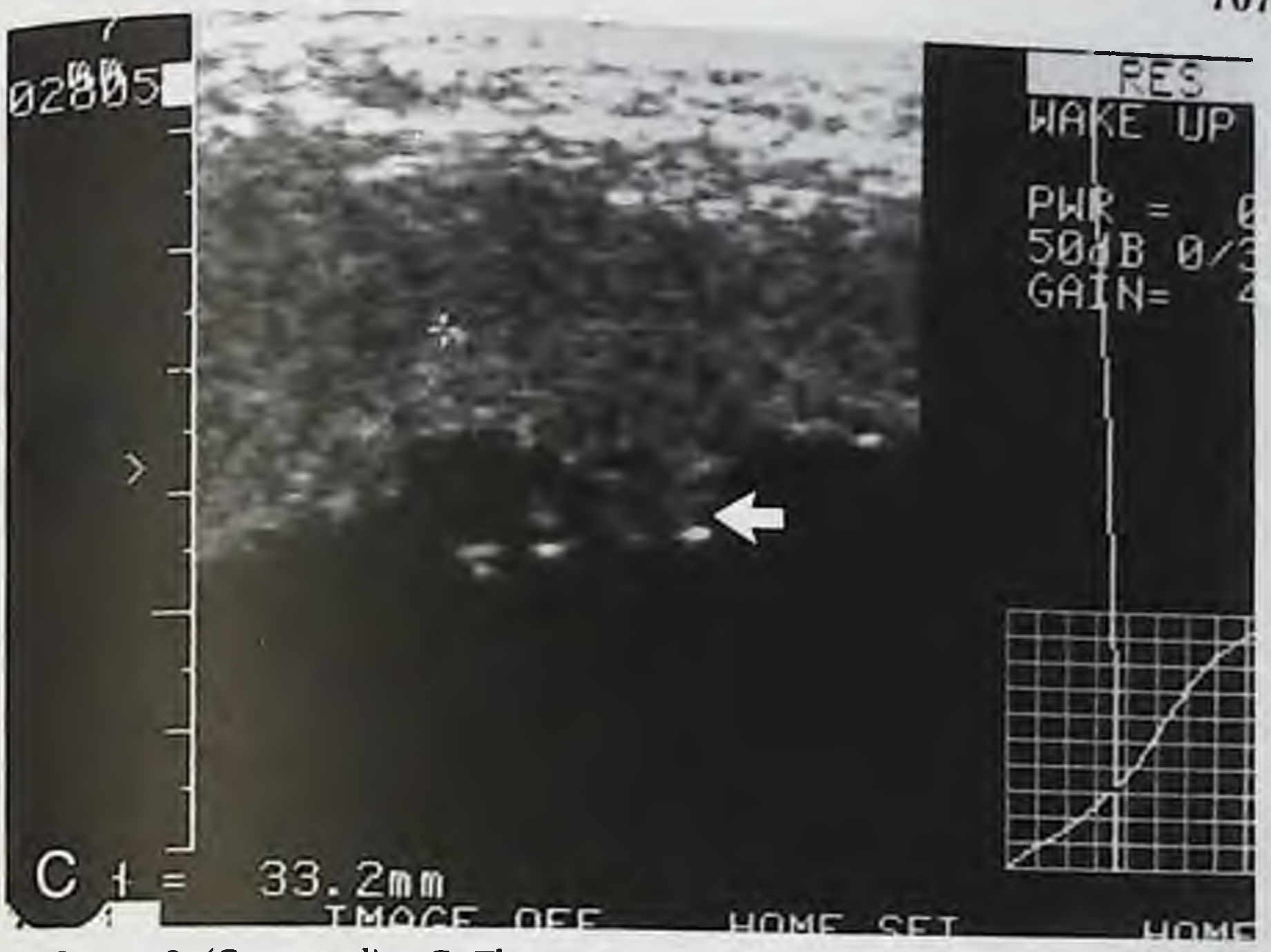

Figure 8 *(Continued).* *C,* The injection of saline is in the umbilical *artery* as it branches to the placenta. The needle is placed properly in the vessel lumen. The only turbulence visible is the small lighted area at the arrow.

gests a great deal of cooperation, and team communication is necessary. It is reassuring to know that such communication is relatively straightforward, as long as it is understood that the ultrasound is the directing force.

When the needle is within the vessel lumen the stylet is removed. (An alternative technique is to perform the procedure with the stylet removed, with the needle filled with citrated saline.[26]) If needle repositioning is necessary, *never reinsert the stylet*—it introduces microbubbles of air: their exaggerated echoes and acoustic shadowing can completely obscure the target and terminate the procedure. The sample is then aspirated and tested at the bedside for fetal origin, and the possibility of maternal or amniotic fluid contamination. Many steps may be taken to ensure a pure sample, but detailed identification of the target site, possible with today's high-resolution equipment, will usually direct adequate sampling.

The volume of fetal blood withdrawn depends on the tests to be performed: 3.2 ml (four tuberculin syringes reasonably full) will suffice for all but the most exotic. Table 4 shows a suggested protocol for fetal blood sampling in alloimmune disease. When this panel of results is obtained (usually on pretransfusion samples of serial IVT as well), unexpected variations in results can be interpreted. Once an adequate sample is obtained, proper placement within the vessel is certified by injection of a small amount of normal saline. This saline turbulence is readily seen in most cases (see Fig. 8*A*), and when the umbilical vein has been sam-

Table 4. *Fetal Blood Tests: Alloimmune Cordocentesis*

Hematologic Indices
Hemoglobin, hematocrit, MCV, WBC, platelet count
Peripheral smear: RBC morphology, N-RBC count and differential, WBC differential, WBC differential, platelet morphology
Kleihauer test: % fetal cells, hemoglobin A : F content
Blood Group Serology
Precise blood grouping
Direct Coombs' (IgG)
Biochemistry
Liver function: albumin, total protein, bilirubin
pH and blood gases
Contaminant Control Tests
beta HCG
I-i RBC antigen

Key: MCV, mean corpuscular volume; WBC, white blood cell count; RBC, red blood cell; N, nucleated.

pled, turbulence moves down the vessel toward the fetus. As long as none of this saline causes turbulence in either amniotic fluid or placenta, it ensures proper placement.

When needle placement is not ideal, even a little extravascular saline may cause cord tamponade, with ensuing bradycardia. This has been produced with as little as 0.5 ml saline infused, emphasizing the difference between the sampling phase, and the infusion portion of intravascular fetal procedures.

LABORATORY EVALUATION

There are many ways of ensuring a pure fetal sample. Several bedside tests are possible, providing useful guidance as to adequacy of the fetal sample. The simple Singer test (alkaline denaturation of maternal hemoglobin) will provide rapid reassurance that the blood is completely fetal. (When the sample is totally fetal, the alkaline solution remains pink or red. When amounts of maternal blood are added, progressive change in color from brown to green is visible to the experienced observer.) The automated cell sorter has been used to good effect at the bedside. (Fetal red cells are much larger than maternal ones, detectable by electronically measured mean corpuscular volume.) On occasion, ABO differences, or specific Rh antisera, may be of use, but generally they are left to detailed testing in the serology lab. The hemoglobin value is readily obtained using an automated instrument at the bedside, providing evidence of proper sampling (assuming maternal hemoglobin is known) and defining the necessity of going straight to transfusion.

In the lab, Kleihauer testing (elution of adult hemoglobin by acid buffer) identifies adult cells in the sample.[30] This may be enhanced with polarized microscopy (Fig. 9). Blood grouping is a further source of confirmation when a unique set of blood groups is identified that differs from that of the mother. Blood gases usually are markedly different between maternal intervillous values and fetal vascular values. Proper vessel identification, artery versus vein, is essential for proper attribu-

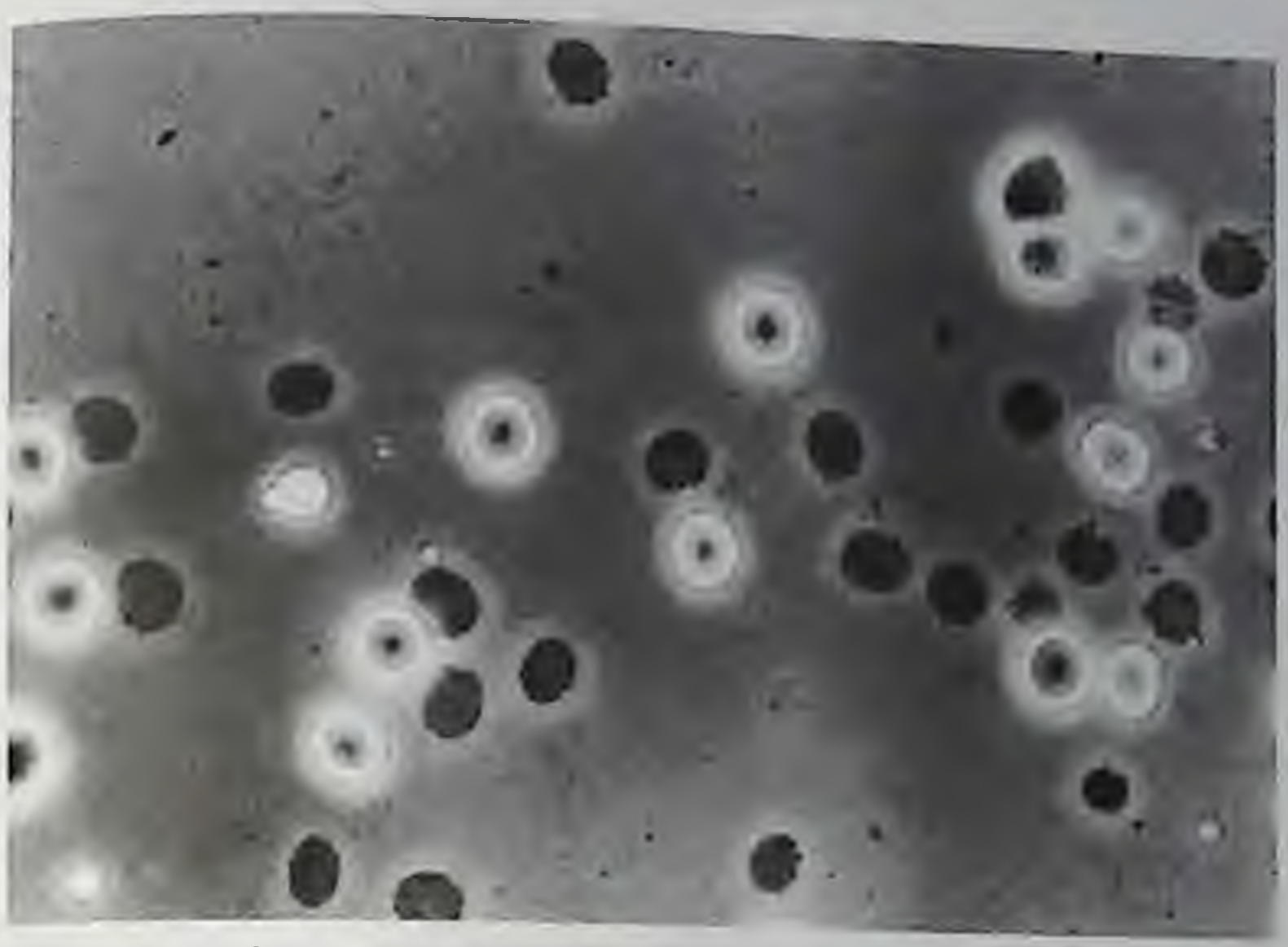

Figure 9. Standard Kleihauer testing may be amplified, using polarized light. Intact fetal cells glow brightly, maternal cells are dark. (Microphotographed courtesy of J. M. Pollock, R.T., who developed the technique with Dr. J. Hoogstraten.)

tion of pH and blood gases (see Fig. 8). Serum bilirubin usually is markedly different between fetus and mother when there is substantial hemolytic disease.[31] Erythrocyte antigen expression (i = fetus, I = mother) and beta HCG (higher in mother) are also significant discriminants of fetal from maternal blood.[32] Amniotic fluid contamination can be shown by activation of coagulation factors, and fetal squames (epithelial cells), on peripheral smear.[32,33] The dilution effect of large amounts (>10 per cent) of amniotic fluid make the bedside results for hemoglobin concentration inappropriately low, pointing the way to repeat sampling. Physical examination of the fetus helps here, suggesting probable hemoglobin ranges based on the extremity of fetal physical changes.

Having proved that the sample is pure fetal blood, action is predicated on the results. Normally, fetal hemoglobin concentration rises during pregnancy, inversely reflecting the po_2. Between 20 and 40 weeks, fetal hemoglobin rises from a mean of 110 to a mean of 150 gm per liter. (At the same time, po_2 is gradually falling, resulting in a maintenance of the same oxygen saturation throughout pregnancy.) Evaluation of the cordocentesis results, therefore, is taken in context with gestational age. Fetuses with hemoglobin greater or equal to the mean, are not transfused. Fetuses within 20 gm per liter of the mean are transfused on occasion: 1) rapid or extreme antibody rise, 2) serial fetal hemoglobin measurements showing rapid decline, or 3) peripheral blood smear with severe hemolytic change, despite maintenance of hemoglobin concentration. Extreme hemolytic damage, affecting virtually every fetal red blood cell, suggests the onset of a hemolytic crisis: fetal hemoglobin may give an inappropriate reassurance of well-being, which will not persist for much longer. Detailed testing is always performed on the appropriate samples in the laboratory.[34,35]

The fetus with no significant hemolysis, and hemoglobin within 20

gm per liter of gestational mean, is followed with serial cordocentesis, rather than transfusion. Considerations such as geographical isolation, difficulty cross-matching blood, and severe previous history, moderate this stance. At the present time, prospectively collected data are not available to be absolute about the progression of these moderately anemic levels of disease.

We have learned that severely anemic fetuses can lose their remaining blood rapidly. Hemolytic loss rates of up to 10 gm per liter per day are seen in some fetuses sampled serially. Based on these experiences, the interval for serial sampling of fetuses with normal hemoglobin concentrations, but significant evidence of hemolysis, is set at 7 days. Of course, detailed serology on fetal blood will illustrate antibody concentration, and avidity of binding. As experience grows with fetal serology, the interpretation of fetal blood smears, and the prediction of fetal hemoglobin concentrations in particular clinical circumstances, more fetuses may be followed serially without transfusion. If transfusion is indicated by low levels, or combinations of the other factors, it usually is carried out the following day. In that case, antibiotic prophylaxis and more definitive maternal sedation are given, as described earlier.

Following cordocentesis, minimal fetal monitoring is necessary. We have not encountered severe thrombocytopenia in any fetus with nonhydropic disease.[36] Further, raised intravenous pressure, possibly related to the combination of massive placental edema and high output cardiac failure, is also restricted to hydropic disease. Thus, the two main elements that predispose to prolonged fetal bleeding after cordocentesis, are generally absent in the nonhydropic fetus. Bleeding exceeding 100 seconds should raise the possibility of a separate entity (e.g., coagulation defect). In general, backbleeding is only observed when the needle entry is via the amniotic fluid, usually a posterior or posterior–fundal cord insertion. We have not observed hematoma formation when the cord has been entered directly via transplacental needle insertion. Once backbleeding has stopped, the procedure is concluded. Depending on the presence of mild bradycardia during the procedure, fetal heart rate monitoring may be instituted. It usually is not necessary to monitor fetal heart rate for more than 60 minutes. During this time, much of the information available from the sampling can be assembled, and the patient can be advised of further management plans and prognosis.

COMPLICATIONS OF INVASIVE TESTING

As indicated in Table 5, both amniocentesis and cordocentesis bear some negative consequences. The possible adverse effects of cordocentesis are more severe for both mother and fetus, but many of these were reported in the first years of experience with the procedure, and their true frequency is likely very low. It remains likely, however, that the range of adverse outcomes with cordocentesis exceeds that with amniocentesis.

Even an uncomplicated procedure may not be free of ill effect. Even with a small-gauge needle, transplacental amniocentesis may cause

Table 5. *Complications of Invasive Therapy*

Maternal supine hypotension•
Maternal infection—superficial
—severe•
Rupture of membranes
Chorioamnionitis•
Abruptio placentae
Fetomaternal bleeding†
Fetal bradycardia•
Fetal distress•
Cord hematoma•
Fetal demise†
Emergency cesarean section†
False-positive test result‡
False-negative test result‡

• Probably higher, or † definitely higher, with cordocentesis.
‡ Higher with amniocentesis.

enough TPH to aggravate maternal antibody production, accelerating fetal disease. With a posterior placenta, the primary risk is fetal or cord injury with leakage to the mother, an uncommon event. With cordocentesis, TPH, and corresponding aggravation of antibody levels, with accelerated fetal disease as a consequence, are all more severe, regardless of placental site (Table 6). This is at least one prominent reason why cordocentesis cannot completely replace amniocentesis in alloimmune monitoring.

FETAL COMPENSATION

As anemia becomes more severe, the fetus attempts to compensate by accelerated hematopoiesis. Presumably, this is regulated as relative renal hypoxemia causes fetal erythropoietin increase, resulting in increased mobilization of red cell precursor lines. This first affects the bone marrow, causing increased reticulocytosis. Accelerated production is unsuccessful; hemolysis continues unabated. Continued hematopoietic demand converts extramedullary sites—liver, spleen, intestinal wall, lymph nodes, and other sites to a lesser extent. Increased promotion of red cell precursors yields a rising proportion of nucleated red cells, and a shift in the differential of those cells to more immature forms (see Fig. 17). Ultimately, circulating hemoglobin in the severely anemic

Table 6. *Maternal Sensitization with Invasive Testing*

	TPH		AB RISE	
PROCEDURE	*Anterior*	*Posterior*	*Anterior*	*Posterior*
Amniocentesis	5.8%	1.2%	3.5%	0
Cordocentesis	39.8%	28.0%	32.6%	21.1%

TPH—Transplacental hemorrhage ≥ 0.1 ml by maternal Kleihauer.
Ab rise—Increased maternal IgG level ≥ 2 dils.

fetus is contained by erythroblasts. Few young red cell forms, and virtually no mature red blood cells, are visible in circulation—hence, the term *erythroblastosis fetalis*.

Other mechanisms of fetal compensation may include increased oxygen extraction, increased cardiac output, and regional diversion of blood flow. Increasing anemia may result in relative diuresis, leading to decreased fetal circulating blood volume and relative hydramnios. The latter, along with placental congestion and increasing liver diameter associated with accelerated hematopoiesis, are the first signs of deterioration in alloimmune disease. This appears at a wide range of fetal hemoglobin concentrations, with hydropic disease at levels as high as 66 gm per liter, and persistence of the nonhydropic state to levels as low as 50 gm per liter.[22] Below 50 gm per liter, the appearance of hydropic changes becomes obvious.

DECOMPENSATION

With further pressure to produce red cells, inevitably met with ongoing hemolysis, anemia deteriorates. This eventually results in cardiovascular compromise in the form of increased demand for output, decreased circulating volume, and increased tissue pressure in the placenta. In concert, hypoxemic endothelial damage is likely, allowing fluid extravasation across the damaged vessels, probably initially in the peritoneal cavity.[37]

As the fetus fails to compensate for ever-decreasing hemoglobin levels, important hepatic structural changes occur. The islands of hematopoietic cells enlarge; liver function is compromised. Compression of intrahepatic vessels causes venous stasis and localized hepatic hypertension, reflected distally as portal and umbilical venous hypertension. Biliary compression results in altered function, with rising enzymatic evidence of hepatocellular toxicity, but more importantly, falling albumin production. Decreasing serum albumin, and total protein content, is associated with more widespread leakage of fluid from the fetal vasculature. Initial phases of ascites may be due to local intraperitioneal factors, but rapid dissemination of anasarca is likely on the basis of marked reduction in systemic oncotic pressure. This spiral ultimately progresses: deepening anemia, liver failure, circulatory compromise, continued elevation in tissue pressure, within both fetus and placenta. Cardiovascular collapse and acidosis follow, culminating in hydropic stillbirth.[5,37]

The mechanisms by which extramedullary hematopoiesis is pushed to such a lethal extent are not fully known. Individual variation is considerable, with fetuses at identical hemoglobin levels manifesting disease ranging from mildly hydropic (just a thin rim of ascites), all the way to the moribund hydrops, with massive edema, effusions, and all the hallmarks of lethal disease.

A gestational age factor is likely—younger fetuses apparently tolerate much lower hemoglobin levels. At a hemoglobin of only 20 gm per liter, a 20-week fetus usually has a normal biophysical profile score. Although he has serious structural changes in the form of massive ascites,

pleural and pericardial effusions, and a massively distended placenta, his cutaneous manifestations of anasarca are frequently not dramatic, and activity is vigorous. On the other hand, the fetus at 30 weeks with a hemoglobin of 40 gm per liter may well be moribund, with severe generalized edema, and little or no activity.[22,38]

Fetal Examination in Hydropic Disease. Most of the findings in the ultimate form of fetal alloimmune disease—hydrops fetalis—emerge in stages. The longer the fetus remains alive with severe anemia, the more likely he is to manifest severe structural changes. Some fetuses may die with extremely low levels of circulating hemoglobin, but only moderate structural hydropic changes; other fetuses may survive for considerable time, having the most dire physical findings. Reasons for this variation in physical response are not known but will likely be clarified as the fetal vascular access now available facilitates further research.

Ascites. Small amounts of intraperitoneal fluid may be undetectable by ultrasound. Observations as donor blood is infused during intraperitoneal transfusion (IPT) suggest the volumes which must be present before we can visualize ascites. As infusion progresses, intraperitoneal appearance changes predictably.[12] Double outlining and separation of bowel loops is apparent at 30 ml. Distinct fluid rims of only a few millimeters are not visible until at least 50 ml have been infused. By the time 100 ml have been given, classic ascites appear, with a large fluid rim (Fig.

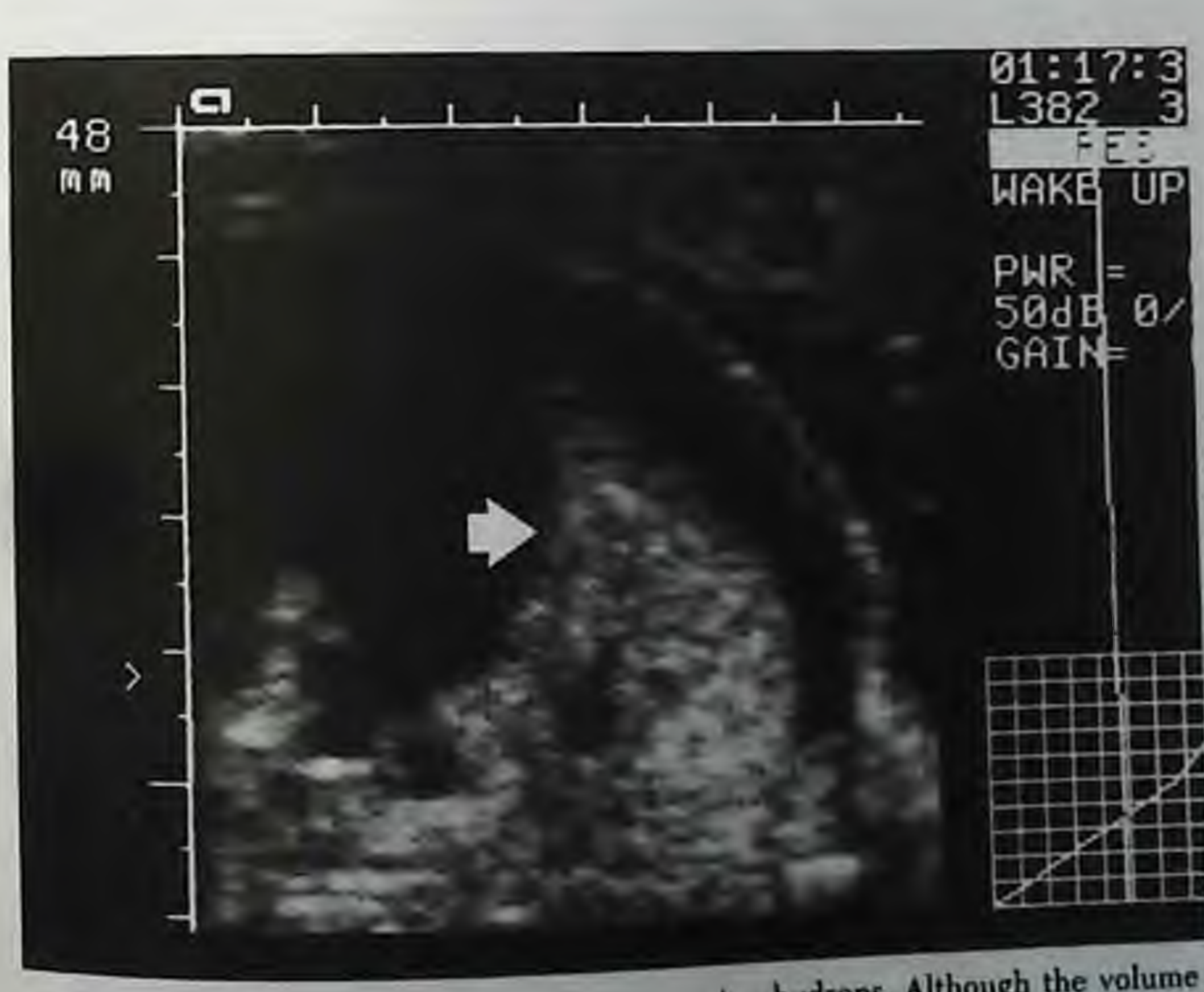

Figure 10. Fetal ascites, 29 weeks, recovering hydrops. Although the volume of ascites within the abdominal cavity remains massive, the liver *(arrow)* has returned almost to normal size, and a sharply defined contour indicates decreased liver swelling. This fetus had just completed his fifth in a series of nine intravascular transfusions.

10). Relatively small fluid rims (10–20 mm) may be present alone or combined with hydramnios and placental edema, and minimal fetal edema. If present at all, fetal edema in these cases is usually restricted to the scalp.

With large volumes of ascites, changes in volume are not obvious. The abdominal cross-section remains much the same. Abdominal wall tension and the free movement of intra-abdominal organs within the fluid mass result in the same ultrasound appearance over a wide range of absolute fluid volumes, as measured when the peritoneal cavity is emptied of ascites at the time of IPT. At both ends of the scale of fetal ascites, the usefulness of any measurements is doubtful. Serial subjective impressions may be more reliable than the use of arbitrary landmarks to "measure" rims of fluid. When these observations are carried out by the same experienced examiner, the overall impression of improvement or deterioration is likely reliable.

Anasarca. Moderate placental edema may be seen fairly early, while fetal edema is a relatively late finding, often seen first as scalp edema (Fig. 11). Assessed at occipital and frontal margins, this may be difficult to interpret based on fetal head position. Scalp thickness > 7 mm is necessary before edema is diagnosed. Scalp edema in any plane may be massive and may be slow to resolve following restitution of fetal hemoglobin. Edema of the face, abdominal wall, hands and feet, and generalized anasarca tend to appear in that order. None of these findings is seen in the absence of significant ascites. As noted, the initial appearance of

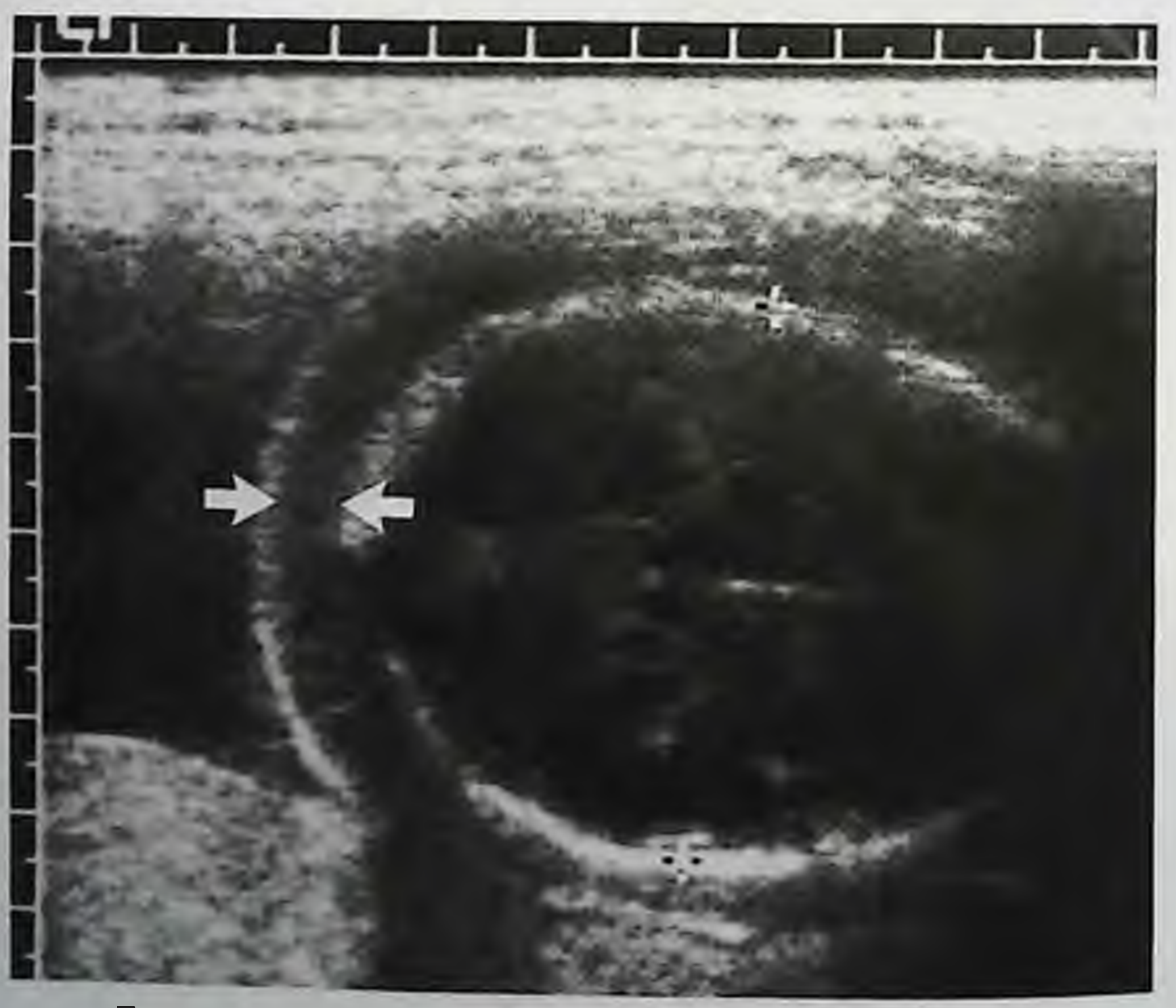

Figure 11. Scalp edema *(arrows)*; hydropic fetus at 24 weeks.

