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TWIN PREGNANCY

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Twin Pregnancy

Stanley A. Gall, MD, *Guest Editor*

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STANLEY A. GALL, MD
GUEST EDITOR

Preface

Few issues in obstetrics create more ambivalent emotions than the diagnosis of a twin gestation. The physician and patient alike are thrilled with the diagnosis, and the immediate thought is the delivery of healthy mature infants. Very rapidly, however, reality returns to the obstetrician and all of the obstetric problems associated with twin gestation become vividly real. As the patient is informed of the tribulations and risks of twin gestation, she also enters the world of reality.

The assembly of complete clinical information on twin gestation in one source is difficult to locate; therefore, the rationale for this issue was to assemble a group of clinicians with expertise in management of twin gestation and neonatal care and bring together all of the newer management techniques available for the obstetrician to use. This issue reviews these techniques and suggests appropriate interventions for each problem.

An area that is vitally important is the need for timely consultation with a maternal–fetal medicine specialist. A well-thought-out "game plan" for pregnancy frequently will allow management by the referring obstetrician. If an adverse event occurs, such as the onset of preterm labor, the referral lines are established for both mother and physician, and effortless transport can occur. This is highly preferable to the "middle-of-the-night/preterm labor/no beds available" scenario that occurs much too often. It is absolutely imperative that the patient with a twin gestation deliver her infants in a facility with proper equipment and skilled personnel. With the inherent morbidity and mortality far exceeding the singleton gestation, no physician should want to contribute to a poor outcome by allowing the ego to overcome good obstetric sense.

The objective of every obstetrician who manages a twin gestation is the delivery of two healthy and intact infants with a healthy mother. This issue begins with a discussion of the morbidity and mortality of twin gestation, incidence of twinning, and diagnosing twin gestations. The fact that the incidence of twins is roughly only 0.8 per cent while

twins represent 11 per cent of the neonatal deaths is very sobering. This is followed by a review of the effects of twins on mother, on each other, and on the process of labor. The antepartum management is of utmost importance, and the roles of ultrasound, fetal growth assessment, tocolysis, and cerclage are discussed. The appropriate role of fetal surveillance, amniocentesis, and management of the death of one fetus is described. The greatest threat to the twin gestation is preterm labor. The place for bedrest and beta-sympathomimetic agents is put into proper prospective.

The placenta in the twin gestation continues to confuse clinicians; therefore, we have presented an extensive review of twinning and approaches to review placental evaluation. Antepartum complications and management of labor and delivery are well represented. The concise discussion of anesthesia management presents a logical approach to the delivery of the twin gestation.

The article presenting the morbidity and mortality in twins uses an epidemiologic approach comprising a database of over 80,000 pregnancies from the University of Illlinois perinatal network. This allows excellent insight into the outcome of a large singleton and twin population. Finally, a discussion of neonatal problems in twins concludes the issue.

It is hoped this issue will be of reference and assistance to the obstetrician caring for the twin gestation. The goal must be to improve perinatal outcome continually.

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Incidence, Morbidity and Mortality, and Diagnosis of Twin Gestations

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The amount of information available regarding twin gestations is astounding. Twins are apparently still as fascinating to obstetricians as they have been to historians and philosophers throughout the centuries. In ancient times, twins were regarded variously as being of celestial or demonic origin. Many American Indian tribes considered twins to be supernatural and developed great rituals involving them. In the last century, interest in twins moved from the ethereal to the scientific, and the study of twins contributed to the fledgling disciplines of genetics and psychology. In the last 30 years, twin gestation has been studied extensively by obstetricians and perinatologists. The literature is replete with information, often contradictory, regarding diagnosis, antepartum management, and delivery. Although undoubtedly related to the inherent interest twins arouse, such abundance also reflects the fact that twin gestation accounts for significant perinatal morbidity and mortality, despite the great obstetrical advances of recent years.

INCIDENCE

It is difficult to state the exact incidence of twinning with authority. Most epidemiologic studies of twins exclude pairs with no liveborn members. When stillborns and spontaneous abortions are thus eliminated, incidence rates reflect successful twin gestations at advanced gestational ages rather than twin conceptions. Livingston has shown that twin gestations have a higher frequency of spontaneous abortion than singleton pregnancies.[19] Alternatively, only one member of the twin gestation may be lost. In an excellent study by Landy,[17]

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1000 pregnancies were meticulously evaluated by ultrasound in the first trimester. The rate of twin conception was found to be 3.29 per cent if two fetuses were identified, and 5.39 per cent if a fetus and a second empty sac was seen. Of the twin conceptions identified, 21.2 per cent subsequently lost one fetus, an event referred to as the "vanishing twin phenomenon." A similar study, in which twin intrauterine fetuses were diagnosed by ultrasound in the first trimester, reported a vanishing twin rate of 63 per cent.[29] Excluding multiple gestation resulting from the use of artificial ovulants, and considering the above single or double first trimester losses, the resultant incidence is usually stated as 3 to 5 per 1000 for monozygotic and 4 to 50 per 1000 for dizygotic twins.

Monozygotic twins result from the fertilization of one ovum, which then divides into two embryonic primordia, usually around the end of the first week. Because the ratio of monozygotic to dizygotic twins is 17.5 to 1 in abortuses, and because malformations and conjoined twins commonly occur, it has been suggested that monozygotic twinning results from a chance teratogenic event. The incidence of this phenomenon remains fairly constant throughout the world. Because of this constancy and its apparent chance occurrence, it was thought that monozygotic twinning could not be influenced by heredity. Although subject to ascertainment bias, several studies have suggested a familial (maternal) predisposition to monozygotic twinning.[29] Such a familial influence must be small, however, because monozygotic twinning occurs at a rate of 4 per 1000 throughout the world and appears to be uninfluenced by race, environmental factors, physical characteristics, or fertility.

The rate of dizygotic twinning, however, varies greatly among different populations. Dizygotic twins result from multiple ovulation and the subsequent fertilization of two ova by two different sperm. Such multiple ovulation is due, at least in part, to overstimulation by follicle-stimulating hormone (FSH) and the surge of luteinizing hormone. In the Nigerian population, mean FSH levels are higher at the peak, and for 4 days before and after the peak, in women who have had one set of twins as compared to women who have had only singletons. In women with two sets of twins, the level is higher still.[27] Such a high peak may cause increased folliculogenesis in the succeeding cycle. It is also possible that a high peak may reflect generally higher FSH levels throughout the cycle, and thus result in multiple ovulation. When one considers the diverse hereditary and environmental factors which seem to predispose to dizygotic twinning, it may be that their common effect is an influence on hormone production.

A familial tendency to dizygotic twinning has long been recognized, inherited predominantly on the maternal side. When women who are dizygous twins, and the female sibs of such twins become pregnant, they demonstrate an increased dizygotic twinning rate among their own offspring. Genetic factors also may explain the variations in twinning frequencies observed between different racial groups. For example, the twinning rate in Scotland is 12.4 per 1000

compared to 57.2 per 1000 in Nigeria.[26] Japan has the lowest rate at 4.3 per 1000. Interestingly, among interracial marriages, the rate of dizygotic twinning most closely resembles that of the mother's race.[37]

Nutritional factors also seem to play an important role in the incidence of dizygotic twinning. In animals, litter size increases with nutritional level. Observations of the twinning rate during different nutritional states suggest that this phenomenon occurs in human beings as well. Nylander has shown a definite gradient in the twinning rate related to nutritional status as reflected by maternal size. Taller, heavier women had a twinning rate 25 to 30 per cent higher than short, nutritionally deprived women.[26] This observation agrees with the experience in post–World War II Europe, when undernourishment was associated with a fall in the dizygotic twinning rate.

Maternal age also exerts a positive effect on the incidence of dizygotic twinning. The rate rises from 0 at puberty, a time of minimal ovarian activity, to a peak at age 37,[1] when maximal hormonal stimulation increases the rate of double ovulation. The fall in incidence as menopause approaches probably reflects exhaustion of the Graafian follicles.

Fertility, and parity as it relates to fertility, also influences the rate of dizygotic twinning. Bulmer demonstrated that the twinning rate is higher in those pregnancies conceived in the first 3 months of marriage than among similar pregnancies conceived later. This may be related to maternal fertility, as he has also shown that the incidence of twinning increases with parity, independent of age.[1] Coital frequency also positively affects the twinning rate.[14]

Finally, it should be mentioned that fertility drugs and in vitro fertilization have resulted in increased numbers of multiple births, due to multiple ovulation after overstimulation. The incidence of multiple gestation after treatment with clomiphene citrate ranges from 6.8 to 17 per cent. It may reach 18 to 53.5 per cent after treatment with gonadotropins.[31]

MORBIDITY AND MORTALITY

Aside from an interest in etiology and incidence, twin gestation is of concern to perinatologists because of its high associated morbidity and mortality. Although the incidence of twins is roughly only 0.8 per cent, twins represent 11 per cent of neonatal deaths.[21]

Malformations

Part of this poor outcome is related to the fact that the frequency of malformation and malformation complexes is increased in twins as compared to singletons. The incidence of major malformations is 2.12 per cent and of minor malformations is 4.13 per cent in twin gestations. This increase is almost entirely due to the high incidence of structural defects in monozygotic twins. Since monozygotic twinning itself may result from a teratogenic event, associated malformations are more

likely. Further, this event may disrupt the developmental time clock and thus cause malformation complexes related to improper timing of embryologic events, or may render the fetus more susceptible to environmental agents. Schinzel[32] has divided these malformations into three categories. The first includes those defects resulting from the teratogenic event of twinning itself, and includes conjoined twins, amorphous twins, sirenomelia, holoprosencephaly, neural tube defects, and anencephaly. The second category of malformations results from vascular interchange between monozygotic twins. Vascular connections may give rise to reverse flow with acardia in one twin. If the death of one twin results in DIC with embolization via vascular connections to the living twin, defects such as microcephaly, hydranencephaly, intestinal atresia, aplasia cutis, or limb amputation may result. The last category is described as those defects that result from intrauterine crowding in late gestation, and are equally common in monozygotic and dizygotic twins. Improper growth and positioning adversely affects phenotype and can result in such defects as talipes or congenital hip dislocation. Finally, it must be noted that some malformations, such as congenital heart defects, may only seem more common in twins because diagnosis in one twin may lead to a more detailed examination of the second apparently healthy twin, and thus result from an ascertainment bias.

Abnormal Growth

Placentation and cord factors also contribute to fetal development and growth. When twin and singleton placentas are sonographically compared, those of twins show advanced maturation with grade III placentas first noted at 29 to 31 weeks.[28] This early maturity may be related to the different intrauterine growth pattern of twin fetuses, or may reflect changes consistent with intrauterine growth retardation. Advanced placental maturation, and an increased fetal mass resulting in relative placental insufficiency, leads to intrauterine growth retardation in two thirds of twin pregnancies.

Twin gestations are also associated with an increased incidence of placental and cord defects such as solitary umbilical artery, velamentous and marginal cord insertions, and vasa previa. Not only do these defects impact on fetal development and nutrition, but they expose the fetus to the risk of exsanguination at the time of rupture of membranes. Monoamniotic twins are at high risk for cord accidents due to entanglement. Monochorionic twins may succumb to the twin–twin transfusion syndrome or suffer injuries secondary to embolization, as previously discussed.

Prematurity

The twin fetuses who are genotypically and phenotypically normal, and who suffer no untoward event during gestation, are still at increased risk as they approach term. Twins deliver prematurely at a rate 5 to 10 times that of singletons. Multiple gestation is complicated by delivery before 35 weeks in 21.5 per cent, with 50 per cent of twins

weighing less than 2500 gm at birth. Further, for unknown reasons, male twin gestations tend to be even shorter than either male and female or female twin pregnancies.[2-4]

One factor leading to preterm delivery may be increased intrauterine volume. It has been observed that, as the number of fetuses increases, the duration of the gestation decreases. It may be that mechanical stretch by increased fetoplacental mass increases intra-amniotic pressure, and thus increases the risk of premature rupture of membranes, as well as stimulates early labor. This scenario accounts for the significantly increased incidence of PROM, preterm labor, and third trimester bleeding observed in twin gestation.

The most significant morbidity due to preterm twin delivery is that related to delivery of the low birth weight infant. Respiratory distress syndrome occurs in 48 per cent and intraventricular hemorrhage occurs in 19 per cent of twins delivered at 25 to 32 weeks' gestational age.[12]

The problems of prematurity and low birth weight/IUGR are of special concern in twins because studies have shown that these infants do not catch up after birth. In an impressive, long-term study that carefully monitored twins up to age 11 years,[22, 35, 36] it was shown that the twins exhibited significant delays in growth and development. They were shorter, lighter, and had smaller head circumferences compared to singletons. They were slower to smile, talk, feed themselves, or learn bladder control. However, as it has been shown that many neurologic and intellectual defects are related to being small for dates,[9] or are aggravated by poor environment, the authors wisely matched the twins to singletons with regard to prenatal and neonatal problems, birth weight, gestational age, and home environment. After this matching, the only remaining developmental differences at age 3 years were delays in achieving the early milestones of talking in single words and sentences. At age 11 years, although the twins still lagged in full scale and verbal IQ scores, their performance IQ scores were comparable to those of the singletons. Although this represents some cause for optimism, it must be pointed out that in terms of physical growth, the twins did not catch up. At each age, they were similar in height to singletons 3 months younger, and similar in weight to those 6 months younger. Head circumference showed the greatest discrepancy; at age 11 years the twins had a mean circumference close to that of singletons at age 7 years.

Trauma at Delivery

Another significant source of morbidity in the preterm and term birth of twins is the delivery itself.

Decisions concerning the method of delivery are based on many factors, not the least of which is the position of the fetuses. If twins present in vertex–vertex positions, most authors agree that vaginal delivery is appropriate. A major source of morbidity, distress in the second twin during labor or following delivery of the first twin, can be diminished by accurate antepartum diagnosis of twin gestation and

by careful monitoring of both fetal heart rates during labor and delivery. The time interval between deliveries of the first and second twins should not contribute to morbidity as long as fetal heart rate monitoring of the second twin indicates continued fetal well-being.[5]

If the first fetus presents as a breech, problems associated with vaginal delivery include entrapment of the aftercoming head and cord prolapse. Preterm breech infants are especially susceptible to skull trauma and asphyxia during delivery. The phenomenon of "locked" twins, in which the chin of the first breech fetus locks with the chin of the second vertex fetus, occurs very rarely. There are few studies to document the safety of a vaginal delivery when the first twin is breech. For these reasons, many authors support cesarean delivery of twin gestations in which the presenting fetus is breech.

The management of vertex/nonvertex twin gestations, however, is the source of much controversy. If delivered vaginally, the breech second twin is likely to have increased mortality and depressed APGAR scores.[16] Some of this morbidity may be related to low fetal weight. It has been shown that breech presentation of the second twin is associated with lower birth weight, and that as birth weight increases the incidence of breech presentations decreases.[21] Therefore, because the breech second twin is more likely to be small, the hazards of breech delivery already mentioned are likely to be compounded by the increased susceptibility of small infants to birth trauma. For this reason, many authors advocate cesarean delivery of the low birth weight nonvertex second twin. However, other authors[5] have pointed out that, above a birthweight of 1500 gm, the incidence of neonatal morbidity and mortality is low and is not significantly different between second twin breeches delivered vaginally or operatively. Another method of management that has been recently popularized is the intrapartum external version of the breech second twin and its subsequent vertex vaginal delivery. Although this method avoids the morbidity associated with either breech extraction or cesarean section, complications such as cord entanglement or placental separation may occur.

MATERNAL MORBIDITY AND MORTALITY

The mother carrying a twin gestation is also subject to a higher morbidity and mortality rate, and, in addition to suffering more physical discomfort, is at a higher risk of undergoing prolonged hospitalization and surgical delivery.

First of all, the rate of spontaneous abortion is twice as high in twins as in singletons. As mentioned earlier, one twin may succumb and be silently resorbed (the "vanishing twin" phenomenon) or become compressed and retained as a fetus papyraceous.

Another first trimester complication is excessive nausea and vomiting. Women with twin gestations have a higher incidence of hyperemesis gravidarum, for reasons not totally clear. Although one theory

implicates the increased placental mass, which produces more human chorionic gonadotropin, other possible etiologies include a relative vitamin B_6 deficiency or mild histamine poisoning.[12]

Increased production of estriol, progesterone, and human placental lactogen will result in increased volume expansion and weight gain. The blood volume in women with singleton pregnancies expands to 45 per cent above nonpregnant levels, and in twin gestation, it will be 500 ml greater than that. Although red cell mass also increases tremendously, reaching a mean of 2272 ml at term in primagravidae with twins compared to 1797 ml in those with singletons, hemodilution will result in markedly decreased serum concentrations of iron and folate, and a more exaggerated pregnancy anemia. Women with twins have an average hemoglobin concentration of 10 gm per dl from 20 weeks onward.[2]

Twin gestation also produces a typical pattern of arterial blood pressure change.[3] Women carrying twins have a lowered diastolic pressure at 20 weeks (74.3 per cent have a diastolic less than 80 mm Hg compared to 66 per cent of singletons) followed by a greater rise in diastolic pressure between midpregnancy and delivery (94.5 per cent had a rise in diastolic pressure $\geq$15 mm Hg compared to 53.6 per cent of singletons). The initial drop in pressure can be attributed to the effects of the endocrine output of the twin fetoplacental unit on peripheral resistance. The late rise is most likely related to the greater weight gain in twin pregnancy compared to singletons, approximately 0.25 lb per week more on average.[4]

Apart from this phenomenon, the risk of proteinuric preeclampsia is five times greater in twin pregnancies compared to singletons. In addition, the twin state seems to negate the relatively protective effect of a previous pregnancy. Even when a first singleton pregnancy is normotensive, a second twin pregnancy has a 13 per cent incidence of preeclampsia compared to 0.1 per cent if the second pregnancy is single.[20]

Hydramnios can be severe, with a uterus containing a twin gestation reaching a volume of 10 liters or more.[6] The resulting overdistention may contribute to premature rupture of the membranes and preterm labor.

The risk of preterm labor with regard to the fetuses has been discussed. The mother in preterm labor may be subjected to cerclage, steroids, or tocolytic agents and thus suffer the morbidity associated with each. She most certainly will be confined to bed rest at some time in gestation, with the most critical period being between 26 and 32 weeks' gestation. Although various authors have reported conflicting results, the one undisputed benefit of bed rest appears to be increased birth weight[15] and an associated decrease in perinatal mortality.

A higher risk of maternal hemorrhage is associated with twin gestation. Although antepartum hemorrhage, largely due to vasa previa and placenta previa, is slightly increased in twins, the greatest risk is

related to uterine atony and postpartum hemorrhage secondary to sudden decompression of the overdistended uterus.

Finally, problems related to the delivery, including failure to progress because of incoordinate uterine action, malpresentation, cord prolapse or entanglement, and fetal distress also increase the maternal risk of undergoing surgical intervention and suffering the associated morbidity.

DIAGNOSIS

Some of the morbidity and mortality associated with twin gestation can be attributed to late diagnosis or failure to diagnose a second twin before delivery.

As recently as 1973 only 51 per cent of all twins were diagnosed antenatally.[8] More current studies indicate an improvement in diagnostic techniques; now 90 per cent of twins are detected antenatally and 95 per cent are detected before delivery.

Clues to multiple gestation are often present in the initial history and physical if the examiner remains alert to this possibility. A history of dizygotic twinning in previous pregnancies or among the patient's female relatives is important. Certainly, a history of taking clomiphene citrate or gonadotropins to enhance fertility should bring the possibility of multiple gestation to mind. Symptoms of hyperemesis gravidarum, more common in twin pregnancy, may be elicited. Likewise, excessive maternal weight gain or sensation of increased girth may be reported. The patient may state that she feels the intrauterine activity of more than one fetus.

Examination may commonly reveal a fundal height that is inconsistent with dates. It is helpful if multiple fetal parts are palpated, but often fetal parts cannot be distinguished before the third trimester. Fetal heart tones should be detectable by Doppler ultrasound before the end of the first trimester; two fetal heart beats, with differences in rate of more than 10 beats per min heard simultaneously and by two examiners, are good evidence of twin gestation.[15]

Certain laboratory values are elevated in the presence of a twin gestation. Twenty to thirty per cent of patients with multiple gestation will have a maternal serum alpha-fetoprotein (MSAFP) level greater than 2.5 multiples of the mean. It must be kept in mind, however, that all elevations of MSAFP cannot be dismissed as secondary to the twin state itself; if the MSAFP is greater than four multiples of the singleton mean, pregnancy complications occur in 90 per cent and such twin gestations have a mortality rate of 40 per cent.[30] Serum human placental lactogen level may also be an indicator of twin status. Ninety-five per cent of twin gestations will have an HPL level greater than 1 standard deviation above the singleton mean for gestational age.[11] Beta-HCG, estriol, and pregnanediol have also been reported to be elevated in multiple gestation, but daily fluctuations make these tests less accurate.

When the physician is confronted with the above physical and laboratory findings, and must confirm multiple gestation as well as rule out other possibilities, including poor dates, hydramnios, hydatidiform mole, myomas, or neural tube defect, ultrasound remains the diagnostic method of choice. It should be noted that prior to the advent of ultrasound, roentgenography was the only reliable method of confirming the contents of the uterus. However, roentgenography is not useful before 15 to 16 weeks' gestation when the fetal skeleton is calcified.[31] Furthermore, it is often postponed until the third trimester because of fears of the effects of ionizing radiation on the developing fetus. Real-time ultrasonography, utilizing a hand-held linear array transducer, obviates these problems and provides a rapid and highly accurate method of identifying and evaluating the twin gestation.[18]

Two gestational sacs can be identified at 6 weeks, and fetal body and heart motion can be detected by 8 weeks.[38] Because of the possibility of false-negative and false-positive diagnoses, and the high rate of methodologic error, a meticulous approach to identification of clearly separate fetal structures must be applied. Information on the number of placentas present, their positions and appearance, and the determination of chorionicity and amnionicity should be obtained, because prenatal prediction of vascular anastamoses and risk of twin–twin transfusion syndrome will be aided greatly by this information. Management of twins found to be discordant for various malformations will also be helped by knowledge of chorionicity. D'Alton and Dudley[7] report the correct determination of chorionicity in 33 of 34 cases by careful visualization of the membrane septum and counting of the fetal membranes.

In addition to diagnosing the twin gestation, ultrasound is especially useful in assessing fetal growth, and therefore in providing early detection of growth retardation or discordance. Although many believe that the growth rate of twin fetuses differs from that of singletons in advanced gestation,[23] body weight and length of twins is comparable to that of singletons up to 21 weeks' gestation. Interestingly, the average body length and biparietal diameter (BPD) of a twin is consistent with an age 6 days younger than menstrual age when compared to singletons. This observation is compatible with the assumption that twins are about 1 week younger than menstrual age would indicate.[12]

Although growth rates of twins are comparable to singletons up to midtrimester, a slowing of both twin BPD and abdominal circumference (AC) growth is then noted at 32 to 34 weeks. The slowing of both these measurements might imply a sort of symmetric growth retardation. However, newborn anthropomorphic data show asymmetric growth retardation, with the actual BPD being larger than that measured by ultrasound. This discrepancy between the actual and the ultrasound BPDs may be due to a slight dolichocephaly seen during gestation due to intrauterine crowding.[38]

For these reasons, it is important to refer to growth charts designed for twin gestation when assessing fetal growth rate. It is also important

to compare the twins to each other. A discrepancy in BPD or AC of 5 mm or greater may be indicative of growth aberration.

In the future, techniques such as magnetic resonance imaging and pulsed Doppler flow velocity wave form analysis may be applied to twin gestations. Data already suggest that analysis of fetal vessels by pulsed Doppler ultrasound may be useful in detecting twin pregnancies at risk for unsatisfactory outcomes.[25] One team of investigators was able to diagnose the small-for-gestational age twin in both intrauterine growth retardation and twin-to-twin transfusion syndrome using this method.[10]

In conclusion, although the lay public may view twins with great interest and excitement, obstetricians should consider with trepidation the various sources of morbidity and mortality inherent in a twin gestation. Both the fetuses and the patient are at high risk for a bad outcome, and monitoring and safeguarding such a pregnancy requires great skill and judgment. As the following articles confirm, there is a tremendous amount of information available upon which to base such judgment.

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Placental Considerations in Multiple Pregnancy

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Identical, or not identical, that is the question.

Our knowledge of multiple pregnancies has crystallized somewhat from seven centuries ago, when in 1276 Margaret, the Countess of Henneberg, as reported by Smalbraak, "went to labor and was delivered of a product of pregnancy which caused the greatest consternation." While this product is now believed to have been a hydatidiform mole, it was misidentified then as a multiple pregnancy. "The strange event made a big impression." It was Smalbraak's translation from the medieval Dutch texts recorded on tombstones and wooden tablets hung at the village church which read in part: "On Good Friday . . . (she) brought to bed 365 children who all together were baptized in basins by Guido Suffragen of Utrecht; the boys were christened John, the girls Elizabeth; who all together, with the mother, died on the same day and buried."[41]

Two issues of fundamental importance should be raised when examining placentas of multiple pregnancies: (1) The first relates to zygosity, which is imperative to document in the light of advances in immunobiology of tissue transplantation, for it is zygosity that determines whether transplanted tissues from one twin to its co-twin are accepted or rejected. The monozygotic, or identical twin, should ordinarily accept tissues from its co-twin as an isograft, whereas the dizygotic, or fraternal twin, not approaching its co-twin any closer than homology, will ordinarily reject its tissue as an allograft.

(2) The second issue concerns structural abnormalities of the placenta, which serve not only as diagnostic elements but also as aids in

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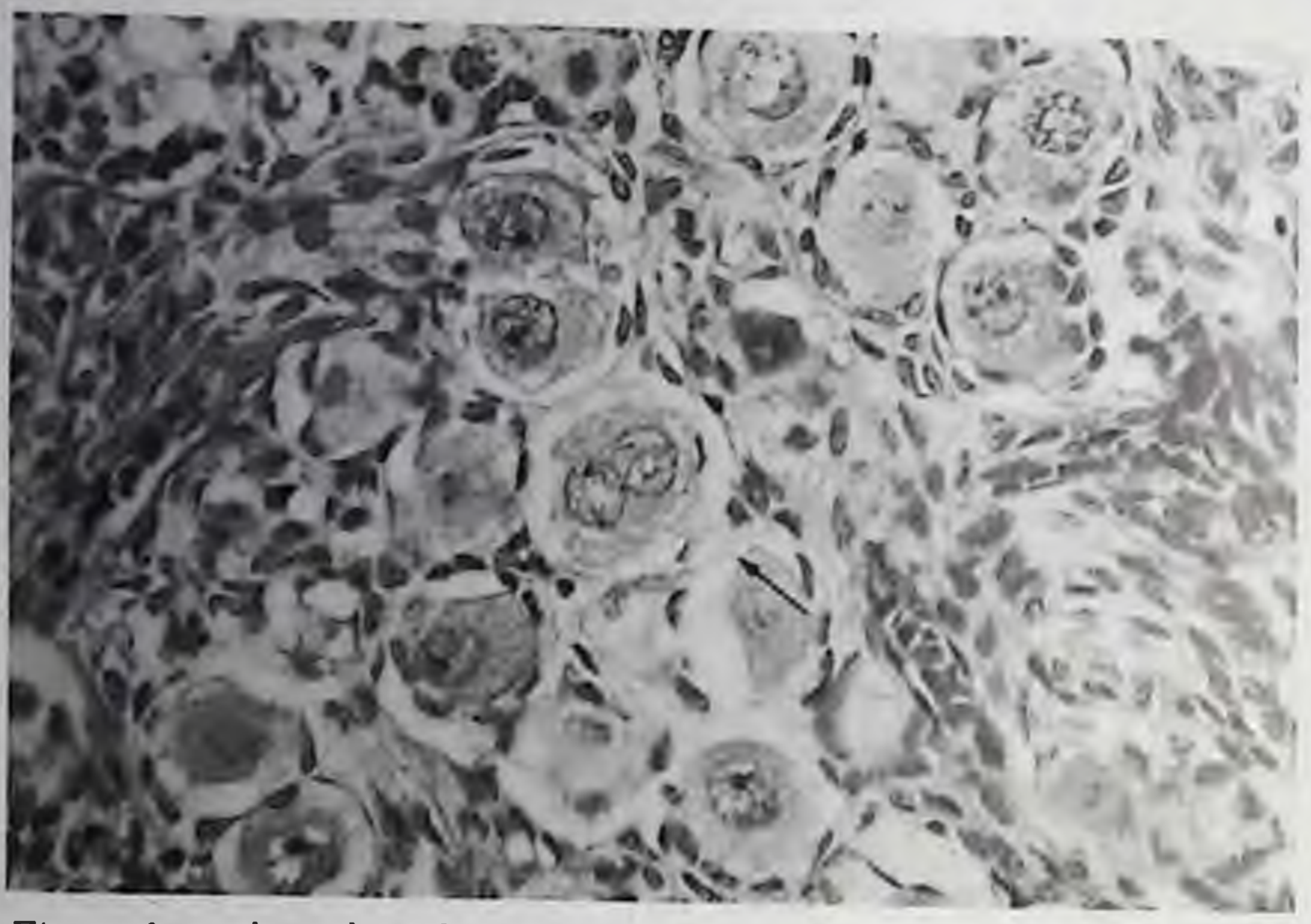

Figure 1. A binucleated oocyte lodged within a single theca (*arrow*). Another theca, just above, houses two oocytes. (mult. × 300, original magnification). What kind of pregnancy will result from fertilization of oocytes such as these (e.g., a third type of twin, an acardiac twin, or another type of monstrosity)?

determining zygosity, because of their index of association with certain types of twinnings (see vascular abnormalities below). The following paragraphs, therefore, primarily discuss the problem of zygosity and anatomic abnormalities of the placenta as they pertain to twin pregnancy, placing emphasis on clinically relevant problems and touching on supporting basic principles.

CLASSIFICATION OF TWIN PLACENTAS

Placentas of twin pregnancies may be classified as monozygous or dizygous. In cases of higher multiple pregnancies, they may be either of single or multiple zygosities as the case may be.