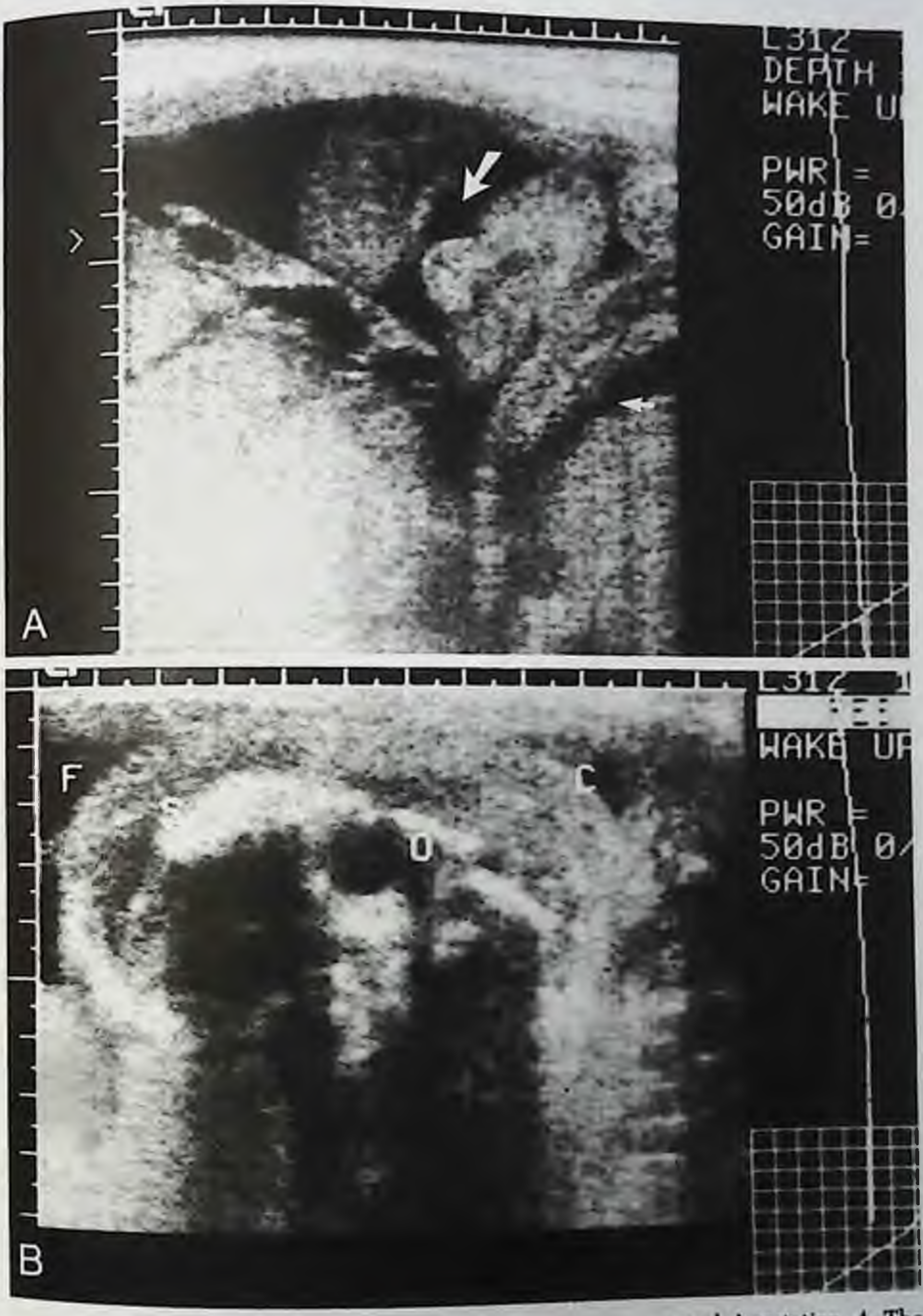

Figure 12. Extreme facial edema, moribund hydrops 23 weeks' gestation. *A*, The "Buddha face." The extreme edema of forehead and cheeks virtually obliterates the eyes *(arrow)*. This fetus has a significant pleural effusion *(small arrow)*, and is using his grossly hydropic placenta as a pillow. This fetus survived intact after nine intravascular transfusions. *B*, The same fetus, in coronal plane. The 3-cm-thick edema took 3 weeks to return to normal appearance *in utero*. *Key:* S = skull, O = left orbit, F = forehead, C = check).

ascites is probably related to hepatic and intraperitoneal factors, rather than the disseminated third-spacing of fluid due to falling albumin levels, which is responsible for generalized anasarca.

End-stage fetal edema results in the Buddha face (Fig. 12). The forehead becomes progressively distended with edema, likewise the cheeks, and eventually they meet, obliterating the orbits. Extensive total body edema results in gross distortion of size and weight, amounting to as much as 100 per cent increase over true, "dry" weight. This extreme edema is associated with swollen extremities, with mechanical reduction of limb flexion. Even when biophysical profile scoring has returned to normal after successful intravascular transfusion, such fetuses move their arms and legs in a very stiff fashion, like paddles, until the edema begins to resolve.[39] Abdominal wall edema can be very severe in association with these findings. However, the gross distention due to ascites may in fact cause enough tension on the abdominal wall to reduce edema.

Pericardial and Pleural Effusions. As part of the presentation of the severely hydropic fetus, these effusions are quite obvious (Fig. 13). Pleural effusions are bilateral, usually moderate in size, and usually do not feature pulmonary collapse. Pleural effusions that are larger, asymmetric, or demonstrate serious pulmonary collapse, may suggest other abnormalities. Pleural effusions presenting prior to onset of ascites or pericardial effusions, likewise suggest fetal abnormality other than alloimmune disease. Examples of severe maternal alloimmunization, accompanied by fetal chromosomal abnormality featuring scalp edema, pericardial and pleural effusions, and other features of non-immune hydrops, are well documented. In the elderly gravida (who was sensitized prior to the routine use of ante- and postpartum prophylaxis), these dual presentations occasionally may be seen. Invasive testing by cordocentesis can provide fetal blood for karyotyping as well as for the alloimmune estimations described earlier. Pleural effusions usually resolve rapidly (5–8 days) after the hemoglobin has been restored to normal.

Pericardial effusions may occur on two levels. Small effusions, as documented by DeVore et al.,[17] may represent increased amounts of fluid generated due to increased contractility or heart rate, associated with the extra cardiac output demanded by the combination of anemia and increased peripheral resistance (due to congested liver and placenta). Although frank cardiac failure due to high output exhaustion is very unusual, even in the dying fetus, there is no doubt that cardiac work is increased. Small amounts of pericardial fluid are, of course, a feature of the normal fetal echocardiogram. The differentiation of normal amounts of pericardial fluid, present in all fetuses, from the small pericardial effusions demonstrated in anemic fetuses, may be very difficult for the inexperienced observer. Real-time ultrasonography is widespread, and the detailed application of M-mode ultrasonography may not be quite so accessible.

Larger pericardial effusions (>4 mm, between midventricular epicardium and pericardium) are generally confined to serious hydrops (see Fig. 13*B*). We have never seen this level of pericardial effusion in a fetus without significant ascites. On resolution, following successful IVT, the pericardial effusion may be the last feature of hydropic disease to re-

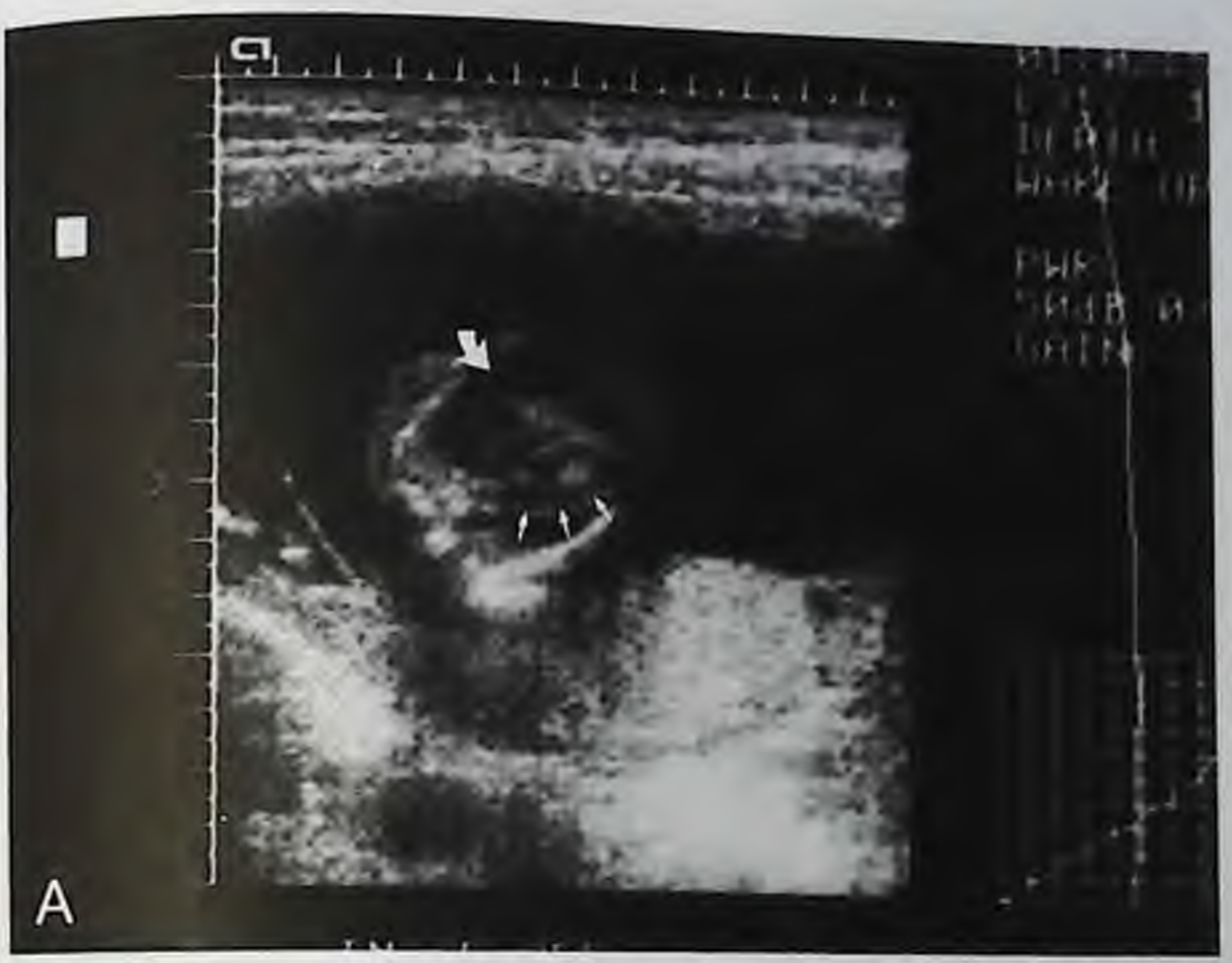

Figure 13. Pleural and pericardial effusions designate class 3 or 4 disease. *A*, Large bilateral pleural effusions *(curved arrow)* at 19 weeks' gestation, clearly outline the fetal heart. In addition, visualization of the heart is enhanced by the presence of a thin pericardial effusion, a thin dark line around the entire perimeter of the heart *(small arrows)*. *B*, A larger pericardial effusion at 24 weeks' gestation, in a hydropic fetus who survived with serial intravascular transfusion. This effusion *(arrows)* occurs at the apex of the heart, directly adjacent to the interventricular septum.

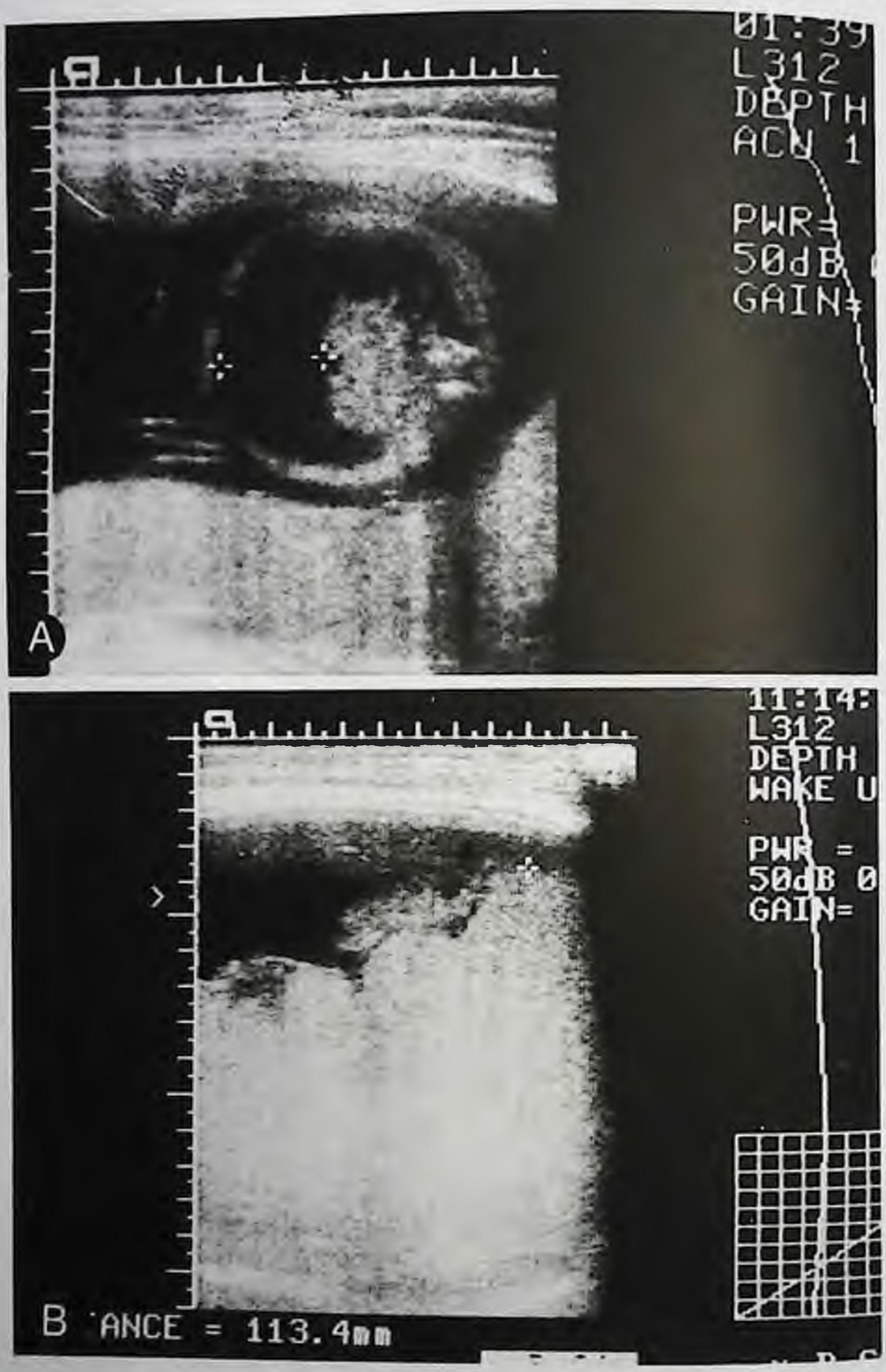

Figure 14. Placental edema is manifest differently at different gestations. *A*, Hydrops at 22 weeks' gestation: posterior placenta is "ground glass," thickened, and homogenous. Note massive ascites (calipers). *B*, At 30 weeks, prolonged hydrops, untreated, yields an enormous placenta, with buckled surface, reaching 12 cm in thickness.

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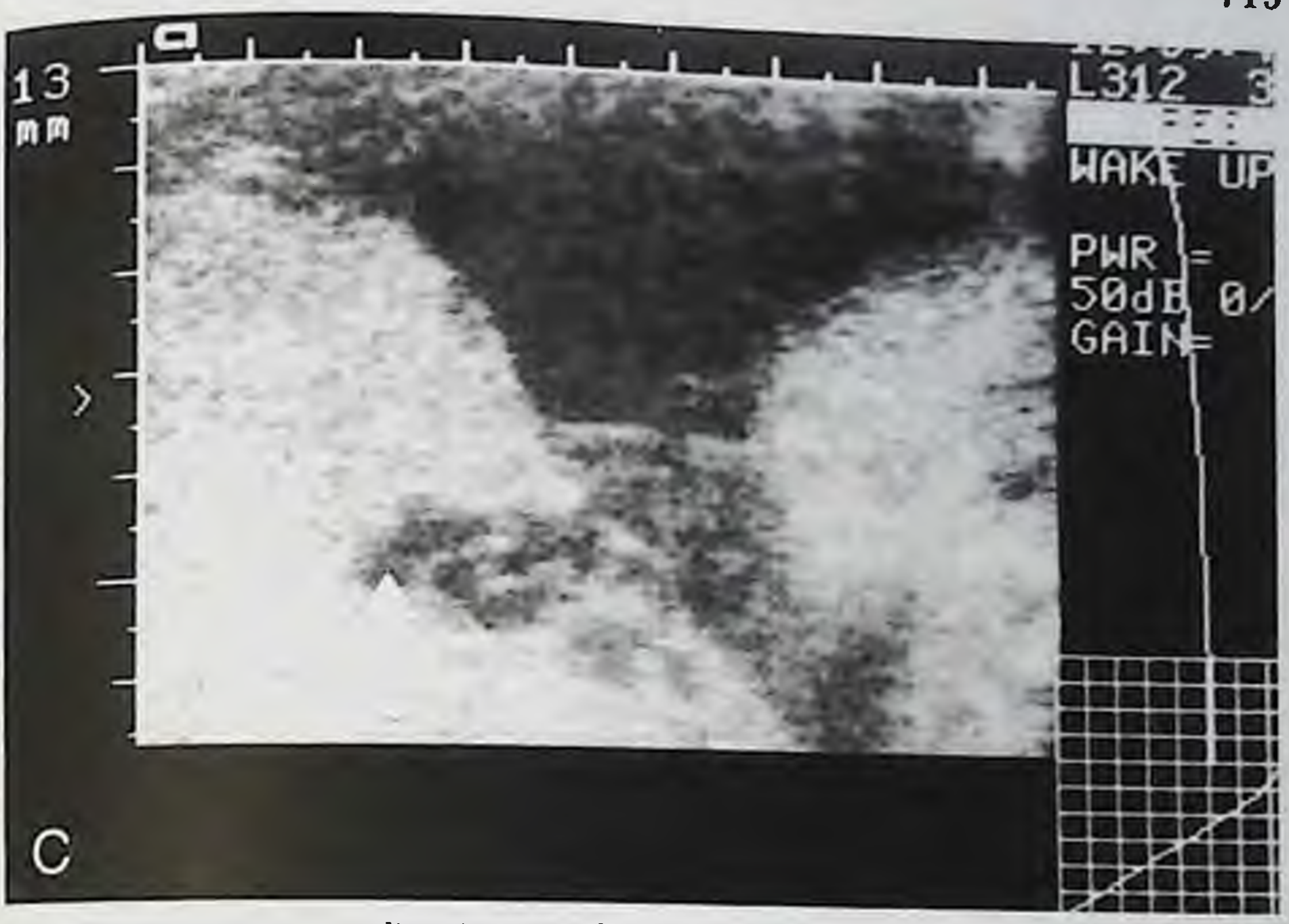

Figure 14 *(Continued).* *C,* In another grossly buckled placenta, the cord insertion *(arrow)* is herniated inwards, lying 3 cm below the surface of the placenta.

solve. Although ascites frequently disappears 2–3 weeks, it is not unusual for a larger pericardial effusion to persist in some degree for up to 5 weeks after restoration of a normal hemoglobin level.

Placental Anatomy. In hydropic disease, placental findings become unequivocal. In nonhydropic disease, subjective aspects of change such as decreased placental markings, assumption of a rounded uniform shape, and a tendency to thickening all may be debatable and highly dependent on the same observer performing the examination. With hydropic disease, placental thickening, bulging, and loss of placental architecture is undoubted (Fig. 14). The placenta is erect, rigid, and very uniform in appearance. Maternal lakes, most notably the usual maternal intervillous vascular spaces found immediately below the cord insertion (e.g., Fig. 7*A*) are often obliterated. The placenta is puckered; total thickness may exceed 10 cm. Placental wet weight may be 2.0 kg at delivery, on which the placenta immediately begins to ooze fluid. The cord insertion may be enfolded as much as 3 or 4 cm below the original placental surface. Clearly, this degree of placental distortion will be associated with alterations in placental blood flow, fluid transport, and decreased efficiency of gas exchange. Such extremes of placental distortion may not resolve completely even when intrauterine therapy is successful and delivery is delayed a number of months.

Umbilical Cord. Visualization of the umbilical cord is important only for the purposes of fetal blood sampling. Serial measurements of umbilical cord diameter are ineffective in monitoring fetal disease. Although significant data exist to suggest that increased venous pressure may be generated by relatively obstructed flow at the level of umbilical and portal venous entry into the liver, there is clearly no physical correlate of this increased pressure.[41] This may be due to several factors.

First, the umbilical vein is encased within the structure of the cord, and therefore limited as to the possible expression of enlargement. Second, measurement of vessel diameter varies significantly with fetal position, tension on the cord, nuchal loops, advancing gestational age, and the angle of the ultrasound plane.

Detailed identification of cord insertion has already been discussed. The placental end of the cord is the primary target for cordocentesis and IVT. If this is unavailable, the abdominal end of the cord, or the intrahepatic portion of the umbilical vein should be considered. The association of significant complications with the intracardiac approach[41] may be completely explicable by the severity of disease involved; nevertheless, we would not consider this for fetal blood sampling in a nonhydropic fetus. Even in serious hydropic disease, the umbilical cord at either end is our primary target. Only if the fetus is moribund and cord access simply is not possible should intracardiac sampling and transfusion be considered.

Other information may be available from cord observations as techniques are developed. One example might be the position of the cord relative to intravascular pressure, and excursion of the cord with pulsations. In end-stage disease, with elevated intravascular pressure, the cord is suspended in the fluid, literally throbbing. Three patients with the most accelerated structural disease had cord excursion with pulsations up to 8 mm. These cord pulsations reduced in amplitude over the course of therapy. In these three fetuses, intravascular pressure was so high that the fetus was able to bleed around the needle while it was inserted in place. When aliquots of intravascular blood were given at the time of IVT, and the intravascular pressure rose, blood leaked around the needle and eventually produced a dramatic "fountain" effect at the point of insertion. This was extremely responsive to infusion, ceasing shortly after infusion was stopped and reappearing 10 to 20 seconds after transfusion was resumed. The slight time delay indicated that this was not the leakage sometimes seen when the needle is incompletely within the vascular lumen.

Amniotic Fluid. Although hydramnios is common in fetuses with serious alloimmune disease, this may be less marked in the severely ill. On occasion there may be reduced fluid or frank oligohydramnios. The outcome in such cases is poor; the implication is that redistribution of blood flow is so extreme in the face of markedly diminished intravascular volume and cardiac output that the fetus has become anuric. Before intravascular fetal monitoring, outcome was universally poor. Recently, one such fetus was treated successfully for a period of 10 weeks with intravascular transfusions, but eventually developed oligohydramnios, repetitive decelerations, and the growth pattern of serious IUGR. That infant survived intact, delivered at 29 1/2 weeks' gestation by emergency cesarean section.

DOPPLER ULTRASOUND

This technique is still in the development stage, especially in correspondence with fetal blood sampling in alloimmune disease. Research is ongoing, and the reports are relatively few, mainly dealing exclusively

with alloimmunized fetuses, without suitable controls. The data may be criticized as being highly selected, and therefore of doubtful significance. By the time of publication, newer work may be available to assist in the interpretation of these data.

Several authors have shown various correlations with elevated velocities in umbilical blood flow waveform analysis.[42,44] These elevated velocities may be expressed in absolute terms (peak systolic velocity, peak diastolic velocity) or as mathematical ratios that describe the relationship between systolic and diastolic velocities (systolic/diastolic ratio [S/DR], Porcelot ratio [PR], pulsatility index [PI], and other calculations). Although considerable statistical debate exists as to the optimal expression of velocimetry data, most authors have dealt with peak systolic velocity and either the S/DR or the PR.

There is a reasonable relationship between increased systolic velocities, and therefore increased S/DRs, and severity of anemia. In some authors' hands, the correlation produced a formula from which reasonable estimations of fetal hemoglobin levels were derived.[45] These correlations may not be definite enough to form a reliable system for indicating therapy, deferring transfusion, or rescheduling planned procedures. There is little correlation between blood viscosity (determined primarily by particle density—hematocrit) and changes in velocity. Such studies have demonstrated that blood viscosity may be increased by up to 60 per cent with little or no effect on either the S/DR, PR, or placental resistance.[46]

Experience with human fetuses before and after transfusion demonstrates that changes, if any, in velocity waveform indices are related at least in part to fetal heart rate changes, responsive more to the volume of the transfusion than to the ultimate change in viscosity. Among a group of fetuses transfused with quantities of densely packed (300 gm per liter) donor red blood cells, there were four typical groups of responses.[20] In 45 per cent, PR and S/DR were not altered substantially. In 33 per cent, systolic peak velocity slowed, diastolic peak velocity varied little, with the result of lower PR and S/DR. Variable changes were demonstrated in the remaining 22 per cent, including absent end-diastolic flow on at least three separate occasions (Fig. 15). In all cases the Doppler blood flow velocity indices returned to normal on all of the 24-hour indices. In most cases, pretransfusion indices and 24-hour post-transfusion indices were very similar. Statistically, there was no significant difference, despite the fact that hemoglobin concentration rose 130 per cent in some fetuses. Volume loads of 40 to 55 per cent of gestationally corrected predicted fetal blood volume were given. In the mature fetus, this results in a mild bradycardia (decrease in baseline fetal heart rate from a mean of 130 to a mean of 110), taking several hours to resolve. During this time, rate-dependent changes occur in Doppler blood flow velocimetry.

Other authors have demonstrated significant changes in blood flow velocimetry, both in umbilical blood flow, and in regional blood flows within the fetus.[46–48] In virtually all cases, alterations in blood flow were normal after 24 hours, and the various indices did not reflect the fact that fetal hemoglobin had been raised dramatically. In summary, Doppler studies presently available indicate a possible role in predicting severe anemia in the untransfused fetus. There is very little role seen at

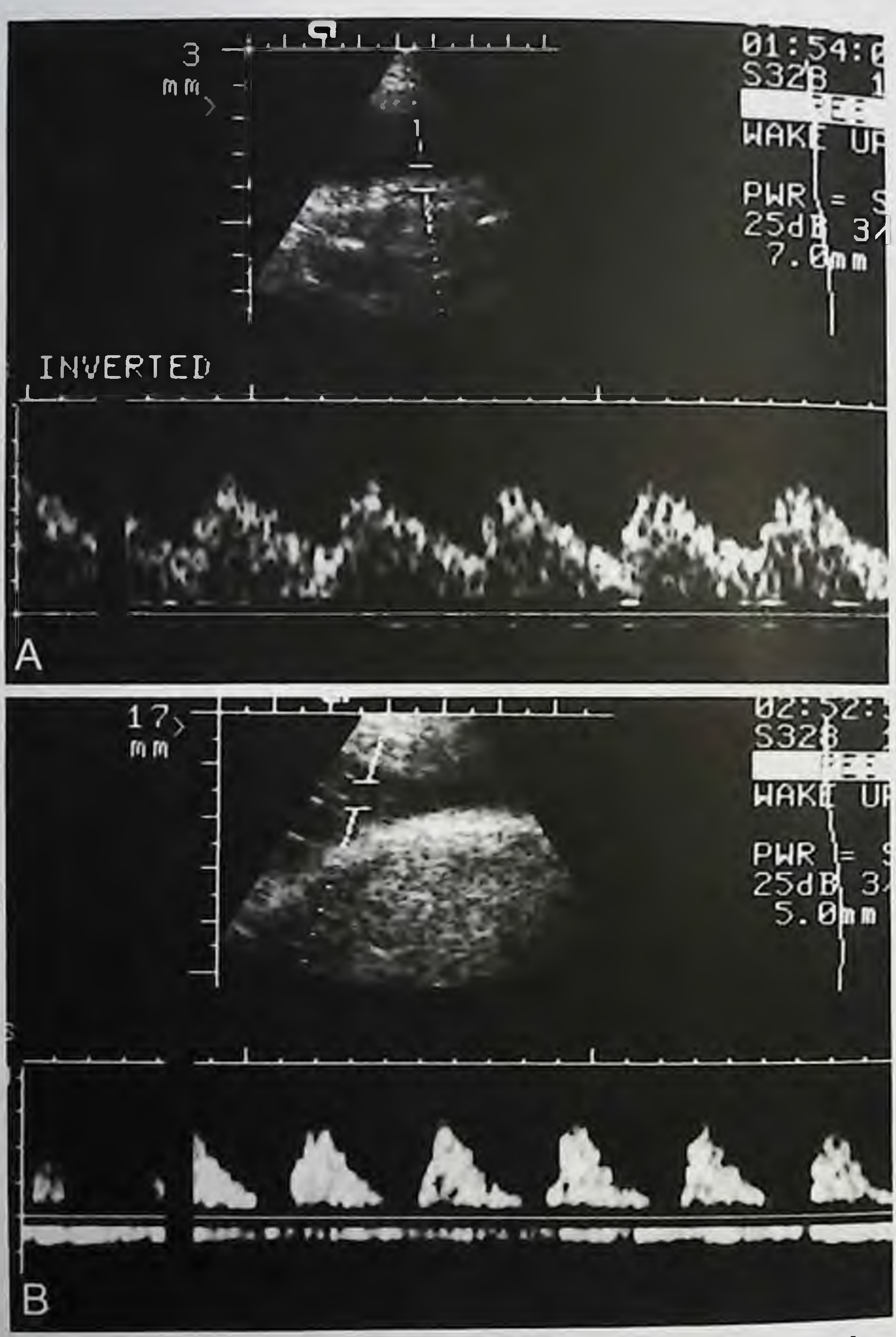

Figure 15. Doppler ultrasound examination at the time of intravascular transfusion, 30 weeks' gestation. *A*, Pretransfusion examination, normal indices. *B*, Absent end-diastolic flow, at completion of IVT, 110 ml, 300 gm per liter donor blood. Fetal heart rate variability and baseline were normal on post-transfusion monitoring. The fetus was normally active. Normal pH and blood gases were obtained in the post-transfusion sample.
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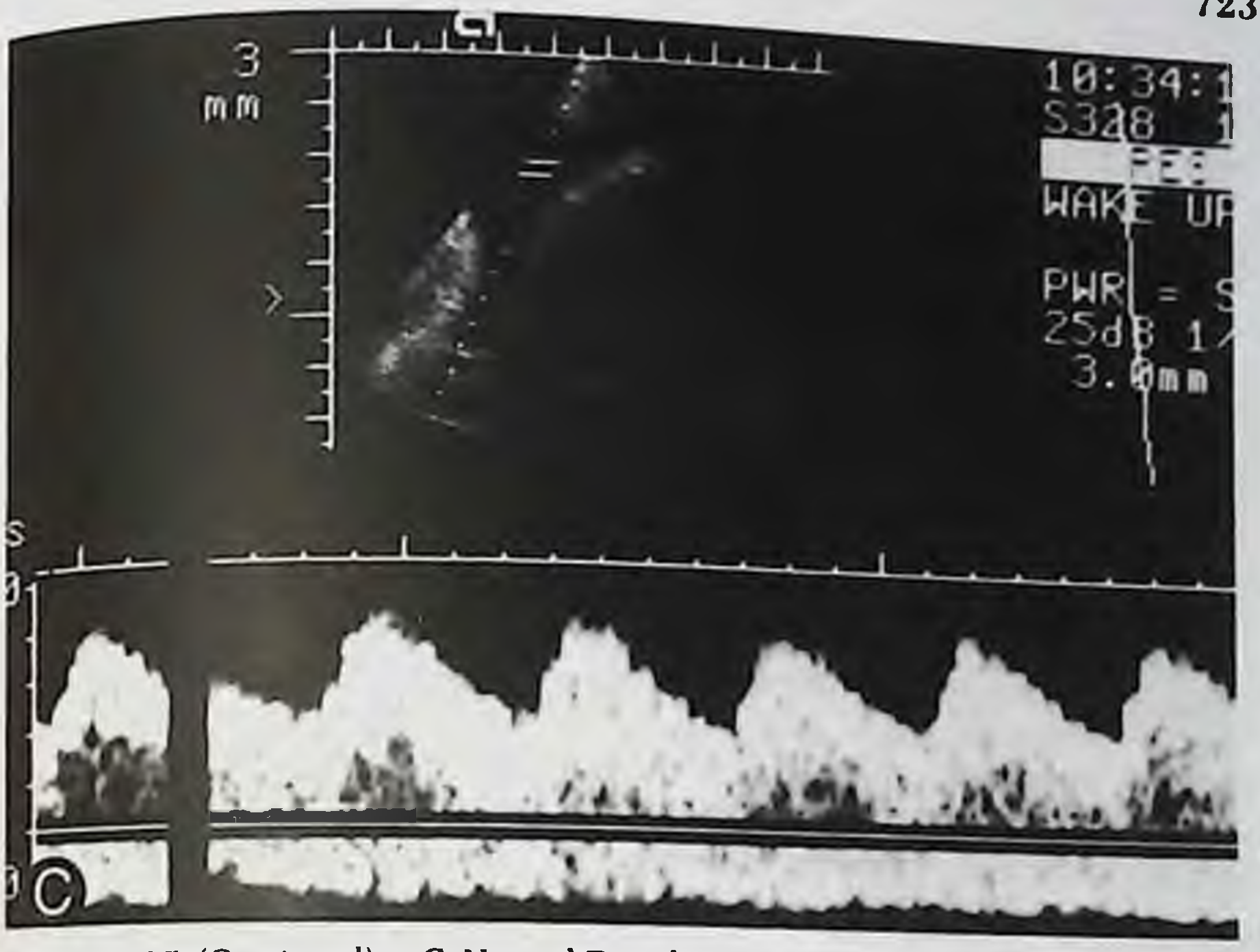

Figure 15 *(Continued)*. *C*, Normal Doppler waveform analysis 24 hours later. This infant was delivered in good health at 38 weeks' gestation.

the present time for determining the basis of ongoing therapy. On the other hand, Doppler ultrasound can be very helpful in proper identification of target vessels.

Fetal Behavior

Fetal behavior is assessed using the biophysical profile score (BPS) as a framework.[49] Parameters observed in the biophysical profile score (fetal tone, gross body and limb movements, breathing movements, amniotic fluid volume, and fetal heart rate variability and reactivity) are evaluated generally as in other high-risk situations. Specific allowances may be made for structural changes "enforced" by extreme disease. That is, the fetus whose limbs are distended with edema cannot properly flex and cannot be expected to demonstrate the normal rapid excursion and return to flexed position normally demonstrated.[50] As noted, amniotic fluid volume is seldom below the minimum criterion for fluid pocket size used in BPS (< 2 cm), so even the moribund fetus usually achieves a score of 2/10. A score of 4/10, representing a fetus who manages a few rolling movements but otherwise demonstrates no normal activity and has a flat, unreactive NST is a severe prognostic indicator.[12,38] Fetuses demonstrating such absent/markedly reduced behavior are classified as moribund hydrops fetalis. In the era before intravascular fetal transfusion, this appearance always meant intrauterine demise, regardless of attempts at treatment (Table 7). At present, this appearance constitutes a fetal emergency, from which the fetus *can* survive if treated urgently, and intensively.

Table 7. *Therapeutic Results*

DISEASE CLASS	CLASS FREQUENCY (%)	SURVIVAL (%)	
		IPT*	IVT†
0	—		99.2
1 Nonhydrops	58	89	96
2 Moderate	16	80	100
3 Severe	13	67	83
4 Moribund	13	0	83

* Intraperitoneal fetal transfusion, 1980–1986.
† Intravascular fetal transfusion, 1986–1989.

As noted previously, intrauterine growth retardation is an occasional accompaniment of severe hydrops fetalis. In such fetuses, and in fetuses recovering from sedation, paralysis, or following resuscitation from severe disease, biophysical profile scoring is an invaluable tool to ascertain fetal normoxemia. Despite the fact that the fetus continues to look horrible, the presence of normal fetal behavior is most reassuring.

In specific circumstances, however, BPS may not in itself offer complete reassurance. In the fetus who has been heavily sedated for the purpose of carrying out the invasive procedure, and especially in the fetus who has been paralyzed for intravascular transfusion, normal fetal behavior may be abolished by various drugs. Such fetuses cannot be distinguished from fetuses asphyxiated as a result of backbleeding, undetected compromise during the procedure, or further progression of their severe disease. In such situations, fetal pH and blood gases obtained from the procedure are most reassuring.

This potential dilemma is one reason the moribund fetus is not sedated. When a fetus is moribund, with virtually no movements, no muscle tone, no postural flexion, sedation is not procedurally necessary. It is rewarding, indeed, to see the fetus "wake up" by the end of the procedure. In several instances, fetuses who have not moved for a number of days, and were acidotic at the time of the procedure, began vigorous body movements, fetal breathing movements, and rapid eye movements, within 30 minutes of transfusion.[38] This may suggest an inactivation role of the CNS in response to severe compromise, but serial convalescent blood gas and other metabolic data are not available. These fetuses are generally not resampled at short intervals. In all cases when subsequent sampling/IVT have been done, pH, po_2, and pco_2 reverted to normal. This aspect of fetal monitoring, during recovery after transfusion, is assisted by maternal counting of fetal movements. In fact, this is a very rewarding experience for the mother, who in most cases has felt only faint rolling movements for some time.

Ultrasound Classification of Disease State[22]

Based on these descriptions of fetal structural and functional changes, fetal disease can be classified as shown in Table 8. This classification is not intended to impose a rigid formula on the interpretation of fetal parameters but to assist in organization of the data, much of which

Table 8. *Ultrasound Classification of Fetal Alloimmune Disease*

Class	ULTRASOUND APPEARANCE				Abnormal BPS <4/10
	Placenta	*Ascites*	*Effusion*	*Anasarca*	
0	−	−	−	−	−
I	+	−	−	−	−
II	+	+	−	−	−
III	+	+	+	+	−
IV	+	+	+	+	+

is subjective in nature. The implication should not be taken that fetal disease proceeds uniformly, by regular steps. Generally speaking, such progression is consistent, and findings in severe disease usually are found together, but progression may be very rapid and occur over a period shorter than the usual observation intervals.

Class 0. These data illustrate a group of fetuses with abnormal amniocentesis results, particularly aggressive historical disease, or suspicious ultrasound findings. Pure fetal blood was obtained but no transfusion was performed because the values indicated a normal hemoglobin concentration. All fetuses were delivered with normal hemoglobin concentrations, at >36 weeks' gestation, and required no intrauterine or newborn therapy. Most of these fetuses were antigen negative; a few were antigen positive, unaffected despite significant maternal antibody titres. This group is illustrated for comparative purposes only, since they were sampled under the same set of indications and conditions as the Class 1 fetuses.

Class 1. These fetuses all had delta OD 450 >80 per cent zone 2 on serial amniocentesis. All eventually required treatment by intravascular transfusion for their anemia. These fetuses were all antigen positive, and showed complete Coombs' reactions in <1 minute. Serum bilirubin was elevated in all, and progressive anemia was documented by serial cordocentesis. By definition, none were hydropic, but hydramnios and early signs of placental edema were common. Fetal hemoglobin values in this class were as low as 52 gm per liter. When serial abdominal circumference measurements were available, most showed centile rise of 20 or more.

Class 2. These fetuses were previously described as moderately hydropic. They have the findings of class 1 disease, as well as progression in the loss of placental architecture, featured by increasing placental thickness, a ground-glass appearance, and a circular uterine shape, signifying increased uterine tone. Ascites of variable amount was documented, the minimum threshold for which is 5 mm fluid rim width, on transverse ultrasound section. Hepatomegaly is clear, but pericardial and pleural effusions, anasarca, and abnormal fetal behavior, were not present. Pretransfusion blood samples demonstrated hemoglobin concentrations of 32–66 gm per liter. As with classes 3 and 4, class 2 disease was managed with concurrent fetal blood sampling and initial IVT. Ascites reversed promptly, and fetal appearance did not deteriorate into class 3 or 4, once therapy was started. The peripheral red blood cell

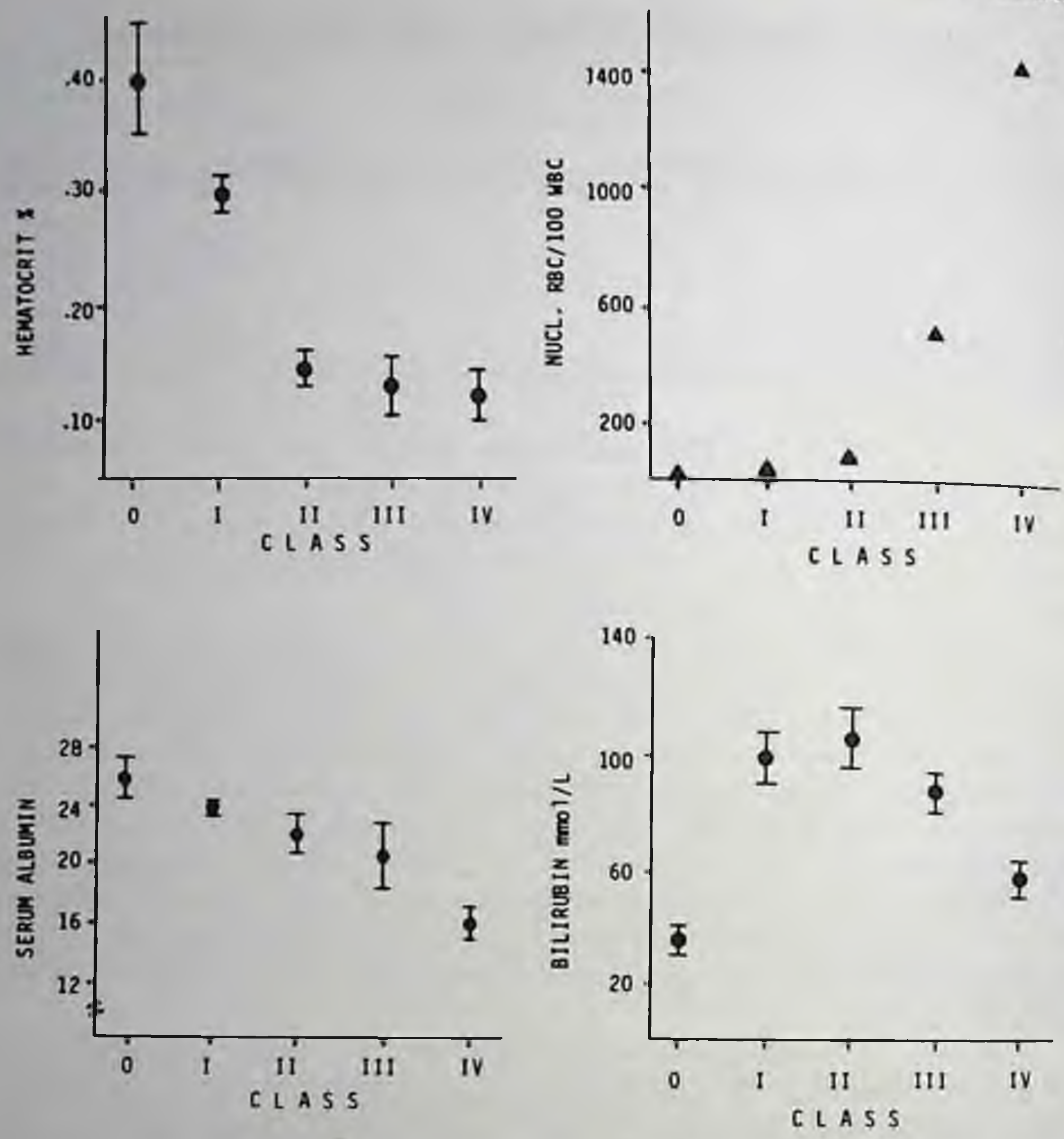

Figure 16. Data collected at first blood sampling in 51 fetuses assessed for severe alloimmune disease. Fetuses were assigned ultrasound class at the time of the blood sampling procedure. Hematocrit reflects advancing disease severity, with significant decline below normal *(upper left)*. The gestational age relationships of these data are illustrated in Figure 20. With advancing class of disease, the presence of nucleated red cells increases dramatically *(upper right)*. In class 4 disease, not only are nucleated red cells the predominant red cell type, most of these are erythroblasts. In earlier stages of disease, macrocytic normoblasts predominate. Serum albumin declines almost linearly as class advances, reflecting severe hepatic impairment *(lower left)*. Fetal serum bilirubin, however, illustrates a paradoxical relationship with advancing class. As disease severity progresses, fetal bilirubin returns toward normal, reflecting the extremely reduced red cell population available for hemolysis *(lower right)*.

smears in class 2 fetuses show significant numbers of nucleated red blood cells, but these are mainly normoblasts compared to the erythroblasts seen in more severe disease. These data correlate with the physical impression of initial phases of decompensation.

Class 3. Disease is at its most severe, in terms of appearance. Massive ascites, gross scalp edema, skin edema (particularly prominent in the face and extremities), and massive placental distortion are features of the ultrasound presentation. Hemoglobin concentrations ranged from 22 gm

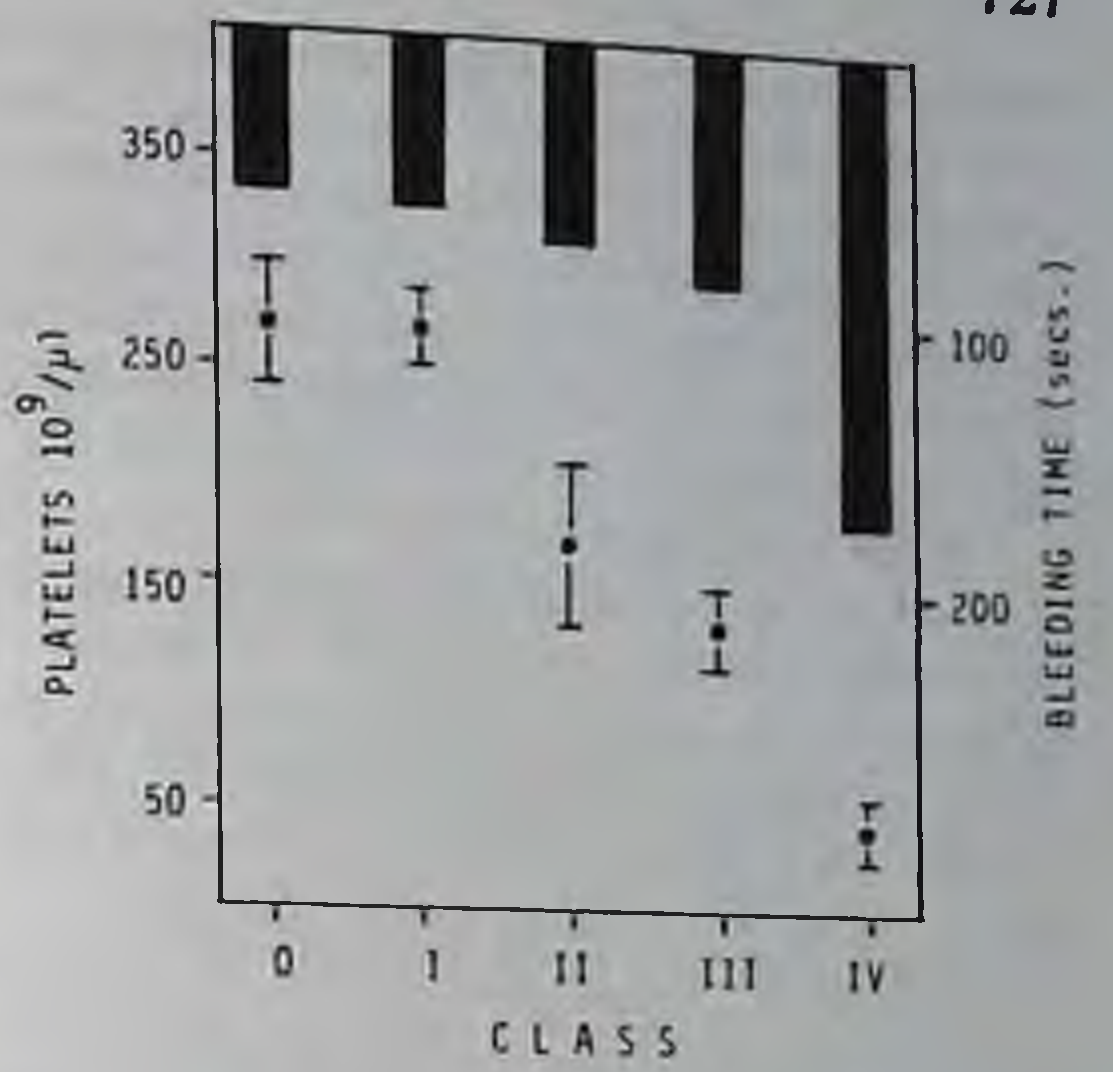

Figure 17. Platelet counts *(circles with standard deviation bars)* and postcordocentesis bleeding time *(solid bars)* displayed according to ultrasound disease class. Classes 2 and 3 demonstrated significant thrombocytopenia compared to classes 0 and 1, but without significant prolongation of bleeding time. In class 4 disease, thrombocytopenia was significant, and profound in three fetuses who had prolonged bleeding time. Two fetuses with class 4 disease required serial platelet transfusion, in addition to their packed red blood cell transfusions.[36]

per liter at 20 weeks' gestation to 55 gm per liter at 30 weeks' gestation. Despite the profound enemia, these fetuses all had normal pH and blood gases, which correlated with normal fetal behavior, biophysical profile scores of 8 to 10/10. Although there is obviously a continuum between classes 2 and 3, the extent of their physical deterioration is quite clear.

Class 4. This stage of disease is not physically different from class 3 but can be differentiated very easily on the basis of fetal behavior. Class 4 fetuses—moribund hydrops fetalis—demonstrate little if any spontaneous behavior. Posture is totally lax, and movements are scarce (if any), occasionally responsive to external stimulation with listless rolling movements. We have not studied the response to vibroacoustic stimuli in such fetuses. Fetal breathing movements are absent; amniotic fluid is normal or increased in most instances; the NST is completely unreactive. Sinu-

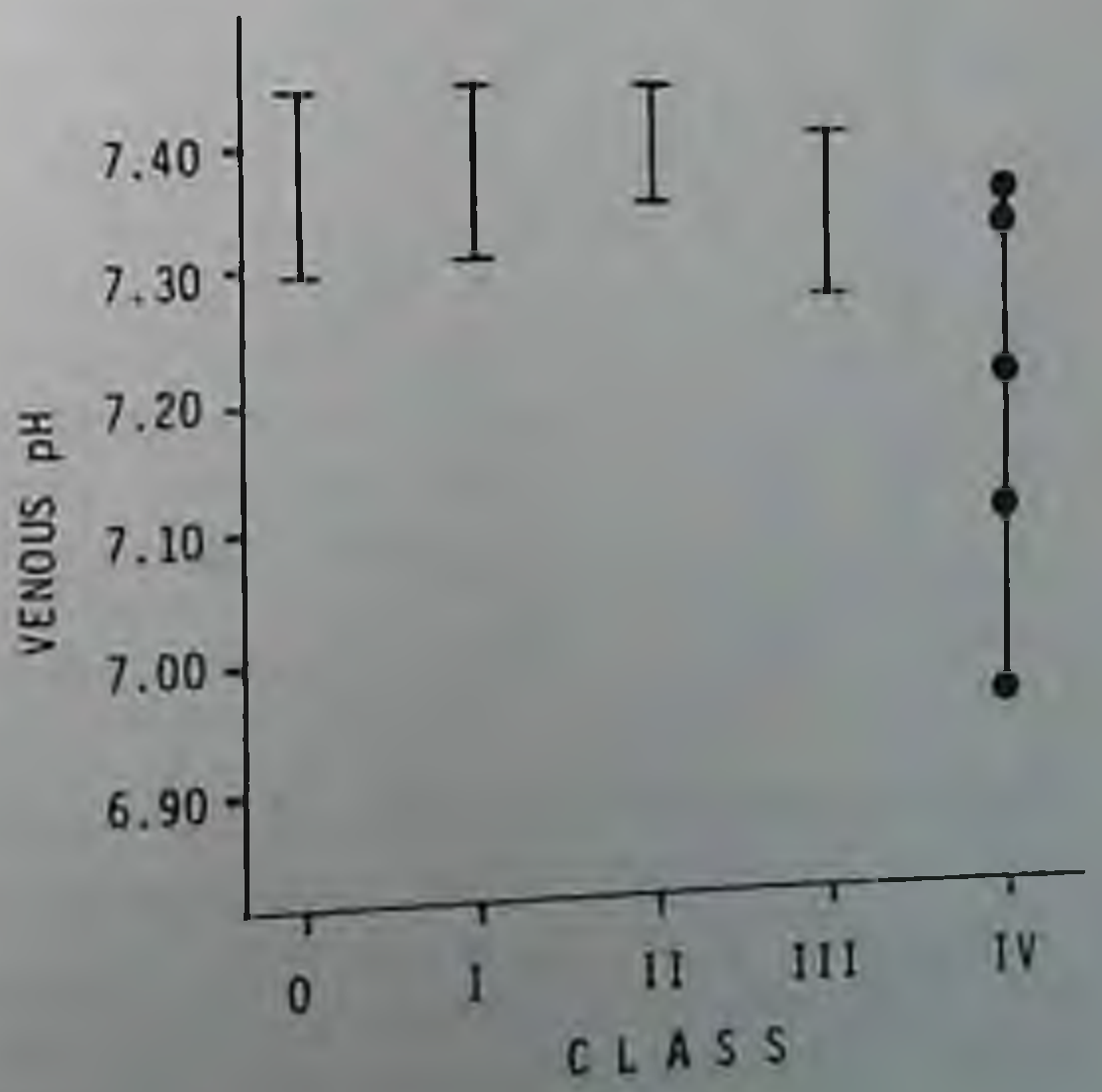

Figure 18. Venous umbilical pH at first cordocentesis in 51 fetuses with serious alloimmune disease. Bars represent ranges observed in classes 0 to 3, statistically identical. Individual data on the five fetuses in class 4 with umbilical venous pH available show substantial acidosis in three. The fetus with pH 6.95 could not be resuscitated at the time of the first procedure, whereas the fetuses with pH 7.11 and 7.23, both survived intact after serial IVT.

soidal heart rate was not seen—baseline heart rate is extremely flat, meeting the criteria of "preterminal trace." Class 4 disease is a fetal emergency. Immediate intrauterine therapy is mandatory.

This classification of physical disease correlates substantially with fetal hematologic and biochemical parameters. Figures 16 through 18 demonstrate values found in the initial blood samples of 51 fetuses managed with intravascular techniques for their apparent disease.

Figure 16 demonstrates the drop in hematocrit, conversion to nucleated red cell precursors, and faltering liver function (albumin production) seen with advancing class of disease. Only in Class 4 was bleeding time after the cordocentesis prolonged; all classes demonstrated a progressive trend to thrombocytopenia (Fig. 17). In Figure 18, umbilical venous pH is documented, showing the individuals in class 4 who were at the acidotic extreme of their disease.

It is clear that disease class if not a foolproof predictor of fetal hemoglobin concentration. At the same time, it is obvious that deteriorating severity of physical signs of disease correlates with hematological and biochemical indices. The converse is that fetal hemoglobin does not necessarily predict ultimate severity of disease. Fetuses with equal circulating hemoglobin concentrations can have very different degrees of disease severity (Fig. 19).

Reference to this scatter plot illustrates several instances in which fetuses with the same hemoglobin had markedly different parameters of disease. Fetuses, some with more severe physical manifestations, but higher hemoglobin, require more transfusions; some did not fully reverse their hydrops, even at birth, and had substantial difficulties in the neonatal nursery. Several fetuses with profound anemia, but modest

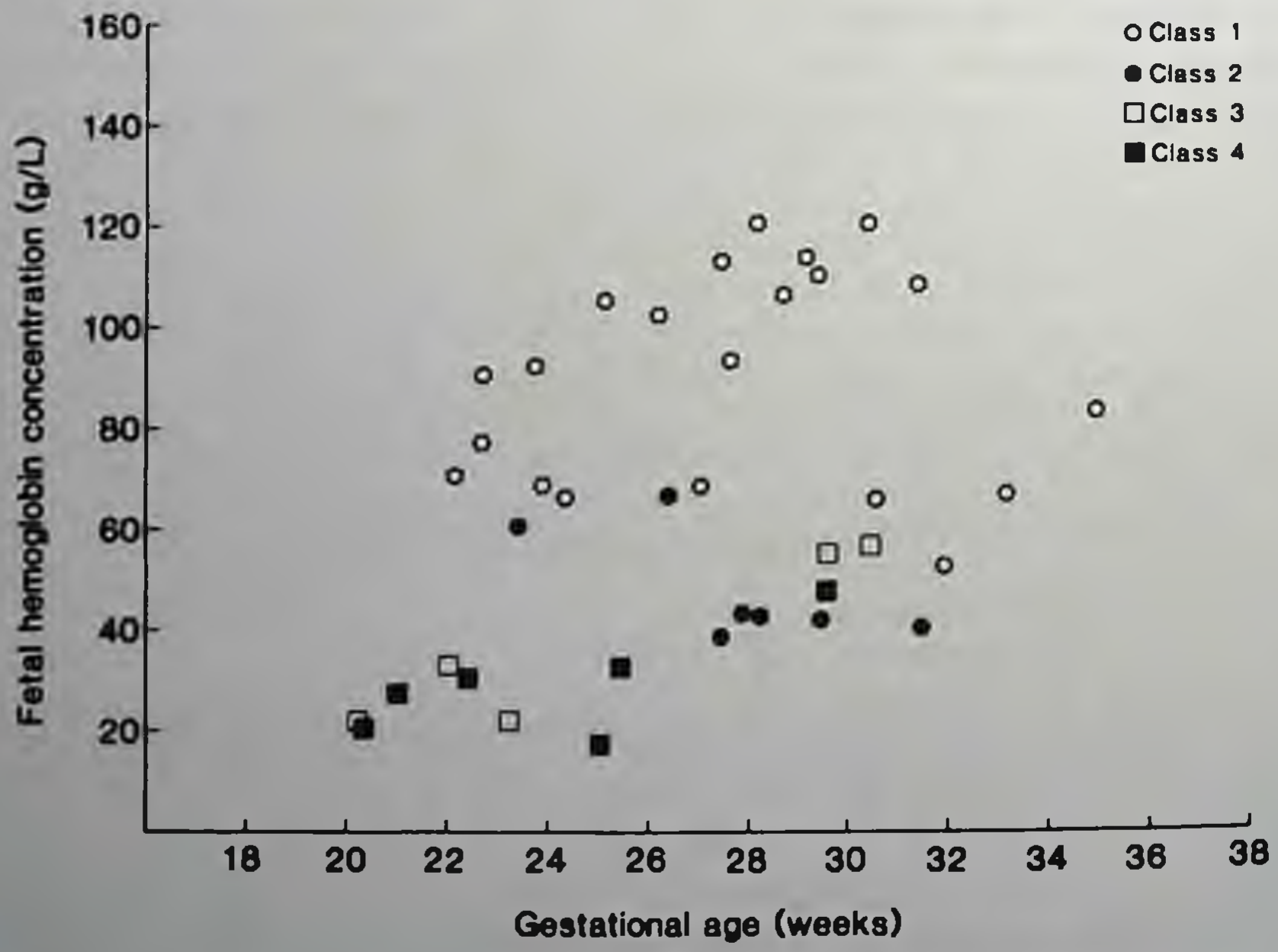

Figure 19. Scatter plot of venous hemoglobin measurements at first vascular access in 51 fetuses investigated for alloimmune disease. Note considerable overlap among class 2, 3, and 4 fetuses, despite significant differences in their levels of compromise.

disease by physical examination, rapidly reversed and were complication free, mature neonates.

This is but one illustration of fetuses with similar degrees of anemia, and markedly different degrees of compromise. This contrast illustrates the importance of recruiting all the available data to formulate a sound management plan and assign a rational prognosis.

FETAL DEATH

The exact cause of fetal death in the severest forms of alloimmune disease is not certain. Many theories have been proposed, unsubstantiated by fetal hematologic and other parameters, and now increasingly demonstrated to be erroneous. For example, the concept that the fetus is in congestive heart failure at the time of death has not been substantiated. As noted in the foregoing discussion, the complex hemodynamic influences in severe disease include increased placental resistance, structural changes secondary to venous obstruction in the liver, and the high output demands of severe anemia. Nevertheless, overt cardiac failure, with chamber dilatation, valvular regurgitation, and aberrant myocardial contractility, have not been observed frequently. Even in moribund fetuses, with profound acidosis, near death, the mechanisms have been those of hypoxemia, acidosis, and abnormal placental respiratory function. The extent to which metabolic acidosis generated by liver failure contributes to this demise is variable.

Many of these observations are based on anecdotal information, with experience only gradually accumulating. In general, the success of IVT in even the sickest fetuses means that terminal data is collected only rarely. For discussion purposes, the data of one such fetus is reviewed.

On first medical attention, at 25 weeks' gestation, the fetus was found to have severe hydropic disease. Immediately referred to our center, the fetus was attended at once. Because of the moribund condition of the fetus (BPS 2/10), transfusion was begun as soon as adequately cross-matched blood could be obtained (< 90 minutes), and the team was assembled. Vascular access to the posterior cord insertion was attained on the first attempt with a 22-gauge needle. The initial venous sample demonstrated an umbilical venous pH of 6.95, a hemoglobin concentration of 17 gm per liter, consisting almost entirely of erythroblasts. Po_2 was 33, Pco_2 was 97, Hco_3 was 15.4, base deficit was 11.0. Oxygen saturation was < 60 per cent. Despite a "successful" intravenous infusion of 30 ml of donor blood (285 gm per liter), the fetus did not respond. Intracardiac adrenalin did not reverse the progressive bradycardia. Fetal heart rate had been 90 bpm at the onset of the procedure, decelerative from that baseline. As the infusion was begun, fetal heart rate rose from 70 to 110, a rate which was maintained for approximately 10 minutes. Following intracardiac adrenalin, the heart rate rose to over 100 bpm for a short period of time. The fetus died shortly thereafter.

Fetal cardiac output at this time was very low: the transfusion mass could be visualized moving very sluggishly along the course of the vein. In this situation, each cardiac contraction moved the more dense transfusion mass < 1 cm along the course of the vein. In a normal situation, the turbulence generated by the transfusion mass in the vein traverses the

entire length of the cord and reaches the intrahepatic portion of the umbilical vein, in two or three cardiac cycles.

This case illustrates our one example of irreversible fetal compromise in severe alloimmune disease. In all other cases, including the fetus whose pH was 7.11 at the time of initial transfusion, improvement in blood gases, pH, and dramatic improvement in fetal behavior, followed soon after the administration of the transfusion.

These data suggest that the terminal events in such fetuses are those of mixed acidosis and asphyxia. Metabolic acidosis was a significant component in this fetus, as well as the other acidotic fetuses who survived (see Fig. 19) It may be that this fetus was too close to death to illustrate adequately the mechanisms of her decompensation. On the other hand, the data available from such fetuses illustrate that they do not die of disseminated intravascular coagulation, bilirubin toxicity, congestive heart failure, or other mechanisms which have been suggested in the past.

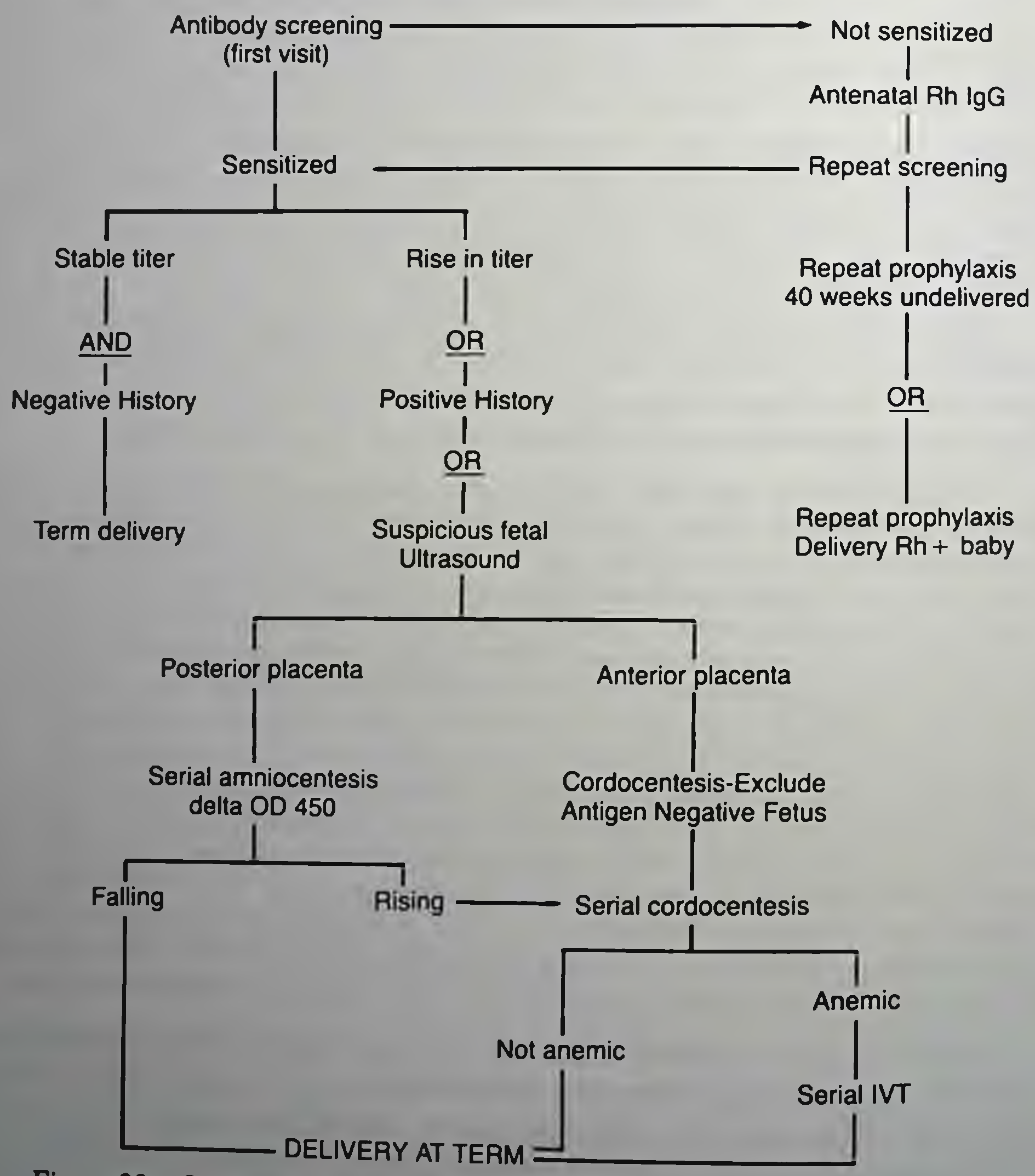

Figure 20. Surveillance of Rh-negative pregnancy.