Monozygotic placentas result from the fertilization of a single ovum by a single spermatozoon. Depending on embryologic factors, these may assume any of the following forms:

1. Monochorionic–monoamnionic
2. Monochorionic–diamnionic
3. Dichorionic–diamnionic, fused or separate
4. Multichorionic–multiamnionic

Dizygotic placentas result from the simultaneous fertilization of two ova which happen to be enclosed in a single follicle or theca,[5,7]

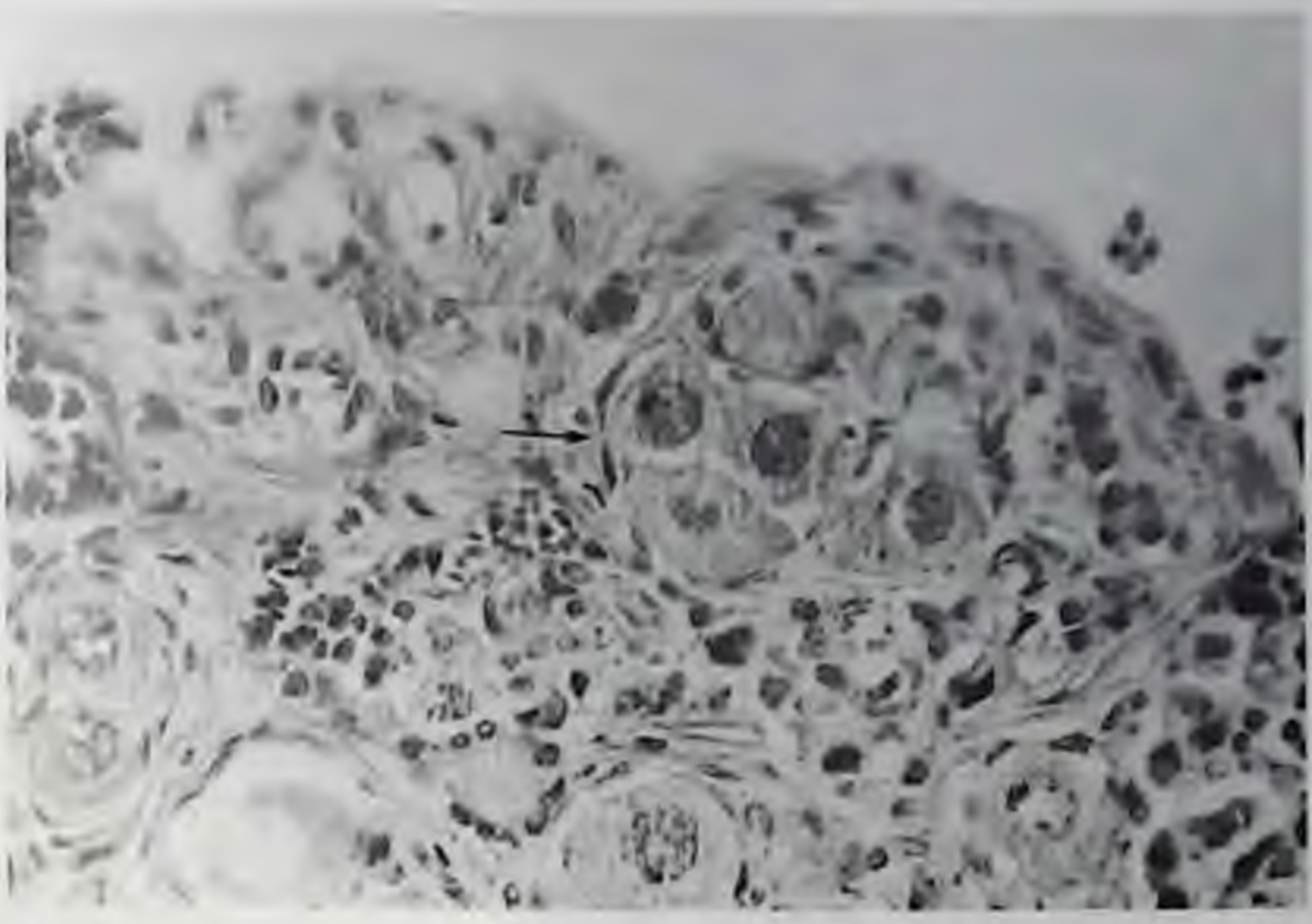

Figure 2. Three ova are seen within a single theca (*arrow*). These ova, originating from a single ovulation site, may be the source of a trizygous pregnancy. (× 300, original magnification).

as in Figure 1, or from the ovulation of two separate follicles in either one or both ovaries, as in Figure 2. Dizygotic placentas must be, by necessity, at least dichorial. These, however, may be either fused (single) or separate (double) and in each case, diamnionic, as follows:

1. Dichorionic–diamnionic fused
2. Dichorionic–diamnionic separate
3. More complex forms in higher multiple pregnancies

Placentas of cases from superfecundation and superfetation, if such occurs, belong to the dizygous category.

Third type of twin: Is there a third type of twin, one based on genetic similarity or disparity intermediate to monozygous and dizygous? Bulmer questioned and surfaced an old concept he attributed independently to Danforth and Thorndike.[13] This type of twin could result from the fertilization of two ova that have not been independently released but have developed from the same primary oocyte (see Fig. 1). Also included in this group would be the dispermic fertilization of a single oocyte or oocyte and its polar body. From factual data available, Bulmer could not substantiate this hypothesis for twins, although he suggested a causal relationship with certain mosaics in single pregnancies like the cases of Race and Sanger.[37] The testing of the hypothesis of dispermic fertilization of oocyte and its polar body, in cases of twins with papyraceous, acephalus, and acardia feti, would be meritorious.

EMBRYOLOGIC CONSIDERATIONS IN TWINNING

Monozygous Twinning

Due to the paucity of monozygotic twin specimens of the early days of development, our knowledge of their embryology is rather inferential and derived mostly from the classic contributions to early human development by Hertig and Rock.[24, 25, 27]

Coulton, Hertig, and Long in 1947 inferred the time of occurrence of embryonic splitting for monozygotic monoamnionic and diamnionic twins.[17] Subsequently, Corner, in 1955, postulated that monozygotic twins are formed by the splitting of the conceptus at any time between days 2 through 15 to 17 of gestation, and that the ultimate morphologic differentiation depends on the embryonal developmental stage at the time this splitting takes effect. In this context, Corner[16] proposed three critical stages at which distinct characteristic morphogenesis may result, namely:

1. Separation of early blastomeres, circa day 2 postfertilization (horizon II)
2. Duplication of the inner cell mass, circa day 5 (horizon III)
3. Duplication of the embryonal rudiment of germ disc, circa day 15 (horizon VI–VIII)

Separation of the Early Blastomeres Stage. The separation of the blastomeres at the two-cell stage, Figure 3*A*, presupposes totipotentiality of the blastomeres. Each cell (or group of cells) is capable of developing sequentially into a morula, blastula, and an embryo with its corresponding membranes, chorion and amnion, with each conceptus implanting at a different site. The resulting placenta(e) will be dichorionic–diamnionic, either separate (double) or fused (single), depending on whether their implantation sites were far apart or close together, respectively. The septal membranes of the fused variety in this group like the dizygous counterpart will be composed of four layers: amnion-chorion=chorion-amnion (see Fig. 9). The totipotentiality of the early blastomeres concept finds support in experimentation on lower animals.[30, 31]

Placentas derived from this type of splitting may not differ morphologically from dizygotic placentas. Therefore, in these cases, zygosity must be ascertained by other parameters such as vascular anastomosis in placentas, fetal sex, blood groups, anthropomorphic characteristics, and, ultimately, tissue typing, transplantation of tissues, and DNA mapping.

Duplication of Inner-Cell Mass. Twinning by duplication of the inner cell mass could occur in the morula to blastula phase at 4 to 7 days postovulation (Figs. 3*B*, 3*C*). At this time of embryonal development, in addition to the inner cell mass, trophoblast is also differentiating and will constitute the chorion. The amnion, on the other hand, is yet to be formed. Its development depends on embryonic inductive forces and subsequently it will be formed with its respective embryo.

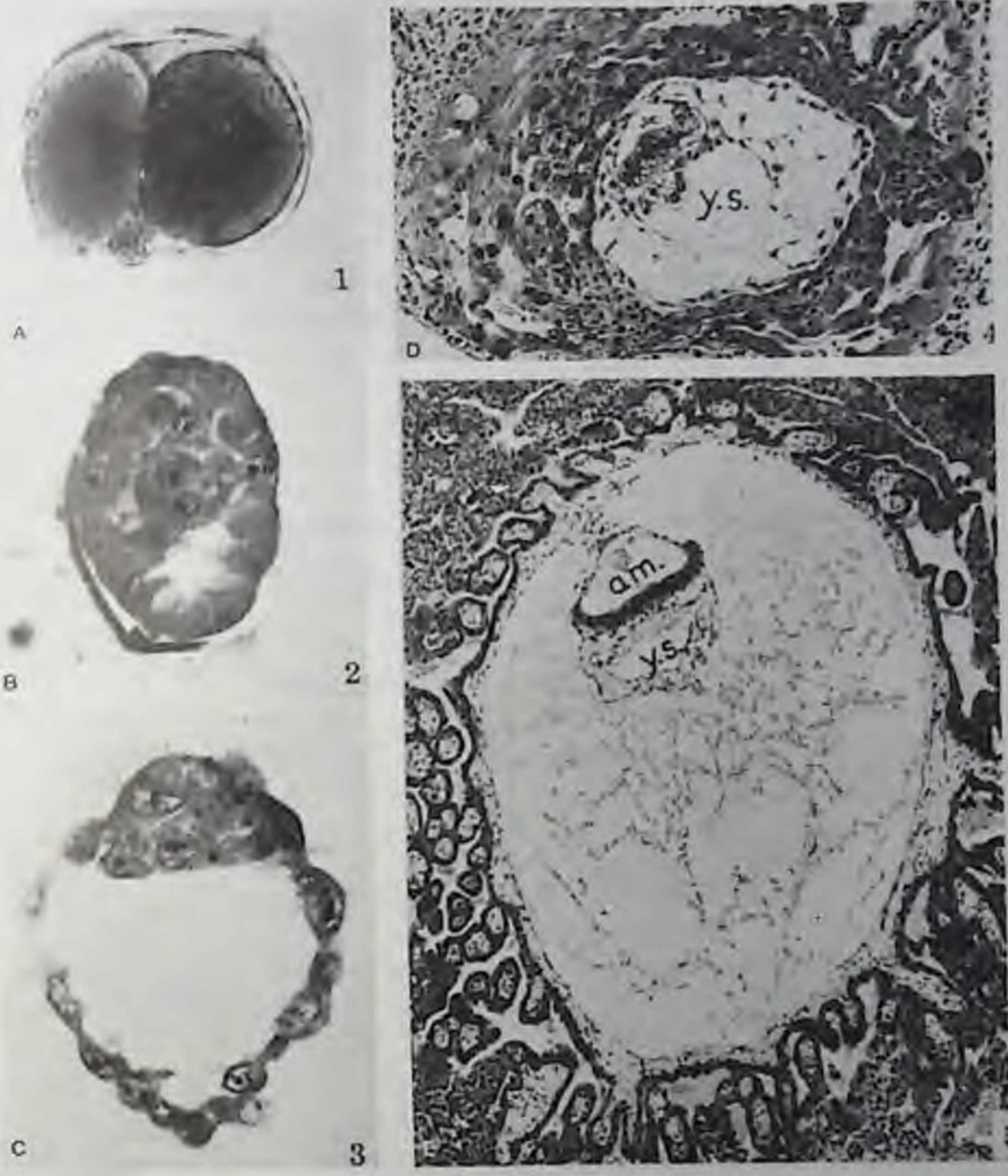

Figure 3. Five stages of early human development illustrating the various phases at which twinning may occur. *Stage* 2, Two-cell stage, from uterine tube about day 2 after ovulation (× 300). *Stage* 3, Morula from uterine cavity about day 4. Blastocyst and inner cell mass begins to be differentiated (× 350). *Stage* 3, Blastocyst from uterine cavity, about day 5. Well-defined inner cell mass (mult. × 500). *Stage* 5*c*, Implanted embryo, previllous stage, about day 11. Embryonic disc has a small amniotic cavity about it and a yolk sac (ys) below (× 100). *Stage* 7, Embryo of about day 16 (mult. × 50). (Courtesy of the Department of Embryology, Davis Division, Carnegie Institution of Washington.)

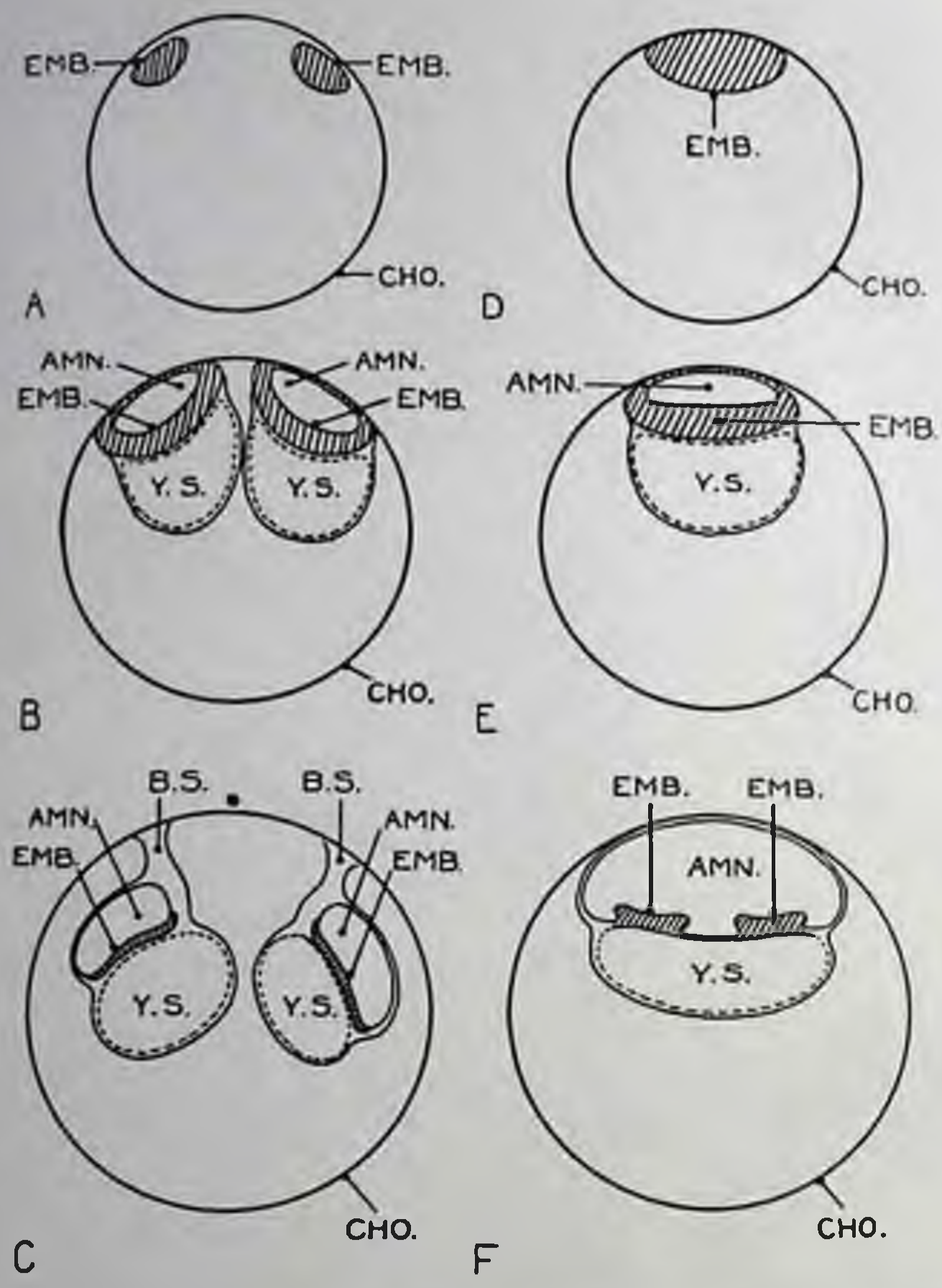

Figure 4. Two types of monozygotic twinning in man. *A–C*, by the formation of two inner cell masses. *D–F*, by the formation of two embryos on a single germ disc. (From Corner GW: Bull Johns Hopkins Hosp 33:389, 1923; with permission.)

Twin placentas of this type will be monochorionic–diamnionic, *single placentas*. The membranes at septum will have two layers, amnion-amnion, without an intervening chorion (Fig. 4*A–C*).

The earliest human twin conceptus on record corresponds to this type of twinning, with an estimated developmental age of 15 to 17 days.[26] Another case, reported by Hamilton et al., had an estimated age of 14 days, however, the conceptus was abnormal.[22]

Duplication of the embryonic rudiment of the embryonal disc: At about days 15 or 16 of human embryonal development and after a single amnion has differentiated (see Figs. 3*D* and *E*), twinning may occur if two embryonic nodes instead of one appear, followed by the development of two embryonic rudiments. The embryos in such a situation will be lodged within a single amniotic cavity. The placenta in this type of twinning will be monochorionic–monoamnionic, and, obviously, a single placenta (Fig. 4*D–F*).

For all practical purposes, all monochorionic–monoamnionic

human placentas are monozygous. The yolk sac should be, and is in most cases, double. On occasion, however, owing to accidents of development, there may be only one yolk sac. For similar reasons, duplication of the embryonic forming cells may be incomplete leading to a variety of bizarre twins, for example, conjoined (Siamese) twins. At times, the embryonic separation is complete, but the cords may be partially or totally fused, resulting in omphalopagus malformation.

Corner indicated that the description of the above phases was made only for the purpose of better understanding the morphogenesis of monozygotic twinning. However, twinning could occur at any time from the stage of the two-blastomere zygote to approximately day 17 of development.

In summary, it appears that the differentiation of trophoblast (chorion) and of the amnion independently are the key as to whether monozygotic twins will be dichorial or monochorial and diamnionic or monoamnionic, respectively; dichorial if the twin is formed before, and monochorial after trophoblast differentiation (postovulatory days 2 to 5). Similarly, placentas may be diamnionic or monoamnionic if the twin is formed before day 7 or after differentiation of the amnion, day 13½ postovulation.

Dizygous Twinning

Dizygous or higher zygosity placentae develop from two or more zygotes implanting at different sites. Their ultimate form will depend on the distance between their implantation sites. If they implant close together, the resulting chorions may fuse, forming what looks like a single placenta. If the implantation sites are distant from one another, two entirely separate placentas are formed. Very rarely these placentas will implant as any other form of twinning, ectopically and orthotopically.[23, 46] Thus, dizygotic placentas will be dichorionic–diamnionic, either single (fused) or double.

ETIOLOGY OF TWINNING

The cause of *monozygotic* twinning is unknown; most writers consider monozygosity as a pathologic entity occurring constantly throughout the world (3.5 per 1000) seemingly to indicate constant causative factor(s), environmental or otherwise. The concept of "twinning impetus" has been proposed. Regarding environmental factors, Bulmer[13] makes reference to Stockard's induction of twinning in sea minnow eggs by retarding their development with oxygen deprivation and low temperatures. He suggests that adverse environmental conditions about the implanting zygote or blastocyst may be the impetus for twinning.

The etiology of *dizygous* twinning is better understood. Endocrine factor(s), exogenous (iatrogenic) or endogenous, capable of influencing multiovulation if fertilization occurs, may lead to multiple

pregnancies, that is, use of gonadotropins such as Clomid or Tamoxifen in the treatment of infertility.[47]

Bulmer, on the basis of his own studies and those of Weinberg that he quotes,[13] concluded that dizygosity is associated with hereditary factors, with a mode of inheritance confined to the mother. They showed that the twinning rate among female relatives of mothers of twins is 19 per cent compared to 10.7 per cent among relatives of fathers.

DIAGNOSING PLACENTAL ZYGOSITY

Having considered the embryonal factors influencing morphogenesis of monozygotic and dizygotic twins, let us now proceed to examine the placenta. First, let us extend Benirschke's plea to the obstetrician concerning recording and expand this plea to the pathologist to record twin placentation accurately by using the best means available for diagnosis.[5]

All twin placentae should be submitted to the pathology laboratories and be deftly examined by the obstetrician or the pathologist, or preferably by both. Unnecessary manipulations of the placenta should be studiously avoided, thus caring to preserve its morphologic integrity for accurate diagnosis.

Benirschke, in 1961,[4] published a guide for the examination and processing of the placenta, basically a modified procedure of Dr. Arthur T. Hertig at the Boston Lying-In Hospital, a procedure we highly recommend. Sander has also proposed a form for the examination of the placenta.[40]

The morphologic determination of zygosity focuses on the membranes: the presence and number of chorion(s), amnion(s), yolk sac(s), and embryo(s).

Twin placentae could be single (one chorion) or multiple (multiple choria). It should be stated categorically that all monochorial twin placentae are monozygous and that multichorial placentae could be either monozygous, dizygous, a combination of both, or multizygous.

If the twin placenta is single, it could be monochorial (monozygous) or dichorial fused. The latter could be either monozygous or dizygous. If the placenta is multichorial (multiple), it could be monozygous, dizygous, or multizygous (higher zygosity). Twins of different sex are dizygous; however, twins of like sex could be either monozygous or dizygous.

If the placentae of twins are separate, as in Figure 5, zygosity cannot be ascertained by gross or microscopic examination of the placentae alone, but rather should be determined clinically and by other means. In the case of fused placentas, the membranes are the single most crucial elements to determine zygosity, in particular, the dividing septal membranes if such are present. Two sets of circumstances may be encountered: the twin may be monochorionic or dichorionic.

If the twin is *monochorionic*, the septum is composed of two del-

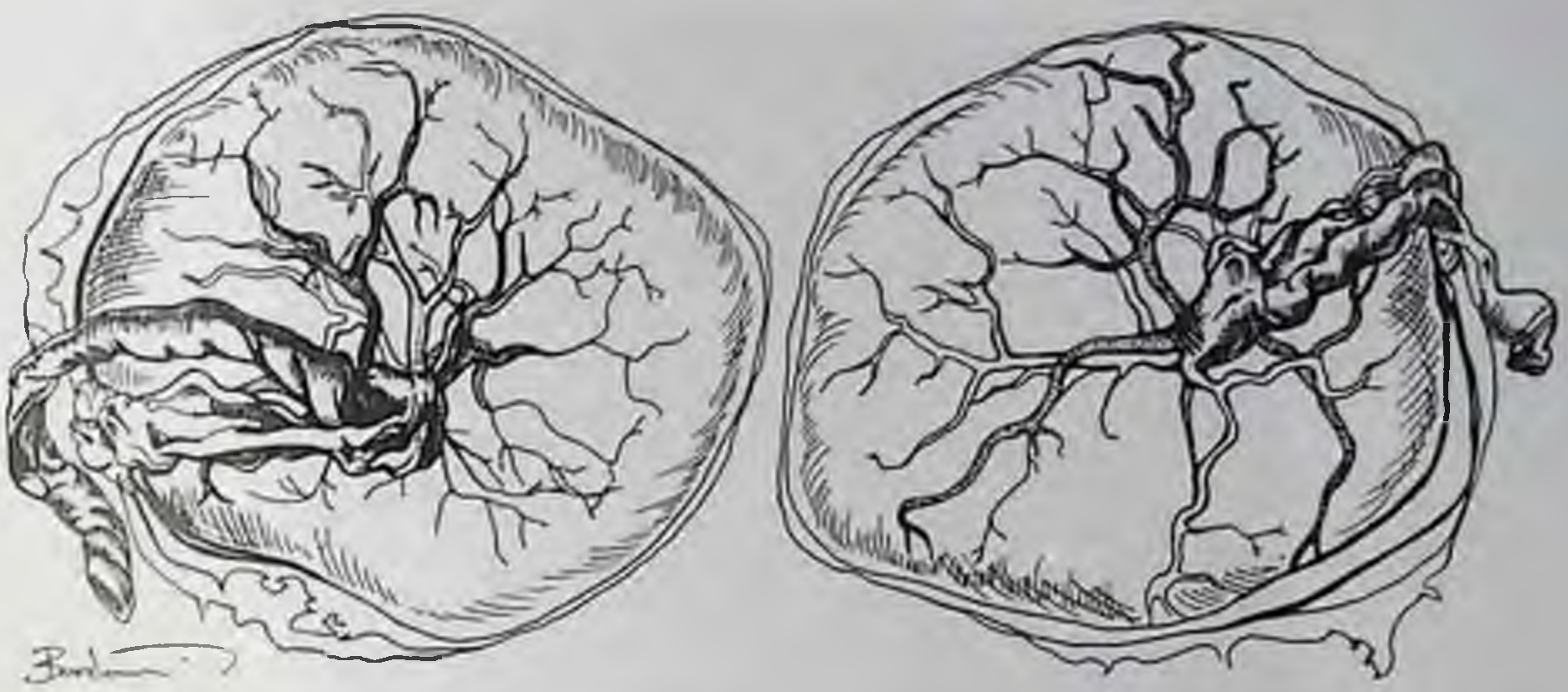

Figure 5. Dichorionic–diamnionic placentae (artistic rendition courtesy of Nancy J. Bardawil).

icate, thin, translucent amnia that can be separated and lifted from the chorionic plate with ease, leaving behind no traces of its attachment, Figure 6. Microscopic examination of the rolled septal membranes or of the T-shaped section of the chorionic plate (horizontal) and septal membranes (vertical) will confirm the presence of two layers or amnia (Fig. 7). These are in opposite position, with a central cleavage space and without chorion. On rare occasions, meager atrophic blood vessels may be seen there. The diagnosis of such a case will be monocho-

Figure 6. Monochorionic–diamnionic placenta. Observe the thin, translucent amnion, which can be lifted easily from the chorionic plate. (*From* Strong SJ, Corney G: The Placenta in Twin Pregnancy. Oxford, Pergamon Press, 1967; with permission.)

Figure 7. T-shaped section of membrane septum in a monochorionic–diamnionic placenta (monozygous). This type of membrane may be seen in a placenta such as in Figure 6.

rionic–diamnionic twin placenta (Fig. 7*A*). This type of twinning results from fission of the inner cell mass at days 3 to 5 postfertilization.

If the twin is *dichorionic*, the septum is thicker and opaque. When separation of the membranes is attempted, resistance is encountered at the junction with the chorionic plate because each amnion is accompanied by a chorion and each chorion is continuous with the corresponding chorionic plate at the site of fusion (Fig. 8). Microscopic examination of the septal membranes or T-shaped section will show

Figure 7. *A*, Diamnionic membranes (monozygous) (× 250, original magnification.)

Figure 8. Dichorial–diamnionic placenta. Note the bile-stained umbilical cord of the fetus delivered last.

four layers: amnion–chorion, chorion–amnion (Fig. 9). Well-developed blood vessels and, on occasion, ghost villi can be seen in the septum. The diagnosis of the placenta in cases such as this will be dichorionic–diamnionic, fused, twin placenta. Approximately ⅔ of dichorionic–diamnionic either fused or separate placentas are dizygous. The remainder are monozygous.

As in the case of dichorionic separate placentas, zygosity should be sought by other parameters, as indicated above.

In dichorionic fused placentae, there are other subtle morphologic findings that may aid indirectly in elucidating zygosity. These include the presence of vascular connections, which for all practical purposes are seen only in monozygotics, and also the association of

Figure 9. Microscopic appearance of dichorionic (C), diamnionic (A) septal membranes. Zygosity not known. (× 125, original magnification.)

Figure 10. Monochorial–monoamnionic placenta. Both umbilical cords attached near one another. No separating membranes were present. (Courtesy of Dr. S. Parulekar.)

certain pathologic complications like transfusion syndrome, which is in the purview of monozygous twins.

Determination of zygosity in monochorial, monoamnionic placentas poses no problem (Fig. 10). This unique form of twin placenta is always monozygous in humans. Included here are the cases of conjoined twins.

For zygosity in higher multiple pregnancies, the same basic principle will apply as in twins. Attention should be focused on the number of placental masses and septae. In triplets for example, the septae of the three compartments are studied as A, B, and C. If A and B are monozygous, and B and C are also monozygous, it stands therefore that A and C are likewise monozygous. The diagnosis in a case such

Figure 11. Monochorial–diamnionic triplet placenta (monozygous). The septum at left was diamnionic. (Photograph courtesy of St. Margaret's Hospital, Boston, Massachusetts.)

Figure 12. Trichorial–triamnionic triplet pregnancy, zygosity not known. Note three placental masses and thick septal membranes. S-63-1229. (Photograph courtesy of St. Margaret's Hospital, Boston, Massachusetts.)

as this would be monochorial–triamnionic triplet placenta. If one, two, or three of the triplets are different, the diagnosis is made accordingly (Figs. 11 and 12).

Potter[35] indicated that zygosity can be established with certainty at birth in approximately 80 per cent of twins. In 22.8 per cent of her 293 pairs, monozygosity was identified by the presence of a placenta with one chorion (monochorionic). In an additional 30.2 per cent, dizygosity was identified in cases of dichorionic placenta with unlike sex babies. Finally, 27 per cent were isosexual babies but were obviously dizygous, because they had different blood groups. Monozygous twins in dichorionic placentas and dizygous twins with like sex babies were not identified by the aforementioned criteria (20 per cent). Possibly, additional zygosities could be identified using the vascular connections and associated pathologic conditions as parameters indicated previously.

PATHOLOGY OF TWIN PLACENTAS

We propose a classification of the pathology of the twin placenta into the following four categories:

a. Specific pathology akin to the twinning process:
   (1) Fetal monstrosities such as conjoined, fetus acardias, acephalus, hollocardius amorphous, fetus papyraceous, and fetus compressus
   (2) Vascular connections
   (3) Bivascular umbilical cords
b. Pathologic lesions or conditions as a consequence of group "a" lesions:
   (1) Entanglement of umbilical cords in monoamnionic twins

(2) Intrauterine transfusion syndrome and related alterations such as polyhydramnions, amnion *nodosum*
(3) Development of chimerous state in dizygous twins

c. Lesions related to physical problems of accommodation due to the limited uterine space
(1) Circummarginate or circumvallate changes (placenta extrachorialis)
(2) Marginal or velamentous insertion of cord, vasa previa

d. Incidental lesions, as they might occur in any other placenta, including abortions

Monochorionic-monoamnionic placenta is a rare form that comprises 1 to 2.11 per cent of monozygous placentae. It is formed by the embryonal disc splitting after differentiation of the amnion, which occurs at 7 to 13½ days of development.[17]

This form of placenta was known to Hippocrates. The dictum "horror incestus" attributed to him attests to his understanding that heterosexual fetuses could not be enclosed within the same cavity.[13] Quigley credits Boccalini in 1612, Jacob von Back in 1648, and Viandel in 1671 for convincing descriptions of this form of placentation.[36]

The monoamnionic twin placenta is easily identifiable grossly (Fig. 10). However, caution should be exercised to avoid artifactual absence of the amnion, which may confound the diagnosis. This type of placenta is generally larger than the average singleton placenta. Its fetal surface shows the presence of two umbilical cords attached at any place in the chorion. At times they attach close together, but quite frequently they have a velamentous type of insertion with the corresponding clinical hazards.

The incidence of monoamnionic twins has been variously reported from 1:6000 to 1:60,000 pregnancies. Relative to twins, Benirschke reports three monoamnionic cases in 250 successive twins[7]; Raphael, 5 in 824[38]; Strong and Corney, 1 in 200[43]; and Potter, 1 in 567.[35] Its true incidence in pregnancy, however, is not known, because many of these twins terminate in abortion.

Twisting, knotting, and entanglement of umbilical cords (group b) is an extremely important and common complication of this type of placentation, which is responsible for its high fetal mortality (Fig. 13).

Vascular anastomoses, so commonly seen in monochorial placentas as expected, may be quite extensive in monoamnionic placentas, in particular those with closely positioned cords.[7] In spite of these anastomoses, polyhydramnios and twin "transfusion syndrome" is not reported in monoamnionic twins. Benirschke attributes these negative findings, in some cases, to the lack of "third circulation" (see below) and in others to the anastomoses that are so extensive that they do not allow for a circulatory imbalance.[7]

The infrequent successful delivery of monoamnionic twins has been the subject of several publications. Quigley reported survival of both fetuses in only 17 of 109 cases collected from the literature[36];

Figure 13. Monozygotic triplets in a monochorial–monoamnionic placenta. The fetuses were macerated. A knot is seen between the two umbilical cords, at the right lower corner, certainly a factor in the demise of this conceptus. Like in the case of "third type of twinning" may we ask whether there is a "third type of killing" placed between homicidal and suicidal that may be applicable to this situation. Could it be isocide? (Photograph courtesy of St. Margaret's Hospital, Boston, Massachusetts.)

Raphael in 51 of 183, including 3 of his own[38]; and Coulton et al., reported the successful delivery of 2 cases.[17]

There are reports in the old and recent literature, of "dizygotic monochorionic" pregnancies,[32] also of monoamnionic pregnancies containing fetuses of heterologous sex. Publications also have appeared suggesting atrophy and dissolution of the septal membranes as a possible cause of some monoamnionic malformation, which may allow unlike sex fetuses to be contained therein. For lack of clear-cut documentation in many of these reports, Benirschke considers both events unlikely *in humans* and presents persuasive evidence to the contrary.[7] However, he presents a monoamnionic placenta with an amnionic fold or plica, which could have been a residue from the septum, and another case of a macerated twin fetus associated with necrosis of the septum.

Monochorionic, Monoamnionic Placenta with Conjoined Twins

Approximately 4 to 5 per cent of monoamnionic placentas contained conjoined twins. This is equal to nearly 1 in 2500 monozygotics. These twins originate, as stated before, by the incomplete splitting of the embryonic disc at days 13½ to 15 of gestation. The conjoined twins that develop could be any of a large variety. The most common forms

Figure 14. Thoracoabdominopagus twin in a triplet set-up. (By permission of Dr. Y.M. Dawood.)

are those fused at the thorax, abdomen, umbilical cords, or a combination of these (thoracopagus, abdominopagus, omphalopagus).