PRACTICAL APPLICATION OF MONITORING PARAMETERS

Figure 20 is a schematic diagram of the discussion in the text. The ultimate goal of such monitoring is to initiate intrauterine therapy when appropriate, defer invasive procedures when it is safe to do so, maximizing pregnancy outcome while minimizing maternal morbidity.[29] In combination with intravascular transfusion techniques, and the evolution of direct fetal monitoring by cordocentesis, the well-practiced approaches of maternal antibody titration and amniocentesis for amniotic fluid bilirubin evaluation form a system by which fetal evaluation can be very precise. Invasive testing is always predicated on the detailed ultrasound examination of the fetus affected by alloimmune disease, and offers new and precise insight.

Through application of these surveillance techniques, and the precise timing of intrauterine therapy thus directed, successful treatment of even the most severely ill fetuses is attainable.

REFERENCES

1. Bowman JM: Suppression of Rh-isioimmunization: A review. Obstet Gynecol 52:385–393, 1978
2. Bowman JM: Controversies in Rh prophylaxis: Who needs Rh immune globulin and when should it be given? Am J Obstet Gynecol 151:289–294, 1985
3. Bowman JM, Pollock JM: Transplacental fetal hemorrhage after amniocentesis. Obstet Gynecol 66:749–754, 1985
4. Harman CR, Manning FA: Alloimmune disease. In CJ Pauerstein (ed): Clinical Obstetrics. New York, John Wiley & Sons, 1987, pp 441–469
5. Bowman JM: Maternal blood group immunization. In Creasy RK, Resnik R (eds): Maternal-Fetal Medicine: Principles and Practice, ed 2. Philadelphia, WB Saunders, 1989, pp 613–649
6. Eklund J: Intensive plasma exchange as an adjunct to management of severe Rhesus disease. Acta Obstet Gynecol Scand 64:7–10, 1985
7. Harman CR: Fetal blood sampling in Rh disease: Even a failed procedure can yield successful results. Am J Obstet Gynecol (in press)
8. Harman CR: Comprehensive examination of the human fetus. Fetal Med Rev 1(2): 1989
9. Liley AW: Liquor amnio analysis in management of pregnancy complicated by Rhesus isoimmunization. Am J Obstet Gynecol 82:1359–1370, 1961
10. Liley AW: Errors in the assessment of hemolytic disease from amniotic fluid. Am Obstet Gynecol 86:485–494, 1963
11. Pollock JM, Bowman JM, Manning FA, et al: Fetal blood sampling in Rh hemolytic disease. Vox Sang 53:139–142, 1987
12. Harman CR: Specialized applications of obstetric ultrasound: Management of the alloimmunized pregnancy. Semin Perinatol 9:184, 1985
13. Harman CR: Ultrasound in the management of the alloimmunized pregnancy. In Fleischer AC, James E, Jeantry P et al (eds): The Principles and Practice of Ultrasonography in Obstetrics and Gynecology, ed 4. Connecticut, Appleton–Lange, 1989
14. Vintzileos AM, Campbell WA, Storlazzi E, et al: Fetal liver ultrasound measurements in isoimmunized pregnancies. Obstet Gynecol 68:162–167, 1986
15. Chitkara U, Wilkins I, Lynch L, et al: The role of sonography in assessing severity of fetal anemia in Rh- and Kell-isoimmunized pregnancies. Obstet Gynecol 71:393–398, 1988
16. Benacerraf BR, Frigoletto FD: Sonographic sign for the detection of early fetal ascites in the management of severe isoimmune disease without intrauterine transfusion. Am J Obstet Gynecol 152:1039–1041, 1985

17. DeVore GR, Donnerstein RI, Kleinman CS, et al: Fetal echocardiography: II. The diagnosis and significance of a pericardial effusion in the fetus using real-time–directed M-mode ultrasound. Am J Obstet Gynecol 144:693–701, 1982
18. DeVore GR: The prenatal diagnosis of congenital heart disease—a practical approach for the fetal sonographer. J Clin Ultrasound 13:229–245, 1985
19. Rightmire DA, Nicolaides KH, Rodeck CH, et al: Fetal blood velocities in Rh isoimmunization: Relationship to gestational age and to fetal hematocrit. Obstet Gynecol 68:233–236, 1986
20. Harman CR: Doppler velocity waveform analysis before and after intravascular fetal transfusion. Proc Soc Obstet Gynecol Canada, Quebec City, 1989
21. Nicolaides KH, Fontanarosa M, Gabbe SG, et al: Failure of ultrasonographic parameters to predict the severity of fetal anemia in rhesus isoimmunization. Am J Obstet Gynecol 158:920, 1988
22. Harman CR, Bowman JM, Menticoglou SM, et al: Ultrasound classification of fetal alloimmune disease: Correlation with fetal hematology. Abstr No. 19. Proc Soc Perinat Obstet, New Orleans, February 1989
23. Nicolaides KH, Rodeck CH, Mibashan RS, et al: Have Liley charts outlived their usefulness? Am J Obstet Gynecol 155:90, 1986
24. Frigoletto FD, Greene MF, Benacerraf BR, et al: Ultrasonographic fetal surveillance in the management of the isoimmunized pregnancy. N Engl J Med 430:432, 1986
25. Nicolaides KH, Soothill PW, Clewell WH: Fetal haemoglobin measurement in the assessment of red cell isoimmunisation. Lancet (May 14)i:1073–1075, 1988
26. Daffos F, Capella-Pavlovsky M, Forestier F: Fetal blood sampling during pregnancy with use of a needle guided by ultrasound: A study of 606 consecutive cases. Am J Obstet Gynecol 153:655–660, 1985
27. MacKenzie IZ, Bowell PJ, Castle BM, et al: Serial fetal blood sampling for the management of pregnancies complicated by severe rhesus (D) isoimmunization. Br J Obstet Gynaecol 95:753–758, 1988
28. Harman CR, Manning FA, Bowman JM, et al: Severe Rh disease—poor outcome is not inevitable. Am J Obstet Gynecol 145:823–829, 1983
29. Harman CR, Bowman JM, Menticoglou SM, et al: Severe alloimmune disease managed with intravascular fetal transfusion: outcome analysis. Proc Soc Perinat Obstet, New Orleans February 1989, Abstr No. 189
30. Kleihauer E, Braun H, Betke K: Demonstration von fetalem hamoglobin in den erythrocytes eines blutausstrichs. Klin Wochenschr 33:637–638, 1957
31. Harman CR, Bowman JM, Manning FA, et al: intravascular fetal transfusion—integration into a successful Rh program. Proc Soc Obstet Gynecol Canada, Vancouver, B.C., June 1988
32. Forestier F, Cox WL, Daffos F, et al: The assessment of fetal blood samples. Am J Obstet Gynecol 158:1184–1188, 1987
33. Egerman R, Richards DS, Dugue RE: Evaluation of a rapid technique for detecting amniotic fluid contamination of fetal cord blood specimens. Proc Soc Perinat Obstet, New Orleans, February 1989, Abstr No. 185
34. Nicolaides KH, Thilaganathan B, Rodeck CH, et al: Erythroblastosis and reticulocytosis in anemic fetuses. Am J Obstet Gynecol 159:1063–1065, 1988
35. Nocolaides KH, Rodeck CH, Miller DS, et al: Fetal haematology in rhesus isoimmunisation. Br Med J 290:661–663, 1985
36. Harman CR, Bowman JM, Menticoglou SM, et al: Profound fetal thrombocytopenia in Rhesus disease: Serious hazard at intravascular transfusion. Lancet ii:741–742, 1988
37. Nicolaides KH, Warenski JC, Rodeck CH: The relationship of fetal plasma protein concentration and hemoglobin level to the development of hydrops in rhesus isoimmunization. Am J Obstet Gynecol 152:341–344, 1985
38. Harman CR, Bowman JM, Manning FA, et al: Moribund alloimmune hydrops—intravascular fetal transfusion is the only hope. Proc Soc Obstet Gynecol Canada, Vancouver, B.C., June 1988
39. Harman CR, Manning FA, Bowman JM, et al: Use of intravascular transfusion to treat hydrops fetalis in a moribund fetus. CMAJ 138:827–830, 1988
40. Reece EA, Gabrielli S, Abdalla M, et al: Reassessment of the utility of fetal umbilical vein diameter in the management of isoimmunization. Am J Obstet Gynecol 159:937–938, 1988

41. Westgren M, Selbing A, Stangenberg M: Fetal intracardiac transfusions in patients with severe rhesus isoimmunization. Br Med J 296:885–886, 1988
42. Trudinger BJ, Giles WB, Cook CM, et al: Fetal umbilical artery flow velocity waveforms and placental resistance: Clinical significance. Br J Obstet Gynecol 92:23–30, 1985
43. Erskine RLA, Ritchie JWK: Umbilical artery blood flow characteristics in normal and growth retarded fetuses. Br J Obstet Gynaecol 92:605, 1985
44. Trudinger B: Doppler ultrasound assessment of blood flow. In RK Creasy, Resnik R (eds): Maternal-Fetal Medicine: Principles and Practice, ed 2. Philadelphia, WB Saunders, 1989, pp 254–267
45. Copel JA, Grannum PA, Belanger K, et al: Pulsed Doppler flow-velocity waveforms before and after intrauterine intravascular transfusion for severe erythroblastosis fetalis. Am J Obstet Gynecol 158:768–774, 1988
46. Fairlie F, Lang GD, Lowe G, et al: Blood viscosity and umbilical artery flow velocity waveform pulsatility index. Abstr No. 286. Proc Soc Perinat Obstet, New Orleans, February 1989
47. Stiller RJ, Ashmead GG, Paul D, et al: Fetal blood flow measurements in severe rhesus isoimmunization: A case report. J Reprod Med 32:453–455, 1987
48. Mari G, Moise KJ, Kirshon B, et al: Doppler assessment of the cerebral and femoral blood flow in the anemic fetus before and after intravascular transfusion. Abstr No. 280. Proc Soc Perinat Obstet, New Orleans, February 1989
49. Manning FA, Menticoglou S, Harman CR, et al: Antepartum fetal risk assessment: The role of the fetal biophysical profile score. Bailliere's Clin Obstet Gynecol 1:55–72, 1987
50. Manning FA, Morrison IR, Harman CR, et al: The fetal biophysical profile score: Functional practical aspects. Contemp Issues Obstet Gynecol 3:83–92, 1988

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Fetal Behavior in Preterm Premature Rupture of the Membranes

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> Although transabdominal puncture of the uterus has been carried out often for therapeutic and experimental reasons without accidents, . . . its practical value is probably limited in the human . . . it might become of great significance in veterinary practice.
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> FUCHS F, RIIS P: ANTENATAL SEX DETERMINATION. NATURE 177:330, 1956

Premature rupture of the membranes (PROM) is a common obstetric complication, occurring in 10 per cent of all gestations,[1-3] and accounting for more than one third of preterm deliveries. Furthermore, 20 per cent of all instances of PROM occur before 37 weeks' gestation, and such preterm PROM precedes 1 to 3 per cent of all deliveries.[4-6]

Although the subject has been the focus of a large body of obstetric literature, PROM and its pathogenesis, management, and incidence of sequelae remain confused and controversial. The origins of this disquieting state of affairs can be traced to the lack of a specific, narrow definition of the condition, and resultant variations both in gestational age and maternal epidemiology in the populations assessed. *PROM* has been broadly defined as rupture of the membranes prior to the onset of uterine contractions.[1]

Amniocentesis, viewed not so long ago as an exotic technique best

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suited to veterinary medicine, has had an impact on many aspects of pregnancy complications. The technique has proved particularly useful in the assessment of preterm PROM and in the prediction and detection of the presence of infection.[5,6]

Although the invasive technique of amniocentesis provides important information regarding the presence of infection, a noninvasive technique that could be easily performed as needed would be preferable. This article discusses recent evidence for an infectious etiology for PROM and methods for the assessment and management of this complex obstetric challenge, and it also presents new data that call into question traditional maternal-centered surveillance schemes for the management of PROM and suggests that, indeed, the fetus itself may be the best barometer of the optimal time of delivery.

PATHOGENESIS

A wide variety of factors have been suggested to cause PROM. Mechanical stress from polyhydramnios, multiple gestations, or exposure to a dilated cervix in cases of incompetent cervix may account for rare cases.[7–9] In addition, qualitative alterations in membrane collagen may explain the increased incidence of PROM in some gestations.[10–12] However, pregnancies complicated by maternal or fetal Marfan's syndrome are not at increased risk for PROM.[13] Conversely, smoking appears to increase the risk of PROM, particularly near term, by as yet unexplained mechanisms.[14] There also appears to be a temporal association between recent coitus and PROM, as well as chorioamnionitis.[15–17]

The hypothesis that chorioamniotic-decidual infection may be a cause and not simply a consequence of PROM has now gained significant experimental support. Naeye and Peters demonstrated that amniotic fluid infections were two- to threefold more common when membranes ruptured just prior to rather than just after the onset of labor.[6] A number of potential vaginal pathogens have been found in greater frequency in women destined to develop PROM.[18] Patients colonized with *Trichomonas vaginalis*, group B beta-streptococcus, and Bacteroides sp. are at particularly high risk for preterm PROM.[19–22] Moreover, an analysis of cord blood immunoglobulin levels suggests that fetal infections precede rather than follow PROM.[23]

A variety of vaginal–cervical microorganisms isolated from patients with preterm PROM have been demonstrated to produce proteases capable of compromising membrane integrity[24,25] and reducing membrane burst pressures.[26] In addition, in these cases vaginal flora include multiple organisms containing phospholipase A-2,[27,28] an enzyme associated with a significant reduction in membrane bursting pressures, secondary to the production of lysolecithin from phosphatidylcholine.[26]

The recruitment of leukocytes to the membranes following bacterial infiltration also results in direct membrane damage. Further, chorioamniotic-decidual bacteria may initiate in situ macrophage peroxidase action, thereby compromising membrane integrity. Moreover, neutrophil-derived trypsin and elastases may reduce the collagen and elastin content

of membranes, resulting in the thinning and loss of compliance noted in PROM membranes.[8,10,11] These leukocytic products may be responsible for the decrease in alpha-1-antitrypsin activity observed in PROM.[29,30]

Endotoxin, a direct bacterial product, as well as the products of bacterial-leukocyte interaction (interleukin-1), and tumor necrosis factor (TNF) are substances that have been demonstrated as eliciting significant elevations in amniocyte monolayer prostaglandin production. Elevated levels of these substances have been found in the amniotic fluid of PROM patients, with especially notable increases in preterm PROM patients.[31,32] Thus, it appears that bacterial infection and the maternal immune response can cause rupture of the membranes and subsequent preterm labor.[33]

Daikoku et al. have noted a higher incidence of postpartum endometritis among women delivering after preterm PROM compared to term deliveries.[34] This suggests that bacterial invasion of the products of conception and maternal decidua may represent an explanation for the mechanism of both PROM and preterm labor. The specific organisms associated with PROM appear similar to those causing postpartum endomyometritis.[34]

Clinical Aspects of PROM

The gestational age at which PROM occurs determines the clinical significance of the problem. At term, PROM is followed by the onset of labor within 24 hours in 80 per cent of patients,[35] and more than 90 per cent of patients will enter labor within 48 hours.[36] There is evidence that after PROM at term, perinatal mortality and morbidity rise significantly when the onset of labor occurs after 24 hours. Such findings may, however, vary with the population under evaluation, as race and socioeconomic status are associated with the risk of chorioamnionitis.[37] Kappy noted no increase in neonatal morbidity in a predominantly clinic population when delivery was delayed until the spontaneous onset of labor after PROM at term.[38] One explanation for these population variables could be the prevalence of high versus low virulence organisms associated with or causing the PROM.[39] Current management of PROM at term generally includes confirming maternal and fetal well-being, with induction of labor following a set latency period.

Preterm PROM, rupture occurring at less than 37 weeks' gestation, presents a clinical dilemma because the dangers of premature delivery (respiratory distress syndrome, bronchopulmonary dysplasia, intraventricular hemorrhage, retinopathy of prematurity, cerebral palsy, etc.) must be weighed against the risk of chorioamnionitis and fetal/neonatal sepsis.

In contrast to PROM at term, the interval from rupture to labor appears to be longer in preterm PROM. In one recent study of preterm PROM occurring prior to 28 weeks' gestation, it was found that 50 per cent of the patients delivered within 1 week of rupture, while 71 per cent of the women delivered within 2 weeks following rupture of the membranes.[40] Daikoku noted latency periods greater than 24 hours were increasingly common as the length of gestation decreased in patients with preterm PROM.[41] Kappy has reported latency periods greater than

24 hours in 57 per cent of patients, and in 19 per cent the interval between rupture and labor extended beyond 7 days.[42]

In the past, the incidence of infection and perinatal mortality was seen to rise with extension of the latent period.[43,44] In contrast, Schutte found no correlation between the incidence of infection and the length of the latent period,[45] a finding confirmed by others.[46-50] Although patients with preterm PROM do not demonstrate a precise correlation between the length of the latency period and the incidence of infection,[36] it is possible that shorter gestations are associated with both an increased latency phase and incidence of infectious sequelae, thus confounding the data.[39,44] The incidence of infectious sequelae in preterm PROM may also vary with the population group under study. Kappy noted a 31 per cent incidence of clinical chorioamnionitis following preterm PROM (compared to 13 per cent in a group at term), but observed no significant fetal–neonatal infectious morbidity.[42]

Complications of prematurity and not sepsis represent the primary cause of perinatal morbidity and mortality in preterm PROM.[1,39,51,52] There is conflicting evidence regarding whether PROM itself, or the use of steroids in this setting, reduces the risk of respiratory distress syndrome.[53] Berkowitz noted that while sepsis did not represent a major threat to the fetus, in those greater than 31 weeks' gestation the incidence of respiratory distress syndrome was diminished if PROM was present for greater than 16 hours.[54] Thus the management challenge is determining the length of time to allow for the prolongation of pregnancy without substantially increasing the risk of maternal or fetal sepsis. With this goal in mind it is necessary to establish the optimal surveillance method for timing delivery in the preterm PROM setting.

SURVEILLANCE IN PRETERM PROM

Maternal Surveillance

Yale–New Haven Hospital provides traditional care for the patient with suspected PROM. First the diagnosis is established using the following criteria: 1) typical history of a sudden flow of fluid from the vagina, 2) physical examination of inappropriate fundal height for gestational age and by observing a moist perineum, 3) speculum examination of the vagina observing a pool in the posterior fornix, 4) alkaline vaginal pH by nitrazine paper, and 5) a characteristic crystallization pattern of air-dried fluid ("fern test"). Manual pelvic examinations are not performed. Patients are evaluated for gestational age (confirmed by first or early second-trimester ultrasound), absence of uterine contractions, and absence of any concurrent maternal complications of pregnancy. Routine vital signs are obtained at admission, and the patient is evaluated for the classic characteristics of chorioamnionitis. These include maternal temperature $>37°C$, maternal tachycardia, leukocytosis, uterine tenderness, or foul-smelling vaginal discharge.[36]

Recently, a prospective and longitudinal study of preterm PROM patients was undertaken at Yale–New Haven Hospital.[55] Forty-five women admitted with PROM in gestations of less than 33 weeks' dura-

tion were evaluated daily until labor. Amniocentesis was performed under direct sonographic visualization on admission, and a fetal behavioral profile was obtained on admission and repeated daily. In all, 372 fetal profiles were performed. The amniotic fluid was assessed by Gram's stain and culture, lecithin/sphingomyelin ratio and phosphatidyl glycerol. Maternal white cell counts were performed daily. Amniocentesis was repeated in those patients suspected of being at high risk for chorioamnionitis. In all, 86 amniocenteses were performed in 45 patients in the study. (Three patients were excluded from the "last amniocentesis prior to delivery" group, as they were transferred to another hospital prior to delivery. One sample was lost in transport.) There were 20 positive amniotic fluid cultures of the 41 patients who had amniocentesis prior to delivery at Yale. Amniocentesis was performed successfully in 96.6 per cent of attempts. In some of the data to be presented here, specifically the "all amniocenteses" group, there are 27 positive cultures. In six patients there were two consecutive positive cultures within a brief period; in each the second amniocentesis was performed before the positive culture returned from the laboratory, and each was delivered after the second amniocentesis.

A fetal biophysical profile, including breathing movements (FBM), body movements (BM), and limb movements, was performed after breakfast each day. Additionally, amniotic fluid volume and the results of nonstress tests were assessed daily. Each examination was recorded on videotape. The videotape was reviewed on the same day, using a stopwatch to count the number and the duration of FBM and BM.

As shown in Table 1, there were no significant differences found in the mean maternal age, parity, gestational age on admission, birthweight, or Apgar scores at 1 and 5 minutes between the two groups. However, there was a significant difference in the gestational age at delivery between the infected and the noninfected groups of amniotic fluid cultures.

Table 1. *Patients Undergoing Biophysical Profiles and Amniocentesis: Comparison According to Amniotic Fluid Culture Results*

	AMNIOTIC FLUID CULTURE RESULTS		
	Negative	*Positive*	*P Value‡*
Gestational age (wks)	26.1 (5.8)	25.3 (4.7)	<0.582*
Parity			<0.772*
Nullipara	16.1%	83.3%	
Multipara	72.5%	27.5%	
Gestational age at admission (wks)	29.6 (2.8)	29.6 (2.9)	<0.471*
Gestational age at delivery (wks)	32.0 (2.1)	29.7 (2.9)	<0.03†
Birthweight (g)	1880 (506)	1464 (575)	<0.140*
Apgar 1 min	6.8 (2.3)	5.6 (2.8)	<0.062*
Apgar 5 min	7.6 (1.9)	6.2 (1.6)	<0.053*

* Not significant.
† Significant.
‡ Analysis of covariance based on pooled ranks, adjusted for gestational age.

Table 2. *Maternal Clinical Signs of Chorioamnionitis in the Infected and Uninfected Groups of Amniotic Fluid Cultures*

	AMNIOTIC FLUID CULTURE RESULTS				
	Negative		*Positive*		
MATERNAL SIGNS	*Mean*	*SD*	*Mean*	*SD*	*P Value*
Temperature	98.7	1.1	98.9	0.8	NS
Pulse	93.4	12.3	101.7	11.5	<0.004
WBC	10.6	3.2	12.8	5.5	<0.02
Bands	4.7	5.1	8.5	7.6	<0.009
Segmented (%)	70.2	9.4	70.4	9.2	NS
Bands/segmented ratio	7%	8%	12%	11%	<0.02

NS, not significant.

Elevated maternal temperature has been considered one of the classic diagnostic signs of chorioamnionitis in cases of PROM.[1] However, the present study revealed no difference in maternal temperature between the infected and noninfected groups, as seen in Table 2. Also shown in Table 2 are the differences that were observed in the maternal pulse, white blood cells, per cent bands, and bands-to-segments ratio between the mothers with infected and uninfected amniotic fluid.

Uterine tenderness has been considered another clinical sign of chorioamnionitis in patients with PROM. Table 3 shows that this sign was confirmed in the present study.

Fetal Surveillance: Amniocentesis

To focus directly on the fetus, a number of investigators more recently have employed amniocentesis in the clinical evaluation of preterm PROM.[56-65] This approach facilitates differentiation between fetuses who could safely remain *in utero* and those at risk for infection, who would benefit from expeditious delivery. The benefit of amniocentesis should lie in its ability to detect occult or incipient chorioamnionitis,[56] and at the same time to provide information about fetal lung maturity.

For the fluid to be of value, it must be obtained by an aseptic technique and via a transabdominal approach. We first identify a pocket of amniotic fluid for needle insertion. The ultrasound transducer is placed inside a sterile glove, and the window of fluid is rechecked. The needle is inserted and advanced while the tip echo is monitored constantly. Once in place, the amniotic fluid is obtained.[66] Based on the preference of the

Table 3. *Uterine Tenderness Compared to Amniotic Fluid (AF) Culture Results*

	UTERINE TENDERNESS	NO UTERINE TENDERNESS
Positive AF culture	28	0
Negative AF culture	2	56

$P < 0.0001$ (Fisher's exact test).

Sensitivity = 100%, positive predictive value = 93.3%, specificity = 96.5%, negative predictive value = 100%, false-positive rate = 6.7%.

Table 4. *Relationship between White Blood Cells in Amniotic Fluid and Culture Results*

WBC IN AMNIOTIC FLUID	NEGATIVE CULTURES (%)	POSITIVE CULTURES (%)
Absent	84.0	16.0
Few	75.0	25.0
Moderate	22.2	77.8
Many	0.0	100.0

operator, either linear or sector transducers may be used. If a sector transducer is used, the needle is inserted from the end, rather than the side.

It has been reported that amniocenteses can be performed successfully on 45 to 70 per cent of PROM patients.[56–58,62–64] Newer data from our institution show a success rate of 96 per cent.[55] Gram stains of amniotic fluid have a sensitivity of 60 per cent in predicting infectious sequelae including chorioamnionitis, or neonatal sepsis, a positive amniotic fluid culture has an 83 per cent sensitivity.[57] Obviously, waiting for culture results may take several days. The combination of two rapid tests, such as the Gram stain together with the Limulus test for endotoxin, can increase the sensitivity to 95 per cent, when positive amniotic fluid cultures are taken as the endpoint.[31,65,67,68]

The presence of a large number of neutrophils suggests a positive amniotic fluid culture. The greater the number of the neutrophils, the higher the incidence of false-negative Gram stain results.[57] In the Yale data, increased numbers of white blood cells also were associated with positive cultures (Table 4).

In contrast to the situation at term, most perinatal deaths in cases of preterm PROM are attributable to hyaline membrane disease and not to infection.[69] If the fetal lungs are immature, the risks of expectant management are relatively less. As established by Gluck, analysis of amniotic fluid phospholipids is an accepted method of evaluation of pulmonary maturity.[70] Cotton has suggested that amniocentesis may be useful in identifying the preterm neonate at reduced risk for respiratory complication: in 69 per cent of cases knowledge regarding pulmonary maturity permitted elective early delivery.[59] Garite reported 50 per cent of patients with preterm PROM underwent successful amniocenteses productive of mature lecithin/sphingomyelin ratios, and the infants were delivered on this basis alone.[56]

The potential danger of amniocentesis lies in either causing delivery or fetal damage. Yeast failed to find any evidence that the amniocentesis itself might induce labor; on the contrary, no maternal or neonatal morbidity could be attributed to amniocentesis.[63]

Fetal Surveillance: Sonographic Assessment

In yet a further step beyond maternal-centered PROM surveillance techniques, and toward a noninvasive fetal-based methodology, several observers have found that the use of a fetal behavioral profile may pro-

vide a sensitive and specific predictor of impending chorioamnionitis.[55,71] It is possible that elevations in interleukin-1 levels in amniotic fluid are responsible for a decrease in fetal electrocortical activity, resulting in decreased fetal breathing and body movements as is observed in fetuses whose mothers subsequently develop chorioamnionitis.

The first steps when performing the ultrasound are to assess dates and size, rule out fetal anomalies, and determine the amount of the amniotic fluid. It may be useful to combine standard fetal biometry (biparietal diameter, femur length, humeral length, head and abdominal circumferences, estimated fetal weight, and transverse cerebellar diameter) with nonbiometric measures of gestational age, including distal femoral, proximal tibial, and proximal humeral epiphyseal ossification centers,[72] and intestinal and placental grades. Real-time scanning for a 30-minute period of observation is suggested for the purpose of the fetal behavioral assessment.

FETAL BIOPHYSICAL PROFILE PARAMETERS IN PROM

Based on the original premise of the "Biophysical Profile,"[75] that the observed behavior of the fetus by ultrasound and fetal heart rate testing could be useful in examining fetal condition, several investigators have evaluated fetuses with PROM using this test. The results of the groups described earlier will be presented for each of the components of the biophysical profile, following which our results will be compared to those found in the literature.

Fetal Heart Rate

Fetal tachycardia (> 160 beats per minute), has been considered one sign of chorioamnionitis.[36] Because major elevations in the baseline fetal heart rate might have prevented the detection of reactivity in the infected fetuses,[76] we first compared baseline fetal heart rates in the infected and uninfected amniotic fluid groups, as shown in Table 5. Although the mean fetal heart rates in the negative and the positive groups differed statistically, the baseline fetal heart rate was in the normal range in both groups.

As Tables 6 and 7 clearly indicate, the nonstress test is highly sensitive to the presence of infection, with moderate specificity. This is similar to the findings of Vintzileos, who reported the sensitivity and the specificity of the nonstress test in predicting infection in patients with PROM

Table 5. *Relationship between Baseline Fetal Heart Rate in Infected and Uninfected Fetuses*

AMNIOTIC FLUID CULTURES				
Negative		*Positive*		
Mean	*SD*	*Mean*	*SD*	*P*
146.6	8.1	152.3	7.6	<0.001

Table 6. *Relationship between Reactive and Nonreactive Nonstress Tests and Amniotic Fluid Cultures (All Amniocenteses)*

	NONREACTIVE NONSTRESS TEST	REACTIVE NONSTRESS TEST
Positive amniotic fluid cultures	23	3
Negative amniotic fluid cultures	15	45

Chi squared = 27.1, $P < 0.001$.
Sensitivity = 88.5%, positive predictive value = 60.5%, specificity = 75%, negative predictive value = 93.8%, false-positive rate = 39.5%.

to be 78.1 and 86.3 per cent, respectively.[75] As with the diagnosis of fetal distress, the NST in this situation is quite reliable when it is normal, and is quite sensitive, but has a high false-positive result rate. Thus, expectant management is safe in the presence of a normal NST, but delivery when the NST is nonreactive alone is likely to cause an unacceptable number of iatrogenic premature births. Considering that the population we are observing is by definition premature, and the likelihood of a nonreactive NST in a healthy fetus is higher at earlier gestations, the problems raised by the use of the NST alone are clear.

The decrease in amniotic fluid volume may itself further complicate interpretation of the NST. This may produce compression of the umbilical cord, and significant variable decelerations, which may lead to the development of fetal distress severe enough to warrant delivery in some patients.[76,77]

Amniotic Fluid Volume

The degree of oligohydramnios has been correlated to the risk of amnionitis by several investigators who found clinical amnionitis to be more common as the amount of amniotic fluid diminished.[78–81] In our own experience, the same relationship has held, as shown in Table 8. Oligohydramnios is less sensitive than the NST and similarly retains a high negative predictive value (i.e., PROM patients with pockets greater than 1 cm in depth had negative cultures in 86.7 per cent of cases). Similarly to the NST, however, the group with oligohydramnios had almost equal numbers of positive and negative cultures. Therefore, oligohydramnios alone cannot be taken as a sign of bacterial invasion, al-

Table 7. *Relationship between Reactive and Nonreactive Nonstress Tests and Amniotic Fluid Cultures (Last Amniocentesis Before Delivery Only)*

	NONREACTIVE NONSTRESS TEST	REACTIVE NONSTRESS TEST
Positive amniotic fluid culture	18	3
Negative amniotic fluid culture	6	14

Chi squared = 10.9, $P < 0.001$.
Sensitivity = 85.7%, positive predictive value = 75%, specificity = 70%, negative predictive value = 82%, false-positive rate = 25%.

Table 8. *Relationship between Amniotic Fluid Pocket Size and Amniotic Fluid Culture Results*

	LARGEST POCKET OF AMNIOTIC FLUID	
	< 1 cm	*> 1 cm*
Positive amniotic fluid culture	21	6
Negative amniotic fluid culture	20	39

Chi squared = 12.6, $P < 0.005$.
Sensitivity = 77%, positive predictive value = 51.2%, specificity = 66%, negative predictive value = 86.7%, false-positive rate = 48.8%.

though positive cultures were uncommon in the group with greater amounts of amniotic fluid.

Fetal Breathing Movements and Labor

Castle and Turnbull first reported that the presence or the absence of FBM in preterm labor with intact membranes predicted whether tocolysis would succeed at preventing delivery.[82] Similar results were also reported by Besinger.[83] Fetal breathing seems to decrease in patients with PROM prior to the onset of labor, whether or not infection is de-

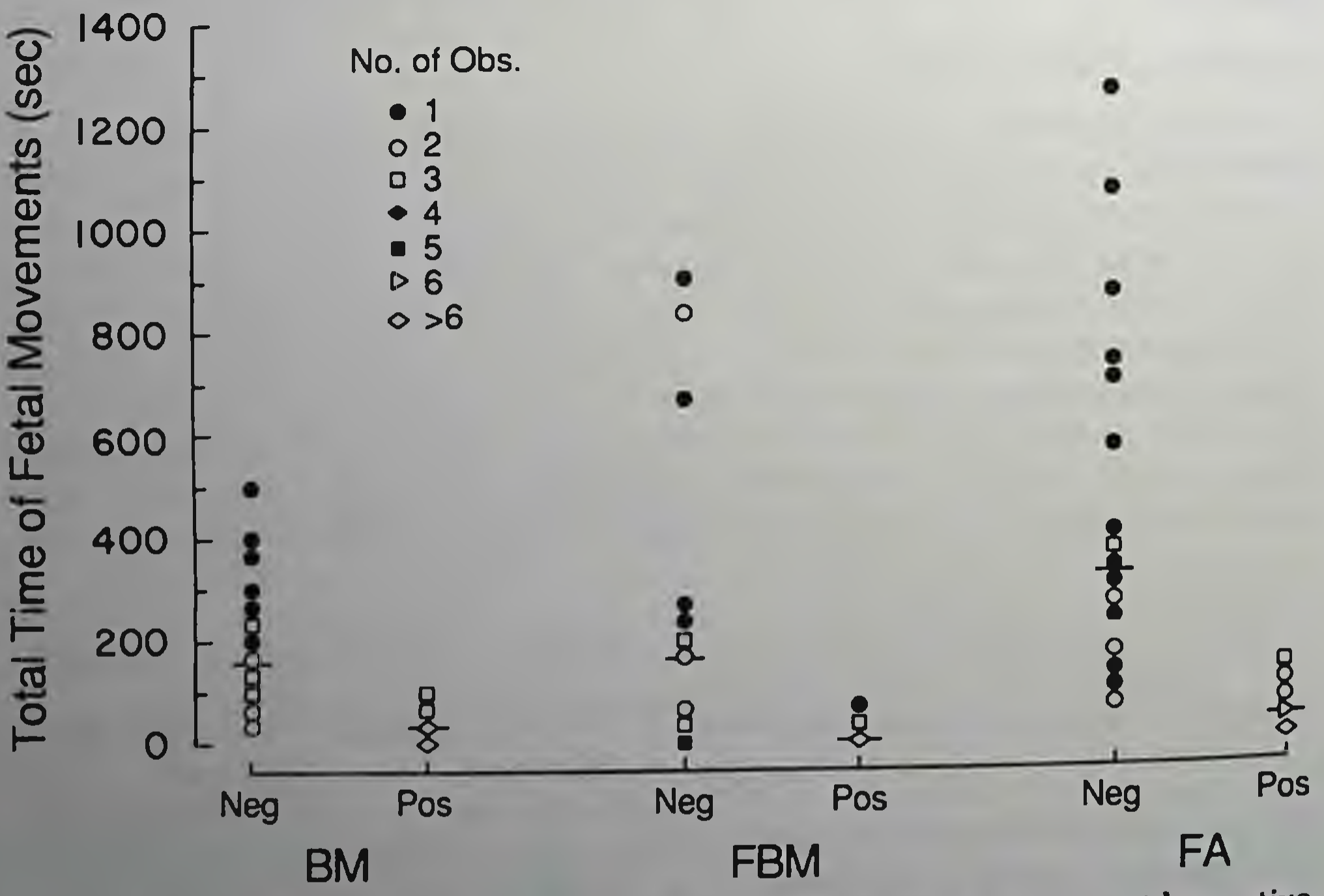

Figure 1. Total time of fetal activities, in seconds, comparing fetuses with negative (NEG) and positive (POS) amniotic fluid cultures. *Key:* BM, body movements; FBM, fetal breathing movements; FA, total fetal activity. All comparisons are highly significant (BM, $P < 0.00001$, FBM, $P < 0.004$, FA, $P < 0.00001$). (*From* Goldstein I, Romero R, Merrill S, et al: Am J Obstet Gynecol 159:363, 1988; with permission.)

monstrably present at that time. In the longitudinal study conducted at Yale–New Haven Hospital, a decrease in BM and FBM was found in PROM patients with or without infection prior to the onset of labor. Two groups were evaluated:

Group A: In the final amniocentesis prior to labor, the amniotic fluid culture was negative. The previous amniocentesis also produced negative culture results.

Group B: In the final amniocentesis prior to labor, the amniotic fluid culture was positive, while all patients in this group had previously had a negative amniotic fluid culture.

The data demonstrated a decrease in the fetal BM and FBM in the group of positive amniotic fluid culture results, when compared to the negative ones. However, in both groups there was a clear tendency toward a decrease in fetal BM, FBM, and FA prior to labor.[55]

Fetal Body and Breathing Movements

To focus more intensively on fetal activity, without the influence of the NST or the amniotic fluid volume, fetal body movements (BM), the fetal breathing movements (FBM), as well as the fetal activity (FA), measured as the sum of BM plus FBM, were assessed. The number of episodes of fetal breathing, body movements, and the sum of these two ("fetal activity") were compared to culture results. Figures 1 and 2 demonstrate the highly significant associations observed. Fetuses with positive amniotic fluid cultures demonstrated less time of gross body

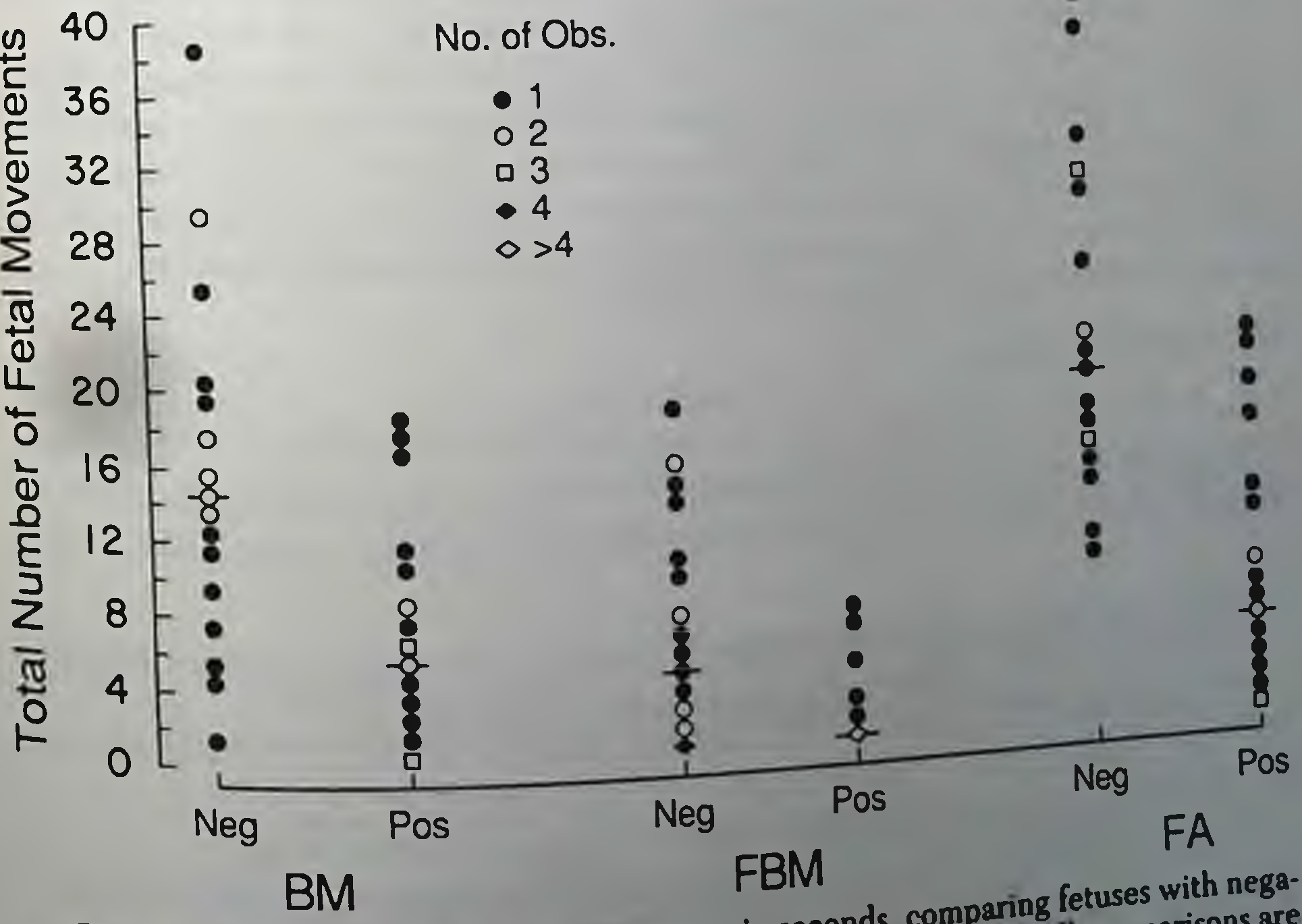

Figure 2. Total number of fetal activities, in seconds, comparing fetuses with negative and positive amniotic fluid cultures. (Abbreviations as in Fig. 1.) All comparisons are highly significant (BM, $P < 0.001$; FBM, $P < 0.0004$; FA, $P < 0.00001$.) (*From* Goldstein I, Romero R, Merrill S, et al: Am J Obstet Gynecol 159:363, 1988; with permission.)

Table 9. *Relationship between Biophysical Profile Score and Amniotic Fluid Cultures (Last Amniocentesis Only)*

	BPS < 6	BPS 6 OR GREATER
Positive amniotic fluid culture	20	0
Negative amniotic fluid culture	8	13

Chi squared = 15.4, $P < 0.0001$.
Sensitivity = 100%, positive predictive value = 71.4%, specificity = 61.9%, negative predictive value = 100%.

movements ($P < 0.00001$), breathing movements ($P < 0.004$), and total fetal activity ($P < 0.00001$) than those with negative cultures (Wilcoxon rank-sum test). Similar reductions were seen in the total number of body movements ($P < 0.001$), breathing movements ($P < 0.0004$), and fetal activity ($P < 0.00001$).

Biophysical Profile

Vintzileos used a modified fetal biophysical score (including placental grading) to predict fetal infection. He suggested that the biophysical profile score was normal in the uninfected fetus; however, a low score (<7/12 possible points) was a good predictor of impending fetal infection with PROM.[71]

In our data, the biophysical score profile was scored as first suggested by Manning, using the five parameters: nonstress test, fetal breathing movements, fetal body movements, fetal tone, and amniotic fluid volume, with 0 or 2 points assigned for each portion of the test.[73] As shown in Table 9, using a cutoff score of six results in sensitivity and negative predictive values of 100 per cent. These findings suggest that a high fetal biophysical profile score in PROM patients seems to correlate well with the absence of amnionitis. A low score, on the other hand, is less able to predict the presence of intra-amniotic infection but does indicate the need for careful surveillance, for example with amniocentesis. These findings are similar to those of Vintzileos.[71]

Neonatal Outcome

In recent years, impressive advances in the field of neonatology have encouraged an aggressive approach to the management of preterm PROM. Survival rates for the very low birth weight infant have risen

Table 10. *Days of Hospitalization of Neonates Born After Preterm PROM According to Results of Amniotic Fluid Culture*

	DAYS IN HOSPITAL	
AMNIOTIC FLUID CULTURE	*Mean*	*SD*
Negative	14	15.3
Positive	28.3	26.7

$P < 0.01$.

Table 11. *Relationship between Amniotic Fluid Cultures and Neonatal Sepsis (Last Amniocentesis Prior to Delivery)*

	SEPSIS	NO SEPSIS
Positive amniotic fluid culture	4	17
Negative amniotic fluid culture	0	20

Not significant (Fisher's exact test).
Sensitivity = 100%, positive predictive value = 19%, specificity = 54%, negative predictive value = 100%.

significantly. However, neonatal hospitalization costs are enormous. Furthermore, as shown in Table 10, neonates born following preterm PROM with positive amniotic fluid cultures spent twice as much time in the neonatal unit as did those born following negative amniotic fluid cultures.

The invasive procedure of amniocentesis may detect chorioamnionitis. However, not all positive amniotic fluid cultures have also neonatal sepsis. Table 11 demonstrates the relationship between the results of amniotic fluid cultures and neonatal sepsis, defined as positive cultures of blood, urine, or cerebrospinal fluid. Amnionitis is primarily a state of infection in the fetal environment,[56,67] which may exist without demonstrable sepsis. The results illustrated in Table 11 must be interpreted in light of the low rate of culture-proven neonatal infection.

While the respiratory distress syndrome is infrequent after 34 weeks' gestation, morbidity before this age is inversely related to gestational age at the time of delivery.[43] The present study did not find correlation between the results of amniotic fluid cultures and respiratory distress syndrome, as shown in Table 12.

Intraventricular hemorrhage is another serious neonatal complication, more common in more premature fetuses. In the present study all five cases of intraventricular hemorrhage occurred in births following findings of positive amniotic fluid cultures (Table 13).

DISCUSSION

The studies of Vintzileos,[71,75,80] as well as those of Goldstein described in greater detail here,[55] confirm the importance of fetal behav-

Table 12. *Relationship between Amniotic Fluid Cultures and Incidence of Respiratory Distress Syndrome (RDS)*

	RDS	NO RDS
Positive amniotic fluid culture	9	12
Negative amniotic fluid culture	7	13

Chi squared = 0.04, not significant.
Sensitivity = 56.2%, positive predictive value = 42.8%, specificity = 52.0%, negative predictive value = 65.0%.

Table 13. *Relationship between Amniotic Fluid Cultures and Intraventricular Hemorrhage (IVH)*

	IVH	NO IVH
Positive amniotic fluid culture	5	16
Negative amniotic fluid culture	0	20

$P < 0.03$ (Fisher's exact test).
Sensitivity = 100%, positive predictive value = 23.8%, specificity = 55.5%, negative predictive value = 100%.

ioral assessment in the management of patients with PROM. Fetuses with good behavioral profiles tend to be uninfected, and infected sacs tend to result in fetuses with lethargic behavior. As fetuses go from uninfected to infected, Goldstein found a diminution in the amount of fetal movement and breathing. Patients presenting with PROM will still benefit from amniocentesis for baseline lung maturity studies, as well as cultures.

A complex network of integrated mechanisms regulates fetal activity. Normal activity indicates an intact and functioning central nervous system.[84] The data from our institution showed a decrease in fetal activity prior to the onset of labor, whether or not infection could be documented at the time. The mechanisms responsible for this decrease are not known. In the infected patient, the mediators of the host inflammatory response may be responsible for this phenomenon. Interleukin-1 (IL-1), the main fever mediator, induces changes in the electroencephalogram that are thought to be the substrate for the decreased motor behavior observed during fever in both animals and humans.[32] Furthermore, IL-1 is capable of stimulating prostaglandin production from macrophages and other cell types. This effect may not only mediate the onset of labor but also the decrease in FBM observed in our studies.[85]

The clinical significance of these findings is clear: fetal behavior assessed with ultrasound can help to identify the presence of intra-amniotic infection. Figure 3 illustrates by a decision tree how amniocentesis and fetal behavioral studies may be used in combination as an aid to the management of PROM. This scheme of management is defined by the experience obtained in our study.[55] Although delivery was the inevitable outcome in those fetuses with absent breathing and total body movements <50 seconds in duration, amniocentesis still may be helpful in this situation. In such a case, the results of the Gram stain may assist in selection of antibiotics to be given to the mother in labor, and the resultant cultures may be of great help in neonatal management.

We currently advocate performing fetal behavioral profiles at least every other day in patients with preterm PROM. In this manner, the fetus itself becomes the indicator of its infectious status. The fetus in fact reacts in much the same way as the young child does. Reduced activity is an obvious sign of illness in the child, who stays in bed with minimal movement. The fetus behaves similarly, reducing movements to a degree discernible by ultrasound examination. Nevertheless, our more recent, admittedly anecdotal, experience has included caring for several pa-

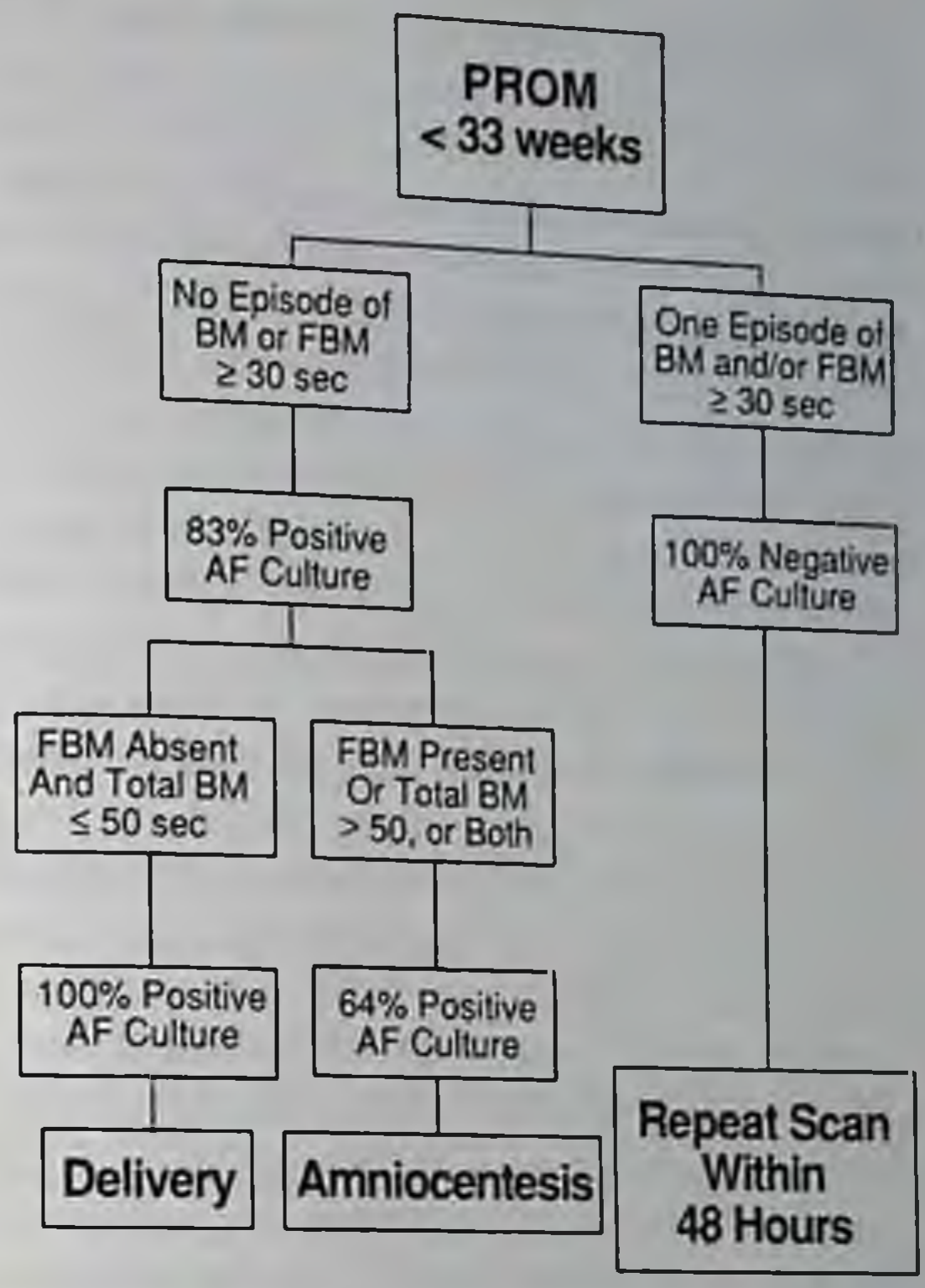

Figure 3. Flow diagram of management of pregnancies complicated by preterm premature rupture of the membranes.

tients who developed clinical chorioamnionitis (contractions, mild fever, fetal tachycardia) within 24 hours after normal fetal behavioral profiles. Therefore, a normal profile cannot *predict* the continuing absence of infection, and clinical signs of infection should not be ignored after a normal profile. We can conclude, however, that once a patient is stable and entered into a long-term expectant management protocol, new infections are uncommon within 48 hours of a normal profile. Life-table analysis of patients with PROM confirms this[55]: few new infections occur in the first 48 hours after a normal behavioral profile.

CONCLUSION

The management of patients with preterm PROM remains controversial. Immediate delivery entails the risk of the immaturity of the infant, resulting particularly in the development of the respiratory distress syndrome. On the other hand, conservative observation may place the mother and the fetus at risk of septic complications.

Increasingly, amniocentesis is being used for the detection of amnionitis, allowing the elective early delivery of fetuses with positive amniotic fluid cultures. An added benefit is the availability of tests of fetal lung maturity, to assist in timing of delivery. While results of the amniocentesis may be quite helpful, the test is practically limited in its applications by its invasiveness, limiting the frequency with which it can be performed.

Real-time ultrasound examination of the fetus has the advantage of being a noninvasive procedure, as well as a readily available and simple test for the presence of fetal infection. It may also provide an indication of the presence of intra-amniotic infection. A decision tree (see Fig. 3) can help us to interpret the value of the information obtained. Fetal behavioral assessments can be used on an ad lib basis to determine the timing of amniocentesis whenever amnionitis is suspected. Whereas the culture results shown here require several days before becoming available, preliminary results suggest that the Gram stain in combination with assays for the presence of endotoxin in amniotic fluid (Limulus test) may provide more rapid results with good specificity.[63,67,68]

The patient with PROM who is being followed expectantly must first be evaluated for the presence of infection. Amniocentesis at the time of PROM is helpful in this regard, and additionally provides baseline information regarding fetal lung maturity. Ideally, management should be undertaken at a facility capable of providing care for the neonate should delivery become indicated, provided that maternal and fetal status is sufficiently stable for transfer. We suggest performing fetal biophysical profiles at least every 48 hours in patients with PROM who are being followed expectantly. Those who develop clinical signs of infection, including labor, or who are found to have poor profiles, should be evaluated by repeat amniocentesis for active infection, with delivery expedited if infection is found. We do not administer tocolytics to patients with PROM, so the value of the amniocentesis is twofold: delivery (induction or cesarean as indicated) is expedited if it is positive; and neonatal culture information can be supplemented, with administration of appropriate antibiotics in labor if the Gram stain is positive.

Clearly, fetuses with intra-amniotic infection behave differently from those free of such infection. By assessing and monitoring fetal behavior, the obstetrician has another tool in the management of preterm PROM, and the prevention of premature birth. Perhaps the time has come when the fetus itself can best tell the physician when to intervene.

REFERENCES

1. Gibbs RS, Blanco JD: Premature rupture of the membranes. Obstet Gynecol 60:671, 1982
2. Daikoku NH, Haltreider F, Johnson FRB, et al: Premature rupture of the membranes and preterm labor: Neonatal infection and perinatal mortality risks. Obstet Gynecol 58:417, 1981
3. Mead PB: Management of the patient with premature rupture of the membranes. Clin Perinatol 7:243, 1980
4. Evaldson G, Lagrelius A, Winiarski J: Premature rupture of the membranes. Acta Obstet Gynecol Scand 59:385, 1980
5. Kappy KA, Cetrulo CL, Knuppel RA, et al: Premature rupture of the membranes: A conservative approach. Am J Obstet Gynecol 134:655, 1979
6. Naeye RL, Peters EC: Causes and consequences of premature rupture of membranes. Lancet 1:192, 1980
7. Eggers TR, Dyle LW, Peperell RJ: Premature rupture of the membranes. Med J Aust 1:209, 1979
8. Artal R, Sokol RJ, Neuman M, et al: The mechanical properties of the prematurely and

non-prematurely ruptured membranes, method and preliminary results. Am J Obstet Gynecol 125:655, 1976
9. Lavery JP, Miller CE: Deformation and creep in the human chorioamnionitis sac. Am J Obstet Gynecol 134:366, 1979
10. Kanayama N, Terao T, Kawashima Y, et al: Collagen types in normal and prematurely ruptured amniotic membranes. Am J Obstet Gynecol 153:899, 1985
11. Skinner SJM, Campos GA, Liggins GC: Collagen content of human amniotic membranes: Effect of gestation length and premature rupture. Obstet Gynecol 57:487, 1981
12. Al-Zaid NS, Bou-Resli MN, Goldspink G: Bursting pressures and collagen content of fetal membranes and their relation to premature rupture of the membranes. Br J Obstet Gynecol 87:227, 1980
13. Pyeritz RE: Maternal and fetal complications of pregnancy in the Marfan syndrome. Am J Med 71:784, 1981
14. Meyer MB, Tonascia JA: Maternal smoking, maternal complication and perinatal mortality. Am J Obstet Gynecol 128:494, 1977
15. Naeye RL: Factors that predispose to premature of the membranes. Obstet Gynecol 60:93, 1982
16. Naeye RL, Ross C: Coitus and chorioamnionitis: A prospective study. Early Hum Dev 6:91, 1982
17. Naeye RL: Coitus and associated amniotic-fluid infection. N Engl J Med 301:1198, 1979
18. Gibbs RS, Blanco JS, St. Clair PJ, et al: Quantitative bacteriology of amniotic fluid from women with clinical intraamniotic infection at term. J Infect Dis 154:1, 1982
19. Miller JM, Hill GB, Welt SI, et al: Bacterial colonization of amniotic fluid in the presence of ruptured membranes. Am J Obstet Gynecol 137:451, 1980
20. Reagan JA, Chao S, James LS: Premature rupture of membranes, premature delivery, and group B streptococcal colonization of mothers. Am J Obstet Gynecol 141:184, 1981
21. Minkoff HL, Sierra M, Pringle G, et al: Vaginal colonization with group B beta hemolytic streptococcus as a risk factor for post cesarean section infection. Am J Obstet Gynecol 142:992, 1982
22. Gravett MG, Nelson HP, DeRouen T, et al: Independent associations of bacterial vaginosis and chlamydia trachomatic infection with adverse pregnancy outcome. JAMA 256:1899, 1986
23. Cederquist L, Zervoudakis IA, Ewool LC, et al: The relationship between prematurely ruptured membranes and fetal immunoglobulin production. Am J Obstet Gynecol 134:784, 1979
24. McGregor JA, Lawellin D, Franco-Buff A, et al: Protease production by microorganisms associated with reproductive tract infection. Am J Obstet Gynecol 154:109, 1986
25. Sbarra AJ, Selvaraj RJ, Cetrulo CL, et al: Infection and phagocytosis as possible mechanisms of rupture of the membranes. Am J Obstet Gynecol 153:38, 1985
26. Sbarra AJ, Thomas GB, Cetrulo CL: Effect of bacterial gestation on the bursting pressure of fetal membrane in vitro. Obstet Gynecol 70:107, 1987
27. Sbarra AJ, Selvaraj RJ, Cetrulo CL, et al: Phagocytosis and onset of human labor. Am J Obstet Gynecol 146:622, 1983
28. Schwartz BE, Schultz FM, MacDonald PC, et al: Initiation of human parturition: IV. Demonstration of phospholipase A-2 in the lysosymes of human fetal membranes. Am J Obstet Gynecol 125:1089, 1976
29. McGregor JA, French JI, Lawellin D: Amniotic fluic trypsin and premature rupture of membranes. Am J Obstet Gynecol 157:1316, 1987
30. Kanayama N, Kamijo H, Terano T, et al: The relationship between trypsin activity in amniotic fluid and premature rupture of the membranes. Am J Obstet Gynecol 155:1043, 1986
31. Romero R, Kadar N, Hobbins JC, et al: Infection and labor: The detection of endotoxin in amniotic fluid. Am J Obstet Gynecol 157:815, 1987
32. Baracos V, Rodemann P, Dinarello CA, et al: Stimulation of muscle protein degradation and prostaglandin E-2 release by leukocytic pyrogen interleukin-1. New Eng J Med 308:553, 1983

33. Cederqvist LL, Zevondakis IA, Ewool LC, et al: The relationship between prematurely ruptured membranes and fetal immunoglobulin production. Am J Obstet Gynecol 134:784, 1979
34. Daikoku NH, Kaltreider FD, Khouzami, et al: Premature rupture of membranes and spontaneous preterm labor: Maternal endometritis risk. Obstet Gynecol 59:13, 1982
35. Duff P, Huff RW, Gibbs RS: Management of premature rupture of membranes and unfavorable cervix in term pregnancy. Obstet Gynecol 63:697, 1984
36. Garite TJ: Premature rupture of the membranes: The enigma of the obstetrician. Am J Obstet Gynecol 151:1001, 1985
37. Johnson JWC, Daikoku HN, Niebyl JR, et al: Premature rupture of the membranes and prolonged pregnancy. Obstet Gynecol 57:547, 1981
38. Kappy KA, Cetrulo CL, Knuppel RA, et al: Premature rupture of the membranes at term: A comparison of induced and spontaneous labors. J Reprod Med 27:29, 1982
39. Minkoff H, Grunebaum AN, Schwarz RH: Risk factors for prematurity and premature rupture of the membranes: A prospective study of the vaginal flora in pregnancy. Am J Obstet Gynecol 150:965, 1984
40. Beydoun SN, Yasin SY: Premature rupture of the membranes before 28 weeks: Conservative management. Am J Obstet Gynecol 155:471, 1986
41. Daikoku NH, Kaltreider DF, Johnson TR, et al: Premature rupture of the membranes and preterm labor: Neonatal infection and perinatal mortality risks. Obstet Gynecol 58:417, 1981
42. Kappy KA, Cetrulo CL, Knuppel RA: Premature rupture of the membranes: A conservative approach. Am J Obstet Gynecol 134:655, 1979
43. Gunn GC, Mishell DR, Morton DG: Premature rupture of the membranes: A review. Am J Obstet Gynecol 106:469, 1979
44. Johnson J: Premature rupture of the membranes and prolonged pregnancy. Obstet Gynecol 57:547, 1981
45. Schutte MF, Treffers PE, Kloosterman GJ: Management of premature rupture of membranes: The risk of vaginal examination to the infants. Am J Obstet Gynecol 146:395, 1983
46. Varner MW, Galask RP: Conservative management of premature rupture of membranes. Am J Obstet Gynecol 140:39, 1981
47. Schreiber J, Benedetti: Conservative management of preterm premature rupture of the membranes in a low socioeconomic population. Am J Obstet Gynecol 136:92, 1980
48. Gillibrand PN: Premature rupture of the membranes and prematurity. J Obstet Gynecol Br Commonw 74:678, 1967
49. Christensen KK, Christensen P, Ingemazsson I, et al: A study of complications in preterm deliveries after prolonged premature rupture of the membranes. Obstet Gynecol 48:670, 1976
50. Andreyko JL, Chen CP, Shennan AT, et al: Results of conservative management of premature rupture of the membranes. Am J Obstet Gynecol 148:600, 1984
51. Fayez JA, Hasan AA, Jonas AS, et al: Management of premature rupture of the membranes. Obstet Gynecol 52:17, 1978
52. Graham L, Gilstrap LC, Hauth JC, et al: Conservative management of patients with premature rupture of fetal membranes. Obstet Gynecol 59:607, 1982
53. Alden ER, Mandelkon T, Woodrum DE, et al: Morbidity and mortality of infants weighing less than 1000 grams in an intensive care nursery. Pediatrics 50:40, 1972
54. Berkowitz RL, Kantor RD, Beck GH, et al: The relationship between premature rupture of the membranes and respiratory distress syndrome. Am J Obstet Gynecol 131:503, 1978
55. Goldstein I, Romero R, Merrill S, et al: Fetal body and breathing movements as predictors of intraamniotic infection in preterm premature rupture of membranes. Am J Obstet Gynecol 159:363, 1988
56. Garite TJ, Freeman RK, Linzey EM, et al: The use of amniocentesis in patients with premature rupture of membranes. Obstet Gynecol 54:226, 1979
57. Broekhuizen FF, Gilman M, Hamilton PR: Amniocentesis for Gram stain and culture in preterm premature rupture of the membranes. Obstet Gynecol 66:316, 1985
58. Cotton DB, Hill LM, Strassner HT, et al: Use of amniocentesis in preterm gestation with rupture of membranes. Obstet Gynecol 63:38, 1984