Vascular connections in monoamnionic placentas have been studied. Boyd and Hamilton described the arteriovenous relationship in two cases of monoamnionic placentas with thoracopagi monsters.[12] The injection of Chromopaque into one of the umbilical cord arteries of the first case filled the entire vascular bed of the placenta, while the injection of the umbilical vein of one side filled only one half of the placenta, as to indicate the presence of two distinct venous districts. In the second case, the authors observed arterial anastomosis as well. Similar findings were obtained in monochorial–diamnionic placentas.[12]

The placenta of conjoined twins is always monoamnionic*; included here are also the rarer cases of conjoined twins of higher order multiple pregnancy. Such are the two cases reported by Tan et al.,[44] Dawood,[18] and Dawood et al.[19] of triplet pregnancies with two conjoined female fetuses contained in one amnionic cavity and one other female baby contained in a separate amnionic sac. The placenta was monochorial. The conjoined twins were lodged in a single amnionic sac. These cases were obviously examples of monozygotic twins (Fig. 14).[18]

Monochorionic–Diamnionic Placenta

This form of monozygous placenta is formed early in human development, approximately at 5 days, by splitting of the inner cell mass.

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* As this article was being written we had the opportunity of examining a monochorial, probably diamnionic, or at least partly septated amnionic cavity placenta associated with conjoined abdomino-omphalopagus feti. This case will be separately reported.[2]

The Zygosity of Twin Pairs according to their Placentation. (Analysis of 200 twin pairs born in the Oxford region.)

Placentation	Monozygotic	Dizygotic	Zygosity unknown	Total
Separate dichorionic	12 (15 %)	69 (85 %)	4	85 (42·5 %)
Fused dichorionic	13 (23 %)	44 (77 %)	9	66 (33 %)
Monochorionic diamniotic	38 (100 %)	—	6	44 (22 %)
Monochorionic monoamniotic	1	—	—	1 (0·5 %)
Unknown	1	1	2	4 (2 %)
Total	65 (36·5 %)	114 (63·5 %)	21	200

The percentages in the first two columns refer only to the groups in which both the placentation and zygosity are known.

Figure 15. The incidence of twin pairs according to their placentation. (*From* Strong SJ, Corney G: The Placenta in Twin Pregnancy. Oxford, Pergamon Press, 1967; with permission.)

The morphology of this type of placenta is similar to the monoamnionic variety except for the presence of two amnionic sacs and their respective cords. The incidence of monochorionic and diamnionic twins is approximately one-half the number of monozygotics, 38 of 65 and 22 per cent of the twins in Strong and Corney's 200 cases (Fig. 15). Benirschke reports that "perhaps 70 per cent of identical" twins are monochorial (77 of 250 total twins were monochorial).[4,5] And Spaeth reports 30 (24 per cent) of 124 twin births to be monochorial.[42]

Monochorionic–diamnionic placentas are larger than the average singleton placenta, but generally less than double the weight of the latter. The constitution of the dividing membranes is amnion–amnion (two layers) without an intervening chorion. The pathologic changes complicating the monochorionic–diamnionic placenta are those specific changes related to monozygosity (groups a and b) as well as those nonspecific changes common to all varieties of twins (group c).

The pathologic changes described below are significantly more common in relative terms to the singleton placentas. Some of these are

1. Marginal/velamentous attachment of the umbilical cord as described before. These changes are estimated to be about three times more common than singletons.
2. Placenta circummarginata or circumvallata
3. Monoarterial (bivascular) umbilical cord malformation. Having considered monozygosity a malformation, it is not surprising to encounter other fetal malformations. The bivascular umbilical cord is a common finding occurring in approximately 1 per cent of pregnancies.[6,7] In twinning, it was seen in 9 cases out

Types of Anastomoses	Total	Survival Number of Infants
Artery to Artery (A–A) (one or more)	17	12
A–A + A–V	17	14
A–A + V–V	2	2
V–V	3	2
A–V	7	3
A–V + V–A	2	1
V–V + A–A	3	1
No shunts	9	6

Figure 16. Vascular connections in monochorial placentae. (*From* Benirschke K, Driscoll SC: Pathology of the Placenta. New York, Springer-Verlag, 1967; with permission.)

of 200 pairs by Strong and Corney[43] and 18 or 19 in 500 fetuses by Benirschke.[7]

4. Displacement of amnionic sacs (trophotropism). The amnionic sacs and the equatorial divisional plane of the placental territories may not correspond. This change (group c), frequently seen in dichorionic placentas, may indeed lack clinical significance.

Vascular Connections. Vascular connections in twin placentas, also referred to as anastomoses, shunts, or vascular fistulas, depending on the type, have been known for many years. The outstanding work by Hyrtl first, and subsequently by Schatz, served as the proper background for the highly meritorious and contributing research by Benirschke and associates in this area.[4, 5, 7] Also noteworthy are Strong and Corney's contributions.[43]

Vascular connections in separate placentas have not been reported. In monochorial twin placentas, however, they are very common. Benirschke reports positive findings in 51 out of 60 (85 per cent) consecutive monochorial twin placentas studied.[7] Strong and Corney, in a study of 39 monochorial placentas, found vascular connections in 35 (90 per cent).

The types of anastomoses found are artery to artery (A–A), vein to vein (V–V), artery to vein (A–V), vein to artery (V–A), artery to vein plus vein to artery (A–V + V–A) (Figs. 16 and 17). The most common connections are A–A and these appear to be inconsequential. There may be, however, also A–V shunts that complicate matters. Benirschke indicates that often an artery finds its path to a cotyledonary villous structure, irrigates it, and then drains via a vein of and to the other fetus. (Schatz's "Third Circulation"). The flow in this type of vascular shunt is unidirectional and unless compensated by some other anastomosis in the opposite direction or by A–A, a hydrodynamic imbalance may result. This is, at least in part, the mechanism of "twin transfusion syndrome" and its accompanying polyhydramnios. (For more details on the mechanism of this syndrome, see reference 33.)

Figure 17. Photograph of a monochorial diamniotic placenta, weighing 1390 gm, associated with two male fetuses, each weighing 3065 gm. On the injection of one umbilical artery of one twin the red injection mass readily passed into the entire arterial system of both twins. The venous system of each twin was separate: one was injected with blue Chromopaque, the other with yellow. (*From* Boyd JD, Hamilton WJ: The Human Placenta. London W. Heffer and Sons, 1970; with permission.)

Twin Transfusion Syndrome. Benirschke credits Schatz (1875) with the first classic description of what is now known as the transfusion syndrome[7] and we quote the description of this case: "The fetuses were born prematurely, fetus #1 was larger and associated with polyhydramnios (3000 ml of fluid), oligoamnios of the other. The placenta was monochorial–diamnionic with A–V anastomosis. The larger fetus was urinating constantly (thus contributing to hydramnios), the other, the smaller twin, was thin, dehydrated and had no urine in the bladder. The placenta showed A–V shunts." Herlitz, quoted by Strong and Corney, reported twins with essentially the same syndrome in 1941.[43] Of historical interest is Corney and Aherne's reference to descriptions in Genesis of the birth of Esau and Jacob, where it is recorded that "the first came out red." The authors' interpretation is that of the birth of the plethoric twin.[14] A description of the second twin was not given.

This syndrome is relatively common in monochorial twins. Strong and Corney, using as criteria the clinical presence of hydramnios, hemoglobin difference of 30 per cent (4.4 gm per 100 ml), and morbid changes, report that some 30 per cent of monochorial twins show evidence of the syndrome. Placentas with fully developed syndrome also will show significant differences in the respective fetal territories. The placenta is edematous, boggy, and pale in relation to the anemic fetus,

whereas it is red and congested in the counterpart. Microscopically, the pale portion of the placenta shows edematous chorionic villi. Their vessels are reduced in caliber and are said to be elongated.[1, 14] Sections of the amniotic membrane may show features of amnion *nodosum* related to oligoamnios of the pale fetus side. Naturally, all placentas involved would have vascular anastomoses as described above.

The degree of clinical severity of the twin transfusion syndrome is regulated by temporal relationships, length of pregnancy, and structural vascular alterations. Such alterations include the caliber of vessels, quality of anastomosis, and the presence or absence of connections in the opposite direction to compensate for circulatory imbalance.

Hydramnios in Twin Pregnancy. Hydramnios is a common expression of the twin transfusion syndrome that may precede its overt clinical manifestation. However, hydramnios also may be seen in dizygous pregnancies. The pathophysiology of this condition is unknown, but several possibilities have been considered. These include excessive urination, heart failure, polycythemia, and transudation of fluids, as well as others. The morphologic changes of the placenta are the same as those described earlier in hydramnios of the twin transfusion syndrome.

Fetal Monstrosities in Relation to Placentation. Because this article is concerned with placental changes, description of fetuses will be reduced to a mention.

Acardia and *acardia amorphii* are fetal montrosities characterized by absence of heart (acardia) or an appearance of a shapeless magma of necrotic tissue and fibrin (acardia amorphii). This type of twin is monozygotic and monochorionic of unknown etiology, although abnormal vascular connections have been considered causative factors. Benirschke and Driscoll indicate that the "development of an acardia monster is allowed only through the vascular support of the normal partner."[9, 15] Their blood supply originates from an aberrant umbilical artery from the normal fetus, while the venous return is effected by an umbilical vein in the opposite direction.

Fetus Papyraceous and Compressus. In a given twin pregnancy, one member of the twins dies in early pregnancy, for whatever reason. Its growth ceases, its tissues shrink and become flattened, mummified, and paper-like, thus the derivation of the name. The estimated date of fetal demise can be determined by proper fetal measurements (Figs. 18*A*, 18*B*, and 18*C*).

Sometimes a fetus, such as that just described, becomes a *fetus compressus* when, under the pressure of the growing twin, it becomes incorporated into and masked by chorionic tissue or membranes, which by the time of delivery, may have undergone fibrosis (Fig. 18*C*). This type of twin frequently is unrecognized. With the advent of sonography and magnetic resonance imaging, these anomalies are being recognized not only more frequently, but before delivery.

It is worth remembering that the normal fetus could, on rare oc-

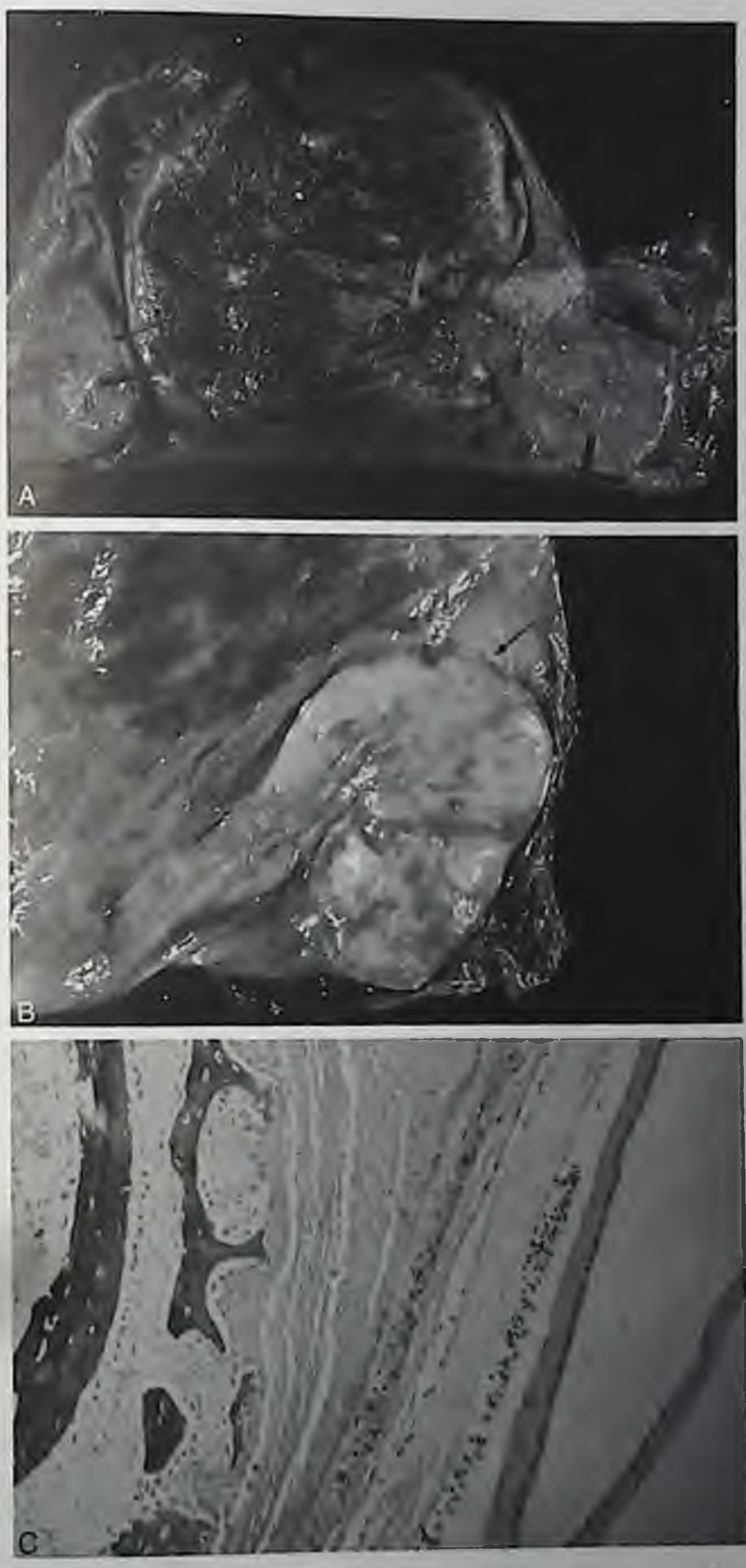

Figure 18. *A*, Placenta with fetus compressus (*arrow*). (Courtesy of Dr. M. Arruza.) *B*, Enlarged view of area containing the fetus compressus. Estimated C.R. 8.0 cm, 13 to 14 weeks' menstrual age. Zygosity could not be determined. *C*, Histologic appearance of fetus compressus, showing bone and cartilage, necrotic epidermis, and amnion.

Figure 19. Photograph of a dichorial diamniotic placenta associated with female fetuses. The arteries of the placenta on the left were injected with red Chromopaque, and vein with yellow Chromopaque; the arteries of the placenta on the right were injected with blue Chromopaque, and the vein with red Chromopaque. (*From* Boyd JD, Hamilton WJ: The Human Placenta. London, W. Heffer and Son, 1970; with permission.)

casions, be affected by products released from a macerated fetus reaching across to the normal fetus via vascular anastomoses. A case in point would be vascular thrombosis (DIC) from thromboplastic fetal products.[8, 9]

Conjoined twins have been discussed previously.

Dichorionic–Diamnionic Fused Placentas

The dichorionic–diamnionic fused placentas could be either monozygous or dizygous. Accordingly, they have different origins. The monozygous variety derives from the separation of the early blastomeres of a single zygote, whereas the dizygous results from two zygotes. The two blastocysts thus formed implant close together and the placentas fuse as they grow larger. The degree of fusion varies considerably from marginal to total, where it mimics a single chorion.

Dichorial–diamnionic placentas comprised 173 of 250 cases in Benirschke's series. One hundred forty of those were estimated to be dizygous. Thirty-three were mono-ovular.[5] Strong and Corney reported 33 per cent dichorionic placentas in their 200 cases. Of these 44 (77 per cent) were binovular, while 13 (23 per cent) were mono-ovular.[13]

Vascular Connections in Dichorionic Placentas. Vascular connections in dichorionic placentas are, at best, very uncommon (Fig. 19). None were found in Benirschke's or in Strong and Corney's series. Many of the cases reported by others are not convincing. There is,

however, an occasional case such as that of Edwards and Cameron. This was a single case in a series of 297 twins, quoted by Benirschke and Strong and Corney, with convincing A–A and V–V anastomoses. In this case the fetuses were male and shared common blood groups (monozygous). (For additional information on vascular connections and on injection of blood vessel techniques, the following references are recommended: 11, 34, 39.)

The infrequency of vascular anastomoses in dichorionic placentas is clearly manifest by Strong and Corney's statement, "If all the prospective cases are regarded as a whole, the incidence appears to be of the order of 1 case in 1000 fused dichorial placentas." "If all the reported cases were accepted, the incidence would be less than 2 per cent and a proportion of these twins would be monozygotic."[44]

The presence of vascular anastomoses in dichorial placentas, particularly the dizygous form, are very important because they may hold the clue for our understanding of blood chimeras or mosaics. These are the subjects carrying in their system blood or tissues from the fraternal twin, which is genetically dissimilar and to whose tissue the infant has become tolerant. Regarding the frequency of this phenomenon, Strong and Corney write, "According to how one interprets the information." referring to the cases gathered from the literature, "the risk ranges from about 1 in 100 fused dichorial placentas to less than 1 in 1000."[43]

Dichorionic-Diamnionic Separate Placentas

The dichorionic–diamnionic separate placenta, like the fused counterpart, can be monozygous or dizygous with a similar rate of distribution (approximately 30 and 70 per cent, respectively). With great frequency, these placentas show pathologic changes corresponding to group c lesions (accommodation). Quite naturally, they may be affected, by chance, by any twinning nonspecific pathologic process (group d). The monozygotic variety, however, because of its greater tendency to prematurity, may reveal features of immaturity of the placenta.

For additional information on the pathology of twin placentas, the reviews by Fox[21] and Lage[28] also are recommended.

HIGHER-ORDER MULTIPLE PREGNANCIES

The incidence of twinning is on average 1 in 85 pregnancies, and this figure is similar in most reports. The incidence of higher-order multiple pregnancy decreases significantly the higher the order. Most authors agree, in general, with Hellin's formula to calculate the incidence of higher multiple pregnancies. According to Hellin, the incidence of triplets would be approximately the square of the number of pregnancies for twins ($1:85^2$), for quadruplets, the cube ($1:85^3$), and so on.

Higher-order multiple pregnancies can be, as indicated before,

Figure 20. Photograph of a tetrachorial tetra-amniotic placenta. Two male infants, weighing 2469 gm and 2298 gm, were associated with the lateral components (*A* and *C*) of the fused placental mass. A female infant, weighing 1844 gm, was attached to component *B*. Another female, weighing 1759 gm, was associated with the isolated placenta. The placental vessels were injected with colored gelatine, and no anastomoses between them were present. The absence of anastomoses was confirmed by histologic examination. All infants survived and are still alive. (*From* Boyd JD, Hamilton WJ: The Human Placenta. London, W. Heffer and Son, 1970; with permission.)

monozygous, dizygous, or multizygous. And they may be associated with one, two, or more placental masses (choria). Boyd and Hamilton in their excellent text on the human placenta[12] review the literature on higher-order multiple pregnancies and make significant contributions of their own. These authors discuss possible placentations in relation to zygosities in triplets, quadruplets, and quintuplets. Quadruplets, for example, "... may arise as the result of the fertilization of one, two, three or four ova, and the following disposition of the placentae and fetal membranes might occur: (1) the fertilization of four ova may give rise to a tetrachorial tetra-amniotic condition; the four placentae may be separate (Fig. 20); there may be three placental masses—two separate and two fused placentae; there may be two placental masses—two pairs of placentae fused; or there may be a single placental mass. (2) The fertilization of three ova may result in three placentae—one monochorial diamniotic and two other placentae, each with a single chorion and a single amnion. If from three ova two

Figure 21. *A*, Septuplets born following human gonadotropin administration in Chiari-Frommel syndrome. *B*, Septachorial–septamnionic placentae, septazygotic pregnancy. Fetuses seen in *A*. (*From* Turksoy RN, Toy BL, Rogers J et al: Obstet Gynecol 30:692, 1967; with permission from the authors and the American College of Obstetricians and Gynecologists.)

Figure 22. Dichorial, diamnionic placenta, missed abortion. Abortion is a common occurrence in multiple pregnancy. (Photograph courtesy of St. Margaret's Hospital.) S-63-1462.

placental masses occur, there are two possibilities—one placenta with single chorion and single amnion, and the other dichorial triamniotic, or one monochorial diamniotic placenta and the other dichorial diamniotic. The fertilization of three ova may also result in a single trichorial tetra-amniotic placental mass.[3] The fertilization of two ova may result in two separate placentae—both monochorial diamniotic—or one single dichorial tetra-amniotic placenta.[4] The fertilization of one ovum may result in a monochorial tetra-amniotic placenta."[12] Similar analysis was made for the triplets and quintuplets.

Berbos[10] has reviewed the literature on pregnancies of 5 or more fetuses and indicates an incidence of 1:371,176 to 1:2,074,306 for quadruplets and 1:15 to 20 million for quintuplets (75 quintuplets reported by 1964). The highest-order multiple pregnancy in humans that we are aware of were octuplets reported by McWhirter and McWhirter in 1967.[12]

The administration of ovulatory agents for the treatment of infertility has on occasion led to multiovulation and multiple pregnancies. We had the opportunity to study at St. Margaret's Hospital in Boston, Massachusetts, when the senior author (WAB) was the director of the Department of Pathology. One case of septuplets reported by Turksoy et al. was born to a patient given gonadotropin for the treatment of a Chiari-Frommel syndrome (Figs. 21*A* and 21*B*).[47] The pathology of placentas of higher-order multiple pregnancies could be the same as those previously described.

This article was introduced with a statement on the immunobiology of tissue transplantation and of the importance of determining zygosity in twins. This importance is underscored by the fact that monozygous twins may, while the dizygous may not, successfully in-

terchange tissues without special manipulations. One exception to this is the chimerous dizygous twin which has become tolerant to the twin partner. This is another reason for adequately studying the twin placenta. (For additional information, see reference 45.)

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Effects of Twins: Maternal, Fetal, and Labor

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During pregnancy, many physical changes, physiologic alterations, and biochemical values have been well established. Twins bring differences to many of these normal pregnancy observations. The mother has exaggerations of normal pregnancy changes. The twin fetuses often respond differently from singletons, and labor in twins presents its own unique problems. The following discussion examines many of the adaptations in a twin pregnancy, assuming knowledge of the normal pregnancy.

MATERNAL

Physical Characteristics

There are physical characteristics in women prior to pregnancy that make the possibility of carrying twins greater. Dizygotic twin pregnancies occur more commonly in women of increasing parity, advancing age, and women that are tall or obese.[36] Not only is the height greater but also their prepregnant weight for height.[5] Corney et al. also found greater height in mothers of dizygotic twins, but the mothers of monozygotic twins were no different from the mothers of singletons.[11] Other characteristics mothers of dizygotic twins have are earlier menarche, earlier menopause, greater susceptibility to ovarian cysts and uterine neoplasms, and greater risk of pancreatic cancer and diabetes.[12, 68]

Maternal weight gain during twin pregnancy not surprisingly is greater than during singleton pregnancy. These are reports that the weight difference starts in the first trimester, indicating that not only the size of the conceptus, but other factors are contributory.[36] After the first trimester, the twin primigravida outgains the singleton by significant amounts: weeks 13 to 20, 0.60 kg per week versus 0.42 kg

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per wk; weeks 20 to 30, 0.54 kg per wks versus 0.47 kg per wk; weeks 30 to 36, 0.64 kg per wk versus 0.40 kg per wk.[39]

The uterus grows larger with twins than with singleton pregnancies. A difference in examination is not usually noted before 12 weeks. By 18 weeks, the 50th percentile of twin uterine heights is above the normal singleton zone (90th percentile). The curve of the 10th percentile is greater than the 90th singleton percentile by 28 weeks' gestation.[31] By serial ultrasound measurements from 12 weeks' gestation in 27 twin pregnancies, a nanogram was constructed of total intrauterine volume (TIUV). The formula for an ellipse

$$TIUV = 0.523 \times L \times AP \times T$$

was used: The TIUV of twin gestations was similar to singletons at the beginning of the second trimester. The TIUV of the twin gestations was twice as large as singletons by the 18th week. At 25 weeks' gestation, the TIUV of twin pregnancies was equal to the size of a term singleton. There was noted to be a showing of the uterine growth prior to the onset of labor.[52]

Cardiovascular System. Pregnant women undergo a decreased peripheral resistance and lower blood pressure during early pregnancy with a rise near the end of pregnancy. Campbell et al. examined the blood pressure patterns in patients carrying twins between 1950 and 1965 in Aberdeen. The diastolic pressure in primiparous women with twins was found to decrease more by midpregnancy and subsequently have a greater rise by delivery than in primiparous women with singletons. These changes were not dependent on age, body size, or weight gain.[5] Closer to delivery, the incidence of preeclampsia in twins was much greater than in singletons (29 per cent vs. 5.8 per cent).

It has been reported for many years that there is a higher proportion of patients with a low hemoglobin level with twins than singletons. This may be due to greater hemodilution in twin pregnancies, a greater demand for iron, a greater demand for folic acid, or some combination of these.

In singleton pregnancies, the increase in total blood volume results in a lower hematocrit and hemoglobin concentration because of the greater increase in blood volume to red blood cell mass. These changes occur in twin pregnancies to a greater degree. By 37 to 40 weeks, the plasma volume increases by 48 per cent in singletons (to 4 liters) and by 67 per cent (to 4.7 liters) in twins in studies by Rovinsky et al.[55] This study included both primiparas and multiparas and may be inaccurate because singleton multiparous patients have a greater plasma volume than singleton primiparous patients (4.2 to 3.7 liters).[8] Looking only at primiparous patients, twins had greater plasma volume than singletons at 34 weeks (4.3 liters to 3.8 liters).[39] The total red cell volume in twins at 34 weeks was found to be 2063 ml compared to 1694 ml in singletons.[39] As in singleton pregnancies, the relative increase is greater in plasma volume than red blood cell volume so hemodilution results.

The plasma volume is important in the growth of the fetus. A positive correlation with plasma volume and infant birth weight in multiparous women with twins has been found. However, the importance of the plasma volume and fetal growth in primiparous twin pregnancies has been conflicting.[8, 39]

Cardiac output was determined by Evans blue dye dilution technique and seemed to be greater in twin than singleton pregnancy. While in singleton pregnancies the cardiac output rose from 5.9 liters per min nonpregnant to 8.6 liters per min in early third trimester, in twin pregnancy the cardiac output rose to 9.0 liter per min.[55]

An increase in heart rate, mean cardiac stroke volume, and mean circulation time were found to be similar in twin and singleton pregnancies.[55]

The greater likelihood of women with twin pregnancies developing folic acid deficiency was suggested by authors finding lower serum folate concentrations in twins, more rapid clearance rate of folate, and a higher incidence of megaloblastic anemia in twins. In a recent report, Ek studied 26 twin mothers and 130 singleton mothers 30 to 40 weeks' gestation receiving iron but no folic acid supplementation.[13] He found that the plasma and red cell folate levels in twin pregnancies were similar to levels in singleton pregnancies. The plasma folate was not lower in twins in contrast to previous studies. It also was found that women with twins had lower hemoglobin RBC volume at 32 weeks than women with singletons, but this returned to normal by 38 to 40 weeks. There was a higher reticulocyte count and MCV in twin pregnancies at term. The twin infants that were born between 30 and 40 weeks demonstrated similar plasma folate levels to singletons at all ages, but there was a lower red cell folate level in the twin infants until 37 weeks. The twin infants had similar hemoglobin, but higher MCV and reticulocyte count than singletons. It was concluded that less folate was transferred to the twin fetuses before term as compared to the singleton.

Coagulation

Plasma fibrinogen levels have been reported to be elevated in twin pregnancies from 24 weeks' gestation compared to singleton pregnancies. No differences were noted of plasminogen, fibrin split products, antithrombin III, alpha I antitrypsin, or alpha II macroglobulin levels.[39]

Respiratory Function

The tidal volume in twin pregnancies has been reported to be increased even greater than in singleton pregnancies.[39]

Renal Function

The already increased glomerular filtration rate in singleton pregnancies is enhanced further in twin gestations with possible increased excretion of amino acids, vitamins, and other substances.[39]

The physiologic changes in pregnancy such as ureteral dilation

by either possible compression by the uterus at the pelvic brim, compression by ovarian veins, or hormonal relaxation of ureteral musculature observed in normal pregnancies may lead to an increased stasis and urinary tract infections in twin pregnancies. An increased incidence of pyelonephritis in twin pregnancy was not found in an earlier study but was found in a later study.[21, 19]

Alimentary System

Many alterations occur in the gastrointestinal tract during normal pregnancy. Some of these may be further altered in twin pregnancies but no clinical evidence of an increased incidence of hyperemesis gravidarum or gastric reflex has been reported. Tests examining liver function with bromsulphthalein by singleton and multiple pregnancies have been performed. The elimination of bromsulphalein from the liver cells in twin pregnancies is reduced as in singleton pregnancies but to a greater degree.[3] A greater transfer to the liver from plasma was noted in twin pregnancy most likely owing to increased blood that flows through the liver.[2]

Carbohydrate Metabolism

Pregnancy is associated with a slightly lower fasting blood sugar and elevated plasma insulin level following a glucose load. Carbohydrate metabolism in a study comparing 24 singletons to 24 twins with an intravenous glucose tolerance test found significant lower fasting, 5- and 15-minute blood glucose levels in the twin pregnancy, and lower 15-minute insulin levels in the twin pregnancy.[60] These data suggest that twin pregnancies do not seem to be at a higher risk than singleton pregnancies for clinical hyperglycemia.

MacGillivray notes that chemical gestational diabetes occurs more commonly in twin than singleton pregnancy.[39] However, Kohl did not find an increased incidence of diabetes in a large clinical study. He found a 2.1 per cent frequency of diabetes in 243,123 singleton pregnancies versus 1.8 per cent in 6503 twin pregnancies.[30] This study suggests that diabetes may not be more common in twin gestations.

Nutrition

The role of nutritional intake and fetal growth is not well established. Some studies have indicated that intakes are not different in patients that are obese or short, or patients that have poor weight gain or normal weight gain in pregnancy.[7] MacGillivray found that the urinary nitrogen output was less in twin pregnancies.[34] This is related to protein and energy intake and may imply that women with twin pregnancies may have less protein energy intake or may more efficiently utilize their diet. Campbell et al. found that energy and protein intake and excretion were not different in twin and singleton pregnancies. This study was performed by weighing dietary intake over a 7-day period and measuring 24-hour urinary nitrogen at 30 weeks' gestation.[9] Although no differences were found in singleton and twin pregnancies, the energy intake was 300 to 400 kcal less than recom-

mended by the United Kingdom Department of Health and Social Security. These data suggest that fetal growth is not directly related to the nutrient intake and that some physiologic adaptation is present in twin pregnancies adjusting the utilization of nutrients.

Dietary Zinc, Copper, and Iron

To evaluate the importance of trace elements zinc and copper in twin pregnancies, maternal plasma levels were measured in healthy primigravida twin and singleton pregnancies.[9] No significant differences were found between twin and singleton pregnancies at 20 or 30 weeks' gestation. At 20 to 22 weeks, plasma zinc concentration was 10.9 ± 3.3 μmol per liter in twins, 11.1 ± 3.3 μmol per liter in singletons, at 30 to 32 weeks 9.9 ± 3.2 μmol per liter in twins and 11.6 ± 3.4 μmol in singletons. At 20 to 22 weeks, plasma copper concentration was 31.1 ± 5.6 μmol per liter in twins, 29.0 ± 5.4 μmol per liter in singletons, at 30 to 32 weeks 33.1 ± 5.8 μmol per liter in twins, and 30.8 ± 5.6 μmol per liter in singletons. However, there was not the expected significant fall in zinc concentration between 20 and 30 weeks, or a significant rise in copper concentration with gestation as reported in previous studies.[23, 24] This previously reported increase in plasma copper has been attributed to estrogenic increase in ceruloplasmin and an increase fetal demand. Further studies are necessary to evaluate these descrepancies.

Serum Protein and Electrolytes

The plasma volume is increased in twin pregnancies over singleton, as shown by Evans blue dye. This reduced the concentration of total protein, but the total intravascular protein mass is the same in twin and singleton pregnancies.[39] There is no significant difference in serum sodium, potassium, chloride, or osmolality between twins and singletons.[39]

Maternal serum human chorionic gonadotropin levels tend to be higher in twin than singleton pregnancies because of the increased placental mass. Thiery et al. found that human chorionic gonadotropin is 2.5 times higher throughout gestation than in singletons.[6] This difference has been attempted to be used clinically for the prediction of multiple pregnancies. Janonovic et al. screened 590 pregnant women at 4 to 5 weeks' gestation for serum human chorionic gonadotropin levels.[27] Nine women had a human chorionic gonadotropin level that was at least 2 times higher than the others. All nine of these women were found to be carrying twins at a 12-week ultrasound examination. However, using serum human chorionic gonadotropin was not found to be as useful as a second trimester test. Vandekerchkhove et al. collected blood on 992 pregnant women between 16 and 20 weeks' gestation.[64] Using the 80 per cent percentile as a cut off, the sensitivity of predicting a twin pregnancy was 60 per cent and the specificity 96.3 per cent. This sensitivity was considered to be too low for useful screening.