59. Cotton DB, Gonik B, Bottoms SF: Conservative versus aggressive management of preterm rupture of membranes. A randomized trial of amniocentesis. Am J Perinatol 1:322, 1984
60. Gonik B, Cotton DB: The use of amniocentesis in preterm premature rupture of membranes. Am J Perinatol 2:21, 1985
61. Leigh J, Garite TJ: Amniocentesis and management of premature labor. Obstet Gynecol 67:500, 1985
62. Zlatnick FJ, Cruikshank DP, Petzold CM, et al: Amniocentesis in the identification of inapparent infection in preterm patients with premature rupture of the membranes. J Reprod Med 29:656, 1984
63. Yeast JD, Garite TJ, Dorchester W: The risk of amniocentesis in the management of premature rupture of the membranes. Am J Obstet Gynecol 149:505, 1984
64. Feinstein SJ, Vintzileos AM, Lodeiro JG, et al: Amniocentesis with premature rupture of membranes. Obstet Gynecol 68:147, 1986
65. Romero R, Roslansky P, Oyarzun E, et al: Labor and infection: II. Bacterial endotoxin in amniotic fluid and its relationship to the onset of preterm labor. Am J Obstet Gynecol 158:1044, 1988
66. Jeanty P, Rodesch F, Romero R, et al: How to improve your amniocentesis technique. Am J Obstet Gynecol 146:593, 1983
67. Romero R, Emamian M, Quintero R, et al: The value and limitations of the Gram stain examination in the diagnosis of intraamniotic infection. Am J Obstet Gynecol 159:114, 1988
68. Cox SM, MacDonald PC, Casey ML: Assay of bacterial endotoxin (lipopolysaccharide) in human amniotic fluid: Potential usefulness in diagnosis and management of preterm labor. Am J Obstet Gynecol 159:99, 1988
69. Miller JM, Pupkin MJ, Crenshaw C: Premature labor and premature rupture of the membranes. Am J Obstet Gynecol 132:1, 1978
70. Gluck L, Kulovich MV, Borer RC, et al: Diagnosis of respiratory distress syndrome by amniocentesis. Am J Obstet Gynecol 109:440, 1971
71. Vintzileos AM, Campbell WA, Nochimson DJ, et al: The fetal biophysical profile in patients with premature rupture of the membranes: An early predictor of fetal infection. Am J Obstet Gynecol 152:510, 1985
72. Goldstein I, Lockwood C, Belanger K, et al: Ultrasonographic assessment of gestational age with the distal femoral and proximal tibial ossification centers in the third trimester. Am J Obstet Gynecol 158:127, 1988
73. Manning FA, Platt LD, Sipos L: Antepartum fetal evaluation: Development of a fetal biophysical profile. Am J Obstet Gynecol 136:787, 1980
74. Freeman RK, Garite TJ: Fetal Heart Rate Monitoring. Baltimore, Williams & Wilkins, 1981, p 63
75. Vintzileos AM, Campbell WA, Nochimson DJ, et al: The use of the nonstress test in patients with premature rupture of the membranes. Am J Obstet Gynecol 155:149, 1986
76. Moberg LJ, Garite TJ, Freeman RK: Fetal heart rate patterns and fetal distress in patients with preterm premature rupture of membranes. Obstet Gynecol 64:60, 1984
77. Smith CV, Greenspoon J, Phelan JP, Platt LD: Clinical utility of the nonstress test in the conservative management of women with preterm spontaneous premature rupture of the membranes. J Reprod Med 32:1, 1987
78. Gonik B, Bottoms SF, Cotton DB: Amniotic fluid volume as a risk factor in preterm premature rupture of the membranes. Obstet Gynecol 65:456, 1985
79. Ferguson MG, Rhodes PG, Morrison JC: Clinical amniotic fluid infection and its effect on the neonate. Am J Obstet Gynecol 151:1058, 1985
80. Vintzileos AM, Campbell WA, Nochimson DJ, et al: Qualitative amniotic fluid volume versus amniocentesis in predicting infection in preterm premature rupture of membranes. Obstet Gynecol 67:579, 1986
81. Vintzileos AM, Campbell WA, Nochimson DJ, et al: Degree of oligohydramnios and pregnancy outcome in patients with premature rupture of the membranes. Obstet Gynecol 66:162, 1985
82. Castle BM, Turnbull AC: The presence and the absence of fetal breathing movements predicts the outcome of preterm labor. Lancet 2:471, 1983
83. Besinger RE, Compton AA, Hayashi RH: The presence or absence of fetal breathing

movements as a predictor of outcome in preterm labor. Am J Obstet Gynecol 157:753, 1987
84. Vintzileos AM, Feinstein SJ, Loderio JC, et al: Fetal biophysical profile and the effect of premature rupture of the membranes. Obstet Gynecol 67:818, 1986
85. Romero R, Durum S, Dinarello CA, et al: Interleukin-1 stimulates prostaglandin biosynthesis by human amnion. Prostaglandin 37:13, 1989

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Cordocentesis: Role in Assessment of Fetal Condition

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Needle aspiration of umbilical cord blood (cordocentesis) was first used to exclude genetic disorders in high risk pregnancies by prenatal diagnosis and abortion of affected fetuses.[1] These diseases included haemoglobinopathies, coagulopathies, severe combined immunodeficiency, chronic granulomatous disease, fetal infection, metabolic disease, and fragile X mental retardation.[2] Although some conditions still require cordocentesis, increasingly DNA analysis of placental biopsy ("chorionic villus sampling") is allowing first-trimester diagnosis (e.g., sickle cell disease and hemophillia A). The ability to prevent a serious uncorrectable abnormality recurring in a family allows some couples to conceive and continue pregnancies they would otherwise have prevented or aborted. Cordocentesis also is used for fetal karyotyping after failure of, or mosaicism in, amniotic fluid or placental cytogenetic analysis.

Cordocentesis for prenatal diagnosis has allowed extensive progress in our knowledge of human fetal physiology by the study of surplus blood taken from fetuses not affected by the condition under investigation.[3,4] This knowledge has led to cordocentesis being used to guide the obstetric management of acquired fetal disease (e.g., timing of delivery and intrauterine therapy), and these applications are the subject of this article. The most established indications for cordocentesis to assess the fetal condition are blood disorders (e.g., fetal anemia and thrombocytopenia) and further investigation of potentially correctable fetal malformation, but it is increasingly being used in placental insufficiency (e.g., fetal hypoxia and hypoglycemia). Other indications in the future will depend on effective lines of treatment becoming available.

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CORDOCENTESIS

Technique

Cordocentesis is done transabdominally, originally under fetoscopic[5] guidance but now by ultrasound-guided needling.[6] It is an outpatient procedure and does not require maternal sedation.[7] The site and direction of the umbilical cord at its insertion into the placenta are identified by ultrasound scanning with a curvilinear transducer. This transducer shape makes orientation and guidance easier by combining the advantages of sector scanners, which enlarge the visual field, and linear array transducers, which allow visualization of the needle path. With the transducer in one hand, held parallel to the intended course of the needle, the chosen site of entry on the mother's abdomen is cleaned with antiseptic solution, and local anesthetic is infiltrated down to the myometrium. A 20-gauge needle is introduced transplacentally when the placenta is anterior or lateral or transamniotically when the placenta is posterior (Fig. 1), and the cord punctured close to its placental insertion. The umbilical cord vessel sampled is identified as artery or vein by the turbulence seen ultrasonically when sterile saline (0.2 ml) is injected via the sampling needle. Intervillous maternal blood, which enables the study of placental transfer, can be aspirated during withdrawal of a transplacentally inserted needle; when the placenta is posterior, intervillous blood may be obtained by placental puncture after fetal blood sampling.

Reported technical problems include contamination of the blood sample with amniotic fluid[8] or maternal blood[6] and inability to obtain the sample when there is extreme excess or absence of amniotic fluid.[9]

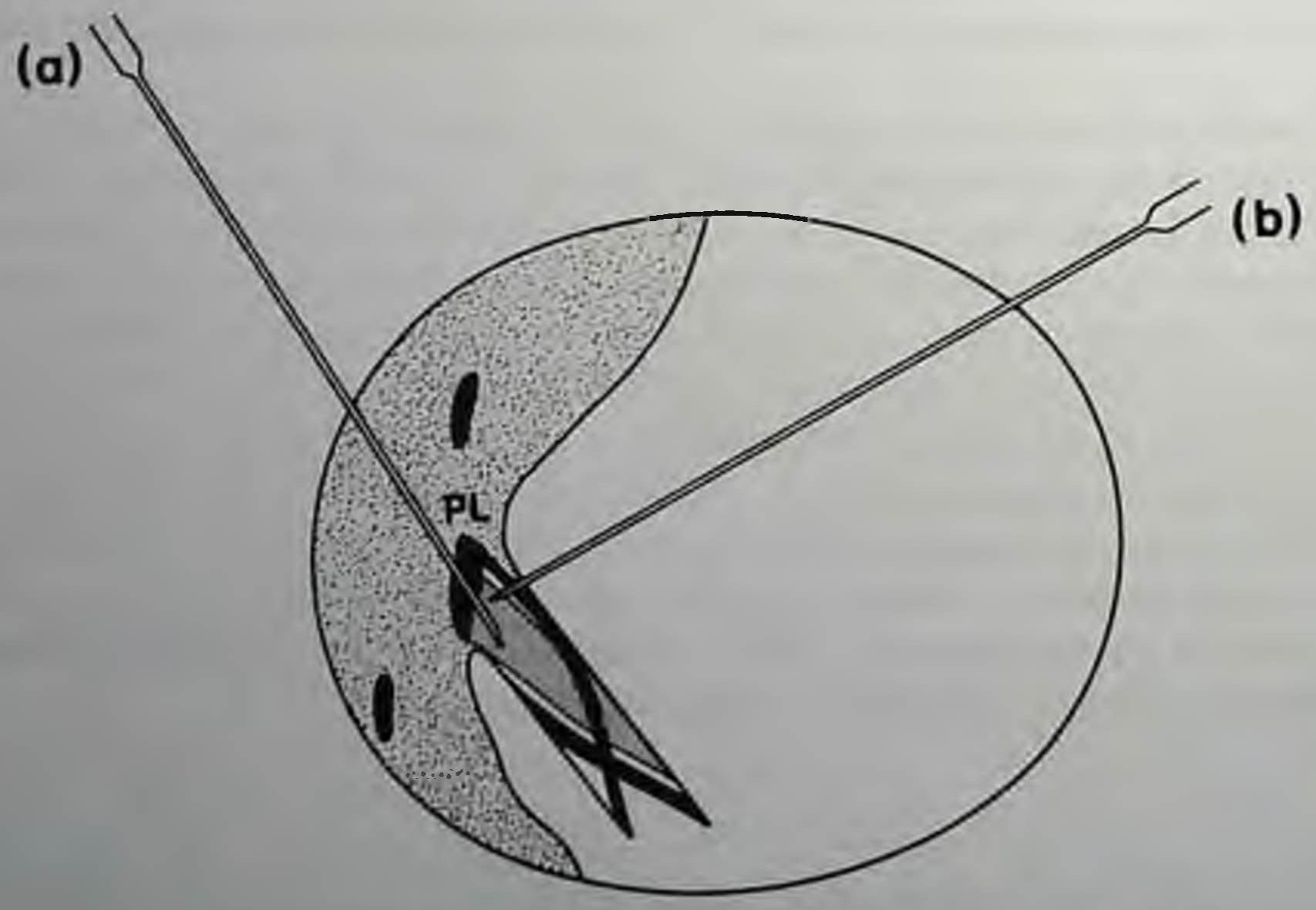

Figure 1. Cordocentesis by the transplacental (a) and transamniotic (b) approaches. Aspiration of blood from placental lakes (PL) allows the study of intervillous blood.

These problems occurred early in the authors' series, and when the needle tip can be clearly seen and the vessel is punctured about 1 to 2 cm along the cord, a pure sample can be consistently obtained with experience. The operator must be sure of the adequacy and purity of the sample at the time of the procedure because subsequent exclusion of samples on the basis of the laboratory results (e.g., low hemoglobin concentration suggesting amniotic fluid contamination) or by comparison with postnatal findings[8] invalidates the use of the procedure to guide obstetric management.

Many obstetricians are now developing skills in ultrasound-guided needle techniques for amniocentesis, placental biopsy, or oocyte recovery. An operator skilled at avoiding the placenta during amniocentesis will require minimal training to hit the placenta and avoid the amniotic membrane in transabdominal placental biopsy.[10] Those skilled in placental biopsy will easily guide the needle through the placenta into the umbilical cord for cordocentesis. Therefore, should cordocentesis prove to be of value for the assessment of fetal condition in the clinical management of high-risk pregnancy, it need not be restricted to a few specialized centers.

RISKS

Fetal

The incidence of fetal death after cordocentesis depends on the indication for sampling and the skills of the operator. Fetuses sampled for indications such as severe early-onset growth retardation and nonimmune hydrops have a poor prognosis, and a high fetal mortality is expected whether a cordocentesis is done or not. Furthermore, it is often not possible to determine whether an abortion occurring after cordocentesis is caused by the procedure or occurred spontaneously. Therefore, the expected mortality must be subtracted from that observed to obtain the procedure-related risk. Fetal death occurred after cordocentesis in 3 of 310 (1 per cent) low-risk pregnancies (defined retrospectively when the fetus was not affected by the condition under investigation.[11] Similarly, Daffos et al.,[12] in a series of 562 cases, sampled primarily for diagnosis of toxoplasmosis, reported 7 fetal losses (1.3 per cent). The spontaneous abortion rate in the second trimester is probably less than 1 per cent but it is not zero. Therefore, for prenatal diagnosis the procedure-related risk is at most 1 per cent in experienced hands and is not much greater than for amniocentesis.[13] The procedure-related risk would probably be even lower than 1 per cent when cordocentesis is undertaken for assessment of fetal well-being because it usually would be done at a gestational age at which the fetus is mature enough to be delivered should fetal bradycardia, hemorrhage, or premature labor occur.

Rupture of fetal membranes and amnionitis probably occur with the same incidence as after amniocentesis.[13] However, these risks may be reduced when the procedure is done transplacentally without puncture

of the amniotic membrane. Revealed antepartum hemorrhage is very uncommon after transplacental cordocentesis.

Cordocentesis carries the theoretic risk of passing a maternal infection to the fetus. This would be a particular concern in a mother infected with human immunodeficiency or hepatitis B viruses, but such an iatrogenic intrauterine infection has not yet been reported.

Maternal

Isoimmunization occasionally will be produced against D or other red cell antigens and, as for all invasive fetal tests, rh-negative mothers should be given anti-D prophylaxis. When a woman who has red cell antibodies undergoes cordocentesis there is a risk of increasing the severity of the fetal disease by boosting the mother's antibody titer.[14,15] The transamniotic route may be preferable to the transplacental in these patients. Maternal intra-abdominal injury is almost never detected clinically and would be expected to occur with the same frequency as for amniocentesis.

INDICATIONS FOR CORDOCENTESIS TO ASSESS FETAL CONDITION

Red Cell Isoimmunization

Traditionally, the condition of fetuses with hemolytic anemia due to maternal red cell isoimmunization is assessed by 1) the history of previous affected pregnancies, 2) the maternal hemolytic antibody titer, 3) the amniotic fluid bilirubin concentration as determined by the Δ optical density at 450 nm, and 4) ultrasonographic findings of fetal hydrops. However, these techniques are inadequate to manage severe disease. Sacrificing a pregnancy to manage the next more actively is unacceptable. Anti-D titers of only 4 IU per ml can be associated with severe disease[11] (fetal hemoglobin concentration of 8.2 gm per dl at 29 weeks' gestation, personal observation, 1988) and titers of antibodies to other red cell antigens are even less reliable in predicting the need for intervention. Amniotic fluid optical density in the second trimester does not define the severity of fetal anemia accurately.[16] Furthermore, in the absence of the preterminal complication of hydrops fetalis, neither ultrasonographic measurements nor Doppler studies can reliably distinguish mild from severe fetal anemia.[17,18]

Fetal Hemoglobin Concentration. The hemoglobin concentration of normal fetuses rises linearly from 17 to 40 weeks' gestation and the reference range is shown in Figure 2.[19] This rise is probably a compensatory response to a fall in po_2, thereby maintaining the blood oxygen content.

Fetal hemoglobin concentration in isoimmunized pregnancies (i.e., fetal red cells positive in the direct Coombs' test) can be classified into three zones (Fig. 2), analogous to those of the Liley chart for amniotic fluid optical density.[19] Zone 1, fetal hemoglobin concentration in the normal range, indicates that an intrauterine transfusion or delivery are

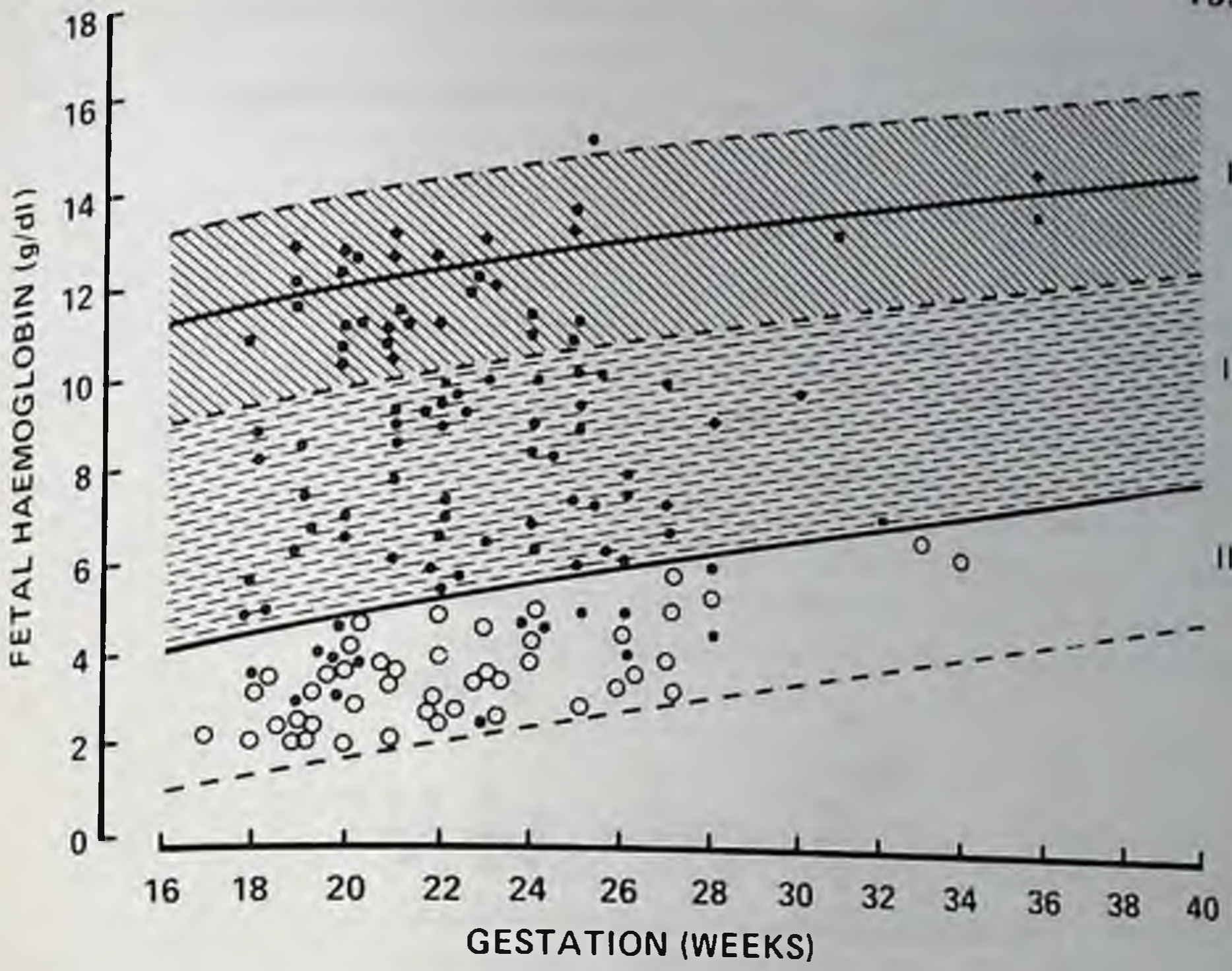

Figure 2. Reference ranges (mean and 95 per cent confidence intervals) for fetal hemoglobin concentration with gestational age from 210 normal fetuses (zone 1 *[shaded area]*). The individual values (●) of 154 fetuses affected by maternal red cell isoimmunization are shown. The hemoglobin concentration of all the fetuses with ultrasonic evidence of hydrops fetalis fell within zone III *(open circles)*. When the fetal hemoglobin concentration is less than normal but above the hydropic range it is in zone II *(broken lines)*.

not yet required. Zone II, between the 2.5th centile for normals and the 97.5th centile for the hydropic fetuses, indicates that either an intrauterine transfusion (intravascular or intraperitoneal) or delivery is required. Zone III, the range for hydropic fetuses, indicates a severely affected fetus, and urgent intravascular transfusion or delivery is required. As well as better assessment of fetal anemia cordocentesis (unlike amniocentesis) allows blood grouping so that if the fetus is antigen negative (e.g., Rh-negative), the patient can be returned to normal care after a single test.

The zones of hemoglobin concentration described earlier reflect the metabolic adaptation of the fetus to anemia. When the fetal hemoglobin concentration is in the normal range (zone 1), fetal lactate concentration is normal, but as the hemoglobin falls to zone II, umbilical arterial lactate starts to rise (Fig. 3).[20] This is because although the po_2 is normal,[21] the oxygen delivery to the tissues is reduced by anemia, and anaerobic metabolism prevents breakdown of pyruvate in the Krebs cycle. In zone II the extra lactate produced by the fetus is cleared from the fetal circulation in a single passage through the placenta because umbilical venous plasma lactate remains normal. In severe fetal anemia, however (zone III), the placenta is unable to clear the extra lactate, and umbilical venous

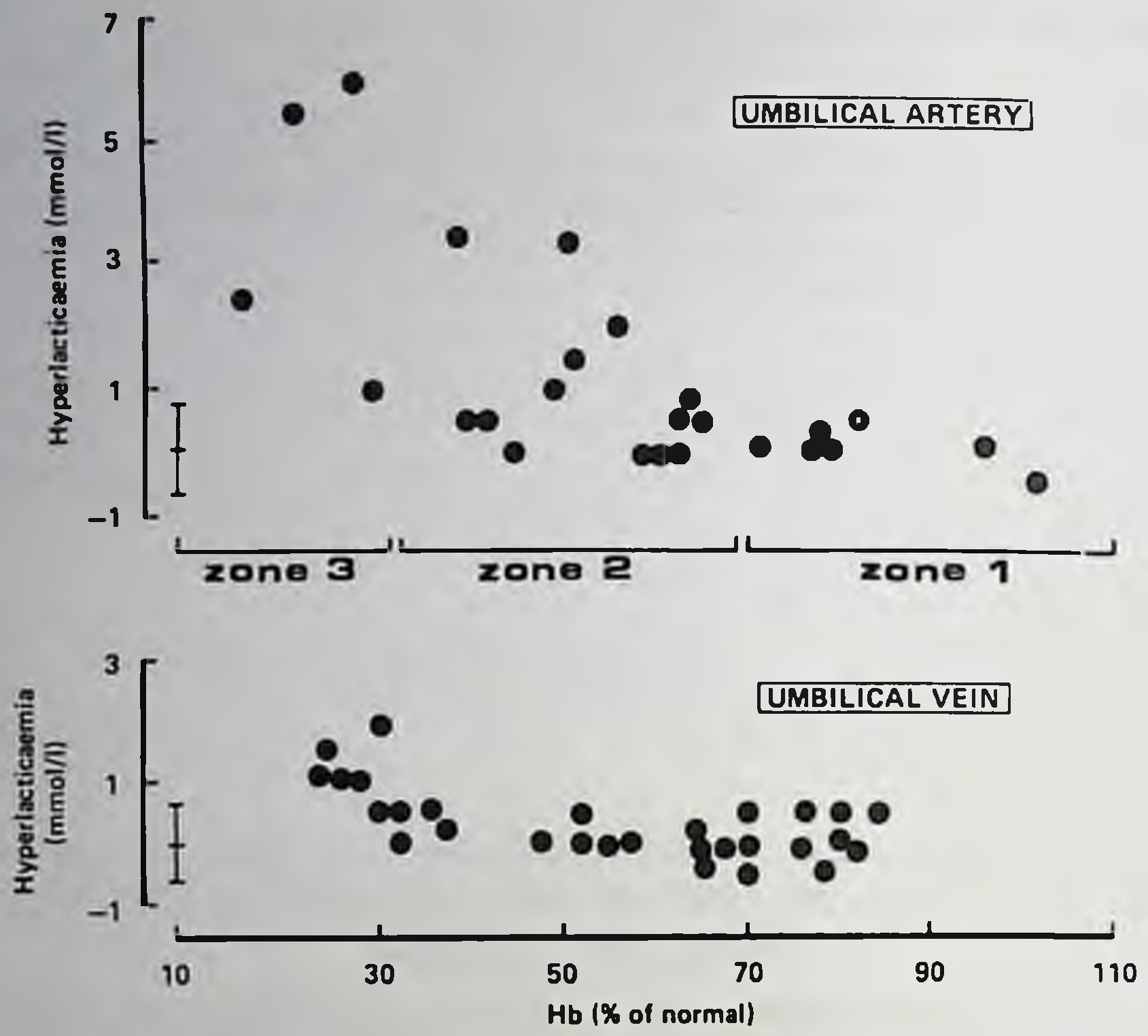

Figure 3. The relationship between fetal anemia (expressed as a percentage of the normal for gestational age) and umbilical arterial and venous hyperlacticemia (observed—normal mean for gestational age). The zones of hemoglobin concentration correspond to those indicated in Figure 2. Umbilical arterial lactate concentration increases when the hemoglobin concentration falls below normal (zones 2 and 3). Umbilical venous lactate concentration increases only when the fetal hemoglobin is in the hydropic range (zone 3). The difference between the lactate changes in umbilical arterial and venous blood indicates that in zone 2 the placenta is clearing the extra lactate produced by the fetus in a single passage of fetal blood (*Modified from* Soothill PW, Nicolaides KH, Rodeck CG et al: Obstet Gynecol 69:268–271, 1987.).

concentration is raised (see Fig. 3) and hydrops fetalis and fetal acidosis occur.[20,21]

It is widely accepted that fetuses with hemoglobin concentration in the hydropic range (zone III) must be delivered or transfused urgently. The observation of metabolic abnormality in many fetuses in zone 2 (see Fig. 3) suggest that these fetuses need transfusion too, but no study of the relative risks entailed has been reported.

When an intrauterine transfusion is required, the volume of blood needed to correct the anemia is determined from the hemoglobin concentration with nomograms using the fetal blood volume and donor blood hemoglobin.[19] The blood is transfused by injecting through the cordocentesis needle.[22] In the United Kingdom, removing blood from the fetus, as in a neonatal exchange transfusion, is not recommended because the fetoplacental circulation can absorb the rapid increase in blood volume without evidence of compromise, and the increased time of the procedure is considered dangerous. Subsequent transfusion is timed by extrapolation from the fetal haematocrit achieved at the end of

the previous transfusion, assuming a fall in the fetal hematocrit of approximately 1 per cent per day. Cordocentesis is undertaken when the estimated fetal hematocrit is 20 to 25 per cent; if the fetus is found not to be anemic transfusion may be deferred. Transfusion is given earlier than predicted if fetal hydrops is detected at weekly ultrasonographic examinations.

There are no controlled studies of the effectiveness of intrauterine blood transfusion. The benefits are obvious when the hemoglobin concentration is in zone III and the fetus is too immature for delivery, but some suggest that the nonhydropic anemic fetus may not require blood transfusion. Studies employing liberal transfusion policies will include less severely affected pregnancies with a better outcome. However, the policy described earlier achieved a survival rate of more than 90 per cent, despite hydrops fetalis being present in 60 per cent of the fetuses,[21] and so it appears that managing fetal anemia by cordocentesis improves the fetal prognosis.

Practical Implications

In mothers who have had previous pregnancies severely affected by red cell isoimmunization or who develop a hemolytic antibody titer greater than 4 IU/ml, the fetal condition should be assessed; previously this was done by amniocentesis, but this test does not permit blood typing, is unreliable, does not allow blood transfusion, and the risks are probably not much less than those of cordocentesis. So we regard cordocentesis as the procedure of choice when experienced operators are available. Intravascular transfusions are timed, given, and monitored by cordocentesis. The decision whether to deliver or transfuse the fetus will depend on the gestational age of the pregnancy and the skills in neonatal and fetal management available in the unit. It seems logical to manage fetal anemia knowing the hemoglobin concentration, however.

ALLOIMMUNE THROMBOCYTOPENIA

Fetal thrombocytopenia, resulting from placental transfer of maternal antiplatelet IgG antibody, is a rare (1 per 5000 births) but serious condition. Intracranial hemorrhage occurs in about 10 per cent of affected fetuses during pregnancy and in another 20 per cent during labor or the neonatal period. The risk of subsequent handicap is substantial. As with maternal red cell isoimmunization, the tests of the mother's blood (e.g., antiplatelet antibody titer and platelet count) do not accurately indicate the severity of fetal disease, and the fetal platelets may not express the antigen to which the mother's antibody binds.

Daffos et al. recommend a cordocentesis at 37 weeks' gestation to decide delivery management.[23] Fetal bleeding appears to be no more than normal even with severe thrombocytopenia.[23] When the platelet count is above 100×10^9 per liter delivery can proceed as determined by normal obstetric management and the maternal condition. If the platelet count is low ($<50-100 \times 10^9$ per liter), a transfusion of concentrated, irradiated maternal platelets can be given through the cordocentesis needle. Delivery is then planned the following day based on obstetric

and maternal factors and usually is possible vaginally. Without a platelet transfusion, cesarean section would be indicated but this still does not always prevent intracranial hemorrhage at delivery or in the neonatal period.[24]

The management described earlier will not prevent intracranial hemorrhage occurring *in utero* before 37 weeks' gestation. A cordocentesis at 20 weeks' gestation allows identification of fetal platelet antigen status, so that if the fetus is not affected the pregnancy care can be normal.[23] The place of weekly platelet transfusion in the second half of pregnancy to prevent intracerebral hemorrhage in thrombocytopenic fetuses is under investigation. A case with a successful outcome after this management has been reported,[25] but the benefit over the risks of repeated invasive procedures requires further study.