Human placental lactogen, one of the placental hormones, is in-

creased in maternal serum levels in twin pregnancies. Spellacy et al. found a higher level at 30 weeks' gestation (7.0 μg per ml vs 6.0 μg per ml) and at 36 weeks (9.2 μg per ml vs 7.4 μg/ml) in twin than singleton pregnancies.[61] Kappel et al. also found that uncomplicated twin pregnancies had higher human placental lactogen levels than singleton pregnancies.[28] Using serial serum human chorionic gonadotropin levels in 145 consecutive twin pregnancies, it was found that significantly more human chorionic gonadotropin levels were below the median in monoplacental than diplacental pregnancies and more human placental lactogen levels were below the median in monozygotic than dizygotic pregnancies.

Similarly, Scheider et al. found in a study of 86 twin pregnancies, that the curve of mean human placental lactogen levels from 27 to 37 weeks' gestation was parallel and higher in dizygotic twins than for monozygotic twins.[58] This difference was significant at 37 weeks. They also found that mothers of dizygotic twins tend to gain more weight than mothers of monozygotic twins, but this was not statistically significant. The difference in weight gain, which was not accounted for by infant or placental weight differences was speculated to possibly be due to an effect of human placental lactogen difference.

Using human placental lactogen as a screening value for twins at 16 to 20 weeks' gestation was found to have a sensitivity of 70 per cent and specificity of 91.9 per cent above the 90th percentile.[64]

Estriol is a hormone that would be expected to be increased in twin pregnancies with its contribution from mother, fetus, and placenta. Urine excretion of estriol has been reported to be increased by 50 per cent in the twin pregnancy over the singleton pregnancy and the plasma value has also been reported to be increased.[39] Maternal estriol levels were significantly higher in twin pregnancies than singleton pregnancies as measured by maternal 24-hour urinary estriol excretion and by maternal serum values.[28, 62, 66] Tamby Raja found that estriol reached the peak about 2 weeks before singleton pregnancies. He speculates that the higher estriol in twin pregnancies may be because of the increase DHEAS produced by the four fetal adrenal glands and two livers producing sufficient 16-hydroxylase.

Serum progesterone levels are increased by a factor of two and serum estradiol levels are increased in twin compared to singleton pregnancies.[39, 62]

Maternal serum alpha-fetoprotein is known to be elevated at 16 to 20 weeks' gestation in several conditions other than neural tube defect, including fetal death, other fetal anomalies, intrauterine growth retardation, and multiple gestation. In twin pregnancy, the median level is at 2 to 2.5 multiples of the singleton pregnancy, placing it at the upper limit of normal for singletons.[18, 53] Different cut off levels for significant alpha-fetoprotein values must be used in screening for neural tube defects. Ghosh et al. suggest using alpha-fetoprotein values greater than five multiples of median for singleton pregnancies because it was exceeded by all 11 of 219 pregnancies tested that had neural tube defects. Redford et al. found that maternal serum

alpha-fetoprotein concentrations greater than four multiples of the singleton median were associated with poor perinatal outcome in the absence of neural tube defects. Further work is being done to further establish abnormal values on the singleton chart and developing values specifically for multiple gestations.

Pregnancy-specific beta 1 glycoprotein (SPI) values in twin pregnancies[59] were above the mean value in 63 per cent of twin pregnancies.

Placental protein 5 has been established as one of the pregnancy-specific proteins that is localized in the syncytiotrophoblast. It is released into the maternal circulation in small amounts and reaches a peak in maternal serum at 34 to 35 weeks. In a study of 58 twin pregnancies by Nisbet et al., placental protein 5 values were above the mean value for singleton in 88 per cent of patients.[44] This is also elevated to a lesser degree in other complications of pregnancy such as diabetes and preeclampsia.

Pregnancy zone protein or alpha-2 pregnancy-associated glycoprotein was drawn in 35 twin pregnancies and 35 singleton pregnancies in the second half of pregnancy.[66] The mean alpha-2 pregnancy-associated glycoprotein was significantly lower in twin pregnancy. An inverse relationship was noted between alpha-2 pregnancy-associated glycoprotein and estriol. It is suggested that alpha-2 pregnancy-associated glycoprotein is regulated by the presence of estrogen.

Serial maternal serum measurements of the enzyme diamine oxidase have found an increased level in twin over singleton pregnancies.[65]

FETUS

Growth

The early intrauterine growth was examined by Iffy in examination of 43 twins 8.5 to 21 weeks' gestation following induced abortions. The body weight compared to length was similar to singletons, but the average crown rump length was less than singletons.[26] Fetal growth has been studied extensively during the past few years with the widespread use of ultrasound, but the abnormal growth patterns of multiple pregnancies have been known for many years. In 1952 McKeown observed that the fetal growth is independent of the number of fetuses present *in utero* until after the 30th week of gestation. After 30 weeks an increasing weight deficit is noted.[41] Erkkola also noted that in 476 twins studied between 1970 to 1981, the growth rates of both twins are similar to singletons until 30 weeks, then slows compared to singletons.[41] A prospective study utilizing serial ultrasound examinations in 35 twin gestations every 3 weeks starting at 15 weeks found that the BPD and abdominal circumference growth maintained a constant velocity from 15 to 28 weeks. At greater than 28 weeks, the growth of the BPD slowed, but the abdominal circumfer-

ences continued to grow at a constant rate. The weights of twins A and B did not appear to differ.[69] A prospective study comparing 150 twins to singletons found that the head circumference and length were following the singleton growth pattern, but the birth weight was similar to IUGR singletons.[15]

Lower birth weights in twins than singletons in the literature have been found to be due to both the more frequent premature deliveries and the problems of feeding two fetuses from the maternal supply.[20, 40] In an evaluation of 1049 twin pregnancies from 28 to 42 weeks' gestation, Leroy et al. also found the difference in twin weights from singletons appearing at 30 weeks. The difference of the 50th percentile in twins versus singletons was 150 gm at 31 weeks, 420 gm at 35 weeks, and 610 gm at 40 weeks. The weights of dichorionic twins was greater than monochorionic twins and male twins weighed more than female twins. The height of twins was also less than singletons. The difference at 31 weeks was 0.3 cm, at 35 weeks 2 cm, and at 40 weeks 2.3 cm.[32]

Other investigators have found differences between twin weights related to the type of twins. There is a greater difference in twin weights with a single chorion than two chorions. Dichorionic twins weigh more than monochorionic twins. Dizygotic twins weigh more than monozygotic twins. Part of the explanation of why dizygotic twins weigh more than monozygotic is that taller women are associated with dizygotic twinning. It has been speculated that the larger size of dizygotic twins may be associated with increased anterior pituitary activity, and increased FSH and GH secretion.

Lung Maturity

Fetal lung maturity has been found to occur several weeks earlier in twin versus uncomplicated singleton gestation as indicated by lecithin/sphingomyelin (L/S) ratios. In 42 twin gestations, the L/S ratios obtained at cesarean section were usually similar to each other and were independent of sex, zygosity, and birth weight.[33] In a study of 30 twins at a mean 37.7 weeks' gestation, Norman et al. found no difference in L/S, phosphatidylinositol (PI), or phosphatidylglycerol (PG) values between the twins before the onset of labor, but with the start of contractions, there was a significant increase in L/S ratios in the first twin.[47] The total protein concentration in amniotic fluid was measured in twin and singleton pregnancies, and no significant difference was found between them.[48]

Umbilical Cord Measurement

Other substances have been measured in the umbilical cord blood to try to gain greater understanding of the interplay between the fetus and mother in twin gestation. Umbilical artery levels of androstenedione, progesterone, pregnenolone, pregnenolone sulfate, and dehydroepiandrosterone sulfate were measured in twins. Before the onset of labor, there was no difference in level of any steroid between the two twins. In the latent phase of labor, the progesterone level was

less in twin 1, and the androstenedione level was greater in twin 1. During active labor, the level of androstenedione was greater in twin 1. It was speculated that the increase in androstenedione, derived from the fetal adrenal gland, may have a role in the onset of labor.[46] In a similar study, cortisol, prostaglandins, ACTH, and prolactin were measured in the umbilical cord blood of 50 twins at cesarean section. Before labor and during latent labor, the cortisol levels were the same. During active labor, cortisol levels were higher in twin 1. Prostaglandin E_2 was not different in twin 1 and 2 before active labor, but in active labor the level was higher in twin 1. 13,14 Dihydro-15-keto-F_2 (PGFM) was increased in both twins in active labor. ACTH and prolactin were the same in both twins and not increased during active labor. It is suggested that differences in prostaglandins and cortisol may have roles either in the initiation of labor or adaptation of the fetus to extrauterine life.[45]

LABOR

Newman et al. examined uterine activity in ambulatory singleton and twin pregnancy. The 18 twin pregnancies demonstrated significantly greater weekly frequency of prelabor uterine activity in outpatients delivering at term than the 22 singleton pregnancies.[42]

The compression of pelvic vessels in quiet standing was found to coincide with uterine contractions by Schneider et al. With left lateral recumbent position, the premature uterine contractions lessened. These uterine contractions which were postulated to possibly relieve venous obstruction were found to occur earlier and more frequently in twin gestations.[57]

This increased uterine activity and possible other factors tend to lead to earlier delivery with twin gestation than with singleton. In a study of 335 twin deliveries, Kaupilla et al. found mean gestational age at delivery 37.2.[29] Houlton et al. found that in 132 twin pregnancies in black African women at greater than 30 weeks, delivery occurred at greater than 37 weeks in 32 per cent.[25]

Reviewing 624 twin pregnancies in Aberdeen from 1968 to 1977, MacGillivray et al. found that the incidence of preterm deliveries was 28.2 per cent of all twin deliveries. He found that the average gestational age at twin deliveries was 260 days and gave possible reasons as overdistention of the uterus or increased hormonal changes over singletons.[38] Preterm delivery has been found to be more common in monozygotic then dizygotic twins because of an increase in preterm rupture of membranes. Preterm delivery was also more common with male than female infants.[37] Newton et al. also looked at the duration of twin pregnancies related to fetal sex. Of 562 twin gestations, he found that by dates and examination, pregnancies with 2 male fetuses had a shorter duration at delivery (36.8 weeks) than either 1 male and 1 female fetus (37.2 weeks) or 2 female fetuses (37.4 weeks). He con-

cluded that the male twin gestation is different in some biologic sense than other twins.[43]

Labor itself presents increased difficulties with twin pregnancies. Malpresentations and overdistention of the uterus have been suggested as increasing problems.[38] In a study examining the length of labor in 100 pairs of twin and matched singleton pregnancies, the duration of labor was found to be the same.[17] Bender also found no difference in the length of labor between twins and singletons in a review of 472 cases.[4] A study by Friedman et al. found differences in both the latent phase and in the active phase in twins.[16] The latent phase in twin pregnancies was found to be shorter than in singleton pregnancies, partially due to the greater cervical dilatation in twins before labor starts. There was a tendency for a longer active phase in twin over singleton pregnancies, possibly due to the uterine overdistention.[16] The net result is a similar total duration of labor in singleton and twin gestations.

The differences of labor between primiparous and multiparous twin pregnancies were examined by Ross et al.[54] They found that the average length of labor in 129 multiparous patients was 8 hours and 19 minutes with no prolonged labor. Of 55 primiparous twin pregnancies 4 had prolonged labor (greater than 48 hrs). In the remaining 51 pregnancies, the average duration of labor was 12 hours and 42 minutes.

Difficult labors also may result from malpresentation. In various reports, the incidence of both twins presenting vertex is no higher in nulliparous than in primiparous patients (44.1 to 47.8 per cent).[49, 50, 70] Other presentations bring a higher risk of complications and operative deliveries. Although difficult to document, there is some belief that labor with twin fetuses has greater discomfort and is more exhausting due to the increased weight and distention of the uterus than a singleton.[38]

There is disagreement on the amount of blood loss during twin delivery. Wood states that although it was thought that postpartum hemorrhage was more common in multiple pregnancies due to overdistention, he did not find hemorrhage to be more frequent after twin deliveries.[67] More recently, in Williams's *Obstetrics* the average blood loss with twin vaginal delivery was reported to be 500 ml greater than after delivery of one fetus.[51]

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Multiple Pregnancy: Antepartum Management

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In approximately 1 per cent of pregnancies, twin gestations are encountered. Despite their infrequent occurrence, they are considered high-risk pregnancies because of the higher maternal and fetal morbidity and mortality associated with them. For example, compared with singleton pregnancies, the perinatal mortality rate is two to five times higher among twins.[1, 6, 8, 14, 18, 22, 28, 30, 57, 60, 71, 78, 82] In fact, perinatal mortality rates as high as 10 per cent have been observed.[28, 57, 60] The leading cause of perinatal morbidity and mortality among twins is prematurity. Additional factors include a higher rate of intrauterine growth retardation (IUGR) and congenital anomalies.[63, 65] Along with these fetal factors, maternal complications are similarly increased. For example, women with twin pregnancies have an increased risk of placental abruption, placenta previa, preeclampsia, anemia, hyperemesis gravidarum, and postpartum hemorrhage.

Early diagnosis is critical to minimize these risks. With early diagnosis, the clinician is in a better position to optimize prenatal care and provide for a more favorable outcome.

EARLY DIAGNOSIS

Even though the importance of early diagnosis of multiple gestation has been documented, many investigators have reported in large series of twin gestations that 20 to 40 per cent of these pregnancies are not diagnosed prior to labor and delivery.[28, 45, 65] Although routine midpregnancy ultrasonography would appear to be the best method for identifying these twin pregnancies and lessening the risk of missed diagnosis, its application is still considered controversial. Persson et al. have reported that 95 per cent of twin gestation could

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Table 1. *Factors Associated With a Greater Likelihood of a Multiple Gestation*

Family history of twins
Ethnicity (black > white > Asian)
Maternal age (>35)
Parity (>3)
Fertility drugs

be detected by routine second trimester ultrasound screening.[75] Of interest, they showed that the average gestational age for twin diagnosis had fallen over the years with the use of routine ultrasound screening. For instance, the average gestational age of diagnosis in 1963 to 1965 was 35 weeks. In 1973, the age of detection had fallen to 30 weeks and by 1977, the average gestational age was 20 weeks. Nonetheless, routine ultrasound screening has not been accepted in America. As a result, obstetricians must rely on clinical factors to establish the diagnosis of a twin pregnancy before prescribing an ultrasound evaluation.

CLINICAL DIAGNOSIS

One cannot underemphasize the importance of considering that every pregnancy has the possibility of twins. Clinical detection of twins by palpation or demonstration of two fetal heart tones is extremely difficult. Reliance on the hallmark of uterine size larger than expected for her menstrual dates is predictive, but not to the same level as ultrasonography. Thus, until routine ultrasound screening becomes acceptable, today's obstetrician must pay close attention to the patient's history and to any signs and symptoms of twins. For example, hyperemesis gravidarum, unexpected anemia, or onset of pregnancy-induced hypertension prior to 20 weeks should alert the clinician to the possibility of twins. In particular, women with a family history of twins are at a high risk for twins. As outlined in Table 1, additional risk factors associated with twins include the patient's ethnic background (black > white > Asian), age (age >35), and parity (>3).[65] Of special clinical significance are women who have undergone ovulation induction; the incidence of twins following clomiphene therapy, for example, is 5 to 10 per cent.[65] This rate is also higher with Pergonal. Thus, patients who have received gonadotropins should also undergo ultrasound evaluation for possiblity of a multiple pregnancy.

An indirect method for detecting twins is alpha-fetoprotein (AFP) screening. With AFP screening at 15 weeks being adopted in many states, more twins will be detected on this basis. In contrast with singleton pregnancies, the AFP level in uncomplicated twins is higher but frequently within the normal range.[32] As demonstrated by Clarke, 30 per cent of twin pregnancies have a maternal serum AFP greater

than 95th percentiles.[13] In most series, however, serum AFP screening will help identify about half of the pregnancies with multiple gestations.[72]

In summary, the importance of early diagnosis of twin gestations is essential and requires close attention to risk factors associated with twinning. Thus, ultrasound evaluation would appear prudent in women with antenatal risk factors associated with twinning (see Table 1) or signs or symptoms indicative of the possibility of twins.

THE ROLE OF ULTRASONOGRAPHY

Diagnosis of Twins

With real-time linear array ultrasonography, two gestational sacs can be visualized as early as 6 weeks' gestation and fetal cardiac motion detected by 8 weeks. With vaginal ultrasound, however, twins can be detected even earlier. Early diagnosis of twins is associated with a much smaller incidence of twins at term. For example, among 118 multiple pregnancies identified before 10 weeks' gestation, 71 per cent of the patients delivered a singleton fetus.[52] Other reports have demonstrated a higher multiple birth rate of 50 per cent with first trimester ultrasound diagnosis.[81, 91] Moreover, Landy, in a group of multiple pregnancies diagnosed by ultrasound prior to 14 weeks' gestation, reported only a 20 per cent spontaneous loss rate.[48]

Subsequent management of twin pregnancies diagnosed in the first trimesters, would appear to suggest the need for a repeat ultrasound to confirm the presence of twins. In those pregnancies in which the sac disappears, the subsequent outcome of the "surviving" twin appears to be related to whether the woman has vaginal bleeding in the first trimester.[52, 81, 91] If she does, the pregnancy is more likely to be lost.

Determination of Zygosity

The incidence of monozygous and dizygous twinning is 20 and 80 per cent, respectively.[8] Of those found to be monozygous, approximately 20 per cent are monochorionic and 80 per cent dichorionic.[8] The incidence of mono- and diamnionic sacs is 1 and 99 per cent, respectively. Furthermore, all dizygotic twins and around 30 per cent of monozygotic twins have dichorionic placentation.[7] When monozygotic twins are compared with dizygous twins, the perinatal morbidity and mortality rates are two to three times higher among monozygous twins. This is frequently due to anastomosis of placental vessels and the resultant unequal sharing of blood flow or twin–twin transfusion. Moreover, monoamnionic twins have the highest rate of fetal demise due to entanglement of the umbilical cords[31, 43, 55, 69, 84] or the presence of conjoined twins.[31, 84] Finally, premature labor risk appears to be higher among monozygous twins. According to Weir,[94] this is due to a higher incidence of acute polyhydramnios[94] among these pregnancies.

Table 2. *Sonographic Diagnosis of Twin–Twin Transfusion (10, 95)*

Marked discordant fetal growth
Fetuses of the same sex
A single placenta
Discordant amniotic sac size
Evidence of hydrops or cardiac failure in either fetus

The antenatal diagnosis of zygosity can be difficult at times, but is essential to clinical management[5, 55] and to optimize fetal outcome. To establish zygosity, ultrasonography is essential. First, ultrasound evaluation of the placental site is done. If there are two placentas, this suggests a dizygous twin. Second, are there two sacs? With ultrasonography, a membrane can be seen between the sacs. Third, ultrasound evaluation of the genital region will allow the clinician to determine the sex of the fetuses. Fourth, what are the fetal positions? If the fetuses are not in the same presentation (e.g., vertex–breech), the probability of conjoined twins is remote. However, if the twins are vertex–vertex or breech–breech, conjoined twins are more likely. In addition, in the absence of a membrane, are the twins connected? In most instances, conjoined twins are connected at the level of the fetal liver, but any combination can occur.

Why is the determination of zygosity important? With monozygous twins, twin–twin transfusion can occur and fetal growth can be affected. In contrast, dizygous twins have their own independent placentas, and as a result, growth of these twins will not be dependent on nor usually affected by the other twin.

If twins are suspected of being monozygous, sonographic criteria to establish the diagnosis of a twin–twin transfusion are illustrated in Table 2.[10, 95] Once growth is considered discordant, subsequent management will depend on the gestational age of the pregnancy and the lung maturity of the fetuses. In these pregnancies, fetal surveillance is warranted. At delivery, the diagnosis of a twin–twin transfusion can be established by identifying an anastomotic vessel, a hemoglobin difference of 5 gm per dl, and a difference in birth weight.[64]

Fetal Growth Assessment

Intrauterine growth retardation is more common among twin than singleton pregnancies (5–7 per cent)[12] and complicates 12 to 47 per cent of multiple gestations. Since twins compete for nutrients, growth discrepancies are not uncommon. The most extreme differences occur with twin–twin transfusion.[12, 34, 72]

For an accurate diagnosis of IUGR, many reports have focused on the biparietal diameter (BPD) of the fetal head as the minimal requirement.[17, 24, 36, 51] However, recent evidence suggests that the BPD alone is insufficient to assess fetal growth adequately. For instance, the fetal head frequently is altered owing to malpresentation and intrauterine crowding.[11, 35] For example, Milne[62] has reported a

Table 3. *Sonographic Criteria for Discordant Twin Growth*

Biparietal diameter difference	>5 mm
Biparietal diameter smaller twin standard deviations from the mean	>2
Head circumference difference	>5%

26.3 per cent failure rate for obtaining a satisfactory BPD measurement in twin gestation, compared to a rate of 8.9 per cent in singleton pregnancies. Moreover, the accuracy of detecting IUGR in twin pregnancies with the use of the BPD alone was found to be 56 per cent.[67] Another issue that complicates the sonographic assessment of fetal growth is whether twins grow at a similar rate as singletons. For instance, Crane[17] has reported that BPD changes in normal twins were similar to singletons. However, many studies have demonstrated a decrease in BPD growth in twin pregnancies after 30 weeks' gestation.[12, 34, 35, 51]

Even though the BPD alone is an insufficient method to assess fetal growth in twin pregnancies, several studies have correlated the differences in BPD measurements in twin pairs with subsequent perinatal outcome. In Houlton's study,[41] the greater the difference in BPD measurements, the greater was the risk of IUGR. For example, if the difference was between 2 and 6 mm, the incidence was 40 per cent. When the predelivery BPD differences exceeded 6 mm, the incidence of IUGR in the smaller twin was 71 per cent. Additionally, Leveno[51] has reported that twins with a BPD difference in excess of 4 mm, IUGR was increased threefold. Fetal death was increased from 2.7 per cent for twin pairs with a 0- to 6-mm BPD difference to 20 per cent when the BPD difference exceeded 6 mm. To provide some uniformity, Crane[17] has suggested the criteria listed in Table 3 for detecting discordant growth.

To assess fetal growth more accurately, a complete fetal physical examination is suggested. This would include the BPD, abdominal circumference (AC), head circumference (HC) and femur length (FL). By determining these measurements, the average gestational age and estimated fetal weight can be determined for each twin.[4, 87, 89]

If discordant fetal growth is suggested by the ultrasound evaluation, fetal surveillance is warranted. If the weight differences between the twins exceeds 25 per cent, the fetal death rate is 6.5 times higher, the neonatal death is increased 2.5-fold, and developmental disturbances in the smaller twin occur at a higher rate.[1, 26]

ANTENATAL CARE

Owing to the lack of properly controlled studies, there is considerable controversy as to the appropriate management of multiple gestations. Nonetheless, the primary clinical objective is the prevention

of prematurity and intrauterine growth retardation. To achieve these goals, early diagnosis, appropriate clinical management that includes fetal assessment, adequate maternal diet, and frequent maternal and aggressive treatment of premature labor or other obstetrical conditions are essential.

In general, clinical management has focused on the following: (1) maternal diet, (2) bed rest, (3) prophylactic tocolysis, (4) cerclage, and (5) fetal surveillance with the nonstress test or biophysical profile, and (6) serial ultrasound evaluations to assess fetal growth.

Diet

Current recommendations are that maternal consumption should be increased a minimum of 300 kcal per day above the current requirements for a singleton pregnancy. Additionally, vitamin intake should be increased to reflect the physiologic adjustments of pregnancy and the demands of the twin fetuses. This requires supplementation with 60 to 80 mg of iron and folic acid (2 mg) throughout the pregnancy. In the event of anemia, the cause for the anemia should be accurately diagnosed and treated with the appropriate hematinics.

Along with these dietary changes, patients should be advised to quit smoking or eliminate any alcohol consumption. Twins of smoking mothers have been found to have lower mean birth weights and a higher risk of perinatal death.[41]

Bed Rest

The role of bed rest in the prevention of prematurity in twin gestations remains controversial.[11, 26, 29, 38, 39, 40, 42, 47, 61, 70, 73, 76, 80, 90] Theoretically, bed rest offers the advantage of improving uterine blood flow and relieving mechanical pressure on the cervix.[64] This should reduce the probability of IUGR and preterm delivery. Recently, Komoromy and Laupe[47] investigated the impact of hospitalization (bed rest) during the third trimester. Their study population of 242 hospitalized twin gestations were contrasted with 249 nonhospitalized twin gestations. The hospitalized group delivered at a later gestational age (37.4 vs 35 weeks) and had higher birth weights (2581 gm vs 1972 gm) than did the control group. More importantly, the perinatal mortality rate among the rested group (54 per 1000) was significantly improved over the nonhospitalized group (217 per 1000).[47] Whereas many studies have corroborated the findings of Komoromy and Laupe,[29, 40, 42, 61, 80] others have failed to demonstrate any lowering in perinatal mortality.[26, 39, 70, 90]

Because more than 50 per cent of the perinatal mortality associated with twin gestation occurs prior to 30 weeks' gestation, recent reports suggest that bed rest should be instituted earlier rather than waiting until 28 weeks.[38, 52, 57, 73, 76] For instance, Hawrylyshyn et al.[40] have recommended hospitalizing with bed rest beginning as early as 25 weeks' gestation, and O'Grady[71] has recommended starting at 24 weeks' gestation.

Regardless of whether bed rest is instituted in a hospital or at

home, the benefits of bed rest clearly outweigh the risks. The optimal time for initiating bed rest is less clear but should begin no later than 28 weeks' gestation. Should complications occur prior to that time, hospitalization would seem prudent.

Prophylactic Tocolysis

Use of prophylactic tocolytics is also controversial. Several authors have failed to demonstrate a benefit from the prophylactic use of ritodrine,[71] terbutaline,[85] or fenoterol.[56] However, in the treatment of premature labor, Rayburn[77] showed similar maternal and fetal physiologic effects from intravenous ritodrine between singleton and twin gestations. Moreover, the average dose, duration of therapy, and delays in delivery were also similar between the two groups.[77] These results are interesting when one considers the known cardiovascular changes associated with twins.[91]

Cerclage

Cervical cerclage for the prevention of premature delivery remains controversial. McGowan found a similar success rate for cerclage in twins (63 per cent) and singleton pregnancies (75 per cent).[93] Other investigators have been unable to demonstrate a benefit in prophylactic cerclage, however.[22, 58] This also is supported by the randomized study by Dor et al.[22] Patients randomized to cerclage had a similar premature delivery and neonatal death rate (45.4 vs 47.8 per cent, 18.2 vs 15.2 per cent, respectively) as those without cerclage.

ANTENATAL VISITS AND FETAL ASSESSMENT

Once the diagnosis of a twin gestation is established, antenatal care will be different from that in singleton pregnancies. At the outset, it would seem reasonable to discuss the risk and potential complications of twin pregnancies during the antepartum and intrapartum periods. With respect to the antepartum period, diet, rest, warning signs of premature labor and frequent clinic visits should be emphasized. Additionally, emphasis on serial fetal growth assessment and the potential use of fetal surveillance should be considered.

Initially, the patient should be seen every 2 weeks until 28 weeks of gestation, and weekly thereafter. The obstetrician should constantly look for changes in the patient's condition. At the first sign or symptom of premature labor or pregnancy-induced hypertension, hospitalization should be considered. If medically necessary, fetal status can be assessed with the nonstress test (NST) and fetal growth monitored sonographically.

The Role of Fetal Surveillance

The NST is the most practical method of antepartum fetal surveillance. Antepartum nonstress testing has been found to be a highly

reliable technique for assessing fetal well-being in multiple gestations[2, 9, 20, 46, 49] and to be more predictive of fetal outcome than urinary estrogens or biparietal diameter measurements.[49] The predictive value of a normal NST is 96 per cent and the predictive value of abnormal NST is 75 per cent.[49] In fact, Devoe[20] has demonstrated that the presence of FHR reactivity, which occurs in about 77 per cent of twins, is associated with low rates of IUGR, neonatal depression, and perinatal morbidity.

Under most circumstances, both fetuses can be tested simultaneously.[20] The major difficulty arises whenever the test results are discordant, such as one twin is reactive and the other nonreactive. Newton[64] has suggested a management scheme for twin gestations with discordant antepartum testing results. First, on the nonreactive fetus do an additional test, such as biophysical profile, to assess more accurately the fetal condition.[54] If the profile score is 6 or suspicious, do a complete maternal and fetal assessment. This should include but is not limited to an evaluation of factors such as the presence or absence of preeclampsia, gestational age assessment (both clinically and sonographically), and determination of zygosity. Third, consider amniocentesis for fetal lung maturity. If the lungs are found to be immature, consider steroid therapy. If fetal lung maturity is documented, delivery would seem reasonable.

AMNIOCENTESIS

Genetic Amniocentesis

The incidence of birth defects among twin pregnancies is approximately twice that of singleton pregnancies. Genetically similar monozygotic twins are nearly 100 per cent concordant for a genetic abnormality, and 2 to 10 per cent concordant for developmental defects.[64] If genetic amniocentesis is indicated, amniocentesis should be performed in both sacs. In diamniotic twins, the success rate for amniocentesis has been reported by several authors and ranged from 80 to 100 per cent.[3, 25, 53, 88, 96, 97] Factors affecting the success of genetic amniocentesis have been described by Librach et al.[53] In that report, the authors found that the success rate was decreased with the presence of two placentas and increased with a gestational age of more than 17 weeks and ultrasound visualization.

If a genetic amniocentesis is indicated, the needle is inserted into the first sac, and after 15 to 20 ml of amniotic fluid has been removed, 1 to 5 ml of 0.08 per cent solution of indigo carmine dye is injected into the sac.[19, 64] The second sac is then aspirated under direct visualization. Successful aspiration of fluid from the second sac is confirmed by presence of clear fluid. However, if the fluid is blue tinged, this indicates that the first sac has been reentered and another attempt would appear warranted. If a separating membrane is not seen, amniocentesis sites are selected as far apart as possible and as close to each respective twin as possible.

Indigo carmine is preferred over methylene blue dye because of the reported complications from the use of methylene blue. The use of methylene blue has been associated with hemolytic anemia and hyperbilirubinemia.

According to the NICHD study, two or more needle insertions are associated with increased frequency of spontaneous abortion.[66] Pelle[71] found a higher rate of second trimester abortion among twin pregnancies undergoing amniocentesis in comparison with singleton pregnancies. However, a recent report by Tabsh et al.[88] could not corroborate Pelle's findings and demonstrated that twin and singleton pregnancies that underwent genetic amniocentesis had an abortion rate of 2 per cent and 1 to 5 per cent, respectively.

Amniocentesis for Fetal Lung Maturation

If there is concern about the lung maturity of a twin gestation transabdominal amniocentesis should be performed and fluid obtained to measure the fetal phospholipid profile.[74, 87] In general, an L/S ratio of 2 or more obtained from one fetal sac is consistent with fetal lung maturity. Does amniotic fluid need to be obtained from both sacs? In circumstances in which the twin growth is concordant, the L/S ratio obtained from one sac is usually similar to that obtained from the other sac. In the case of discordant twins, amniotic fluid should be obtained from the sac of the larger twin. Dobbie et al.[21] reported that concordant L/S ratios were more likely among monozygotic than dizygotic twins. Leveno et al.,[50] however, have shown that the lung maturation among twin fetuses is independent of zygosity, sex, and birth weight discordance. Moreover, they found in contrast with singleton pregnancies that fetal lung maturation occurred several weeks earlier in twins.[68]

The Role of Doppler Ultrasound

Continuous wave Doppler ultrasound has been suggested as a reliable technique for detecting IUGR in twin gestations. When combined with careful ultrasound assessment of fetal size, Gilles et al.[33] reported that in 33 pregnancies one or both of the live born infants was small for gestational age (SGA), and, in 78 per cent of these, at least one fetus had an elevated systolic/diastolic (S/D) ratio. Discordancy in birthweight and an abnormal S/D ratio were associated with fetal growth retardation. Moreover, they reported that the finding of discordant twins with an abnormal umbilical blood flow was associated with twin–twin transfusion. In contrast, twins that are appropriately grown for their gestational age have been found to have normal umbilical artery wave forms[33, 79] but a higher umbilical artery vascular resistance when compared to singleton pregnancies.