The value to the fetus of other therapeutic approaches during the pregnancy (e.g., treatment of the mother with intravenous injections of γ-globulin) is being assessed by cordocentesis.[26]

Practical Implications

Cordocentesis to assess the fetus in alloimmune thrombocytopenia and guide appropriate therapy such as *in utero* transfusion with platelets may prevent intracerebral hemorrhage and subsequent handicap and reduce the need for cesarean section.

Fetal Structural Abnormalities

When fetal or neonatal treatment is possible for ultrasonically diagnosed structural abnormalities, cordocentesis will help to exclude associated untreatable abnormalities. Karyotyping should be undertaken before intrauterine surgical procedures such as the insertion of a vescicoamniotic shunt for obstructive uropathy.[1] It should also be considered to guide delivery policy when the lesion (e.g., exomphalos or diaphragmatic hernia) requires neonatal intensive care. Should the fetus have a lethal chromosomal abnormality, both the maternal dangers of an intensively monitored labor or operative delivery and distressing pediatric intervention can be avoided.

When hydrops develops in a fetus cordocentesis is indicated to determine the cause.[27] Should cytogenetic, hematologic, biochemical and virologic studies be negative, treatable diagnoses (e.g., managing a chylothorax by a thoracoamniotic shunt[1]) should be considered.

Placental Failure

The placenta is the fetus's organ of respiration (gas exchange). Hypoxia is the common end pathway of fetal death in conditions such as preeclampsia,[28] abruptio placentae,[29,30] and some cases of fetal growth retardation,[31] maternal diabetes mellitus,[32] and unexplained stillbirths.

The polycythemia of neonates affected by these conditions suggests that the hypoxia is chronic and that the fetus attempts to maintain its blood oxygen content by increased hemopoesis. Placental failure leads to a spectrum of fetal damage, including growth retardation, death before or during labor, distress in labor, neonatal asphyxia, and long-term brain damage.[33] Therefore, failure of placental respiration is a major clinical problem and results in the complications of pregnancy that are currently most difficult to manage. Study of fetal blood gas and acid–base parameters by cordocentesis can provide information about fetal condition which may improve clinical management.

Fetal Blood Gas and Acid-Base Measurements

Reference ranges of blood gas and acid–base parameters in umbilical venous, umbilical arterial and intervillous blood before labor or delivery have been established by analysis of cordocentesis samples obtained for prenatal diagnosis from 208 normal fetuses at 18 to 38 weeks' gestation.[34,35] The po_2 of both umbilical venous and arterial blood decreases linearly with advancing gestation (Fig. 4); this appears to be the result of increased consumption of oxygen by the placenta.[34] Despite this decrease, the umbilical venous blood oxygen content remains constant because the fetal hemoglobin concentration rises with gestational age (see Fig. 2).[34] Umbilical venous and arterial blood pco_2 rises and pH falls (Fig. 5) with advancing gestational age.

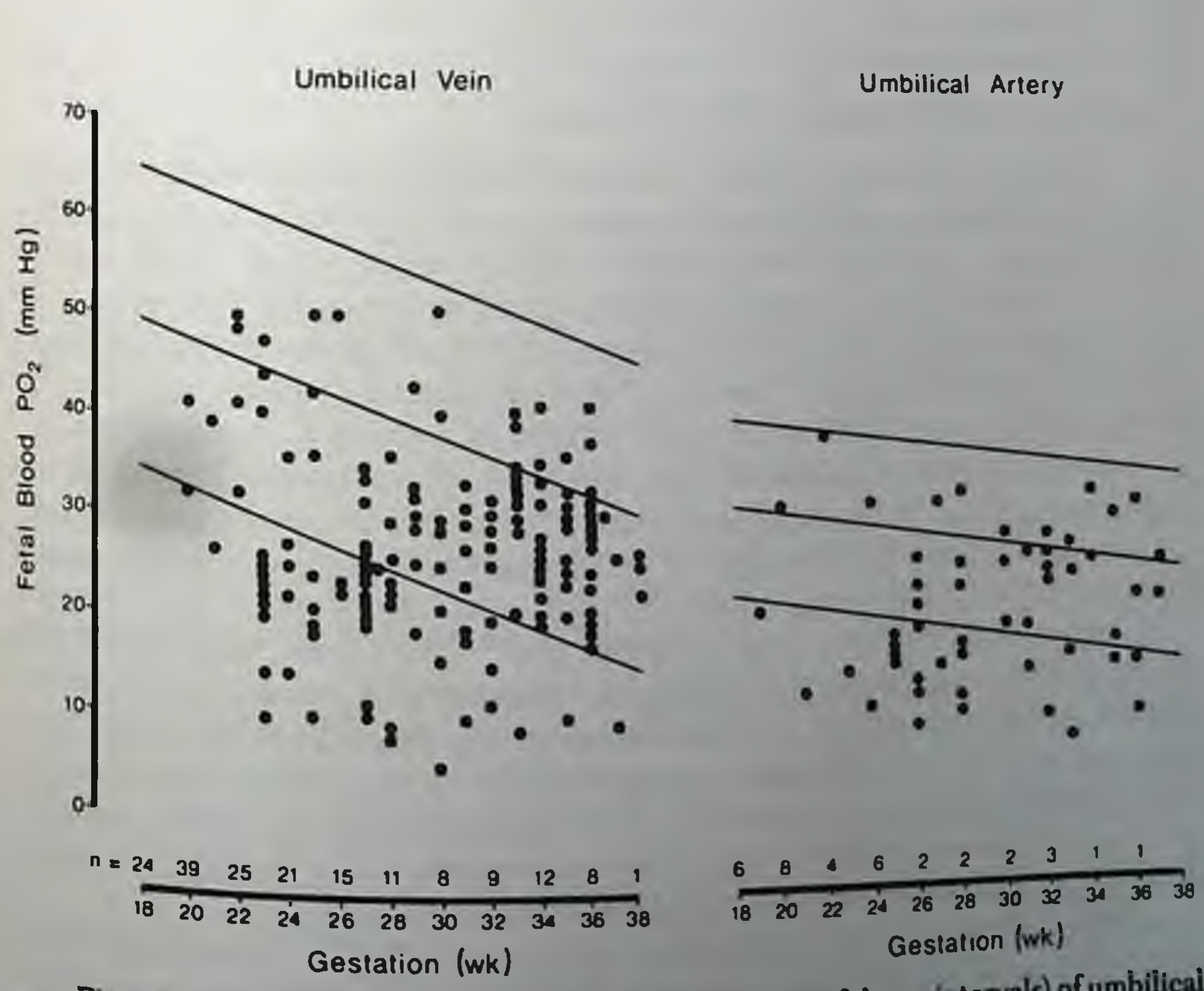

Figure 4. Reference ranges (mean and 95 per cent confidence intervals) of umbilical venous and arterial po_2 with gestational age. The individual values of small-for-gestational-age fetuses are shown (●).[35]

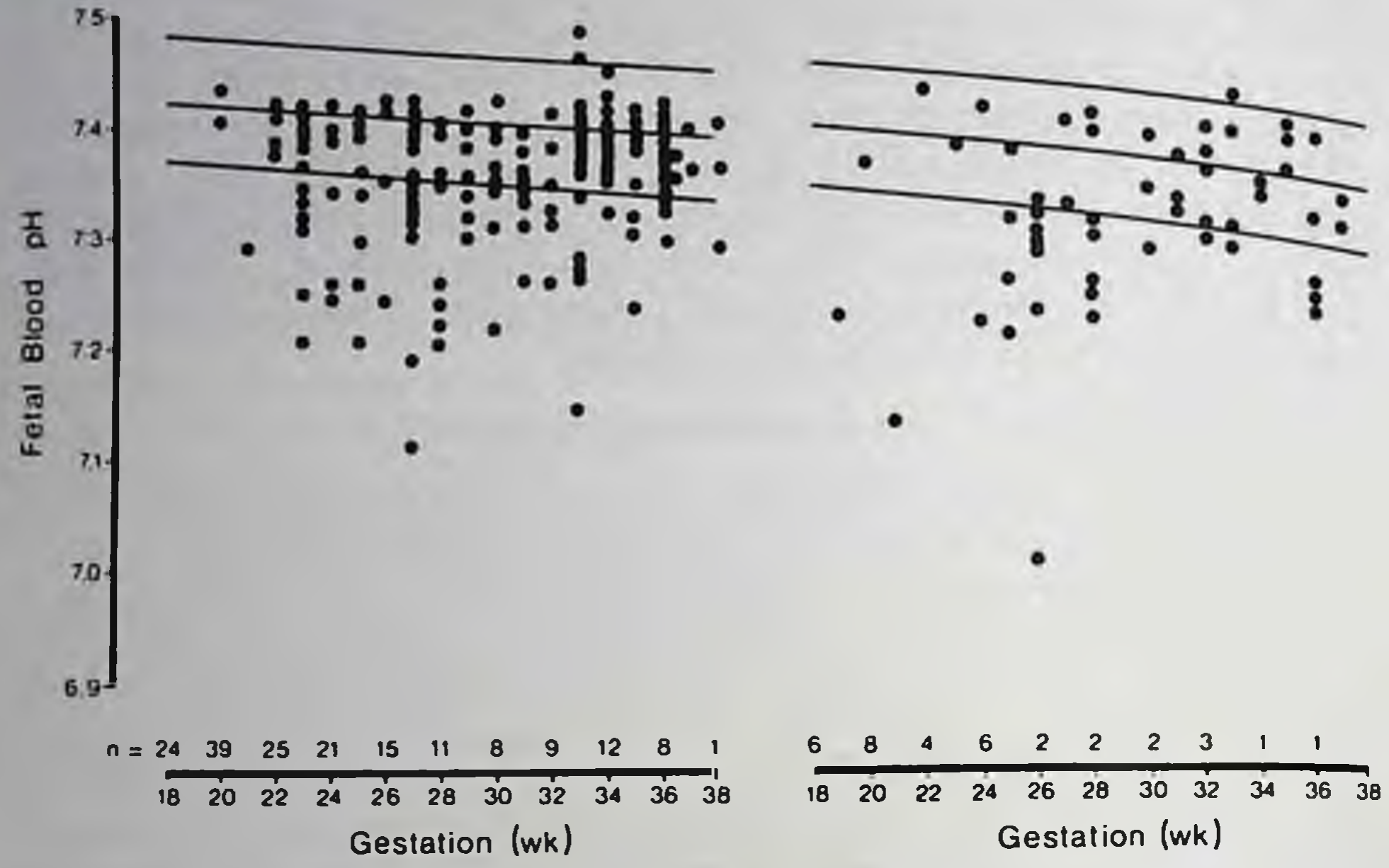

Figure 5. Reference ranges (mean and 95 per cent confidence intervals) of umbilical venous and arterial pH with gestational age. The individual values of small-for-gestational-age fetuses are shown (●).[35]

Small-for-Gestational-Age (SGA) Fetuses

SGA fetuses can be 1) constitutionally small, owing to racial or familial characteristics, which entails no increased risk of perinatal mortality or morbidity; or 2) growth retarded, either owing to a) "fetal insufficiency," the result of genetic disease or environmental damage, or b) "uteroplacental insufficiency," the result of inadequate maternal blood supply. Distinguishing between normal small and growth-retarded fetuses remains one of the major challenges of antenatal management.

Analysis of cordocentesis samples from chromosomally and structurally normal SGA fetuses has shown that some are hypoxic (see Fig. 4), hypercapnic, acidotic (see Fig. 5) and hyperlacticemic when compared to appropriate reference ranges.[36] Pardi et al. sampled 12 SGA fetuses and suggested that they had a normal po_2.[8] This conflicting result was because they compared the results to ten normally grown babies delivered by cesarean section at term. Because the po_2 falls with gestational age, some of their SGA fetuses considered to have a normal po_2 were in fact hypoxic. Asphyxia manifested at birth may not be due to the process of birth itself, but rather it may exist antenatally. This finding has management and medicolegal implications.

The fall in po_2 in the umbilical venous or arterial blood correlates significantly with an increase in pco_2, lactate, and hydrogen ion concentration. Acidosis of both the respiratory (raised pco_2) and the metabolic

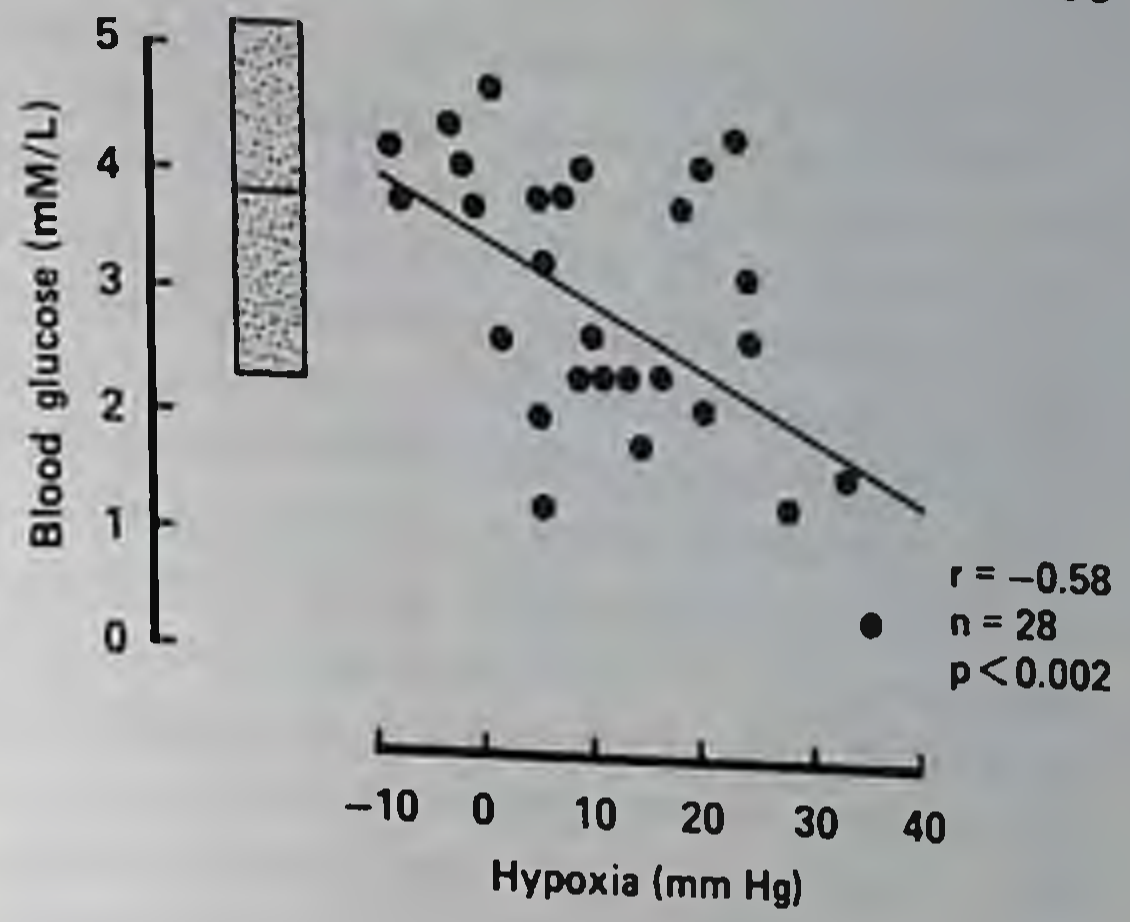

Figure 6. The relationship between umbilical venous blood hypoxia (normal mean po_2 for gestational age − observed po_2) and glucose concentration showing that hypoxic fetuses tend to be hypoglycemic before labor.[36]

(raised lactate) type occur with fetal hypoxia. In the umbilical venous blood the po_2 can be low with normal pco_2 and pH. In umbilical arterial blood, however, when the po_2 falls the pco_2 and hydrogen ion concentration rise immediately.

Growth-retarded fetuses are also hypoglycemic *in utero*, indicating that neonatal hypoglycemia can be the result of chronic fetal hypoglycemia.[36] The low levels of po_2 and glucose (which correlate significantly; Fig. 6) could both be due to poor uteroplacental perfusion leading to reduced placental transfer. Alternatively, the low glucose could result from increased anaerobic metabolism in hypoxia. This would explain the hypoglycemia of hypoxic SGA fetuses and low glycogen stores of small-for-date neonates.

Fetuses of Diabetic Mothers

Intrauterine fetal death, without warning from the conventional tests of fetal well-being, remains a problem in diabetic women. Assessment of fetal growth may be unreliable in detecting placental failure in these pregnancies because the macrosomic effects of maternal diabetes may mask growth retardation. An apparently normally grown fetus of a diabetic mother was shown to be hypoxic by cordocentesis following abnormal Doppler blood velocity studies.[32] Cordocentesis may be helpful in managing pregnancies in which noninvasive techniques are unreliable indicators of the need for early delivery.

Correlation with Noninvasive Tests

There are established noninvasive techniques that are thought to indicate placental sufficiency. The extent to which they might render fetal blood gas measurement unnecessary, once they are calibrated by cordocentesis studies, depends not only on the precision of the correlation but also the nature of the discrepancies.

Doppler Studies of the Maternal Circulation. The uteroplacental blood velocity resistance index determined by Doppler ultrasound scanning is abnormal in some pregnancies complicated by fetal growth retardation.[37] This is consistent with the histopathologic findings that in some

such pregnancies there is failure of the normal change of maternal placental bed arteries from high to low resistance vessels.[38,39] The concept that one of the causes of fetal growth retardation is poor maternal blood supply leading to fetal malnutrition was supported by the significant correlation between uteroplacental resistance index and blood gas results at cordocentesis.[40] Abnormalities in uteroplacental blood velocity may exist for many weeks before fetal growth retardation, however, and so this technique is not a useful way of timing delivery.

Doppler Studies of the Fetal Circulation. A combined linear array and pulsed Doppler ultrasound system allows calculation of the mean velocity of blood in the fetal thoracic descending aorta.[37] In SGA fetuses a decrease in aortic blood velocity correlates strongly with fetal hypoxia (Fig. 7), acidosis, hypercapnia, and hyperlacticemia.[41] When the fetal po_2 was raised by maternal hyperoxygenation, the mean velocity of blood in the fetal aorta increased so blood velocity measurement not only permits diagnosis of fetal hypoxia but also may be used as a dynamic indicator of fetal conditions.[42] The reduction in the blood velocity within the aorta is probably secondary to a compensatory redistribution of blood flow in response to hypoxia. These results are very encouraging, but the pulsed Doppler system required for this investigation is expensive and requires experienced, well-trained personnel.

The continuous-wave Doppler equipment required to record umbilical arterial blood velocity waveforms is much cheaper and easier to use. The failure to detect Doppler shift frequencies at the end of diastole in the umbilical artery (absent end-diastolic flow) nearly always indicates that fetal hypoxia or acidosis will be demonstrated by cordocentesis.[43] This simple quick test is useful for screening pregnancies with SGA fetuses but is nonquantitative and therefore indicates further investigation, for example, by cordocentesis.

Fetal Heart Rate Traces and Biophysical Score. Fetal heart rate traces and biophysical assessment, usefully applied to prolonged pregnancy, have been widely used for timing the delivery of premature SGA fetuses but this has yet to be substantiated. Cordocentesis has demonstrated that fetuses with normal fetal heart rate traces can be severely acidotic before labor.[7,8] Systematic studies comparing fetal heart rate

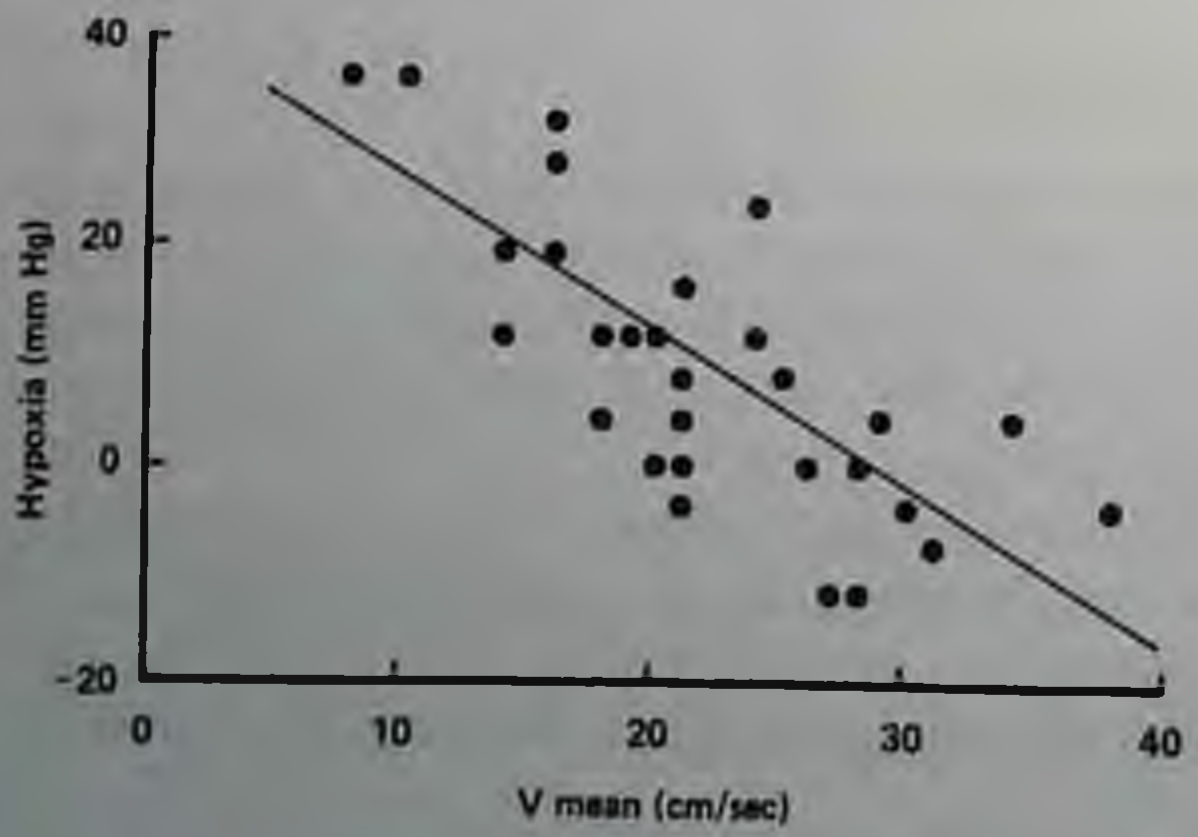

Figure 7. The relationship between umbilical venous blood hypoxia (normal mean po_2 for gestational age − observed po_2) and the mean velocity of blood in the fetal aorta (V_{mean}); $r = -0.73$, $n = 29$, $P < 0.0001$.[41]

traces and biophysical profile scores with cordocentesis results are underway and the results are eagerly awaited.

Treatment for Fetal Hypoxia?

The diagnosis of hypoxia when the fetus is too immature for delivery has stimulated attempts at *in utero* therapy. Mothers of hypoxic, SGA fetuses were given humidified oxygen (55 per cent) continuously by face mask. In five cases, maternal hyperoxygenation raised the fetal po_2 to or near to the normal range and prolonged hyperoxygenation resulted in a sustained rise in the mean blood velocity in the fetal thoracic aorta.[42] These preliminary observations suggest that if a hypoxic or acidotic fetus is too immature for delivery, maternal hyperoxygenation may prevent fetal death and allow the pregnancy to continue long enough for the fetus to be viable after delivery. The improved po_2 might reduce anaerobic metabolism of glucose and allow the fetus to replace its glycogen stores and so prevent fetal and neonatal hypoglycemia. Fetal blood measurements will stimulate further therapeutic trials and permit their proper assessment.

Does Fetal Hypoxia or Acidosis Matter?

If one extrapolates from the experience of fetal scalp blood sampling in labor, a fetal pH less than 7.20 at cordocentesis would indicate immediate delivery by cesarean section. However, the observation that the po_2 and pH can be abnormal in fetuses who appear well on conventional testing suggests that chronic hypoxia and acidosis may be much more common than previously suspected. If the fetal metabolism can compensate for these abnormalities, the disadvantages of prematurity may outweigh those of chronic hypoxia. There are substantial data showing that pH and lactic acid concentration in cord blood at birth are very poor predictors of adverse pediatric outcome.[44] This observation must make us question the policy of making delivery decisions on the basis of pH or po_2 measurements, although it may still be valid because the cases of damaging chronic intrauterine fetal acidosis may be statistically swamped by the more common, nondamaging, acute acidosis of labor.

When discrepancies between the different tests of fetal well-being occur we will not know which is the better indicator of the need for delivery. Some will argue that fetal heart rate traces and biophysical assessments are brain function tests and therefore may be more important than cord blood biochemistry. The only way to answer this debate will be studies involving many years of pediatric followup. Perinatal mortality, cord pH at delivery, and Apgar scores are too crude outcome parameters to resolve this question.

Practical Implications

Cordocentesis is useful in the investigation of SGA fetuses allowing fetal karyotyping, infection screening, and blood gas assessment. Diagnosis of the cause of poor fetal growth often results in improved obstetric management. It also may be useful in pregnancies in which other methods of assessing placental function are less reliable such as in diabetic pregnancies.

Cordocentesis also can be used like fetal scalp sampling in labor. When noninvasive tests of fetal well-being indicate premature delivery in the fetal interest, cordocentesis can exclude false-positive results. If the fetal biochemistry is normal the pregnancy could be allowed to continue, thereby reducing the neonatal risks. If the results confirm fetal hypoxia or acidosis, delivery would proceed. Direct chromosomal preparation of a placental biopsy taken during the cordocentesis procedure[10] can often provide a fetal karyotype the same day. This is important because placental failure can be associated with fetoplacental chromosomal abnormalities.

CONCLUSIONS

The applications of cordocentesis to assess fetal condition described in the text can be divided into current uses, those of probable value and future possibilities.

Current Uses

Following the demonstration of the inadequacies of indirect methods of assessing fetal anemia in red cell isoimmunization, the place of cordocentesis is established because it allows successful intrauterine diagnosis and therapy. More accurate assessment of alloimmune fetal thrombocytopenia and appropriate platelet transfusion is likely to improve the perinatal outcome while reducing the maternal risk of unnecessary obstetric intervention. The management of most potentially treatable fetal malformations may involve cordocentesis to exclude associated untreatable abnormalities before intensive intrauterine, delivery, or postnatal intervention.

Probable Value

The potentially most important application of cordocentesis is in assessing placental function, although its full value has not yet been determined. Many pregnancy complications that are currently the most difficult to manage (e.g., growth retardation, preeclampsia, maternal diabetes mellitus, and unexplained mature fetal death) are associated with fetal hypoxia. Should the noninvasive methods of assessing fetal hypoxia prove to be as inaccurate as the traditional methods of assessing fetal anemia, cordocentesis may have a major role in clinical obstetrics. At the very least the incidence of unnecessary elective premature delivery and cesarean section in the "fetal interest" could be reduced.

Future Possibilities

With precise fetal diagnosis and intravascular access, treatment of severe inherited disease by gene therapy or bone marrow transplantation may become possible; the special immunologic status of the fetus could make it an especially suitable recipient of these treatments. The study of fetal endocrinology by cordocentesis may help improve our understanding of the causes of premature labor. If the human fetus has as much control over labor as some animal species, cordocentesis could have an impact on this major obstetric problem.

The ability to sample fetal blood with relative ease and safety has many implications for the practice of obstetrics because it allows more precise fetal diagnosis and therapy. Cordocentesis already has increased our understanding of human fetal pathophysiology before labor and provided parameters with which to assess noninvasive tests. The value of using cordocentesis to assess fetal condition clinically depends on the results changing obstetric management (e.g., timing of delivery or intrauterine treatment) so as to improve the fetal outcome.

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REFERENCES

1. Soothill PW, Nicolaides KH, Rodeck CH: Invasive techniques for prenatal diagnosis and therapy. J Perinat Med 15: 117–127, 1987
2. Nicolaides KH: Cordocentesis. Clin Obstet Gynecol 31:123–135, 1988
3. Soothill PW, Nicolaides KH, Rodeck CH: Blood gas and acid-base status of the human fetus. In Rodeck CH (ed): Fetal Medicine Review, Vol 1. Meridian & Univers, Oxford, 1989
4. Soothill PW: Human fetal blood gases. MD Thesis, London, University of London, 1988
5. Rodeck CH, Campbell S: Umbilical cord insertion as a source of pure fetal blood for prenatal diagnosis. Lancet i:1244–1245, 1979
6. Daffos F, Cappella-Pavlovsky M, Forestier F: Fetal blood sampling via the umbilical cord using a needle guided by ultrasound: Report of 66 cases. Prenatal Diagnosis 3:271–277, 1983
7. Nicolaides KH, Soothill PW, Rodeck CH, et al: Ultrasound-guided cord and placental blood sampling to assess fetal well-being. Lancet i:1065–1067, 1986
8. Pardi G, Buscaglia M, Ferrazzi E: Cord sampling for evaluation of oxygenation and acid–base balance in growth-retarded human fetuses. Am J Obstet Gynecol 157:1221–1228, 1987
9. Weiner CP: Cordocentesis for diagnostic indications: Two years experience. Obstet Gynecol 170:664–667, 1987
10. Nicolaides KH, Soothill PW, Rodeck CH, et al: Why confine chorionic villus (placental) biopsy to the first trimester? Lancet i:543–544, 1986
11. Nicolaides KH, Soothill PW: Cordocentesis. In Studd J (ed): Progress in Obstetrics and Gynecology, Vol 7. Edinburgh, Longman, 1989, pp 123–43
12. Daffos F, Capella-Pavlovsky M, Forestier F: Fetal blood sampling during pregnancy with use of a needle guided by ultrasound: A study of 606 consecutive cases. Am J Obstet Gynecol 153:655–660, 1985
13. MRC Working Party: An assessment of the hazards of amniocentesis. Br J Obstet Gynaecol: (Suppl II)85: 1978
14. Bowell PJ, Selinger M, Ferguson J, et al: Antenatal fetal blood sampling for the management of alloimmunized pregnancies: Effect upon maternal anti-D potency levels. Br J Obstet Gynaecol 95:759–764, 1988
15. Nicolini U, Kochenour NK, Greco P, et al: Consequences of feto-maternal hemorrhage after intrauterine transfusion. Br Med J 297:1379–1381, 1988
16. Nicolaides KH, Rodeck CH, Mibashan et al: Have Liley charts outlived their usefulness? Am J Obstet Gynecol 155:90–94, 1986
17. Nicolaides KH, Fontanarosa M, Gabbe S, et al: Failure of ultrasonographic parameters to predict the severity of fetal anemia in rhesus isoimmunization. Am J Obstet Gynecol 158:920–926, 1988
18. Rightmire DA, Nicolaides KH, Rodeck CH, et al: Midtrimester fetal blood flow velocities in rhesus isoimmunization: Relationship to gestational age and to fetal hematocrit in the untransfused patient. Obstet Gynecol 68:233–236, 1986
19. Nicolaides KH, Soothill PW, Clewell CH, et al: Fetal hemoglobin concentration to assess the severity of red cell isoimmunization. Lancet i:1073–1075, 1988

20. Soothill PW, Nicolaides KH, Rodeck CH, et al: The relationship of fetal hemoglobin and oxygen content to lactate concentration in rhesus isoimmunized pregnancies. Obstet Gynecol 69:268–271, 1987
21. Soothill PW, Nicolaides KH, Rodeck CH: The effect of anaemia on fetal acid-base status. Br J Obstet Gynaecol 94:880–883, 1987
22. Nicolaides KH, Soothill PW, Clewell W, et al: Rh disease: Intravascular fetal blood transfusion by cordocentesis. Fetal Therapy 1:185–192, 1986
23. Daffos F, Forestier F, Kaplan C, et al: Prenatal diagnosis and management of bleeding disorders with fetal blood sampling. Am J Obstet Gynecol 158:939–946, 1988
24. Simm CG, Amigo NC, Harper RG, et al: Failure of cesarean section to prevent intracranial hemorrhage in siblings with isoimmune neonatal thrombocytopenia. Am J Obstet Gynecol 153:79–81, 1985
25. Nicolini U, Rodeck CH, Kochenour NK, et al: In-utero platelet transfusion for alloimmune thrombocytopenia. Lancet ii:506, 1988
26. Bussel J, Berkowitz R, McFarland J, et al: Antenatal treatment of neonatal alloimmune thrombocytopenia. N Engl J Med 319:1374–1378, 1988
27. Nicolaides KH, Rodeck CH, Lange I, et al: Fetoscopy in the assessment of unexplained fetal hydrops. Br J Obstet Gynaecol 92:671–679, 1985
28. Low JA, Pancham SR, Worthington D, Boston RW: Clinical characteristics of pregnancies complicated by intrapartum fetal asphyxia. Am J Obstet Gynecol 121:452–455, 1975
29. Hibbart BM, Jeffcoate TNA: Abruptio placentae. Obstet Gynecol 27:155–161, 1966
30. Pritchard J, Mason R, Corley M, et al: Genesis of severe placental abruption. Am J Obstet Gynecol 135:639–646, 1970
31. Low JA, Boston RW, Pancham SR: Fetal asphyxia during the intrapartum period in intrauterine growth-retarded infants. Am J Obstet Gynecol 113: 351–357, 1972
32. Bradley RJ, Nicolaides KH, Brudenell JM, et al: Early diagnosis of chronic fetal hypoxia in a diabetic pregnancy. Br Med J 296:94–95, 1988
33. Pasamanick B, Lilienfeld AM: Association of maternal and fetal factors with development of mental deficiency. JAMA 159:155–160, 1955
34. Soothill PW, Nicolaides KH, Rodeck CH, et al: The effect of gestational age on blood gas and acid-base values in human pregnancy. Fetal Therapy 1:168–175, 1986
35. Nicolaides KH, Economides DL, Soothill PW: Blood gases and acid-base status in appropriate and small for gestational age fetuses. Submitted for publication
36. Soothill PW, Nicolaides KH, Campbell S: Prenatal asphyxia, hyperlacticaemia, hypoglycaemia and erythroblastosis in growth retarded fetuses. Br Med J i:1051–1053, 1987
37. Griffin D, Cohen-Overbeek T, Campbell S: Fetal and utero-placental blood flow. Obstet Gynecol 10:565–602, 1983
38. Brosens I, Dixon HG, Robertson WB: Fetal growth retardation and the arteries of the placental bed. Br J Obstet Gynaecol 84:654–664, 1977
39. Sheppard BL, Bonnar J: An ultrastructural study of the utero-placental spiral arteries in hypertensive and normotensive pregnancy and fetal growth retardation. Br J Obstet Gynaecol 88:695–705, 1981
40. Soothill PW, Nicolaides KH, Bilardo C, et al: Utero-placental blood velocity resistance index and umbilical venous po_2, pco_2, pH, lactate and erythroblast count in growth retarded fetuses. Fetal Therapy 1:176–179, 1986
41. Soothill PW, Nicolaides KH, Bilardo C: The relation of fetal hypoxia in growth retardation to mean velocity of blood in the fetal aorta. Lancet ii:1118–1120, 1986
42. Nicolaides KH, Campbell S, Bradley RJ, et al: Maternal oxygen therapy for intrauterine growth retardation. Lancet i:942–945, 1987
43. Nicolaides KH, Bilardo CM, Soothill PW, et al: Absence of end diastolic frequencies in the umbilical artery: A sign of fetal hypoxia and acidosis. Br Med J 297:1026–1027, 1988
44. Ruth VJ, Raivio KO: Perinatal brain damage: Predictive value of metabolic acidosis and the Apgar score. Br Med J 297:24–27, 1988

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Doppler Ultrasound Fetal Velocimetry and Its Role in Obstetrics

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It is just over 10 years since Doppler ultrasound was used to monitor blood velocity in the human umbilical artery.[4,16] Since then the technique has become relatively inexpensive, simple to perform, and the velocity patterns in the umbilical artery are often dramatic when fetal compromise is present.[3] This apparent potential has lead to Doppler velocimetry being introduced as a routine investigation for fetal assessment in many centers. Although the technique has enormous promise for clinical investigation, its true place in obstetric practice has yet to be assessed. This article explores the physiological basis of Doppler velocimetry and assess how human fetal velocity waveforms should affect obstetric decision making.

HISTORY

Doppler ultrasound was first used to measure blood velocity in peripheral arteries[24] and was subsequently developed to evaluate occlusive arterial disease.[10] It was not until 1977, however, that Doppler ultrasound was first used to measure velocity changes in the human umbilical artery, thereby introducing a new noninvasive method of assessing fetal hemodynamics.[4,16]

Fitzgerald and Drumm suggested in their original paper that changes in the velocity waveform might be important in the assessment of the growth-restricted fetus. Much of the subsequent work was directed toward determining absolute blood flow, both in the fetal aorta and the umbilical vein, because of the probability that fetal cardiac output might be altered when the fetus is compromised.[2,8,13,15] In practice absolute blood flow measurements have been found to be too imprecise

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to be useful clinically.[3,14] The velocity waveforms alone, however, may provide valuable information regarding fetal condition.

UMBILICAL ARTERY WAVEFORMS AND INTRAUTERINE GROWTH RETARDATION

A strong correlation is now established between abnormal umbilical artery velocity waveforms and intrauterine growth retardation.[3,5,11,26] In these initial studies pregnancies were identified in which growth restriction was present and the umbilical artery waveforms were shown to be substantially different from waveforms observed in the normal fetus (Fig. 1). Abnormal waveforms were characterized by a decrease in diastolic velocity relative to the systolic value. More extreme waveform changes were also observed in growth-retarded fetuses characterized by absent or reversed diastolic velocity. The perinatal outcome in these initial studies was usually poor, but this may have been at least in part because of the severity of the cases that were chosen for study.

A more recent study[1] assessed the value of abnormal umbilical Doppler waveforms in predicting intrauterine growth retardation. They found that as a screening test the presence of abnormal Doppler waveforms had a poor predictive value for intrauterine growth retardation. Nevertheless, fetuses identified as having abnormal waveforms had a less favorable prognosis than the general population.

RELATIONSHIP WITH PLACENTAL PATHOLOGY

Analogy with other vascular beds suggests that changes in the umbilical artery waveform might relate to increased resistance to blood flow "downstream" from the umbilical artery (i.e., the vessels of the placental vascular bed). Traditional examination of the placenta shows no specific

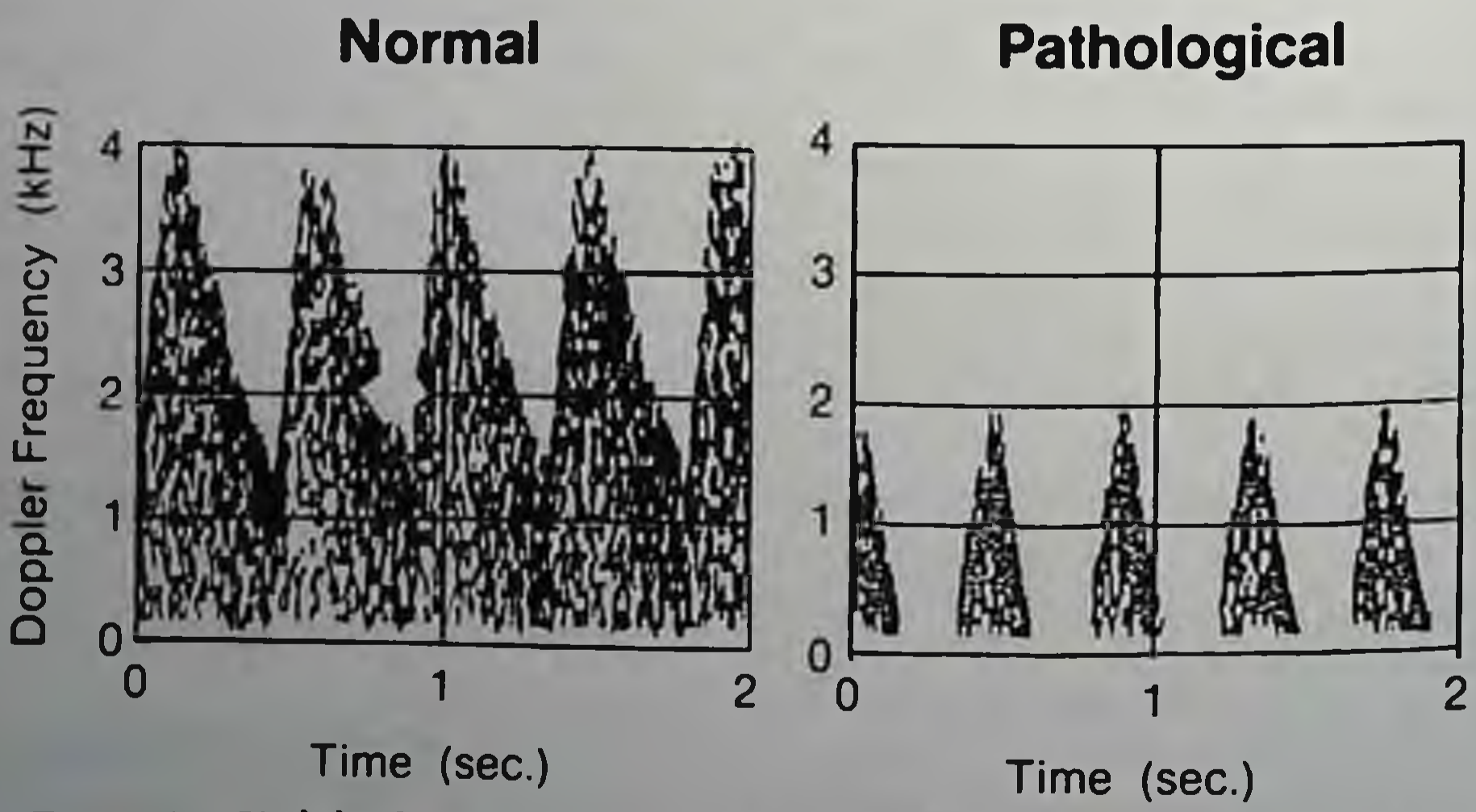

Figure 1. Umbilical artery waveforms in a normal and a growth-restricted fetus at approximately the same gestational age.

histopathologic changes in the presence of fetal growth restriction,[6] but the argument for a lesion at this level is strong.

The major arterial pressure change in the placenta occurs at the level of the arterioles in the tertiary stem villus. In 1985, Giles and his colleagues[7] reasoned that increased placental resistance would result if the number of vessels in the tertiary stem villi was reduced. They were able to establish that the tertiary stem villus in the placenta of the growth-restricted fetus does in fact contain fewer arterioles. A quantitative relationship between changes in the umbilical artery waveform shape and the number of small arterial vessels in the tertiary stem villi was subsequently confirmed by McCowan and her co-investigators (1987).[17] It is not clear whether these placental changes are due to defective placentation or embolic phenomena that result in obliteration of the vessels. In the long run this type of placental pathology could clearly impede the fetoplacental circulation to the extent that the ability to exchange nutrients and gases across the placenta is reduced.

Initially it was hoped that the Doppler technique might permit the distinction to be made between intrinsic (symmetrical) and extrinsic (asymmetrical) causes of fetal growth restriction. Although the pathologic changes in the placenta have not yet been clearly identified, it is now evident that growth restriction owing to chromosomal abnormality can produce waveforms indistinguishable from those seen in association with other causes.[12]

UMBILICAL ARTERY WAVEFORM AND FETAL WELL-BEING

It has been suggested that umbilical artery waveforms are a sensitive indicator of fetal hypoxia and may therefore provide a useful way of assessing fetal well-being. Several studies have demonstrated a correlation between abnormal waveforms and poor perinatal outcome, but it is not yet clearly established how abnormal velocity waveforms relate to fetal condition.

Soothill et al. (1986)[25] studied a group of growth-retarded fetuses and measured fetal blood gases by cordocentesis as well as aortic blood velocity patterns using the Doppler technique. They were able to demonstrate a negative correlation between the severity of fetal hypoxia, hypercapnia, acidosis, and hyperlactemia with reduction in mean blood velocity in the fetal aorta. They suggested this might reflect increasing placental impedance in response to hypoxia. They subsequently reported[21] that the aortic velocity in growth-restricted fetuses could be increased by maternal oxygen therapy, thus reinforcing the view that abnormal aortic velocity in some way reflects the oxygen status of the fetus. More recently Nicolaides (1988)[22] observed it was the growth-restricted fetus with absent end-diastolic velocity that was more likely to be hypoxic or acidotic.

A recent study[12] assessed umbilical artery waveforms in fetuses dying with congenital abnormalities. All eight fetuses had either absent or reversed diastolic velocity, and two were found to be hypoxic and acidotic when blood was sampled by cordocentesis. The authors con-

clude that "once the diastolic component of umbilical artery flow velocity waveforms become absent or reversed, the fetus is in a state of hypoxia and acidosis, and fetal death is impending." Another report[27] stressed "the need for immediate delivery" with zero end-diastolic flow. It is not clear from any of these studies whether the Doppler waveforms reflect hypoxia per se or some other physiologic phenomenon associated with deterioration of fetal condition. It is also impossible to establish whether hypoxia occurs in fetuses with normal waveforms or to know whether abnormal waveforms antedate hypoxia.

We assessed outcome in a series of 32 fetuses with absent diastolic velocity in our own unit in Toronto (Ryan G: Unpublished observations, 1989). Delivery was always undertaken on criteria other than the Doppler waveforms. Of the 32 fetuses, 8 required delivery within 3 hours of assessment and a further 8 between 4 and 24 hours. The remainder, however, were followed for up to 42 days before delivery was indicated. Although absent diastolic velocity in this group was associated with poor obstetrical outcome this data does not support the view that immediate delivery is required solely on the basis of absence of diastolic velocity. In fact, in some cases the fetus may be unnecessarily exposed to the hazards of prematurity if absent diastolic velocity is used as the sole criterion for delivery.

INFLUENCE OF HEART RATE ON UMBILICAL WAVEFORMS

It has become apparent that fetal heart rate can affect the indices used to quantitate the umbilical artery waveforms.[19,20] This is important because a change in fetal heart rate might cause changes in the indices that could be incorrectly ascribed to changes in placental resistance. We

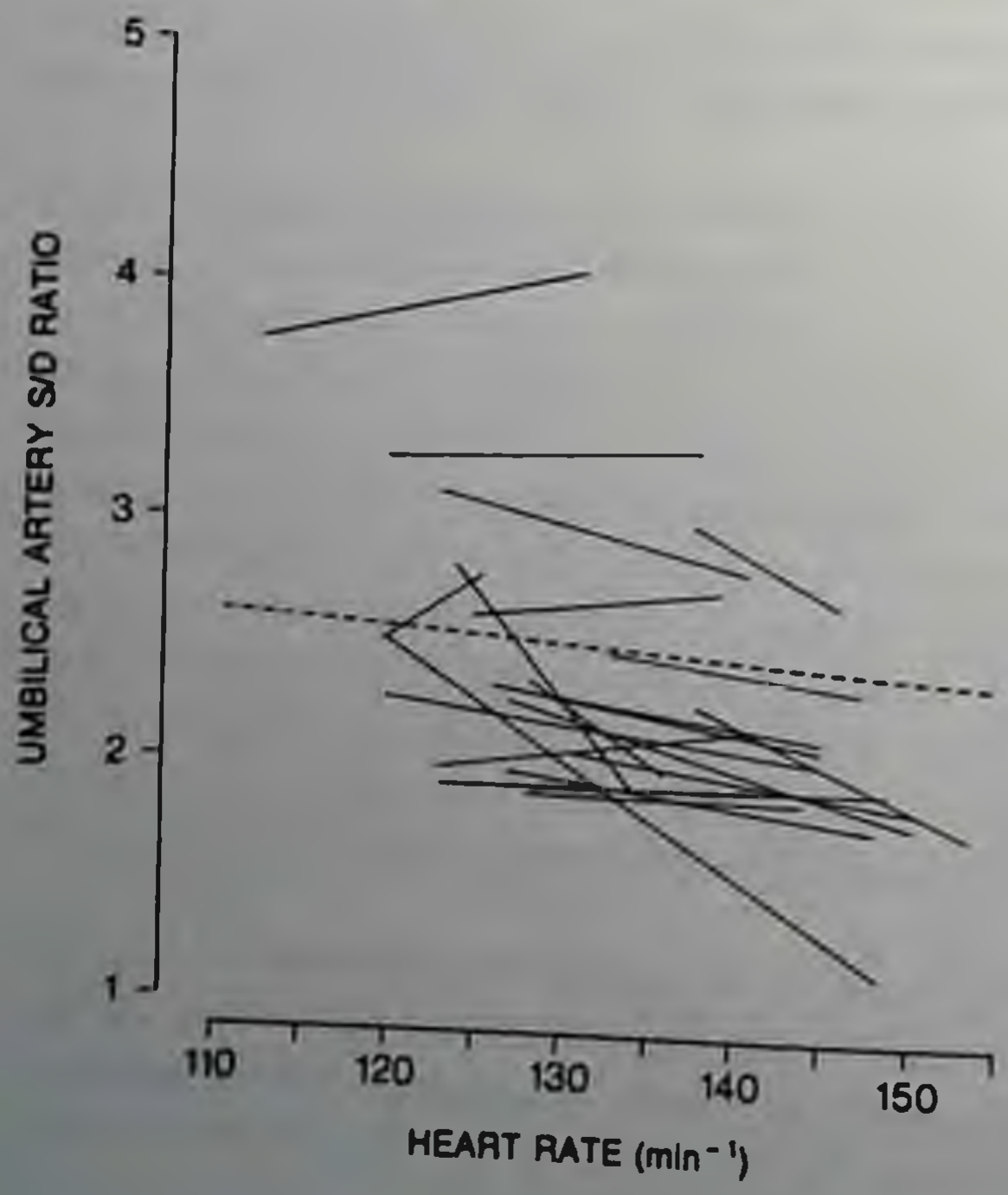

Figure 2. The relationship between the S/D ratio and fetal heart rate during spontaneous accelerations.

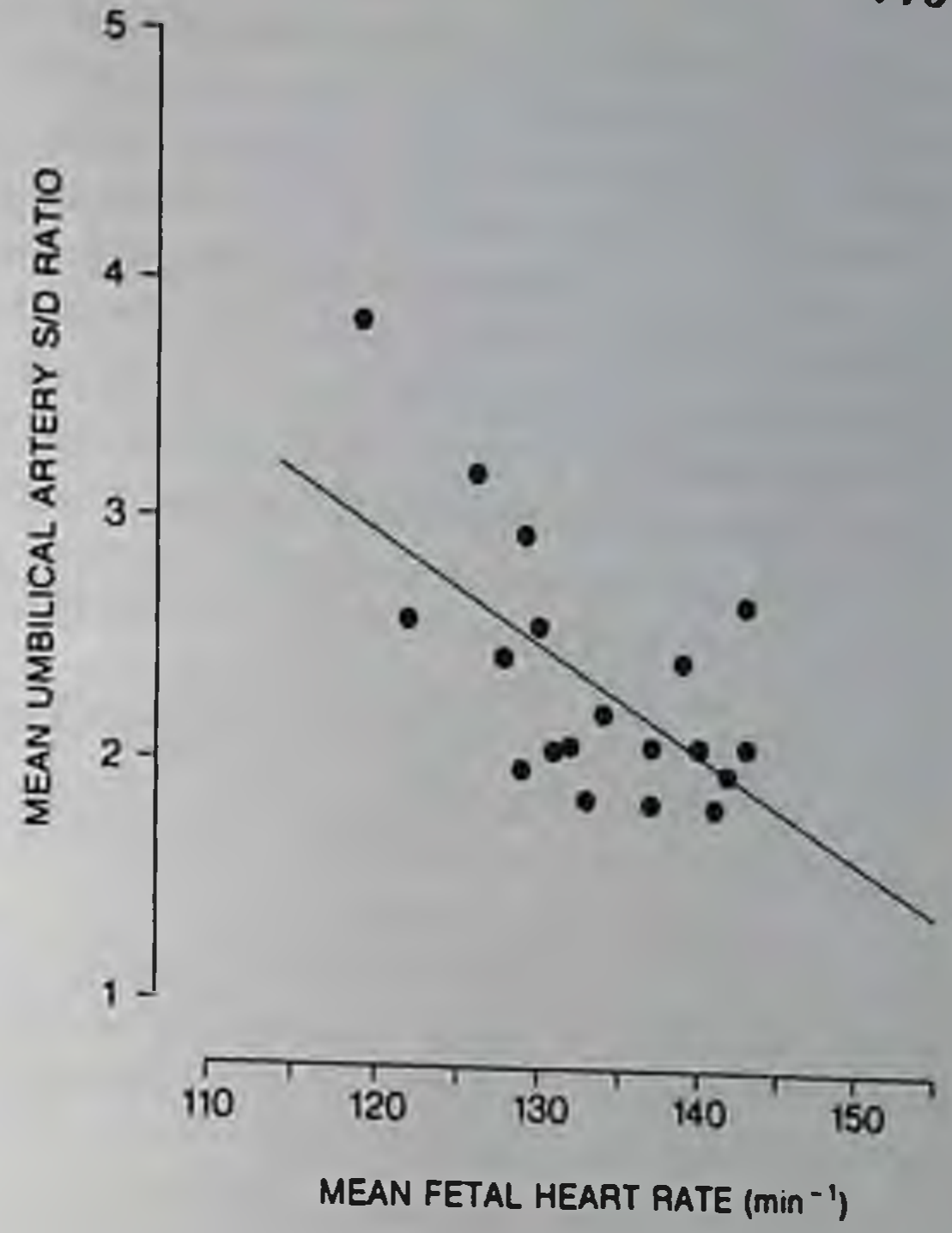

Figure 3. The relationship between mean heart rates and mean S/D ratio in each fetus.

studied changes in the ratio between the systolic and diastolic peaks (S/D) that occurred in normal fetuses during spontaneous acceleration of the fetal rate (Fig. 2). We found that acceleration of the fetal heart rate in an individual fetus caused only a small change in the S/D ratio. By comparison there was a stronger negative relationship between the mean heart rate of an individual fetus and the mean S/D ratio (Fig. 3). This suggests that high heart rate and low S/D ratios are associated but not causally. It is interesting to speculate what causes this association; perhaps increased placental vascular resistance causes both high S/D ratio and lower heart rates.

Because the changes in S/D ratio within the range of normal heart rate are small, we would suggest no adjustment to the S/D value is required for most clinical purposes. On the other hand, it is a phenomenon that should be taken into account in research studies, for example, when the effect of drugs on S/D is being assessed. Here a small change in S/D ratio may be due to a change in heart rate rather than other physiologic causes. The effect of heart rate on S/D ratio becomes more dramatic when at extremes of heart rate, for example when fetal heart block is present.

THE USE OF ANIMAL MODELS TO INVESTIGATE DOPPLER VELOCIMETRY

In attempting to unravel the causes of abnormal umbilical artery waveforms, it is apparent that there are many complex pathophysiologic changes that may contribute to such changes. It is impossible to isolate individual pathologic changes in the human fetus and thus difficult to

establish whether waveform alterations reflect changes in blood gas status, placental pathology, blood viscosity, blood flow alterations in the fetus, or changes in the pattern of cardiac contraction.

In an attempt to assess the effects of some of these pathologic changes, we have developed an animal model based on a chronically catheterized sheep preparation. To measure the umbilical artery waveform we have implanted Doppler crystals on the umbilical artery. Such a model also allows fetal blood pressure and blood gas status to be monitored continuously. Placental vascular resistance and blood flow can also be calculated. In human studies[7,17] there is a correlation between waveform changes and a decrease in the number of vessels at the level of the tertiary stem villi. Although this suggests a causal relationship, the waveform changes may result from asphyxial changes that may or may not be related to changes in placental pathology. To test whether abnormal waveforms could be created by occlusion of these vessels in the placental bed, we embolized the fetal side of the placenta with plastic microspheres. We found that this first caused reduction in diastolic velocity until it was absent and eventually reversal in direction of flow. These waveform changes bear a close resemblance to those observed in growth-restricted human fetuses.

Because abnormal waveforms have been reported in hypoxic human fetuses we examined the effect of hypoxemia on the umbilical waveform in the sheep model. We found that hypoxia had no effect on the systolic/diastolic velocity ratio. In fact even when we exposed the fetuses to prolonged periods of hypoxemic acidosis the waveforms remained unchanged. In a similar experiment we also found that increasing fetal hematocrit and viscosity by up to 100 per cent had little effect on the velocity patterns.

This series of animal experiments suggest that abnormal umbilical artery waveforms reflect primarily changes in the placental vascular bed rather than asphyxial changes in the fetus.

DOPPLER ULTRASOUND AND OBSTETRIC DECISION MAKING

If Doppler ultrasound is to find a role in obstetric practice, then its impact on obstetric decision making must be assessed. Trudinger et al. (1987)[26] carried out a prospective trial in 300 high-risk patients and randomized them either into a control group or a group in which the umbilical waveform was available to the clinician. When the Doppler analysis was available to the clinician there were fewer cesarean sections performed for fetal distress and fewer cases of fetal distress in labor. This suggests first that compromised fetuses were identified earlier by the presence of abnormal Doppler waveforms and delivered earlier, and second that normal waveforms were taken as reassurance of fetal health so that delivery could be postponed. There was a trend toward improved neonatal outcome in the study group but no individual measures of outcome achieved statistical significance.

It is not clear how obstetric decisions would be altered by a different group of obstetricians. In this Australian study the overall cesarean sec-

tion rate even in this high-risk population was only 15 per cent. In populations in which the threshold for cesarean section is much lower, Doppler studies might serve only to further increase cesarean section rates that are already much higher. Thus it is necessary to establish which waveform changes should change management and how.

The answers to these problems can be achieved only by the use of large randomized prospective trials in which management is altered in a specific fashion by strict criteria. Such studies are now needed to place the role of Doppler investigations finally into perspective.

CONCLUSIONS

Doppler ultrasound examination of the umbilical artery has undoubtedly given a new insight into changes in fetal cardiovascular physiology. The interpretation of abnormal waveforms is still somewhat problematic.

It is clear that abnormal waveforms are associated with less favorable perinatal outcome. Reversed diastolic velocity is a rare finding and almost always accompanied by an adverse outcome. Absent diastolic velocity is a more common finding and identifies fetuses that need close surveillance. Abnormal waveforms with less pronounced changes are more difficult to interpret. It is not clear which pregnancies should be screened using Doppler ultrasound; screening the whole population would certainly prove expensive and initial studies suggest that it may not be effective.[1]

Thus it remains to be established who should be subjected to Doppler examination, when should they be assessed, and what action should be taken in response to the results. It is our opinion that these issues should be addressed before Doppler velocimetry of the umbilical artery is adopted into routine obstetric practice.

Umbilical artery waveforms have been shown to be abnormal in the presence of intrauterine growth retardation, although at present it would seem to be a poor screening test to identify unrecognized cases. Placental vascular changes have been associated with abnormal waveform patterns. Hypoxia and acidosis also have been associated with abnormal waveforms. Animal studies show that placental embolization causes waveform changes, but asphyxial insults do not. Heart rate has a small effect on waveform indices at normal heart rates but a longer effect at more extreme rates. The precise place of Doppler velocimetry in clinical practice is not yet established, but we suggest that it should be used only as an indicator for increased surveillance, and further interventions should be made only when conventional test results become abnormal.

REFERENCES

1. Beatty RB, Dornan JC, Clements CWA, et al: Umbilical artery velocity waveform assessed as an antenatal screening tool for intrauterine growth retardation and poor fetal outcome. (abstr). Br J Obstet Gynaecol 95:534, 1988
2. Eik-Nes SH, Brubakk AO, Ulstein M: Measurement of human fetal blood flow. Br Med J 1:283, 1980

3. Erskine RLA, Ritchie JWK: Umbilical artery blood flow characteristics in normal and growth retarded fetuses. Br J Obstet Gynaecol 92:605, 1985
4. FitzGerald DE, Drumm JE: Noninvasive measurement of human fetal circulation using ultrasound: A new method. Br Med J 2:1450, 1977
5. Fleischer A, Shulman G, Farmakides G: Umbilical velocity waveforms in intrauterine growth retardation. Am J Obstet Gynecol 151:502, 1985
6. Fox H: Pathology of the placenta. In Bennington JL (ed): Major Problems in Pathology, Vol 7. Philadelphia, WB Saunders, 1978, p 250
7. Giles WB, Trudinger BJ, Baird PJ: Fetal umbilical artery flow velocity waveforms and placental resistance: Pathological correlation. Br J Obstet Gynaecol 92:31, 1985
8. Gill RW: Pulsed Doppler with B-mode imaging for quantitative blood flow measurement. Ultrasound Med Biol 5:223, 1979
9. Gill RW, Trudinger BJ, Garrett WJ: Fetal umbilical venous flow in utero by pulsed Doppler and B-mode ultrasound. Am J Obstet Gynecol 139:720, 1981
10. Gosling RG, King DH, Newman DL, et al: Transcutaneous measurement of arterial blood velocity by ultrasound. In Ultrasonics for Industry Conference Papers. Guildford, IPC Press, 1979, p 16
11. Griffin D, Cohen-Overbeek T, Campbell S: Fetal and uteroplacental blood flow. Clin Obstet Gynaecol 10:565, 1983
12. Hsieh FJ, Chang FM, Ko TM, et al: Umbilical artery velocity waveform in fetuses dying with congenital anomalies. Br J Obstet Gynaecol 95:478, 1988
13. Kurjak A, Rajhvajn B: Ultrasonic measurements of umbilical blood flow in normal and complicated pregnancies. J Perinat Med 10:3, 1982
14. Laurin J, Lingman G, Marsal K, et al: Fetal blood flow in pregnancies complicated by intrauterine growth retardation. Obstet Gynecol 69:895, 1987
15. Lingman G, Marsal K: Fetal central blood circulation in the third trimester of normal pregnancy: A longitudinal study: I. Aortic and umbilical blood flow. Early Human Development 13:137, 1986
16. McCallum WD, Williams CS, Napel S, et al: Fetal blood velocity waveform. Am J Obstet Gynecol 127:491, 1978
17. McCowan IM, Mullen BM, Ritchie JWK: Umbilical artery flow velocity waveforms and the placental vascular bed. Am J Obstet Gynecol 157:900, 1987
18. McCowan IM, Erskine LA, Ritchie JWK: Umbilical artery Doppler blood flow studies in the preterm small for gestational age fetus. Am J Obstet Gynecol 156:655, 1987
19. Mires G, Dempster J, Paten NB, et al: The effect of fetal heart rate on umbilical artery flow waveforms. Br J Obstet Gynaecol 94:665, 1987
20. Morrow RJ, Adamson SL, Lewin M, et al: The influence of spontaneous accelerations of fetal heart rate on umbilical artery velocity waveforms. Am J Obstet Gynecol (in press)
21. Nicolaides KM, Bradley RJ, Soothill PW, et al: Maternal oxygen therapy for intrauterine growth retardation. Lancet 1:942, 1987
22. Nicolaides KM, Bilardo CM, Soothill PW, et al: Absence of end diastolic frequencies in umbilical artery: A sign of fetal hypoxia and acidosis. Br Med J 297:1026, 1988
23. Ryan G, Morrow RJ, Kelly EN, et al: Absent umbilical artery diastolic flow using Doppler ultrasound: Clinical implications. Presented to the Society of Perinatal Obstetricians, New Orleans, 1989
24. Satomura S: Study of the flow pattern in peripheral arteries by ultrasonics. J Acoust Soc Japan 15:151, 1959
25. Soothill PW, Bilardo CM, Nicolaides KH, et al: Relation of fetal hypoxia in growth retardation to mean blood velocity in the fetal aorta. Lancet 2:1118–1119, 1986
26. Trudinger BJ, Giles WB, Cooke CM, et al: Fetal umbilical artery flow waveforms and placental resistance: Clinical significance. Br J Obstet Gynaecol 92:23, 1985
27. Woo JSK, Liang SI, Lo RLS: The significance of an absent or reversed end diastolic flow in Doppler umbilical artery waveforms. J Ultrasound Med 6:291, 1987

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