MATERNAL COMPLICATIONS

Maternal complications in twin gestation are increased for a variety of reasons. Physiologic changes such as uterine and cardiovas-

cular adjustments to twins appear to contribute to these problems. It is believed that the large placental mass associated with twin pregnancies predisposes the mother to pregnancy-induced hypertension, abruption, previa, and thus to prematurity.[72] As previously stated, the obstetrician should constantly look for changes in the patient's condition. At the first sign or symptom of premature labor or pregnancy-induced hypertension, the patient should be hospitalized.

Preterm Labor

Prematurity to preterm labor is the leading cause of neonatal death among twin gestations. About 10 per cent of preterm deliveries are twin gestation[83]; and 20 to 50 per cent of multiple gestations are complicated by premature labor and delivery.[60, 83] Of note, preterm deliveries in twin gestations account for 25 per cent of perinatal deaths in infants delivered prematurely.[83] In twins, approximately 50 to 70 per cent of the perinatal mortality occurs before 30 weeks' gestation.[63] Thus, antepartum management, as previously discussed, is critical to the prevention of premature labor.

Even though a twin mother may follow instructions closely, premature labor still may occur. If the patient presents in premature labor with intact membranes and cervical dilatation less than 4 cm, consideration should be given to suppressing labor with tocolytics. With patients in advanced labor with cervical dilatation of 4 cm or more with evidence of chorioamnionitis, delivery should be considered regardless of gestational age.

Pregnancy-induced Hypertension

McMullen's[59] prospective study demonstrated that the incidence of preeclampsia among twins was 37 per cent, and was accompanied by a significant increase in small-for-gestational age infants. Patients with mild pregnancy-induced hypertension (PIH) before 36 weeks should be placed at bed rest and followed in the hospital with a weekly NST. As long as the NST remains reactive or the fetal biophysical profile score is 8 or 10 and the patient's condition remains stable or improves, delivery may be delayed until fetal lung maturity is achieved. Delivery is warranted, however, at any time the maternal–fetal condition deteriorates.

Patients admitted after 36 weeks with mild PIH may be candidates for delivery. If there is any question regarding fetal maturity, a transabdominal amniocentesis should be performed to determine fetal lung maturity.

Any patient with a multiple gestation who presents with severe pregnancy-induced hypertension or eclampsia is a candidate for delivery regardless of gestational age. Under these circumstances, the patient's condition will need to be stabilized. During this time, magnesium sulfate is administered. If medically necessary, antihypertensives to lower the patient's blood pressure also would appear prudent. When lowering the blood pressure, care must be taken to maintain adequate uterine blood flow and not lower maternal blood pressure

below 150/90 mm Hg. After stabilization, delivery should be considered.

Polyhydramnios

The situation of acute polyhydramnios, in which a large amount of amniotic fluid accumulates in a short period during the second trimester, frequently is associated with monozygotic twins.[94] In contrast with chronic polyhydramnios, which is associated with a high incidence of fetal abnormalities,[44] acute polyhydramnios does not appear to be associated with a high incidence of fetal abnormalities. Because of the high rate of premature labor, however, a high fetal mortality rate is encountered.[94]

When acute polyhydramnios is encountered, Weir et al.[94] have suggested an active management approach that includes frequent amniocentesis to reduce the amniotic fluid volume. Usually, 200 to 800 ml of fluid can be withdrawn at any one time. Removal of too much fluid may result in placental abruption and multiple taps might result in premature labor.[64]

MANAGEMENT OF THE DEATH OF ONE FETUS

The frequency of single fetal demise in multiple gestation is reported to range from 0.5 to 6.8 per cent.[23] However, the probability of harm to the remaining twin appears low.[37] Death in the remaining twin has been described to be due to intravascular coagulation. Moreover, maternal consumption coagulopathy also is infrequently observed when one twin dies *in utero*. Intrauterine fetal death in twin gestations is more frequently observed in monochorionic than with dichorionic placentation.[15]

Once a single fetal death is diagnosed, the gestational age of the pregnancy and the condition of the surviving fetus will dictate clinical management. Hanna and Hill have suggested that a pregnancy less than 34 weeks should undergo close fetal surveillance of the surviving twin and weekly maternal clotting profiles. If the pregnancy is 34 weeks or beyond, delivery when the fetus is mature would seem reasonable.

SUMMARY

The critical aspects of twin pregnancy begin with early diagnosis. After that, diet, bed rest, and frequent visits to the physician's office will enhance fetal outcome. Additionally, frequent ultrasound evaluations to assess fetal growth and fetal surveillance are also invaluable adjuncts. Prompt treatment of any medical or obstetrical complications will contibute to an overall improvement in maternal and fetal outcome.

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Prevention and Treatment of Preterm Labor in Twins

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Although there has been a significant decrease in the perinatal mortality in singleton pregnancies over the past two decades, perinatal mortality for twins remains high.[1] The primary reason for this increased perinatal mortality, compared to singletons, is premature labor and delivery.[1–7] The most significant etiology of premature labor in twins is probably uterine overdistention,[8] and possible increased exposure of membranes from premature dilation of the cervix,[9] although decreased uterine blood flow also may play a significant role.[8, 10] Other causes of perinatal mortality[8] are summarized in Table 1, and a full discussion of their relative roles and interaction with prematurity is available.[9]

Because of this increase in perinatal mortality, several different treatment modalities have been proposed and have been directed primarily toward the prevention and treatment of premature labor. These have included prophylactic bedrest,[1, 6, 12–14] progesterone therapy,[8] cervical suture placement,[7, 15, 16] and beta-sympathomimetic agents (Table 2).[17–19] There is a great deal of controversy surrounding the use of these treatment regimens in singleton pregnancies, and there have been very few well-designed studies to evaluate them in this setting. Thus, there is even less information regarding their use in twin pregnancies. Additionally, it is unknown if evaluations in singletons can actually be applied directly to twin pregnancies. The focus of this review will be on these modalities and their use in twin gestation, rather than an overall discussion of each in the broad sense.

PROPHYLACTIC BEDREST

There is no unanimity of opinion regarding the benefit of prophylactic bedrest in the prevention of prematurity in twins. Whereas

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Table 1. *Recognized Causes of Increased Perinatal Mortality in Twin Gestations*

Premature labor
Intrauterine growth retardation
Congenital anomalies
Pregnancy-induced hypertension
Prolapsed umbilical cord
Premature placental separation

some[1, 6, 11–14] have reported a beneficial effect of bedrest in twin gestation, others[7, 20–23] have questioned the benefit of such a policy. There are several reasons for this diversity in opinion on the benefits of bedrest in twin gestations. Foremost being that there is no "standardized" protocol for the management of twin gestations and there is marked variation from center to center. Probably the most significant variable is the gestational age used for recommending hospitalization—which ranges from 24 to 32 weeks' gestational age.[1, 14, 24] Another major problem is that there is a paucity of prospective randomized studies of twins comparing hospitalized to nonhospitalized women. For example, Saunders and colleagues,[24] in the only prospective randomized study published thus far, did not routinely use hospitalization for twins until 32 weeks' gestation or greater, although 50 per cent of perinatal losses in twins occurs before 28 weeks' gestation.[1] There have been only two published reports to date in which prophylactic hospital ward rest was used before 28 weeks' gestation.[1, 14] In one of these studies, Komaromy and Lampe[14] reported both improved perinatal survival and increased birth weight in twins delivered of women admitted for prophylactic ward rest. In the second study, Gilstrap and associates[1] reported on their experiences of prophylactic hospital ward rest at an early gestational age—beginning as early as 23 to 26 weeks' gestation. In this study of 132 twin pregnancies, 51 per cent were hospitalized at, or before, 28 weeks, while 49 per cent were not hospitalized until after 28 weeks' gestation, or until a specific pregnancy complication arose. Although not a randomized prospective study, there was a significant difference in perinatal mortality between the two groups (2 per cent for the hospitalized group compared to 8.5 per cent for the nonhospitalized group).[1]

Obviously, a large, randomized prospective study of prophylactic

Table 2. *Prophylactic Modalities That Have Been Proposed for the Prevention of Prematurity in Twin Gestations*

Bedrest
Progesterone
Cervical cerclage
Beta-sympathomimetics

hospitalization and ward rest at an early gestational age (prior to 28 weeks) is needed before the role of hospitalization and benefit in preventing prematurity in twin gestations can be definitively addressed. Unfortunately, it is unlikely that such a study will ever be done, and the clinician is still faced with the "motivated" patient who might accept hospitalization, as opposed to the nonmotivated patient who might refuse hospitalization in such a study. Additionally, the economic aspects of maternal hospitalization must be weighed against the economic burden of infant prematurity. In this era of cost containment, hospitalization is not a popular therapeutic modality. Thus, it is unlikely that hospitalization at an early gestational age will ever prove to be an acceptable management plan to either physician, patient, or third-party payers until medical and economic efficacy is proved.

PROPHYLACTIC PROGESTERONE THERAPY

There is also controversy concerning the efficacy of progesterone in the prevention of premature labor and delivery in women at risk for preterm delivery. Although Johnson and colleagues[25] reported a decrease in premature delivery in women treated with 17α-hydroxyprogesterone caproate compared to controls, Hauth and associates[26] were unable to demonstrate any beneficial effect of this medication in a randomized prospective study of active-duty pregnant women at high risk for premature delivery. Also, Hartikainen-Sorri and associates[8] demonstrated that progesterone administration was ineffective in the prevention of prematurity in a randomized, prospective, placebo-controlled study of 77 women with twin pregnancies.

CERVICAL CERCLAGE

In a retrospective study, Zakut et al.[15] reported that elective cervical suturing may be effective in preventing premature delivery in multiple pregnancies, although results from a randomized, prospective study of cervical cerclage in 50 women with twin gestations from the same institution indicated that cerclage was not effective in prolonging gestation.[16] Weekes and associates,[7] in a study of 133 twins, found no significant differences in the incidence of premature labor, mean gestational age at delivery, birth weight, or growth retardation in 37 women treated with cervical cerclage compared to either women who were treated by bedrest (60 women) or who received no special treatment (36 women). Unfortunately, this was not a randomized prospective study. Thus far, the use of cerclage for prevention of prematurity in twins is not encouraging.

BETA-SYMPATHOMIMETIC AGENTS

The beta-sympathomimetic agents are currently used extensively in this country for the prophylactic treatment of premature labor, although there is less than unanimity of opinion regarding their efficacy. The prophylactic administration of these agents has also been used in an attempt to prevent premature labor in both singleton and twin pregnancies.[17–19] For example, Marivate et al.[17] conducted a prospective, randomized, double-blind trial of fenoterol in 46 women with twin gestations. They were unable to demonstrate any beneficial effect (i.e., prevention of premature labor) from this drug. Likewise, O'Connor and associates,[18] as well as Skjaerris and Aberg,[19] also were unable to demonstrate any beneficial effect from prophylactic administration of beta-sympathomimetic agents. Ritodrine was used in the former study and terbutaline in the latter study. A newer concept regarding the prophylactic treatment of premature labor with oral tocolysis involves the ambulatory monitoring of uterine contractions with a mobile tocodynamometer.[27] As is true of other potential treatment modalities, this also has not been proved efficacious in randomized controlled trials. However, studies involving the use of these monitors for baseline uterine activity in both singleton and twin pregnancies have suggested that the baseline uterine activities in twins is increased; thus, this baseline activity should be taken into consideration when considering institution of higher tocolytic doses.[28]

TREATMENT OF PREMATURE LABOR

Despite measures at prevention, the clinician is often faced with the dilemma of managing active premature labor in twins. Unfortunately, there is no consensus of opinion regarding the efficacy of tocolytic agents currently available for the treatment of premature labor in general, let alone in the case of twins. The two most commonly used tocolytic agents in the United States are ritodrine hydrochloride and magnesium sulfate, although others have been advocated. The indications, dosage, and duration of therapy are the same for twin pregnancies as for the singleton pregnancy; however, it should be pointed out that the risk and potential complications are also the same if not greater, due to increased plasma volume.

To date, there is no large, prospective randomized study of the use of these tocolytic agents in the treatment of premature labor in twin gestation.

DECISION TO ALLOW DELIVERY

Fetal Lung Maturation

Although preterm labor is often spontaneous, it is often necessary to consider premature delivery due to other obstetric complications.[9]

Table 3. *General Guidelines for the Prevention and Treatment of Premature Labor in Twins*

Limited activity throughout pregnancy
Bedrest beginning at early gestational age
Hospitalize if feasible from 24 to 30 weeks' gestation
Home rest with frequent clinic visits if hospitalization not feasible
± Oral ritodrine for mild contractions
Hospitalize for identified complications (premature labor, premature cervical dilatation, hypertension, premature rupture of the membranes, etc)
± Parenteral tocolytic agents for premature labor
Ritodrine
Terbutaline
Magnesium sulfate
Confirm fetal lung maturity in both twins if preterm delivery is contemplated but not clearly indicated

Although many complications associated with twins are straight forward, common, and not within the scope of this discussion, some of them are peculiar to twin pregnancies. The most noticeable of these would be the twin discordancy, or twin–twin transfusion syndromes. This particular situation can be predicted sonographically,[29] although care must be taken before intervention is suggested. This recently reported experience at Parkland Memorial Hospital suggests that fetal lung maturation should be confirmed before intervention is undertaken.

Leveno and colleagues,[30] in a study of 42 twin gestations, reported that fetal lung maturation, as measured by the lecithin/sphingomyelin (LS) ratio, was independent of sex, zygosity, and birth weight discordance, suggesting that both amnionic sacs be sampled if possible. They also found that in their population, fetal lung maturation occurred several weeks earlier in twins compared to singletons. Spellacy and associates,[31] as well as Sims and co-workers,[32] reported that lung maturation was similar within twin pairs.

In the event of indicated or imminent delivery with immature lungs, the question of steroid administration is an important dilemma. Unfortunately, the beneficial effect of antenatal administration of steroids in preventing the respiratory distress syndrome in twins is less than clear, as is still the case with singleton pregnancies. In a large, prospective, randomized double-blind trial, antenatal administration of dexamethasone was no more effective than placebo in preventing the respiratory stress syndrome in twins.[33]

SUMMARY

It is well established that mothers with twin gestations are at a significant risk of giving birth to a premature infant and, compared to singletons, the perinatal mortality and morbidity are significantly in-

creased. Unfortunately, it is clear that little progress has been made over the past two decades in either the prevention or the treatment of premature labor in twins. The clinician is left with more questions than answers. This latter aspect needs to be recognized by the legal profession. Obviously, more studies regarding the possible beneficial effect of either bedrest or prophylactic beta-sympathomimetics are needed before meaningful recommendations can be made on a universal basis. It is also obvious that more potent tocolytic agents are needed to actually treat premature labor once it occurs. Taking all of these facts into consideration, the authors would recommend the protocol outlined in Table 3 for the general management of twins with regard to premature labor.

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Antepartum Complications in Twin Pregnancies

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The studies of pregnant women with a single fetus and their associated diseases are legion, but there are very few studies of similar type in women carrying more than one fetus. As a result, while the textbooks suggest several problems in the woman with a twin gestation, the support for many of these statements is weak. Some antepartum problems, however, are either unique to or significantly more frequent for the woman with twins. These will be reviewed and their management discussed. Included are fetal discordance, anomalies, hydramnios, single fetal death, hypertension, and anemia. Other problems, such as preterm labor, are reviewed elsewhere in this volume.

THE "VANISHING TWIN"

Many studies have now been done using routine early pregnancy ultrasound scanning, and these have shown a higher frequency of twin pregnancies (2–4 per cent) than was recognized from prior delivery data. The ultrasound studies have demonstrated that many of the early twin gestations result in a loss of one of the gestations, in which it reabsorbs partially or completely, and this phenomenon has been termed the "vanishing twin" syndrome.[1, 9, 18, 36] Landy and associates found 28 of 54 twins "vanished"; however, many of these were only sacs without a recognized fetus.[18] In those cases in which two fetuses were seen, disappearance occurred in 21.2 per cent.[18] There is usually some vaginal bleeding noted in the pregnancies in which a loss occurs, and this can serve as a useful clinical clue for reevaluation of the gestation with ultrasound scanning.[9, 18] There are no reports of an adverse outcome for the surviving infant or for the mother in vanishing twin pregnancies, and therefore no treatment seems necessary.

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CONGENITAL ANOMALIES

There are many studies demonstrating that the frequency of congenital anomalies is significantly increased in twin infants.[2, 17, 20] Kohl and Casey as well as others have noted a twofold increase in the anomaly rate.[2, 17] No specific anomaly is characteristic for this group of infants. The cause of the higher rate of anomaly is unknown, but the increase seems to be principally owing to the higher frequency noted in monozygotic infants. It is important to inform parents of this in prenatal counseling and to look for these when surveying the pregnancy with later ultrasound scans. The maternal blood alpha-fetoprotein levels generally are not useful in detecting these cases because they are elevated because of the twin gestation itself. The perinatal morbidity and mortality of twins clearly will be adversely affected by the presence of an increased frequency of anomalous infants.

TWIN DISCORDANCE

When the growth rate of twins is altered so that their birth weights differ, the infants are said to be discordant.[3] This may produce fetal growth retardation if an infant's weight remains in the lowest ten percentile for gestational age. The cause for the most marked examples of this usually involves a twin–twin transfusion. This is diagnosable when the infants' birth weights differ by more than 1000 gm and when the infant hemoglobin levels differ by more than 5 gm per dl[27] Kohl and Casey noted this difference in birth weight to occur in 2.9 per cent of 6503 twins.[17] Others report frequencies of 5 to 10 per cent.[27] A vascular connection between fetuses with dichorionic placentas is very rare, whereas it is common in monochorionic placentas.[2] Indeed in those cases in which both placental circulations were injected after delivery, almost all monochorionic placentas demonstrated vascular connections.[21] Therefore, only the latter type of twins is at risk for this problem. When there is a significant twin–twin transfusion, the donor twin will be small, pale, and may suffer hypoxia, whereas the recipient twin will be large, plethoric, and may develop heart failure with hydrops and acute polyhydramnios. The polyhydramnios is thought to be due to the excess water transferred in the vascular anastomosis being excreted by the fetus as urine. Twin pregnancies contribute significantly as the cause of hydramnios, and in one large series of patients with hydramnios, twins have accounted for 8.4 per cent of the cases.[29] The hydramnios usually is treated conservatively with bed rest and diuretics, but if severe or acute it may need to be treated with periodic and frequent amniocentesis. When a significant twin–twin transfusion occurs, both twins are potentially compromised and may need intensive care management immediately after delivery. Those mothers should be transferred to a delivery site, where such care will be available.

The diagnosis of the twin–twin transfusion problem can be

helped with ultrasound studies. Low-risk dichorionic placentas can be predicted by seeing either opposite sex twins or two separate placentas. For the others, serial ultrasound studies of fetal growth are helpful. Several studies have shown that fetal growth retardation and twin weight discordance are predictable. Measurements of head size, femur length, and abdominal circumference have all been published. The curves for twin infants lag behind those for singletons generally after 31 weeks' gestation, especially those of biparietal diameter and abdominal circumference and less so for femur length.[10, 13] The most common diagnostic criteria used for predicting discordance has been biparietal diameter differences, and suggested criteria have varied from 3- to 7-mm discrepancies.[6, 14, 19, 35]

When discordance is suspected, it suggests that fetal distress may be a risk due to placental insufficiency. Assessment of fetal well-being should then be done with serial fetal–placental function tests such as weekly nonstress tests (NST).[16] Weekly real-time ultrasound studies of fetal growth and amniotic fluid volumes are also helpful. The occurrence of oligohydramnios puts the fetus at very great risk for acute cord compression accidents and usually needs delivery as management. Because mothers of twins tend to deliver prematurely, there has been a concern about performing a contraction stress test (CST) as the primary surveillance method. A nonreactive NST must be followed with a contraction stress test, however, and if late decelerations are found consistently, consideration must be given to delivery.[27] Labor rarely is precipitated by the CST. If the fetuses are possibly immature, then some assessment of fetal lung maturity should be done. Twins with similar growth curves have similar lung maturation studies, and in those cases only one amniotic sac needs to be sampled for the L/S ratio.[33] If, however, the twins are discordant, probably both sacs need to be tapped because the amount of stress on each fetus cannot be assessed accurately, and stress may accelerate lung maturation. The decision for delivery will be related to the degree of maturity that exists in the least mature fetus. Mature fetuses in severe distress need to be delivered. If there is fetal distress and immature fetal lung maturation, then consultation with a maternal–fetal medicine subspecialist is needed to determine the best management plan for the patient and her infants. In general, glucocorticoid treatment of the fetus for the acceleration of lung maturity has had little success in twin gestations.[5]

DEATH OF A FETUS

Many twin pregnancies are now reported in which one of the infants dies *in utero* and the pregnancy continues with the other infant surviving.[4, 8, 12, 15, 23, 24, 27, 38, 40] This is an uncommon problem. Melnick reviewed 188 monozygotic twins in one series and found seven cases for an incidence of 3.7 per cent.[23] In other series the frequency of this has been reported to vary from 0.5 to 6.8 per cent for all twin

gestations.[8] Many of these cases have maternal hypertension as a high-risk complicating problem.[15, 27] Occasionally, a cord accident is responsible, particularly if it is a monoamniotic pregnancy or has a velamentous insertion of the cord. Biochemical monitoring shows that estriol levels routinely decrease in these cases after the death, whereas human placental lactogen levels may be little affected.[38] The complications for the mother in this situation are minimal, and serious disseminated intravascular coagulation (DIC) is not a risk, although a slight fall in fibrinogen levels has been reported.[12] The surviving infant is at very significant risk, however. This seems to be due to either the adverse intrauterine environment that was responsible for the first infant's death or to DIC in the survivor, especially when twin–twin placenta vascular anastomoses exist, allowing blood products from the dead fetus to reach the survivor. Again, such vascular anastomoses are limited to monochorionic placentation, and ultrasound studies may be useful to attempt to exclude this problem from consideration. Hagay and associates reported a death rate for the surviving twin of 50 per cent (2 of 4) with monochorionic placentas and 0 per cent (0 of 17) with dichorionic placentation.[12]

DIC also has been reported in the surviving neonate.[24] Another major problem for the survivor is brain damage, especially multicystic encephalomalacia.[4, 15, 40] The frequency of this varies, but one review showed that only about half of the surviving twins were "normal" on followup examination.[8] Death of one fetus clearly demonstrates the possible seriousness of the abnormal intrauterine environment and suggests that when the diagnosis is made, if the pregnancy is in the late third trimester and the surviving infant is mature, then it should be delivered as soon as possible to attempt to prevent these problems. If it is immature, then serial fetal well-being studies, such as weekly NST and ultrasound evaluations of growth and amniotic fluid volume, need to be done while it remains in the uterus to prevent its death as well.

MATERNAL HYPERTENSION

Many large series of twin pregnancies have been published looking at the frequencies of maternal problems, and most of these reports show an increased frequency of maternal hypertension, which also tends to occur at an earlier gestational age when compared to singleton pregnancies. Unfortunately, many of these studies do not have comparable control groups or statistical analysis of their data to indicate whether the changes noted are significant.[30, 37, 39] Kohl and Casey reported the increased risk to be doubled; Guttmacher found it to be tripled; MacGillivray reported it to be five times greater.[11, 17, 22] Commonly hypertension frequencies from 20 to 30 per cent have been reported in twin pregnancies.[17, 30, 37, 39] Clearly this serious complication of pregnancy is increased in twin gestations and accordingly the prenatal visits for these women should be closer together to detect

the problem early. These women should have less physical activity and more bed rest to help to minimize the disease occurrence and severity. When hypertension complicates the pregnancy it poses a risk for both the mother and the fetus. The main fetal risks are abruption and placental insufficiency, leading to growth retardation, hypoxia, and death. Maternal complications are related to acute vascular events, and the more serious ones are seizures, cerebral vascular bleeding, renal and hepatic failure, and hemolysis. Management of hypertension complicating twin pregnancies is similar to that in singleton gestations. If the infants are mature, then delivery is accomplished, otherwise consideration of medical management and prolongation of the gestation must be considered if the process does not become severe. During the time that the pregnancy is progressing, careful assessment of fetal health is necessary, using at least weekly serial testing with electronic fetal heart rate and real-time ultrasound studies. Biochemical tests such as estriol and human placental lactogen levels are not useful because there are no established criteria for their evaluation in twin gestations.[32]

ANEMIA

Another maternal complication with increased frequency in twin pregnancies is anemia, with frequencies reported to be as high as 40 per cent.[11, 21, 30] In Guttmacher's series, anemia was four times more common in twin compared to singleton pregnancies.[11] The two major causes for this increased anemia are (1) increased fetal drain on maternal iron and folate stores, and (2) increased hemodilution that accompanies twin gestations. These women need supplemental prophylactic iron (60 mg per day) and folic acid (1 mg per day) during their antepartum period, and they also need to have their hemoglobin level evaluated in each trimester. There are few published reports on the frequency of anemia in twin gestations under this type of combined preventive medical management. It is extremely important that these women enter labor with an adequate red blood cell mass since they are also more likely to have an increased blood loss with delivery owing to more frequent use of cesarean sections and more frequent postpartum uterine atony with hemorrhage secondary to overdistention of the uterus.

CARBOHYDRATE METABOLISM—DIABETES MELLITUS

It is well recognized that pregnancy creates a state of "insulin resistance" and therefore stresses the maternal beta cell mass in the pancreas to grow and to produce more insulin.[34] While the exact cause of this metabolic change is not known, most investigators think that the activities of the placenta play a key role. Accordingly it has been

suggested that women with two or more placentas are at an even greater risk for developing gestational diabetes.[7] Some have suggested that women with twin gestations should be screened more carefully for this problem than is the usual procedure in singleton gestations.[21]

Studies of carbohydrate metabolism in pregnant women with twins have shown normal to lower glucose levels and normal insulin levels during glucose tolerance testing.[7, 25, 26, 31] Therefore, the carbohydrate metabolic stress of a twin pregnancy does not seem to be excessive. It is reasonable to recommend that these women have the same glucose screening as is done on those with singleton pregnancies, namely, using a blood value 1 hour after a 50-gm oral glucose load at the end of the second trimester. If that plasma value exceeds 140 mg per dl, then a 3-hour oral glucose tolerance test using a 100-gm load should be done. There are no published data to suggest that insulin-dependent diabetes mellitus is more common or more difficult to control in twin versus singleton gestations.

OTHER MATERNAL ANTEPARTUM PROBLEMS

Few data are available to support the conclusion that a twin gestation significantly increases the mother's risk for other complications of pregnancy. The frequency of urinary tract problems like infection and hydronephrosis is not increased. Placental problems of previae and abruption are reported to be at increased frequency, but carefully controlled studies are scarce. Abruption will increase as the frequency of hypertension increases. The overall antepartum bleeding frequency is not significantly increased in twin pregnancies.

SUMMARY

Women with twin pregnancies have some unique problems and some that occur more frequently than those seen in singleton pregnancies. Examples of the former are the vanishing twin and death of one fetus. Examples of the latter are congenital anomalies, hydramnios, hypertension, and anemia. Prenatal care must be altered because of these complications, and perinatal morbidity and mortality are increased.

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The Management of Labor

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The management of labor in a pregnant mother of twins usually provides an interesting break from the routine management of singleton pregnancies. The same principles of management of labor that apply to singletons apply to twins. The pregnant mother of twins requires the same consideration of fluid management, analgesia, anesthesia, electronic fetal monitoring, and attention to the course of labor. Twin pregnancies are, however, more complicated than singleton pregnancies by virtue of having two fetuses. Although it is difficult to separate the management of labor in twin pregnancies from management of delivery, this article will endeavor to address issues that concern strictly the course of labor in twin pregnancy.

The incidence of congenital anomalies is higher in twin pregnancies than among singletons, and the fact that one or both fetuses are affected by congenital defects may affect the decision of whether to allow labor. The frequency of anomalies in twins among spontaneous abortions ranges from 21 to 88 per cent.[15, 24] At term, however, the ratio of twin to singleton anomalies ranges from 0.5[22] to 3.2.[12] If twins are known to be conjoined, the delivery will be accomplished by cesarean section. The best route of delivery for abdominal wall defects such as omphalocele and gastroschisis is unclear. The obstetrician might choose to deliver a twin with an abdominal wall defect by cesarean section to minimize possible trauma. A twin gestation may be affected by twin–twin transfusion syndrome. The incidence of twin–twin transfusion in twin gestations ranges from 7.5 per cent[23] to as high as 15 per cent.[20] Depending on the severity of the blood transfer from one fetus to another, one twin may be extremely growth retarded while the other is normal. Thus, one twin may not tolerate labor as well as its healthy twin may, and an abdominal route of delivery may result.

The decision of whether to allow labor also may be affected by the presentation of the twins. The presentation of the twins may be different, and this may affect the decision of whether to allow labor.

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Both twins will be in vertex presentation only 47 per cent of the time.[1] In 37 per cent of twin pregnancies, one twin will be vertex and the other breech. In 16 per cent of pregnancies, the twins will be in various breech and transverse lie combinations. Some authors recommend liberal use of cesarean delivery for all twins that are not in vertex–vertex presentation.[2] Others recommend that if the first twin is vertex and the second is breech, external cephalic version be performed on the second twin following vaginal delivery of the first.[3] Cetrulo et al. found in their study that of 295 twin pregnancies, 69 per cent were delivered by cesarean section, a much higher incidence than the singleton population. As a result, more twins will undergo cesarean birth than vaginal births; many will never go through labor.

Although more and more twins are delivered by cesarean section, it is still important to understand the labor patterns associated with twin pregnancies. First, the overall length of labor with twins has been shown by Friedman[6,7] to be the same as with singletons. Differences in the lengths of different stages of labor were found, however. Friedman noted in his study of twin labors that whereas the latent phase of labor was shorter in twin pregnancies, the active phase and second stage of labor were lengthened. Latent phase was thought to be shortened due to the fact that women with twins usually present in labor with advanced cervical dilatation.[5,7] The cervix was dilated less than 2 cm on admission in 62 per cent of singleton pregnancies as compared to 25.8 per cent of multiple pregnancies.[7] In contrast, 39.4 per cent of multiple pregnancies presented with a cervix dilated greater than 3 cm, whereas only 7.2 per cent of singleton pregnancies were 3 cm or more dilated. As a result, Friedman showed that the average latent phase labor was 2.7 hours in twin pregnancies compared to 5.6 hours with singletons. Whereas latent phase was shortened, the active phase a second stage of labor tended to be prolonged in twin pregnancies.

In considering why the active phase and second stage of labor would be prolonged in twin gestations, Friedman examined such factors as fetal weight, dysfunctional labor, maternal sedation, and the incidence of cephalopelvic disproportion. Cephalopelvic disproportion was found to be very rare, occurring only 3.0 per cent of the nulliparas and never in the multiparas. Heavy sedation was administered more often during the course of labor to mothers of twins as compared to mothers of singletons. It was thought that this was a potential influence on the course of labor. As the combined fetal weight increased, there was a slowing of active phase of labor. In addition, since twin pregnancies often deliver prematurely, the possibility was raised that prematurity could be a factor in causing dysfunctional labor. Friedman[9] was able to demonstrate a correlation between dysfunctional labor and prematurity. One of the more obvious etiologies of prolonged active phase, however, was the increased incidence of dysfunctional labor in multiple pregnancies. One third of all nulliparas had some form of dysfunctional labor (compared to 7 per cent in the singleton population) and 16 per cent of all multiparas (compared to 0.8 per cent) had dysfunctional labor.

Why multiple pregnancies should have an increased incidence of dysfunctional labor is uncertain. Physicians have long assumed that overdistention of the uterus is responsible for prolongation of the active phase. Polyhydramnios is one situation besides multiple pregnancy in which the uterus is distended. Cadyro-Barcia[1] showed that the contractions of a uterus distended by polyhydramnios were of low intensity. It was presumed on the basis that these labors with contractions of low intensity were longer. Furthermore, it was asserted that if the fluid was withdrawn, the uterine contractility and labor pattern would return to normal. Friedman,[8] however, was unable to show that hydramnios was associated with prolonged labor. On the contrary, active phase labor in nulliparas with polyhydramnios at term appeared to be shorter in duration. When fetal size and time of membrane rupture were taken into account, no difference in the length of labor could be found in those pregnancies with polyhydramnios and without.

Knowing that twin labors may be associated with dysfunctional labor, there is an increased likelihood that the obstetrician may be required to use oxytocin in a pregnant woman with twins. Clinically, there appears to be a reluctance to use oxytocin with an overdistended uterus. Perhaps the fear should be more with the use of oxytocin than with twin pregnancies, per se. Golan et al.,[10] in reporting on 93 cases of spontaneous rupture of the uterus, noted that 42 per cent of the cases were associated with oxytocin usage. Cephalopelvic disproportion and grand multiparity were the next most common factors associated with rupture. Other studies[16, 25, 26] confirm the ominous association of oxytocin and grand multiparity with spontaneous uterine rupture. Leroy[14] studied oxytocin treatment in 483 twin labors. Among their cases, 30 per cent required oxytocin during the first stage of labor. An additional 13 per cent received oxytocin to assist in delivery of the second twin. It was noted that the decision to use oxytocin was more common with increasing cervical dilatation. There was no significant morbidity associated with oxytocin usage and no instance of uterine rupture. In the management of a twin pregnancy with dysfunctional labor, oxytocin can be used safely by relying on intrauterine pressure catheter readings and careful titration of the oxytocin dosage to avoid overstimulation.

Since twin pregnancies have a perinatal mortality that is five times that of singleton pregnancies, the twin pregnancy involves very high risk and requires fetal monitoring during labor. Pernoll and Carnes, in 1973, reported the technique for electronic fetal heart rate monitoring of twin pregnancies, whereby twin A is monitored by scalp clip electrode, whereas twin B is monitored by external ultrasonic transducer. An intrauterine pressure catheter is inserted to monitor the uterine contraction pattern. Using this technique, both twins can be monitored safely during labor.

A laboring mother with twins will require pain relief of some form during the course of labor. Maternal narcotics and sedatives may be used. These medications have fetal central nervous system and res-

piratory depressant effects. Because twins often deliver prematurely, they are especially susceptible to drug depression. Avoidance of the use of these drugs is desirable.

Lumbar epidural anesthesia also has been advocated for use of pain control. Initial reports cited an increase in perinatal mortality with regional anesthesia. Jaschevatzky et al.[13] in a study of epidural anesthesia in 58 twin pregnancies noted that the mean duration of labor in twins was shorter in the epidural group as compared to non-epidural. They also noted that 88 per cent of the patients with epidurals required oxytocic stimulation due to an increased incidence of hypotonic uterine dysfunction (compared to 6.8 per cent of the control group). Although there was no difference in the perinatal mortality rates between the term epidural group and term control, there was an increased perinatal death rate in the preterm epidural group compared to the control preterm twins (12 per cent versus 8 per cent). Other authors, however, reported good success with lumbar epidural anesthesia. Pearson and Davies[17, 18] in studying the fetal acid–base effects of lumbar epidural anesthesia in single pregnancies noted that although epidural anesthesia provided less alteration in fetal acid–base status during the first stage of labor (compared to control nonepidural groups) the second stage of labor was associated with progressive fetal acidosis. Fetal acidosis developed in both the control and epidural groups. More recently, Crawford[4] carried out a prospective study of 196 twin labors in which 58 per cent of the laboring patients delivered vaginally under epidural anesthesia. The acid–base status of the second twin was as good or better than that of the first twin at delivery. In the twin nonepidural vaginal deliveries, the acid–base status of the first twin was always superior to the second. These data would suggest that epidural anesthesia can be used very safely in twin labors, providing comfort for the parturient.

In summary, management of twin labors is more challenging than labors of single pregnancies. Fetal monitoring can be technically more difficult in twin pregnancies. More dysfunctional labor will be experienced requiring judicious oxytocin administration. However, epidural anesthesia can be administered safely with close observation of fetal status during labor, thereby providing a pleasant labor experience for the mother.

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Management of Delivery

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Although twins account for only about 1 per cent of all deliveries in the United States, they are responsible for nearly 10 per cent of all perinatal deaths.[18] Most of the morbidity and mortality associated with twins can be attributed to complications of prematurity, placental insufficiency, fetal abnormalities, polyhydramnios, twin–twin transfusion, and to maternal diseases, such as preeclampsia and diabetes.[17, 19] It is estimated that 25 per cent of all twins suffer from intrauterine growth retardation.[8] These factors may influence but are otherwise independent of the delivery process itself. Careful and thoughtful management of labor and delivery is necessary, however, to ensure the best possible outcome for both babies with the least risk for the mother.

Despite considerable attention over the years, there is still no consensus on the best means of managing twin deliveries. Algorithms based on gestational age, estimated fetal weight, and fetal presentation frequently are used to guide delivery plans.[2, 6, 7, 16] In recent years, innovative uses of fetal monitoring and ultrasound have expanded our options for management of the twin delivery and made it more of a dynamic process than a fixed decision from the outset.[6] At the same time, remarkable advances in neonatal management of the preterm infant have made it imperative to include the very low birth weight infant, in the 26- to 27-week range, in our decision-making process.

It is conceivable a consensus on management of the twin delivery under certain circumstances may never be reached. Indeed, such a concensus may be undesirable owing to differences in skill levels of obstetricians, sophistication of hospital facilities, and availability of neonatology and anesthesiology services. In addition, when the time for decision about delivery is imminent, it has become equally important to consider the needs and desires of the individual patient.

Presented herein is the approach to the problem of the twin delivery adopted by the author in recent years. It is relatively balanced and stresses the preparation, which allows flexibility to modify plans

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Table 1. *Accessories for Management of the Twin Delivery*

Umbilical cord clamps (×3)
Suction bulbs and DeLee traps (×2)
Syringes for umbilical arterial and venous blood sampling
Forceps (e.g., Simpson, Kielland or vacuum extractor, Piper)
Tocolytics (e.g., terbutaline, ritodrine)
Oxytocin, methergine, 15-methyl-$PGF_2\alpha$

with changing circumstances. It is recognized that, because of the dynamic nature of our field, as well as external influences such as the medicolegal climate, information or technology may arise to challenge this approach even during the time prior to publication. It is also recognized that despite best efforts at preparation and careful planning, situations will still arise when the obstetrician is "surprised" by an unfortunate outcome. The approach described will minimize these occurrences, but our inability at present to eliminate them lies in our failure to identify and prevent all those factors that contribute to fetal and maternal morbidity, as well as our difficulty in quantitating those "intuitive" factors on the part of the experienced obstetrician who makes decisions under critical circumstances as much art as science.

GENERAL PREPARATIONS FOR DELIVERY

Ideally, the patient carrying twins will have had the benefits of antepartum diagnosis and conscientious prenatal care prior to presentation for delivery. Under these circumstances, actual preparations for delivery can begin with admission to the labor suite. Such preparations establish the foundation for a successful outcome.

To take advantage of past experience, and to allow time for their input and preparation, senior-level obstetricians, neonatologists, and anesthesiologists must be alerted at the outset of the patient's presence. Information should be transmitted to them regarding gestational age, pregnancy complications, and current indications for delivery (e.g. labor, ruptured membranes, fetal distress, polyhydramnios, oligohydramnios, fetal abnormalities, and preeclampsia). Included early in the preparatory process should be an honest evaluation of adequacy of facilities and personnel to handle the delivery, and any special requirements suspected for maternal or fetal care. Many tragic consequences may be avoided if the ego is sublimated from the decision to transfer the patient to a more appropriate facility if indicated.

Once the patient is admitted, intravenous access should be started as a routine, with at least one large-bore indwelling catheter. At the same time, in addition to routine laboratory studies, the patient should be crossmatched for two units of compatible blood. Although transfusion is rarely needed, the patient with twins is at significantly higher

Table 2. *Deciding the Route of Delivery: Maternal Factors*

Obstetrical History
Parity
Size of previous infants
Complications of previous deliveries (e.g., Cesarean section, midforceps, shoulder dystocia, prolonged active phase)
Clinical Pelvimetry
Overall shape
Prominence of ischial spines
Measurements
Anteroposterior diameter (diagonal conjugate ≥12.5 cm or obstetrical conjugate ≥11.5 cm)
Transverse diameter of inlet ≥13.5 cm
Sum of anteroposterior diameter of outlet, intertuberous, and interspinous diameters ≥32.5 cm
Cervical Condition
Dilation, effacement, station, consistency
Medical Problems
Preeclampsia, diabetes
Cooperativeness of Patient
Informed Consent
Patient's desires for delivery

risk for requiring the same, and circumstances under which it becomes necessary do not permit much lag time.

Regardless of the delivery plan ultimately chosen, an operating room should be readied and personnel alerted for the possibility of immediate cesarean section. Extra supplies often useful during the delivery and immediate postpartum period are shown in Table 1. In addition, fetal monitors or hand-held Doppler units, and, if possible, an ultrasound machine, should be available for use in the delivery room. Facilities to handle the simultaneous resuscitation of two infants should also be prepared.

If cesarean section is deemed necessary from the outset for fetal or maternal indications, this should be done as soon as sufficient preparations can be made to ensure a safe delivery. If immediate cesarean is not indicated, then a decision still needs to be made regarding the best plan for delivery. Factors that are often considered

Table 3. *Deciding the Route of Delivery: Fetal Factors*

Gestational Age
Presentations
Attitude of fetal parts (e.g., flexion of head)
Ultrasound evaluation (e.g., biparietal diameters, head circumferences, abdominal circumferences, femur lengths, amniotic fluid, presence of anomalies)
Estimated and relative fetal weights
Complications (e.g., hydrops fetalis, IUGR, fetal distress)
Monoamnionic versus diamnionic

when this course is taken are shown in Tables 2 and 3. What has not been entirely agreed on is how to use the information gathered by assessing these factors to arrive at a delivery plan under all circumstances. (Management of labor in patients in whom this is deemed appropriate is discussed by Zuidema elsewhere in this volume.)

MANAGEMENT SCHEMES FOR DELIVERY

When developing management schemes for the delivery of twins, it is useful to have an overview of the entire problem and a concept of how certain factors listed in Tables 2 and 3 can be used to develop a delivery plan.

Although the ideal time to deliver twins from the standpoint of perinatal mortality appears to be at 37 to 38 weeks' gestation, more than 50 per cent of patients, in round numbers, will be less than 37 weeks at delivery.[4, 18] Indeed, about one third will be less than 34 weeks' gestation. Consistent with the high incidence of prematurity, more than 50 per cent of twins will weigh less than 2500 gm at delivery, with about 10 per cent weighing less than 1000 gm. This latter group is of particular importance because it constitutes more than 65 per cent of the mortality and a significant proportion of the long-term morbidity resulting from all twin pregnancies. Overall, 90 per cent of perinatal mortality in multiple gestations occurs in twins weighing less than 2000 gm.

When route of delivery has to be decided, the traditional concern has been that related to head entrapment of the breech resulting from insufficient molding, particularly when head circumference exceeds abdominal circumference, as in the premature or low birth weight infant. Special additional concerns to keep in mind are the high incidence of intrauterine growth retardation, and also the 25 to 40 per cent incidence of second twins outweighing the first. In our experience, this difference exceeded 250 gm about one third of the time. The impact of this difference achieves greater significance when looked at as a percentage of birth weight in the low birth weight (under 1500 gm) infants. Fortunately, several equations have been developed to estimate fetal weight using ultrasound parameters, and these are most reliable in estimting the low birth weight infant.[12, 27] It is recommended the individual physician employ the formula that most accurately reflects fetal weights using their own measurement techniques and patient population.

Assessment of fetal presentations of twins has yielded, fairly consistently, the following observations. Seventy-five to eighty-five per cent of first twins will present as vertex, and 20 per cent as breech or transverse.[4, 7] When the first twin is vertex, only about half of second twins will be vertex and half nonvertex. Overall, 40 per cent of twins will be in combined vertex–vertex lies and 40 per cent in vertex–nonvertex lies. From another perspective, 60 per cent of the time, one or both babies will be malpresenting. Interestingly, in preterm infants,

although the first twin is still vertex about 75 per cent of the time, there is a greater tendency for malpresentation of the second twin to occur. For example, Cetrulo found only 22 per cent of twins of 34 weeks' or less gestational age were in combined vertex–vertex presentations.[4] This has been typical of our own experience. It is important to remember also that, regardless of initial presentation, up to 20 per cent of second twins will change position spontaneously once the first twin has delivered.

Because of the concerns detailed above, the major controversy influencing the plans for twin deliveries still lies in the approach to the preterm infant, particularly when the second twin is in a nonvertex lie. Generally, management of preterm twins has tended over the years to follow the trends for management of the preterm or intrauterine growth–retarded singleton infant. Even for preterm singleton pregnancies, however, the issue is not at all clear. Generally, in the well-managed preterm vertex singleton infant, there is no advantage of cesarean section over vaginal delivery.[28] However, many reports have cited an increase in both morbidity and mortality for the malpresenting low birth weight (≤1500 gm) singleton delivered vaginally.[13, 15, 20, 30] Although disconcerting, general criticism of these reports has focused on their retrospective nature and possible selection bias with regard to fetal monitoring and cesarean section. Others have demonstrated no particular advantage of cesarean section over vaginal delivery in the carefully managed labor and delivery of the preterm breech singleton once labor has begun.[22, 29]

Observations on second twins presenting as nonvertex yield equally uncertain conclusions. In a retrospective review, Barrett looked at the effect of route of delivery on neonatal outcome in preterm twins.[2] Neonatal mortality of second twins weighing less than 1000 gm delivered vaginally by either the vertex or breech extraction was twice that of first twins. However, there were not enough cesarean sections done in this group of very low birth weight infants to draw the conclusion that this would have improved outcome. In the same study, among infants in the 1000- to 1499-gm weight range, there was a higher incidence of hyaline membrane disease and patent ductus arteriosus. Although it was theorized these adverse outcomes were related to birth asphyxia, there was no evidence to support this conclusion. Indeed, this would be a difficult conclusion to evoke considering most of the second twins were delivered within 8 minutes of the first.

In another study, Chervenak reviewed 135 twin pregnancies presenting as vertex–nonvertex.[5] Although second twins weighing less than 1500 gm delivered vaginally by breech extraction had a higher incidence of 5-minute Apgar scores less than 7, they did not have a higher incidence of intraventricular hemorrhage, neonatal death, or birth trauma when compared to their first-born siblings. Again, no side-by-side comparison with nonvertex second twins born by cesarean was done, retrospectively or prospectively, to conclude that this would have improved outcome.

Table 4. *Pros and Cons of Routine Cesarean Section of Twins*

PROS	*Cons*
20–30% of all deliveries already done by cesarean; twins constitute only 1% of all deliveries	Maternal mortality increased over vaginal delivery (4–8×)
High incidence of malpresentation and prematurity	Increased infectious morbidity (2–4×)
Preterm infants at greater risk for consequences of birth asphyxia (e.g., RDS, intraventricular hemorrhage, persistent fetal circulation)	Greater blood loss, risk of transfusion, and transfusion-related infections
Preterm infants are more susceptible to birth trauma	Increased risk of subsequent pregnancy
Minimize complications of labor and difficulties of fetal monitoring	Prolonged recovery time
Diminishes complications resulting in emergent surgery (e.g., cord prolapse, placental separation, failed version)	Longer hospital stay
Generally less traumatic delivery	Increased medical costs
Planned surgery has lower surgical and anesthetic complications	Increased risk of thromboembolism
Less risk from legal community for suits related to "birth asphyxia"	Increased risk of anesthetic complications
Declining obstetrical skills	Increased population needing "repeat" cesareans
	Does not ensure less traumatic delivery, or improvement in neonatal morbidity and mortality

The safest conclusion to be drawn from these disparate results is that the truth probably lies somewhere in between. Malpresenting preterm infants may be at greater risk for trauma from delivery and also for complications unrelated to the delivery process itself. Until further data are available, it is still probably best to continue the policy of the "liberal use of cesarean section" for preterm twins; however, one must be continually aware of both maternal and fetal risks when weighing the decision to perform cesarean. Even from the standpoint of "defensive medicine" it is not wise to turn the liberal use of cesarean section into invariable use of cesarean section. Compiled in Table 4 are arguments that have been put forth over the years for and against the liberal use of cesarean section of twins. Although compelling arguments can be made from both positions, the bottom line at this point is that cesarean is not necessary or desirable in all or even most instances. Fetal outcome will not necessarily be improved, and maternal risks are significant.[1, 9, 10, 18, 22, 23, 29] The onus is still on us, however, to define more clearly those instances when fetal risks indicate an advantage to cesarean over vaginal delivery and outweigh maternal risks.

The delivery scheme used by the author over the past several years is shown in Table 5. The rationale for the options indicated, extenuating circumstances influencing choice of delivery route, and specific details of handling the delivery itself are detailed below.

For twins clearly less than 26 weeks' gestational age and EFW

Table 5. *Management of Twin Delivery by Estimated Fetal Weight and Presentation*

PRESENTATION TWIN A/TWIN B	EFW <600 gm; <26 WEEKS	EFW 600–1500 gm	EFW >1500 gm
Vertex/Vertex	Vaginal	Vaginal ? / ECV IPV C/S	Vaginal / ECV IPV C/S
Vertex/Nonvertex	Vaginal	Vaginal / ECV IPV C/S	Vaginal / ECV IPV C/S
Nonvertex/X	Vaginal	Cesarean	Cesarean

Key: EFW = estimated fetal weight; ECV = external cephalic version; IPV = internal podalic version/breech extraction; C/S = cesarean section.

less than 600 gm, vaginal delivery is indicated regardless of fetal presentation. The viability at this gestational age and weight is extremely low, and long-term morbidity and mortality so invariable that maternal risks from cesarean section outweigh the fetal disadvantages of vaginal delivery. In addition, it is not unusual to have to perform a "classic cesarean," involving a vertical incision in the uterus, which places the mother at risk for uterine rupture in a subsequent pregnancy and virtually necessitates a repeat cesarean section.

For twins weighing up to 600 gm in a combined vertex–vertex lie, it is reasonable to consider a vaginal delivery with a carefully monitored labor. If there is any question of gestational age, which might place the infants in the range of 26 to 27 weeks or if estimated fetal weight exceeds 600 gm, it is best to err on the side of safety and to use the management scheme for the 600- to 1500-gm infants. When vaginal delivery of any preterm infant is anticipated, it is valuable to keep the membranes intact as long as possible to help maximize their contribution to cervical dilatation and to minimize trauma of labor.

When the first twin is in the nonvertex presentation with EFW ≥ 600 gm, cesarean section probably is the safest route of delivery under most circumstances. This will virtually eliminate the complications of cord prolapse, "interlocking twins," and other types of fetal entanglement above and below the pelvic brim. In addition, most sets of monoamnionic twins and most conjoined twins are best delivered by cesarean section.

When the first twin is vertex, the second nonvertex, and EFW exceeds 1500 gm, generally a vaginal delivery is planned. In skilled hands, short- and long-term morbidity in the term singleton breech infant appears comparable for vaginal and cesarean delivery.[11,23,25,26] Similarly, in the well-managed delivery of the term (≥ 37 weeks; ≥ 2500 gm) twin pregnancy, and even in most situations when the pregnancy is near term (≥ 34 weeks, ≥ 1500 gm), and the first twin is presenting as vertex, vaginal delivery can be considered with the nonvertex second twin.[1,5] Exclusions to this approach include, among others, suspected fetal macrosomia, fetal distress, discordancy, par-

Table 6. *Indications for Cesarean Section of the Second Twin*

Fetal macrosomia
EFW discordancy >500 gm
Failed external version
Failed internal version
Cervical contraction
Placental abruption
Cord prolapse
Fetal distress
Failure of descent

ticularly when weight of the second twin exceeds that of the first by 500 gm, and deflexion of the fetal head. Our preferred progression of management for the delivery of the second twin under these circumstances has been external cephalic version, internal podalic version and complete breech extraction, and, finally, cesarean section. Chervenak has outlined the approach to external cephalic version and the results have proved highly successful.[6] In his earliest publication on this subject, 18 of 25 version attempts were successful and resulted in vertex deliveries. Of 25 infants in this series, 4 were delivered by breech extraction with good outcome and only 3 of 25 required cesarean section. The success of any manipulative delivery under these circumstances seems to be facilitated greatly by anesthesia, and our choice for this has been regional block by epidural anesthesia.

When external cephalic version or internal podalic version fails, or extenuating circumstances prevent their completion, the second twin should be delivered by cesarean section expeditiously. There has been an increasing frequency of combined vaginal–abdominal deliveries for twins, and the delivery room must be prepared for this eventuality.[3, 10, 21] In our own experience, 7.5 per cent of 276 twin deliveries resulted in a cesarean section for the second twin. This outcome is consistent with results published elsewhere and probably reflects more of a consciousness for safety than declining obstetrical skills, as has been proposed by others.[21] Indications frequently cited for cesarean section of the second twin are shown in Table 6. Cesarean section for the second twin after a vaginal delivery of the first has been associated with maternal morbidity exceeding that usually found for cesarean section alone.[3]

When the first twin is vertex, the second nonvertex, and EFW is 600 to 1500 gm, our general approach has been that used for the >1500-gm infant. This group of patients is certainly the most controversial, as has been detailed previously. In general, the smaller the baby, the more difficult a trial of external cephalic version and the more likely the need for internal podalic version and complete breech extraction. The liberal use of cesarean section for this group cannot be discouraged, and the threshold for the same tends to decrease with the size of the infants, the presence of intrauterine growth retardation, discordancy, and the experience of the obstetrician. Also, when the

cervix is very unfavorable at the onset of labor, the patient is a primagravida, there has been prolonged rupture of membranes, or there is maternal disease (e.g., preeclampsia) that is evolving rapidly, early cesarean section is probably the option of choice.

TECHNIQUE OF DELIVERY

When vaginal delivery of twins is anticipated, the patient should be taken to the delivery room in time for the preparation of obstetricians, neonatologists, and anesthesiologists. The delivery room should be one in which cesarean section can be performed if necessary. At least two obstetricians, ones skilled in the techniques of identification of fetal parts, breech extraction, internal podalic version, and external cephalic version, should be scrubbed for the delivery. It is helpful to have a third person skilled in ultrasound evaluation of fetal presentation and attitude. It is our preference that the patient have a working continuous lumbar epidural anesthetic on board prior to entry into the delivery room, although, if time and circumstances permit, a spinal anesthetic is a reasonable alternative. If the patient has declined regional anesthesia, she must have a cooperative attitude and also understand that general anesthesia may be required for delivery of the second infant.

In most instances when vaginal delivery is planned, the presenting infant will be in the vertex lie. Delivery of the vertex is carried out in the routine fashion, with continuous careful monitoring of both infants during the delivery process. If oxytocin has been used to augment labor, this should be stopped just before or immediately on delivery of the first twin. Patience should be exercised throughout delivery of the first infant, which should never be forced through an incompletely dilated, effaced, and retracted cervix. With all other factors being equal, the course of delivery for both babies often can be judged by the ease of delivery of the first. In this regard, we have adopted a general policy that if it is thought that a midforceps extraction is necessary for delivery of the first twin, the entire delivery is probably best done by cesarean section.

With delivery of the first twin, the umbilical cord is singly clamped and cut, and the infant immediately passed to the awaiting pediatrician. At this point, a section of cord can be isolated, clamped, and blood gases obtained if desired. Usually, routine sampling of the umbilical vein for fetal blood type should be deferred until the second twin is delivered.

The position of the second twin must then be quickly ascertained. If the vertex is presenting or is close to the pelvic inlet, the fetal head can be guided into the pelvis using combined abdominal and intrauterine manipulation. During a contraction, or with the head held against the pelvic inlet by abdominal pressure, membranes are ruptured and a fetal scalp electrode applied to facilitate continuous monitoring. If uterine contractions have ceased, oxytocin augmentation is

begun. With adequate descent of the vertex, the second stage of labor can be shortened by the use of forceps or vacuum extraction, although with careful monitoring, heroics here can be safely avoided.[7, 24] Following this delivery, both the fetal and placental sides of the umbilical cord are doubly clamped to indicate birth order. At this point, blood gas samplings from the second umbilical cord and routine blood samples from both umbilical cords can be obtained.

When the second twin is breech or transverse or when a vertex second twin has unexpectedly changed to a nonvertex lie, it is absolutely necessary to assess fetal position rapidly and to decide a plan of action for delivery of the second twin. If ultrasound is available, this should be used immediately to confirm fetal position and assess attitude (i.e., flexion) of the fetal head. If ultrasound is unavailable, Leopold maneuvers prior to rupture of membranes are recommended.

Because delivery of the vertex places both fetus and obstetrician at the least risk, we have opted for a trial of external cephalic version prior to proceeding with internal podalic version and complete breech extraction. It is at this point that maternal cooperation, uterine relaxation, and adequate anesthesia become crucial for a successful outcome. A regional anesthetic under most circumstances provides sufficient uterine relaxation and maternal cooperation to accomplish external cephalic version. Even under these circumstances, however, if maternal cooperation is interfering with the manipulation, a general anesthetic may need to be administered. The patient should be made aware of this possibility prior to entering the delivery room.

If necessary, uterine relaxation can be achieved using terbutaline (0.25–0.5 mg) administered intramuscularly or intravenously. Once the uterus is relaxed, fetal position ascertained, and fetal well-being confirmed, external cephalic version can be tried using the standard techniques of abdominal manipulation. As recommended by Chervenak, it is useful to attempt the shortest arc of rotation as a first trial.[6] Undue force should be avoided at all times. If version is successful, the infant's head should be guided into the pelvis and membranes ruptured as described previously.

If external cephalic version fails, or is accompanied by fetal distress, or inadvertent rupture of membranes has occurred prior to achieving version, then a decision needs to be made immediately regarding delivery by internal podalic version and breech extraction or cesarean section. With an adequate maternal pelvis, fetal concordancy, and a completely dilated and effaced cervix, complete breech extraction usually can be accomplished quickly and safely by the skilled obstetrician. Under ideal circumstances, when this is done, both feet are identified and firmly grasped through the intact membranes and drawn into the pelvis. The membranes are then ruptured and the baby delivered by steady gentle traction assisted in the end by suprapubic pressure to maintain flexion of the fetal head or by the use of Piper forceps to facilitate delivery and minimize trauma. Expect the baby delivered by breech extraction to be more depressed initially; however, if the selection criteria and delivery technique have been ade-

quate, most infants will respond to a prompt resuscitative effort.[14] Indications for proceeding with cesarean section for the second twin have been detailed previously (see Table 6).

Traditional teaching has recommended delivery of the second twin between 5 and 20 minutes following delivery of the first. However, risks from premature placental separation, cord prolapse, cervical contraction, and placental insufficiency can be minimized with the use of careful monitoring techniques.[7, 24] With these techniques, delivery of the second infant can be delayed; however, it has been our experience that prolonged delays associated with failure of descent appreciably increase the risk for cesarean section of the second twin.

Following delivery of the babies, delivery of the placenta can be awaited or accomplished by manual removal. The placenta should be inspected carefully to aid determination of zygosity and to assess pathologic conditions such as abruption and vascular communications. After visual inspection, the placenta should be submitted for formal evaluation by the pathologist.

Once the placenta is delivered, an oxytocin infusion is begun with a fluid load of lactated Ringer's solution or normal saline. The uterus should be manually explored to confirm its integrity, particularly if any manipulative delivery has been done, and to rule out retained products of conception. Gentle fundal massage can be performed while the examining hand is in the uterus to promote uterine contraction. The cervix and vagina then should be carefully inspected for lacerations.

The patient is at high risk for hemorrhage from uterine subinvolution resulting from overdistention or trauma, as well as residual anesthetic and tocolytic drugs. If control of hemorrhage is not achieved with oxytocin and fundal massage, then methergine (0.1–0.2 mg IV or IM) or 15-methyl-$PGF_2\alpha$ (250 μg) can be given. If hemorrhage cannot be controlled, then laparotomy may be necessary. Even prior to delivery, the patient with twins should be aware that hysterectomy may be necessary to control hemorrhage if conservative measures fail.

MANAGEMENT OF UNSUSPECTED TWINS

Despite efforts to encourage prenatal care and sometimes even with otherwise good prenatal care, 10 to 15 per cent of all twin pregnancies will be undiagnosed at the time of presentation to labor and delivery. This group contributes significantly to morbidity and mortality associated with twin gestations. A policy of routine ultrasound examination of any patient arriving on the labor suite who has not had an ultrasound performed during the pregnancy can help to avert many disasters. If unsuspected twins are found under these circumstances, the time frame for evaluation, preparation for delivery, and assessment of adequacy of facilities must be greatly compressed. Often these pa-

tients will present in preterm labor with significant cervical dilatation, having had no prenatal care.

Unfortunately, 5 to 10 per cent of all twin pregnancies will actually get to the delivery room before a diagnosis of multiple gestation is made.[8] The scenario is often one in which the attending physician is alone at the time, delivers an infant smaller than expected for the uterine size, and suddenly realizes that the uterus is still larger than expected, with membranes palpable on cervical examination. Under these circumstances, pediatricians and anesthesiologists need to be alerted immediately. Resuscitation of the first-born infant should be begun promptly. At the same time, the presence of fetal heart tones in the uterus should be documented and a fetal monitor attached if one is available. If immediate delivery of the second infant is not indicated or imminent, the attending physician should await arrival of assistance prior to further intervention. If an ultrasound unit is available on the delivery suite, a rapid assessment of fetal position and fetal size can be performed. Once the anesthesiologist, pediatricians, and, if available, another obstetrician have arrived, the second infant can be delivered using the approach detailed previously.

POSTPARTUM CARE

Once the patient with twins has delivered, she is still at risk for hemorrhage from complications of uterine subinvolution, infection, fatigue, and depression. Maternal–fetal bonding may be difficult, especially if the infants are premature or require intensive care nursery admission. The patient who has anticipated breastfeeding may be frustrated by the concerns about milk production and occasionally by sheer exhaustion. Extended hospitalization frequently is required to ensure the patient sufficient recovery from her delivery to handle the day-to-day problems with which she will be confronted.

Prior to discharge, the patient should have a discussion with her physician about contraceptive management. Contact with a local support group for parents with multiple pregnancies should be arranged. Careful followup and availability of the obstetricians and pediatricians should be encouraged. If the patient comes from an environment in which the babies will be at high risk for neglect and abuse, social services should be contacted and followup scheduled prior to her discharge from the hospital. The care and attention given to the postpartum patient with twins can be as critical to their long-term outcome and development as the delivery itself.

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Anesthesia for Twin Delivery

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Many anesthesiologists unfortunately have an aversion to provision of obstetric anesthesia services. The problems are related to unscheduled needs and emergencies, all-hours coverage, the variability and changing of needs during labor and delivery, the medicolegal climate, and feeling of inadequacy for the service, the latter perhaps related to lack of experience and training.[18] Multiple gestation, twins or more, add anxiety and apprehension. However, delivery of patients with multiple gestation especially demands the availability of anesthesia services—the smart obstetrician should insist on anesthesia service presence at delivery.

This article approaches the anesthetic problems presented by multiple gestation with an overview of some of the physiologic and pathophysiologic aspects, then develops clinical aspects of labor and delivery analgesia and anesthesia management for the anesthesiologist and obstetrician.

PHYSIOLOGIC CONSIDERATIONS

Normal physiologic functions change in all organ systems with any pregnancy, and these are not changed further appreciably by multiple gestation. The changes in the central nervous system (CNS) and the renal and hepatic systems are relatively unchanged from normal singleton pregnancy, and an excellent review of these are found in chapter 1 of *Anesthesia for Obstetrics*, by Cheek and Gutsche.[7]

The respiratory physiologic changes with pregnancy are summarized in Table 1. Multiple gestation, especially if and as carried to near term, may have some small effect in decreasing total lung capacity further, as well as functional residual capacity, expiratory reserve volume, and residual volume because of the increased size of the uterus and contents. Minute ventilation may increase slightly. Patients may complain of increased shortness of breath and difficulty breathing,

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Table 1. *Respiratory Changes*

VARIABLE	AVERAGE CHANGE	
	Singleton	*Twins*
Total lung capacity	0–5%	−5%
Functional residual capacity	−20%	−25%
Expiratory reserve volume	−20%	−25%
Residual volume	−20%	−25%
Minute ventilation	+50%	+55%
Alveolar ventilation	+70%	+75%
Tidal volume	+40%	+40%
Respiratory rate	+15%	+15%
Oxygen consumption	+20%	+25%
Blood gases		
Arterial pO_2	+10 mm Hg	Same
Arterial pCO_2	−8 mmg Hg	"
Arterial pH	No change	"
Serum bicarbonate	−3 mEq/L	"
MAC, inhalation agents	−10%	−10%

especially in the supine position. The respiratory distress may require adjustment in maternal position during labor and prior to and with induction of anesthesia for cesarean section.

Cardiovascular system changes of pregnancy may be enhanced with multiple gestation. The general changes, summarized in Table 2, tend to occur earlier in multiple gestation and may change to a slightly greater extent. There is an increased tendency to relative or actual anemia compared with singleton pregnancies.[42] Increased occurrence and extent of aortocaval compression produced by the increase in size and weight of the uterus and contents is of greater concern.[5, 29, 33]

Table 2. *Cardiovascular Changes*

VARIABLE	*Increase*	*Decrease*
Total blood volume	40%	—
Plasma volume	50%	—
Red cell volume	30%	—
Cardiac output	40%	—
Renal blood flow	15%	—
Hepatic blood flow	5%	—
Hematocrit	—	6%
Total proteins	—	10%
Albumin concentration	—	20%

Changes with multiple gestation tend to be increased and occur earlier in pregnancy than singleton pregnancy.

PATHOPHYSIOLOGIC CONSIDERATIONS

It is not the purpose of this article to review all the pathophysiology that may complicate pregnancy, especially multiple gestations, and the management of these complications. There are, however, conditions more apt to complicate multiple gestations. Pregnancy-induced hypertension (PIH or preeclampsia) increases to perhaps twice the incidence of singleton pregnancies.[22] The severity of the syndrome likewise may be increased. The potential for a prolapsed umbilical cord is increased, especially between the vaginal delivery of the first and subsequent fetuses. Blood loss increases to about twice that of singleton deliveries because of the increased distention and reduced contractility of one uterus following delivery.[3]

Preterm labor and resulting premature delivery is increased, perhaps as a result of uterine distention and initiation of uterine contractions by normal pathways. Early diagnosis of multiple gestation with close prenatal care are the first steps for prevention of preterm labor.[22] Prevention and treatment of preterm labor may involve the use of beta-2 agonists, such as ritodrine, terbutaline, or isoxsuprine, magnesium sulfate, or other agents, including alcohol, morphine, calcium channel blockers, and prostaglandin inhibitors, such as indomethacin and aspirin.

Beta-adrenergic therapy introduces the maternal risk of a relative fluid overload and pulmonary edema. The maternal tachycardia produced may cause cardiac failure in the patient with a compromised cardiac system, and perhaps cause subendocardial ischemia in normal patients. Hypotension may occur, particularly postural hypotension. Naturesis is reduced, with resultant fluid retention, which coupled with possibly increased pulmonary capillary leak may contribute to pulmonary edema. Plasma hypokalemia and hyperglycemia have been reported.[4, 9, 51, 56] Fetal effects include hyperglycemia, tachycardia, and hypocalcemia. The neonate may show generalized hypotonia, and there is an increased incidence of ileus.[6, 15] Anesthetic agents sensitizing the myocardium to adrenergic stimuli, such as halothane, should perhaps be avoided in the patient receiving beta-adrenergic agents. Discontinuing administration of these agents is recommended for at least 30 minutes, preferably 4 hours, prior to delivery if possible.[6]

Alcohol and morphine produce a CNS depression of both mother and fetus, and require consideration in relation to anesthesia.[16, 47] Elevated blood magnesium concentrations[46, 47] to the therapeutic range or above cause increased sensitivity of neuromuscular junctions to the muscle relaxants used in anesthesia, which requires considering dose reduction and careful monitoring to prevent further problems. Prostaglandin inhibitors may inhibit platelet activity, which may be of concern when consideration is given to regional anesthesia, and a bleeding time test may be desirable. Experience with calcium channel blocking agents is limited but may cause decreased myocardial and uterine contractility in the presence of potent inhalational agents.

The premature fetus usually has a lower concentration of plasma proteins, and therefore reduced protein-binding capacity, of potential significance with the amide group of local anesthetics and some intravenous agents such as thiopental. Elevated bilirubin levels may compete with or block protein-binding sites. The premature fetal brain may have a reduced blood–brain barrier, and accordingly may be more depressed by anesthetic agents. Although these considerations are worthy of concern, there is perhaps little that can be done from the practical standpoint; that is, a mother for cesarean section with premature fetuses requires anesthesia. Regional anesthesia will result in less drug presenting to the fetus and less depression than with general anesthesia. With the latter, however, an attempt to limit exposure of the fetus(es) should be made.

With the increased uterine distention, and perhaps related to whether there are one or two (or more) placentas, uteroplacental insufficiency is more apt to develop. *In utero* twin–twin transfusion and the potential of difference in development and size of the fetuses, discordant twins may develop.[21, 40] *In utero* death of one of the fetuses may occur, the extreme discordancy, perhaps a result of twin–twin transfusion or placental insufficiency. There is an increased tendency to umbilical cord problems; twisting, knots, and compression especially in monoamniotic twins.

All of these factors, and more, will influence the obstetric and anesthetic management. These do occur in singleton pregnancies and should be familiar to most anesthesiologists, and will not be addressed specifically in the following discussions of anesthesia management.

LABOR AND DELIVERY

The decision for the basic plan for delivery is an obstetric one, based on many factors. One of the aspects considered is the positions of the twins, especially twin A. If twin A is breech, the decision may be to deliver by cesarean section, especially if a footling breech, prematurity, or if locking of chins is possible. If there is discordancy, cesarean birth may be advisable, especially if twin B is larger. Intrauterine death of one fetus may be an indication for cesarean section without labor. Presence of twin–twin transfusion, erythroblastosis, or prenatal diagnosis of congenital deformities are often causes for cesarean delivery. If antenatal testing suggests reduced uteroplacental reserve, for example, positive nonstress or contraction test results, or if fetal cardiac decelerations of either twin appear with spontaneous contractions, cesarean section must be considered. Prematurity itself may be an indication for cesarean delivery without labor.[11, 31, 43]

In reviewing our management of multiple gestations for the past 9 years, there has been an increase in "primary" cesarean section management, from 34 per cent in the first 3-year period (1978–1981) to 50 per cent in the last 3-year period (1984–1986) (Table 3). We have

Table 3. *Anesthesia Interventions for Multiple Births*

	Duke Univ.	*Crawford*[11]
"Primary" cesarean section		
1978–80	34%	(1983–85)
1981–83	42%	29.5%
1984–86	50%	
Total twins	266	196
>Twins	10	
Cesarean section for twin B	7.6%	6.2%*
General anesthesia for internal version, breech extraction, B	12.7%*	
Other supplemental anesthesia, B	2.5%*	
Total anesthesia for twin B	22.8% (after vaginal delivery A)*	
Internal version, breech extraction, twin B:		
Epidural anesthesia only	15.8%	
Spinal anesthesia only	0.6%	
Pudendal block only	5.1%	
General anesthesia for internal version, breech extraction, B		
Number of epidural anesthesia,	A: 72, 45.6%*	
General anesthesia,	B: 7, 9.7%	

* Based on vaginal delivery, twin A.

not been able to document outcome, but it is hoped that there is improvement.

The next sections will discuss some aspects of the anesthesia management of labor for anticipated vaginal delivery and then for delivery vaginally or by cesarean section.

LABOR ANALGESIA

Birth preparation for labor and delivery, as for any other pregnancy, is advocated (e.g., Lamaze classes and practice). The patient with multiple gestation must be prepared for the possible need for anesthesia for delivery either vaginally or by cesarean section of either one or more fetuses at any time during the labor and delivery process. Some patients may desire and expect to experience labor without use of analgesics or regional anesthetic techniques. However, I strongly urge the early rather than late use of regional anesthesia for the benefit of both mother and babies.

Several studies document that pain and anxiety of labor cause a marked rise in circulating endogenous catecholamines, both epinephrine and norepinephrine, in mother and the fetus.[2, 28, 45] The extent of this varies with individual patients, but potentially this stress is sufficient to cause hypertension, increased peripheral resistance, and uterine artery constriction, with resultant reduced maternal placental blood flow. This is perhaps more apt to occur in the primiparous or relatively young, and especially the very anxious patient. Proper use of analgesia will reduce this response and may improve the intrauterine environment for the fetus.[20, 25, 44, 45]

There is recognition and some concern that a preterm fetus may potentially be more depressed by narcotics used in labor than a full-term fetus. The judicious use of narcotics for analgesia is permissible, especially if regional anesthesia is not available or contraindicated. The selection of drug seems to be of little consequence: all are about equally depressant in equivalent analgesic doses, and all are delivered to the fetus in equivalent amounts for equivalent maternal effects. The agonist–antagonist analgesics, namely butorphanol, nalbuphine, and pentazocine, offer no advantage because the ceiling effect of no further respiratory depression occurs at doses above therapeutic and depressant doses. The sometimes-seen psychotomimetic effects and sedation of the agonist–antagonist drugs may be undesirable. The addition of adjuncts, such as promethazine for reduction of nausea and vomiting, must be viewed with some caution. Adjunctive use of tranquilizers produce little additional analgesia, may reduce fetal autonomic response (i.e., reduced beat-to-beat variability), and may reduce the patient's ability to cooperate and cope with labor pain. The best choice is that drug with which the participants are most familiar. Dose should be kept as little as possible, and preferably should be given intravenously so that effect is readily seen and evaluated, and further dosing is adjusted appropriately. Judicious use has not been shown to cause clinically significant neonatal effects, rather, in some patients a beneficial effect of reduction of catecholamines as described above has been seen.

Continuous regional anesthetic techniques, primarily and especially lumbar epidural anesthesia, are highly recommended for labor analgesia, and can readily be continued into the delivery.[12, 19, 20, 26, 27, 49] This may be initiated when the patient becomes a bit uncomfortable and contractions are regular, usually at 4 to 5 cm or more of cervical dilation in the natural course of labor. There is no reason to withhold epidural analgesia until a cervical dilation of 4 to 5 cm if labor is induced or augmented with oxytocin infusion, and delivery is committed.

Standard techniques are used, with an upper segmental level of T10 desirable. Local anesthetic agents and concentrations are those usually used for labor epidurals, and are the choices of those administering the anesthetic: 0.25 per cent bupivacaine, 1 per cent lidocaine, and 2 per cent chloroprocaine (concentration may be adjusted as per usual practice) are generally accepted standard agents, with very minimal or no fetal effect. The goal is to provide analgesia with a minimal loss of motor power. Standard maintenance with continuous infusion or intermittent top-up techniques are equally satisfactory.

Caudal anesthesia/analgesia has fallen into some disfavor for labor, as the dose of local anesthetic necessary for producing adequate levels is more than that for lumbar epidurals, and is less readily extended for cesarean section. In experienced hands, and as a part of the two-catheter technique, when the caudal catheter is used for delivery, the caudal approach to the epidural space is acceptable.

It is especially important to nurse these patients in a lateral po-

Table 4. *Therapy for Hypotension*

Determine cause:
- A. If secondary to regional anesthesia, i.e., sympathetic block:
  1. Oxygen by mask.
  2. Change position to increase venous return.
  3. IV fluid bolus, saline, or lactated ringers.
  4. Ephedrine or mephentermine, 10 mg IV bolus, repeat p.r.n.
- B. If other causes:
  1. Hypovolemia: treat accordingly, fluid and/or blood.
  2. Cardiac: treat hemodynamic cause.
  3. Reflex: reduce surgical stimulation.
  4. Other: treat accordingly.

sition because of the increased tendency toward aortocaval compression in multiple gestation, and as epidural analgesia with attendant sympathetic block enhances aortocaval compression.[24] Hypotension is more apt to occur, and close monitoring of blood pressure is important, with prompt treatment of hypotension with a bolus of intravenous fluid and ephedrine or mephentermine as necessary (Table 4).

VAGINAL DELIVERY

As labor progresses, and vaginal delivery becomes imminent, anesthesia or analgesia may become essential for satisfactory completion of delivery. There is no need to allow an epidural to "wear off" when cervical dilation is complete, and in fact this may be undesirable.[1, 2, 8, 26, 32, 37, 50, 52] Perineal distention, possible episiotomy, and possible use of forceps suggest the need for some form of anesthesia for delivery. Regardless of the anesthetic/analgesic technique, the patient should be receiving supplemental oxygen at 50 per cent or more concentration to improve fetal oxygenation, as shown by Ramanathan and colleagues (Fig. 1).[14, 38]

If continuous lumbar epidural analgesia has been instituted for labor, this can be readily extended for delivery. With the patient in a 15- to 45-degree head-up position, a volume of 10 to 14 ml of appropriate local anesthetic is injected. As forceps delivery may be necessary, especially for the second twin, I recommend 1.5 per cent lidocaine, 0.5 per cent bupivacaine, or 3 per cent chloroprocaine as the agent. Perineal anesthesia should be obtained in less than 10 minutes, if not already present from labor dosing, and should last for the delivery and any perineal repair. The upper segmental level of anesthesia obtained may produce adequate analgesia for internal manipulation of the second twin, that is, version and breech extraction, although uterine relaxation is not produced.

Spinal anesthesia, or saddle block, is very effective for producing anesthesia and muscle relaxation of the perineum. I recommend the

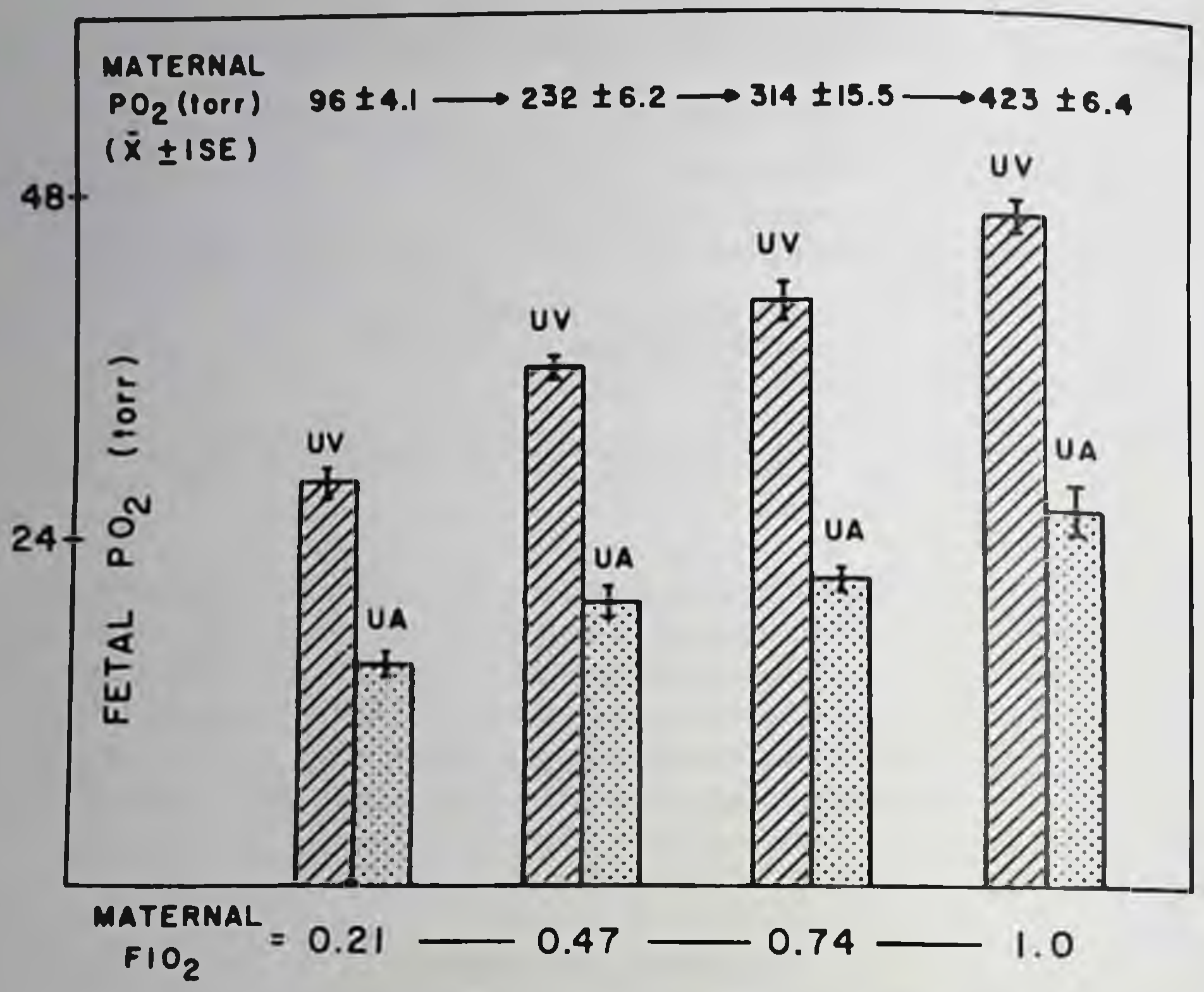

Figure 1. Histograms showing umbilical vein (UV) and umbilical artery (UA) po_2 levels at different maternal levels of Fio_2. Maternal pao_2 at four levels of Fio_2 is shown at top. Values are means ± 1 SE (n = 10). (*From* Ramanathan S et al: Oxygen Transfer from Mother to Fetus During Cesarean Section Under Epidural Anesthesia. Anesth Analg 61:577, 1982; with permission.)

use of 5 mg hyperbaric tetracaine, by standard techniques, which should provide adequate duration for delivery and repairs. True saddle block, such as achieved by keeping the patient in a sitting or upright position for 2 to 3 minutes or more after injection, may not be satisfactory. A period of about 60 to 90 seconds of sitting after injection will produce good perineal anesthesia yet provides some lower abdominal analgesia for intrauterine manipulation if needed.

Caudal anesthesia may be instituted for vaginal delivery and will provide excellent conditions. The agents and concentrations are the same as for lumbar epidurals, although the volume is reduced to 8 to 12 ml.

Bilateral pudendal block by standard techniques, using 1 per cent lidocaine, 0.25 per cent bupivacaine, or 2 per cent chloroprocaine or equivalents, will provide perineal anesthesia and some perineal relaxation, with minimal discomfort for low forceps. Should further manipulation or internal version be necessary, the analgesia may be inadequate. Local infiltration of only the perineum is minimally adequate, thus I do not recommend this approach.

Inhalation analgesia, using nitrous oxide or other suitable agents (almost all inhalation agents can be given in less than anesthetic but yet analgesic concentrations), may be useful to supplement a pudendal block, if indicated.[48] With this method, the hazard of vomiting and aspiration can be avoided, as the patient is not anesthetized to the point of loss of protective reflexes. The technique is to administer about 40 per cent nitrous oxide, or 0.75 per cent enflurane, or 0.25 to 0.5 per cent isoflurane, or 0.25 to 0.3 per cent halothane in oxygen by mask. Constant patient interaction is maintained, as loss of patient contact indicates deepening anesthesia level. This will not provide uterine relaxation for intrauterine manipulation of the second twin, although the analgesia may be satisfactory. General anesthesia per se should not be used unless necessary as dictated by the progress of events, as will be discussed below.

The vaginal delivery of twins is fraught with many uncertainties and potential problems during the course of delivery. These include the need for internal version and breech extraction of subsequent fetuses, and the potential of a cesarean section if the second (or third) fetus cannot be delivered, an umbilical cord prolapses, or severe fetal distress intervenes. It is for these potential problems that the thoughtful obstetrician will have anesthesia personnel standing by at the time of vaginal delivery of multiple gestations.

Over the past 9 years, in our institution, general anesthesia for attainment of uterine relaxation for internal version and breech extraction was required in 12.7 per cent of vaginal deliveries of twin B, when twin A was delivered vaginally. Cesarean section was required for the second twin in 7.6 per cent. Supplemental analgesia was given for an additional 2.5 per cent. Thus, anesthesia service intervention was required in 22.8 per cent of the attempted vaginal delivery cases (see Table 3). Crawford has reviewed their experience, and reports similar numbers (see Table 3).[11] This problem is compounded because the incidents requiring the interventions are not predictable and may occur at any time during the course of any vaginal delivery of multiple births.

When the course of events requires uterine relaxation for internal version, general anesthesia is the quickest and most consistent approach. Uterine relaxation using beta agonists in this situation is unpredictable and slow. Amyl nitrate by inhalation may be of some use but again is unpredictable. The induction of general anesthesia to produce uterine relaxation may be necessary in addition to and on top of a perfectly functional epidural or spinal anesthetic. This occurred in 7 of 72 cases, 9.7 per cent, in our experience (see Table 3). As the patient must be considered to have a full stomach, the induction of general anesthesia must be accomplished with techniques to reduce the potential of vomiting and aspiration.

Rapid sequence induction with endotracheal intubation is recommended. Thiopental, about 4 mg per kg, or ketamine, 1 mg per kg (approximate normal body weight), is administered rapidly intravenously, followed immediately by succinyldicholine, 80 to 120 mg, and

the trachea intubated. (It is assumed that the mother will already be receiving oxygen, and if not, why not?) When ventilation is assured, the selected inhalation agent is added to the inhaled oxygen. The halogenated agents appear to be faster and perhaps better. Halothane has been most widely used, but all potent inhalation agents will produce uterine relaxation. The concentration of the agent needs to be at least two and preferably three times the MAC (MAC is the minimum anesthetic alveolar concentration: halothane = 0.78 per cent, enflurane = 1.68 per cent, isoflurane = 1.15 per cent, in oxygen, in non-pregnant patients, pregnant patients may require 10 per cent less).[36] Nitrous oxide up to 50 per cent may also be administered. It will take 2 to 3 minutes to deliver the agent to the uterine musculature at the concentration to produce relaxation. Once the manipulation is accomplished, the concentration of the agent should be reduced to a low level, less than 50 per cent MAC, as now return of some uterine tone is desirable. It may not be wise to turn off all anesthetic agent(s) since the delivery may not yet be accomplished, and it is desirable to maintain the endotracheal tube in place until the delivery is complete—cesarean section has been required at this point in time.

Should cesarean section become necessary for the second or subsequent delivery, the above rapid sequence induction of general anesthesia is carried out, except the concentration of inhalation agent can be kept to about one half to one MAC, with up to 50 per cent nitrous oxide added. Management of general anesthesia in this circumstance is the same as for any cesarean section under general anesthesia. On many occasions, a functional epidural which has been "topped up" appropriately for delivery with a higher concentration of local anesthetic has been adequate for the incision and initial progress of a cesarean section, while a supplemental injection of a cesarean section dose is taking effect. A more rapid onset of surgical anesthesia may be obtained by the addition of sodium bicarbonate to the local anesthetic.[41]

CESAREAN SECTION

In reviewing our experiences over 9 years, we found that 34 per cent of multiple births underwent initial cesarean section in the first 3-year period (1978–1980), and this increased to 50 per cent in the last 3-year period (1984–1986) (Table 3). This may reflect the general trend of increasing cesarean section rate, or may reflect a change in philosophy to deliver by cesarean section premature fetuses, breech presentations, or other potential problems. In our experience in this period, all but one of the deliveries of triplets and all quadruplets have been by cesarean section. The following is a brief review of anesthesia management for cesarean section for multiple births.

The choice of anesthesia for cesarean section is based on many aspects of the patient and the presence of other problems. Table 5 lists contraindications for regional anesthesia: spinal and epidural.

Table 5. *Contraindications to Regional Anesthesia*

Absolute contraindications
Patient refusal
Coagulopathy
Thrombocytopenia, platelet count <70,000
Tumor of spinal cord or at site
Infection in area of insertion
Generalized infection, bacteremia
Active primary herpes infection
Hypovolemia, hemorrhage
Shock, due to any cause
Significant spinal deformity or lower spine problems
Moderate to severe generalized neurologic disease (i.e., multiple sclerosis)
Drug allergy
Inadequate time available (i.e., severe fetal distress)
Relative contraindications
Significant anemia
Fever, temperature greater than 38°C
Active but secondary herpes infection
Prior back surgery, backache
Increased intracranial pressure (i.e., pseudotumor cerebri)
Mild neurologic disease
Low cardiac output disease states
Pregnancy-induced hypertension if inadequately treated
Fetal distress
Inexperience of anesthetist

Assuming no contraindications are present, selection of the anesthesia plan becomes the choice of the patient with the concurrence of the obstetrician and anesthesiologist. Relative urgency may preclude regional anesthesia because of time required to place and achieve anesthesia. The choice of regional versus general remains controversial. There are data to suggest that general anesthesia may be more depressing to the fetus than regional anesthesia; however, this is notable for only the first 24 hours following delivery.[10] Biochemical studies suggest that general anesthesia may be less stressful if only measured cord blood pH is considered.[25] There may be an element of improved uterine relaxation with general anesthesia, which may be beneficial for intrauterine manipulation and delivery of a premature fetus or fetuses, or for intrauterine manipulation of abnormal presentations. Conversely, well-managed regional anesthesia, spinal or epidural, with measures to prevent and immediately treat hypotension, should result in good fetal status on delivery. Multiple births as such do not preclude either regional or general anesthesia.

Attention must be given to avoidance of the aortocaval compression syndrome, maintenance of blood pressure, and provision for patient comfort with whichever anesthetic technique. The enlarged uterus and contents may make lying supine very uncomfortable for mother, regardless of technique as preparations for the section are underway. After delivery, the relative overdistention of the uterus

may reduce its ability to contract, and an increased blood loss should be anticipated.[3] Therefore, an adequate intravenous line (or lines) is essential, and blood for transfusion should be immediately available.

Standard procedures for spinal anesthesia is used, using either 8 to 11 mg tetracaine (expected duration 1.25–1.5 hours); 10 to 15 mg bupivacaine (expected duration 1.5 hours); or 75 mg lidocaine (expected duration 1 hour) in hyperbaric solution, with a minimal upper segmental level of T6 desirable. Epinephrine 0.1 to 0.2 mg may be added to prolong duration by another 30 to 50 per cent. The patient should have a vascular space preload of 20 ml per kg of saline or balanced salt solution to reduce the potential of hypotension. These solutions should be glucose free or may contain at most 2 per cent glucose.[30, 34] Any indication of hypotension should be treated with 10 mg ephedrine (or mephentermine) intravenously.[13, 23] Supplemental oxygen is administered. Once satisfactory anesthesia is obtained, the surgical procedure and delivery should be carried out expeditiously.

Lumbar epidural anesthesia is induced by standard techniques, using 1.5 to 2 per cent lidocaine, 0.5 per cent bupivacaine, or 3 per cent chloroprocaine,[55] preferably with 1:200,000 to 1:300,000 epinephrine, and a volume to achieve a minimal upper segmental level of T6 (range 12–20 ml). Recent reports suggest that the addition of a small amount of fentanyl, 25 to 50 μg, will provide better analgesia for mother, with less nausea and vomiting from intra-abdominal manipulation, without significant fetal effect.[17] Again, a vascular space preload of 20 ml per kg of normal saline or lactated Ringer's solution is administered, and any indication of hypotension is further treated with ephedrine or mephentermine 10 mg. Supplemental oxygen is administered. When anesthesia is satisfactory, the surgical procedure and delivery should be carried out expeditiously.

General anesthesia is carried out in a standard fashion—monitors applied, preoxygenation begun, the abdomen prepped, and draping accomplished, and when all is ready, anesthesia is induced. Nondepolarizing muscle relaxant pretreatment may be given at the time of draping but should not be used if magnesium sulfate is being given for preeclampsia. Thiopental, 4 mg per kg, or ketamine, 1 mg per kg, is given rapidly intravenously, followed by 1 to 1.5 mg per kg (80–120 mg) succinyldicholine; the trachea intubated; ventilation begun and endotracheal tube position verified; and surgery commenced. A potent inhalation agent, halothane, enflurane, or isoflurane, at about 0.5 MAC is given, with or without 50 per cent nitrous oxide in oxygen. More than 0.5 MAC may be used if increased uterine relaxation is desired. Once the babies are delivered and the cord(s) clamped, the anesthesia may be supplemented with intravenous narcotics, and the nitrous oxide increased to 60 to 70 per cent, but the potent inhalation agent should not be increased as the effect of reducing uterine tone may further increase bleeding. Muscle relaxants may be added as indicated or desired.

With any technique, oxytocin should be given immediately after delivery to enhance uterine contraction. Bolus IV injection of oxytocin

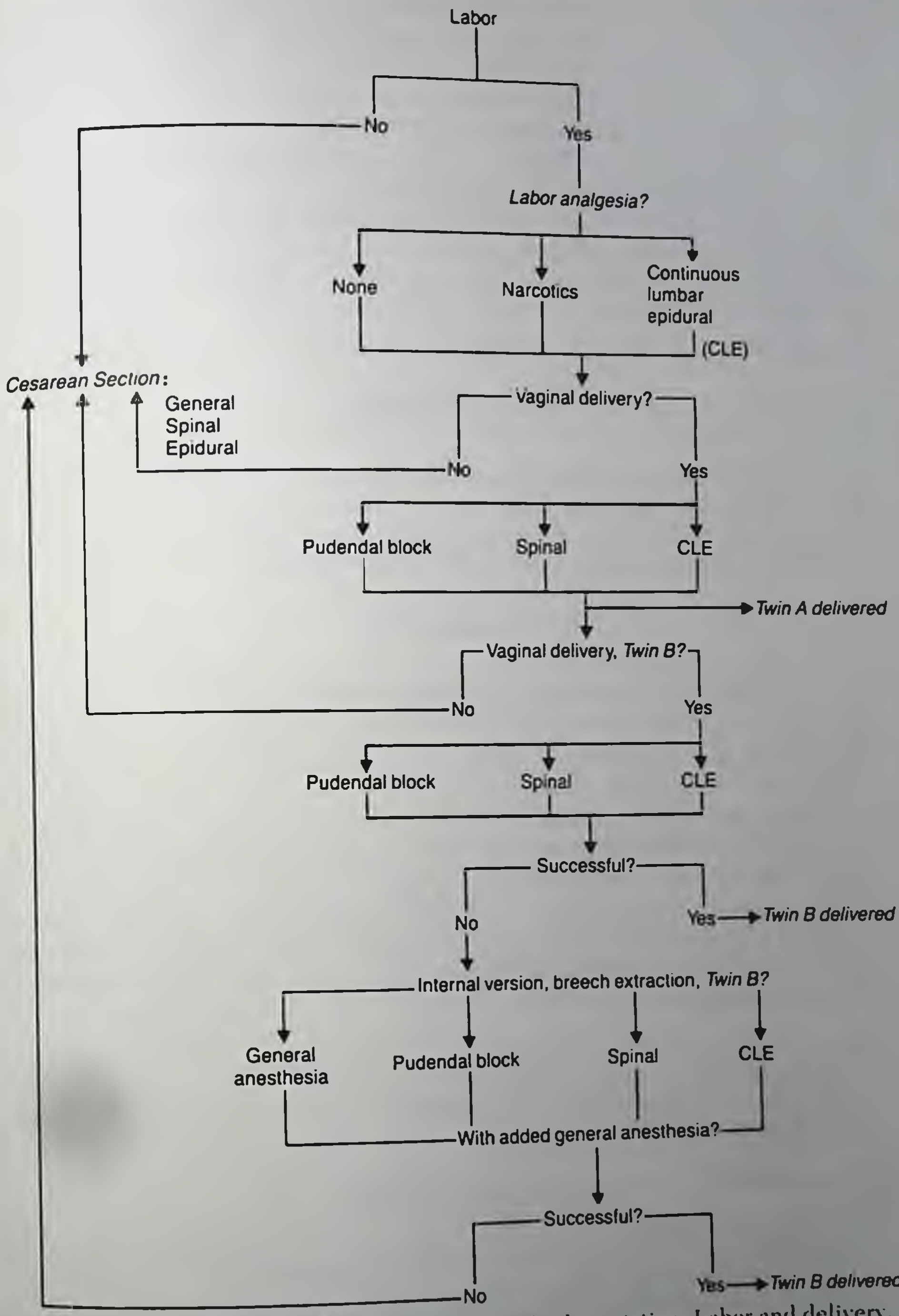

Figure 2. An algorithm for anesthesia for multiple gestation: Labor and delivery.

has been shown to produce hypotension in 20 per cent or more of patients, and may induce ventricular arrythmias; therefore oxytocin should be given as a continuous infusion of 20 to 30 units per liter of intravenous fluid.[35, 53, 54] If response is thought to be inadequate, 10 units of oxytocin may be given by direct injection into the uterus. On rare occasions, the addition of 0.2 mg intramuscular methergine may be required to attain good uterine tone.

No discussion of anesthesia for cesarean section would be complete without mentioning the potential of use of local infiltration anesthesia. This is essentially unheard of in our institution, but it may be the best or only choice in some circumstances, and all obstetricians should have a cursory knowledge of the techniques required.[39]

ALGORITHM

To help in developing the approach to anesthesia for twin or multiple births, an algorithm has been developed (Fig. 2). Again, there is the element of surprise, unpredictability, and need for sudden change to plans and expectations for delivery of multiple gestations.

SUMMARY

The patient presenting for delivery with multiple gestation often produces extreme anxiety for those involved with her care. From the standpoint of anesthesia service, knowledge of what to expect, and better, the knowledge of what to do if and when the various potential problems present is paramount. With close communication and cooperation with the obstetrician and patient, a satisfactory anesthetic and obstetric outcome is achievable. Lumbar epidural anesthesia is highly recommended for pain management when labor and vaginal delivery is anticipated. However, the knowledgeable obstetrician and the knowledgeable anesthesiologist must be present and prepared for all circumstances.

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Morbidity and Mortality Factors in Twins

An Epidemiologic Approach

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Historically, twins have been the subject of awe and speculation. At various times and in various geograhic or racial groups they have been the cause of wonder and veneration or, conversely, hostility, to the point of infanticide. Twin births and their epidemiologic characteristics probably have been better recorded than the general rule; the result of their relative rarity, and the sense of wonder which has accompanied this phenomenon. The scientific study of twinning, however, is of relatively recent origin,[17] despite the fact of their high mortality and morbidity, which make them an important risk group for study.

In this study we wish to review the mortality and morbidity of twins and the factors contributing to this and also to present some of our own data from the University of Illinois perinatal network.

MATERIALS AND METHODS

We studied all singleton and twin pregnancies and their products at the 12 hospitals which comprise the University of Illinois perinatal network, from 1982 through 1986. For our study the database consisted of information abstracted from the obstetrical and neonatal charts of the network hospitals during the study period. Data were transcribed onto a perinatal abstract form, consisting of 73 variables and more than 300 items. The data were then entered into a computer. The data collecting system has been previously described.[59]

The purpose of our study was to assess the mortality and morbidity among twin pregnancies, within the University of Illinois perinatal

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Table 1. *Variables Analyzed*

Fetal, neonatal, and perinatal mortality rates
Incidence of low (<7) Apgar scores at 1 minute and 5 minutes after birth
Incidence of hyaline membrane disease (HMD)
Incidence of respiratory disorders other than HMD
Transient tachypnea of the newborn
Apnea
Pneumonia
Meconium aspiration syndrome
Persistent pulmonary hypertension of the newborn
Air leak syndromes
Incidence of neonatal seizures
Incidence of congenital malformation
Incidence of all nonrespiratory morbidity all significant diagnosis
Seizures, CNS malformations, other neurologic diagnosis
Congenital heart disease, heart failure, arrhythmia, shock, other cardiovascular diagnosis
Necrotizing enterocolitis, gastrointestinal malformations, gastrointestinal bleeding, other gastrointestinal diagnosis
Hepatitis, cholestasis, hyperbilirubinemia
Anemia (hematocrit <40), polycythemia (hematocrit >65), other hematologic diagnosis
Renal failure, genitourinary anamolies
Endocrine disorders
Congenital anamolies, chromosomal abnormalities, other syndromes
Infections

network system and compare these data with the existing literature. For this purpose we compared the data for twins and singletons; first- and second-born twins; male and female twins; twin pairs segregated by sex as MM, MF, FM, and FF. We analyzed data by gestational age and by birth weight groups (group I: 500–1499 gm; group II: 1500–2999 gm; group III: 3000+ gm). The perinatal, intrapartum, and neonatal factors analyzed are depicted in Table 1. Statistical analysis was performed using the Fisher's exact test (two-tailed) and the Chi-square test.

INCIDENCE

The incidence of twinning varies widely throughout the world. The highest rate has been reported in black populations, with Nigeria having a rate of 1 in 20 to 25 pregnancies[1, 31, 33] and the lowest rate in Oriental populations.[34] The rate in Japan is 1 in 150 pregnancies.[33] The rate in white populations is intermediate, at 1 in 100 pregnancies.[7, 33] Worldwide, twinning appears to occur in approximately 1 per 80 pregnancies.[3]

In our study there were 80,906 singleton pregnancies and 998 twin pregnancies during the study period, giving a rate of 1 per 82 pregnancies. The rates in black, Hispanic, Oriental, and white races in our population are given in Table 2.

Table 2. *Twinning Rates by Race*

Black	*Hispanic*	*Oriental*	*White*
1:76 13/1000	1:100 10/1000	1:105 9.5/1000	1:76 13/1000

* Data from University of Illinois.

Interestingly, the rate of monozygotic twinning is fairly constant throughout the world, at 3 to 5 per 1000 deliveries.[31] The monozygotic twinning rate in a population is determined by analysis of placental morphology or by genotyping. In approximately 30[51] to 40 per cent (our population) different sex establishes dizygosity. Twenty to twenty-five per cent of twins may be diagnosed as being monozygotic by virtue of their having a monochorial placenta.[3, 51] The remaining 35 to 45 per cent must be studied systematically, using blood groups, enzymic markers, or dermatoglyphics. Cameron distinguished 8 per cent out of an undiagnosed remainder of 45 per cent in his study as monozygotic using these markers.[5]

Another method of determining zygosity in populations is by using the Weinberg rule,[31, 51] which states that the number of monozygotic pairs is equal to the total number of pairs minus two times the number of unliked sexed pairs. Potter,[51] in an elegant study, put this assumption to the test using placental morphology and blood grouping and proved it to be valid. Our study instrument was not designed to record placental morphology. However, using the Weinberg formula, the monozygotic twinning rate in our population was calculated to be 4.9 per 1000 pregnancies.

There are biologic differences in monozygotic twinning and dizygotic twinning. Monozygotic twinning is thought to be due to chance, unrelated to heredity, resulting from a delay in implantation associated with nutritional, hypoxic, or other stress.[3, 31] This delay leads to monozygotic twins, generally with monochorionic placenta. If the twinning process starts later, during cleavage (but before the blastocyst stage), a dichorionic placenta results.[25] This hypothesis also may help explain the reportedly higher incidence of congenital malformations in monozygotic twins.

Dizygotic twinning is due to multiple ovulation possibly related to increased levels of follicle-stimulating hormone or luteinizing hormone. Racial and familial tendencies to dizygotic twinning may be related to variations in gonadotropin production.[3, 31] Exogenous gonadotropins or clomiphene used in the treatment of infertility may induce multiple ovulations.

Incidence of twinning is thought to increase with maternal age and parity.[31] In our study, the median maternal age for singletons was 27 years and for twins, 31 years. The twinning rate for primigravidas was 21.3 per 1000 and 26 per 1000 for multigravida ($p < 0.001$).

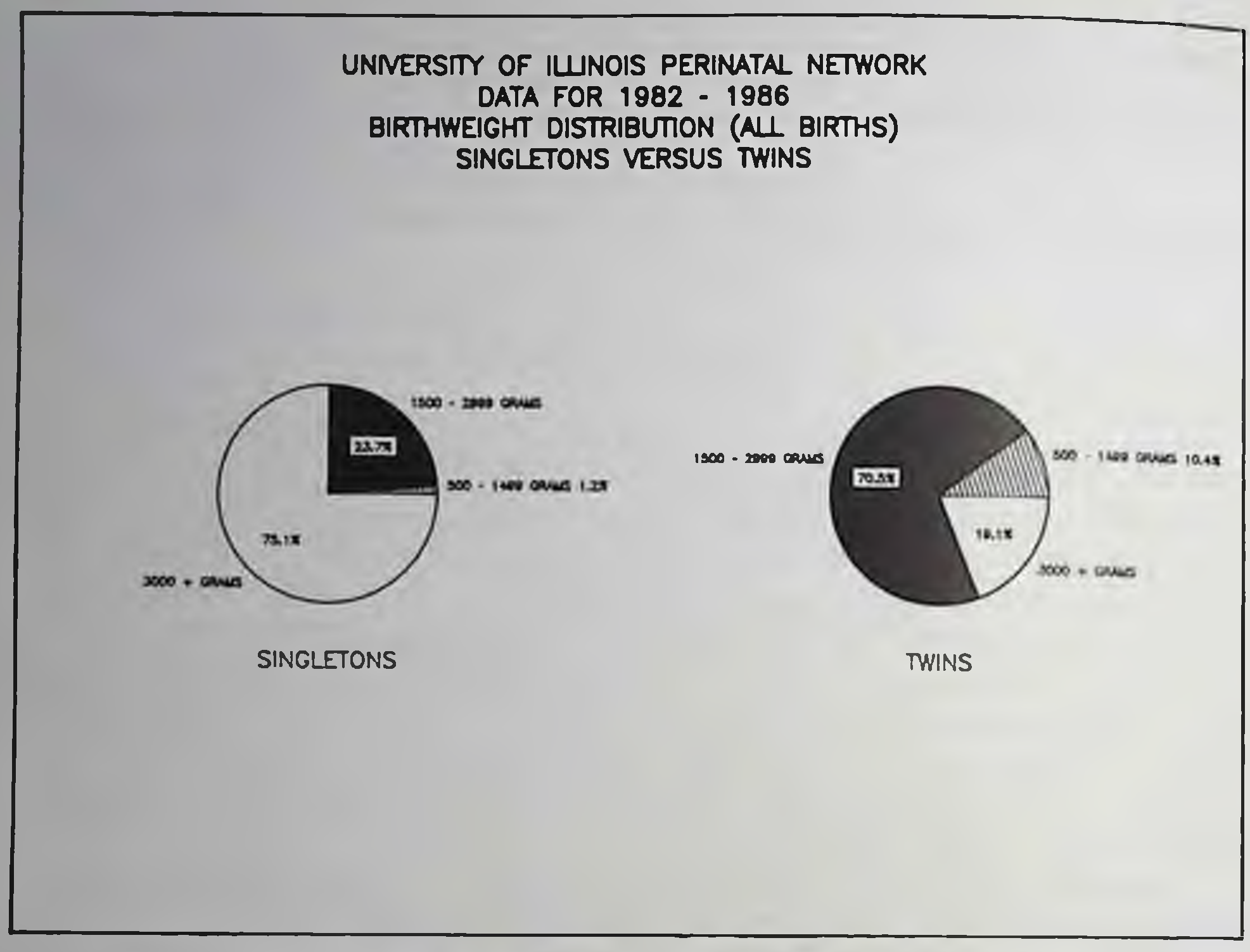


Figure 1. Birth weight distributions of twins and singletons.

INCIDENCE OF PREMATURITY/LOW BIRTH WEIGHT RATE/ INTRAUTERINE GROWTH RETARDATION

Twins are well known to be born prematurely compared to singletons.[6, 9, 19, 21, 23, 27, 33, 39, 41, 47, 49, 50] The mean gestational age at birth for twins has been reported to be 3 weeks earlier than for singletons.[2] In our population, 42 per cent of twins and 8 per cent of singletons were born at a postconceptional age of less than 37 weeks.

Low birth weight is a common problem in twins.[19, 23, 27, 32] It is reported that greater than 50 per cent of twins will have a birth weight less than 2500 gm.[35, 41] It is evident from Figure 1 that twins have lower birth weights compared to singletons. In our study, 10.1 per cent of twins and 1.2 per cent of singletons had a birth weight of less than 1500 gm. Bletcher et al.[4] reports that the average birth weight of twins at term is 600 gm less than that of singletons.

Low birth weights in twins are the result of prematurity[20, 32] as well as intrauterine growth retardation (IUGR).[4, 9, 20, 23] Intrauterine growth of the twin fetus more or less follows the pattern of growth of singleton fetuses until 30 to 34 weeks' gestation.[15, 23, 29, 39] Following this period, the mean birth weight for twins progressively deviates from the curve for singletons. Figure 2 illustrates the intrauterine growth curves of twins and all infants during the period of study.

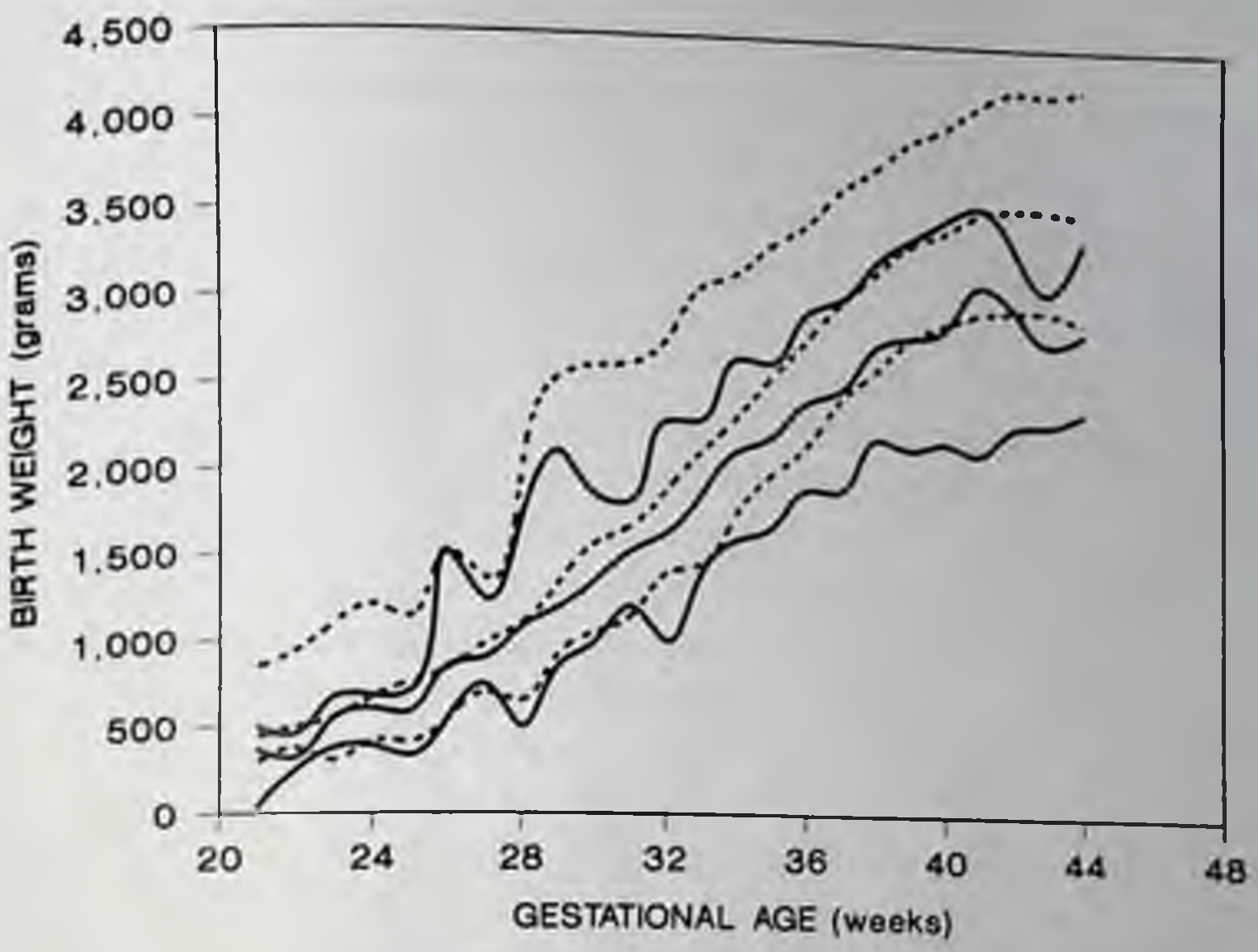


Figure 2. Intrauterine growth curves for twins and singletons.

The peak of mean birth weight is reached at 37 to 38 weeks rather than 41 to 42 weeks as is the case with singletons. This is consistent with the contention of Heluin[21] and others[12, 20] that twins beyond 37 to 38 weeks should be considered postmature.

Intrauterine environmental factors are considered to be responsible for this growth retardation. It has been reported that the uteroplacental system can support unrestricted fetal growth up to a combined fetal weight of 3000 gm (1500 gm each), beyond which point there is progressive deviation from the normal growth pattern.[20, 36] Whether placental factors play a role in this growth retardation is a subject of controversy. Gruenwald[20] and others[23, 40] have found a normal fetal–placental weight ratio. More recently, however, Blecher[4] found in a large series of twins that there is a smaller amount of placental tissue available to each twin. The importance of environmental factors in this form of growth retardation is illustrated by the fact that twins tend to have an accelerated rate of growth postnatally and by 1 year are equivalent in weight to their singleton counterparts.[43] The decrement in intrauterine growth is evident in most major organs. Organ weights of the heart, lungs, kidneys, liver, spleen, as well as the brain progressively deviate from the normal growth pattern in the last trimester of pregnancy.[43] Head circumference and body length do not follow this general pattern and are better maintained until later in the pregnancy.[15, 29]

Monochorionic twins tend to be lighter than dizygotic twins.[39] Male twins tend to be slightly heavier at birth.[4] Second-born twins are reported to weigh slightly less than the first-born twin.[19]

BIRTH ASPHYXIA

Twins are known to be more prone to birth asphyxia as compared to singletons.[9] This is largely due to the increased prematurity rate in twins.[9] Operative delivery and abnormal presentation,[8] both of which are more common in twins, also may account for this. Within twin pairs the second born twin is more prone to birth asphyxia.[14, 23, 33, 57] This is related to delayed delivery,[20, 51] cord prolapse,[14] placental separation,[14] placental infarcts,[41] abnormal presentation,[2, 14, 33, 57] and operative delivery.[14] The relationship between delayed delivery and low Apgar scores is weak.[14, 19] As long as a normal fetal heart tracing is present, there is no need for haste in delivering the second twin operatively.[6] It is reported that the neonatal depression seen in the second twin is rapidly reversible. The incidence of low 5-minute Apgar scores[57] or low heel-stick capillary blood pH at 15 minutes[14] is no different between the first- and second-born twins.

In our study (Fig. 3), twins had a higher incidence of low Apgar scores (<7) at 1 and 5 minutes as compared to singletons. At 1 minute, there was a higher incidence of low Apgar scores in twins with birth weight greater than 1500 gm (groups II and III). In twins with birth weight greater than 3000 gm (group III). This difference persisted even at 5 minutes, despite resuscitative efforts. This seems to indicate a severer or prolonged asphyxial insult to the larger twins.

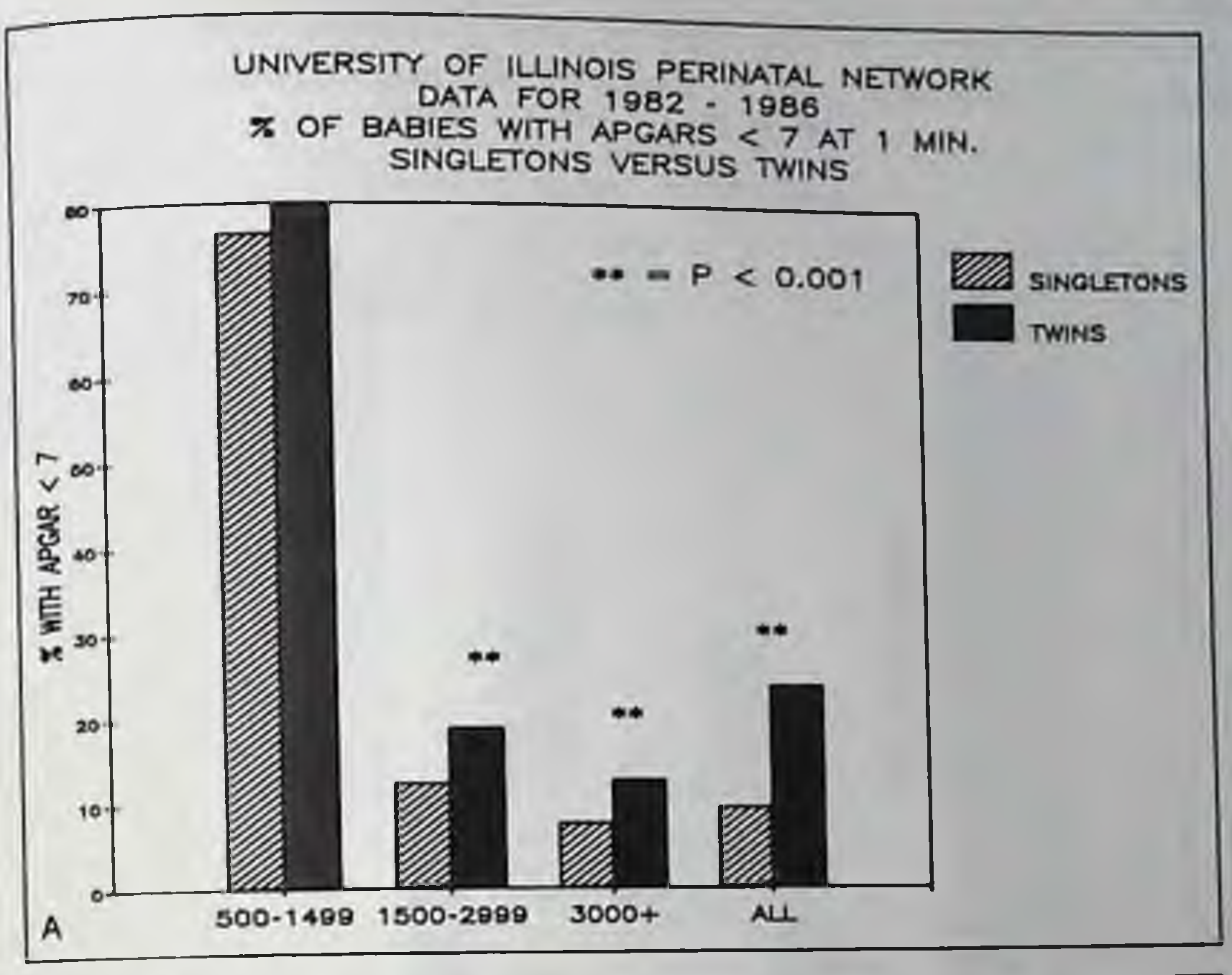
When we compared the first- and second-born twins, the second-born twins had a higher incidence of low Apgar scores (<7) at 1 minute (19.1 vs 28.7 per cent), but by 5 minutes no differences were observable (7.8 vs 10.0 per cent). However, when only the vaginally delivered twins were compared the second-born twins did indeed have lower Apgar Scores at 5 minutes (9.2 vs 14.2 per cent).

MORBIDITY

Hyaline Membrane Disease (HMD)

Ho and Wu[23] reported an overall 8.5 per cent incidence of HMD in twins, with 29 per cent of premature twins (<37 weeks) being diagnosed as having HMD. No differences were found in the incidence of HMD between the first- and second-born twins. Stahlman[56] and others,[2,6] however, report a higher incidence of HMD in the second-born twin. Spellacy et al.[55] and others[34] showed a close correlation between the lecithin-to-sphingomyelin ratios between first and second twins. Olsen, however, could not demonstrate this relationship.[46] It seems more than likely that any increased incidence of HMD that may be occurring in the second-born twins may be the result of birth asphyxia.

In our study twins had a higher incidence of HMD as compared to singletons (Fig. 4). The differences were largely accounted for by birth weight. However, there was a higher incidence of HMD in group



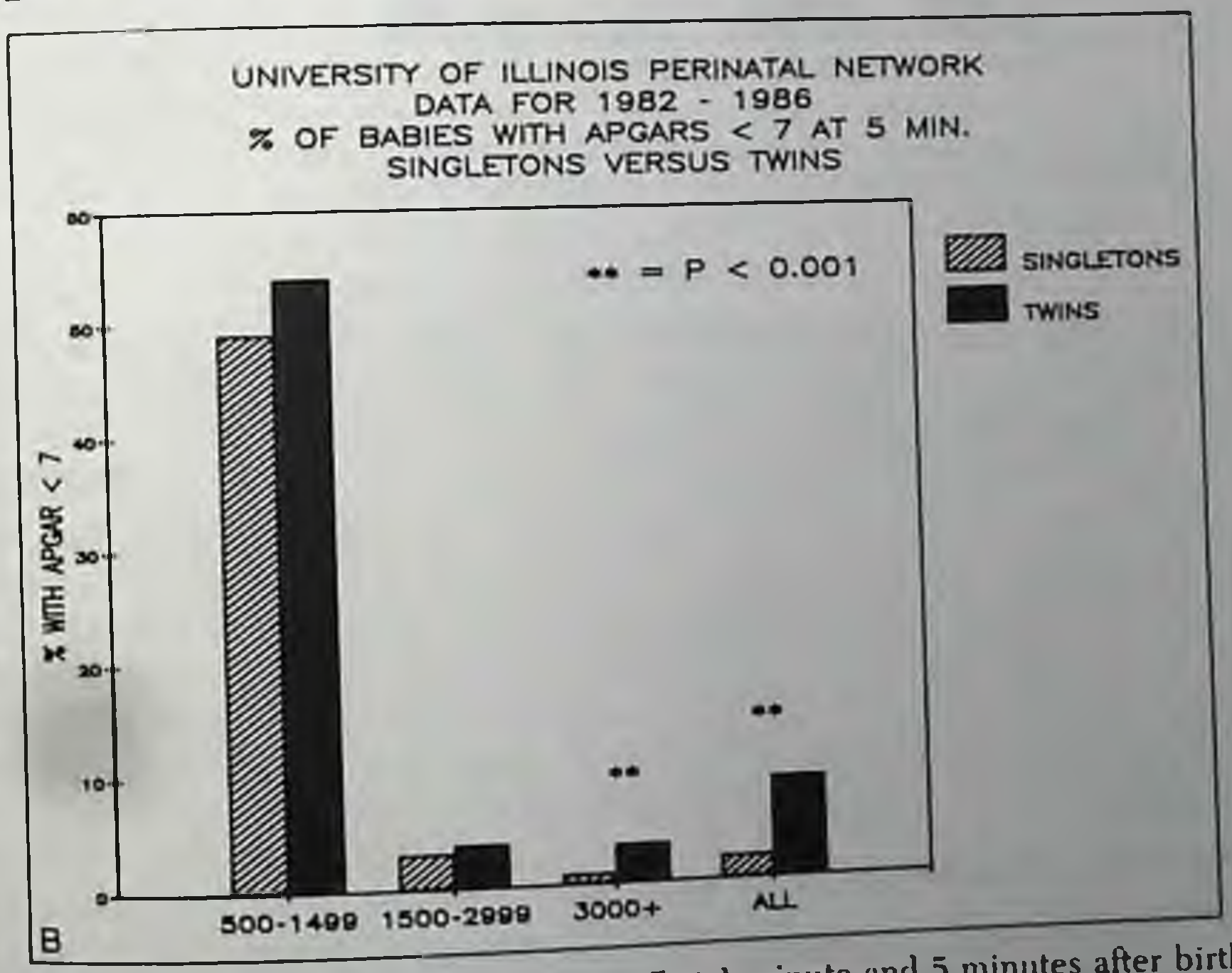


Figure 3. Incidence of Apgar score <7 at 1 minute and 5 minutes after birth in twins and singletons (* = $p < 0.05$; ** = $p < 0.001$).

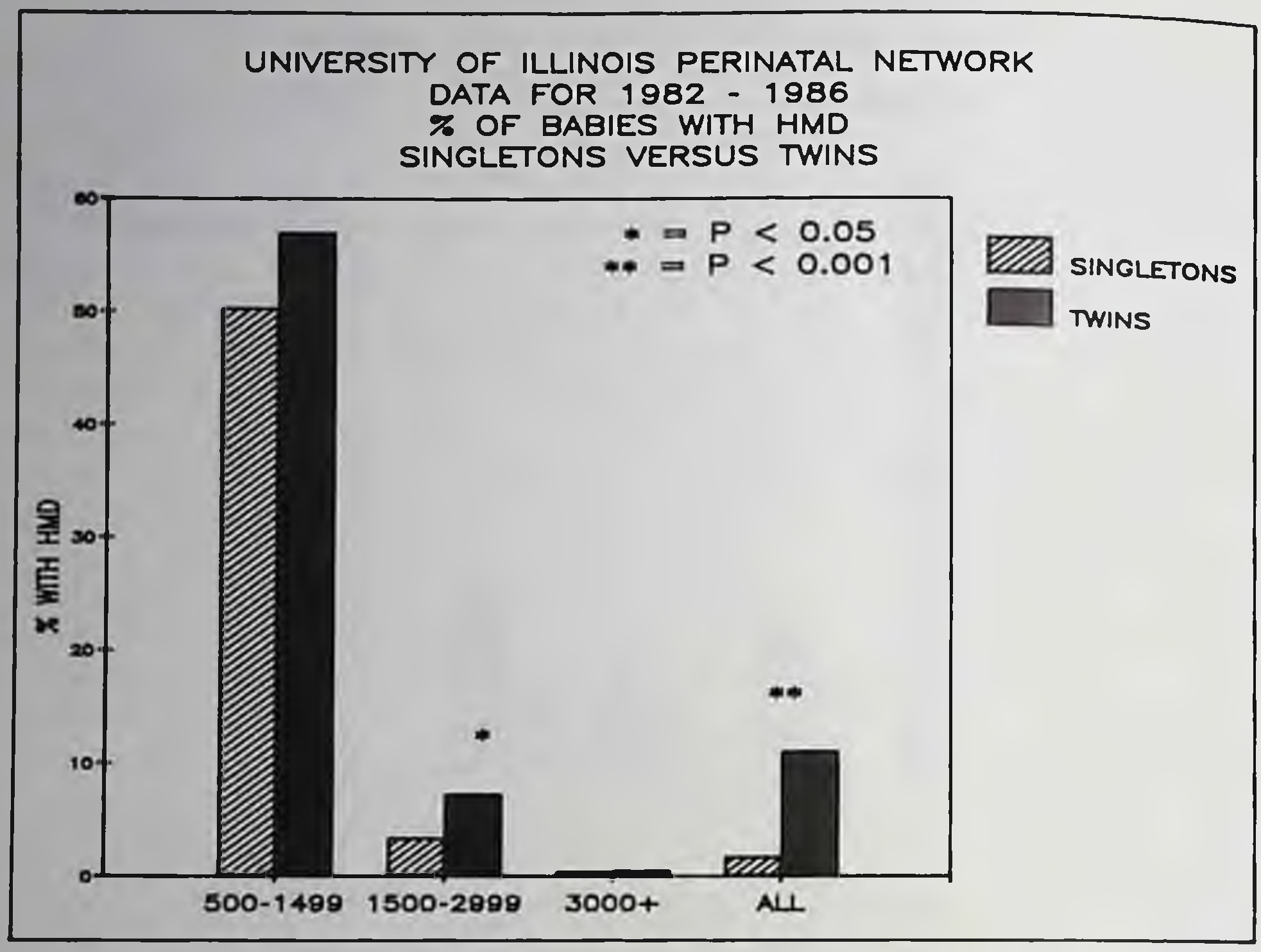


Figure 4. Incidence of hyaline membrane disease in twins and singletons (* = $p < 0.005$; ** = $p < 0.001$).

II twins (birth weight 1500–3000 gm). There was no significant difference in the incidence of HMD between the first- (10.2 per cent) and second-born twins (12.1 per cent).

Male infants are known to have a higher incidence of HMD and severer disease. In our study there were no differences in the incidence of HMD between male (11.5 per cent) and female (11 per cent) twins. We also found no difference in the incidence of HMD when twins were segregated as MM, MF, FM, and FF. The presence of a female in the twin pair did not protect the male twin from HMD. No differences in the incidence of HMD were found when we compared FF, MF, and FM twin pairs with the MM twin pairs.

Respiratory Morbidity

We assessed the incidence of respiratory disorders in our population. Infants with any of the disorders shown in Table 1 were included.

Respiratory morbidity (other than HMD) was noted to be strikingly increased in twins. After adjusting for birth weight no differences were found in group I twins, but group II and group III twins had significantly ($p < 0.001$) higher incidence of respiratory disease. In the largest twins (group III) the incidence of respiratory disease was three times that for singletons (Fig. 5).

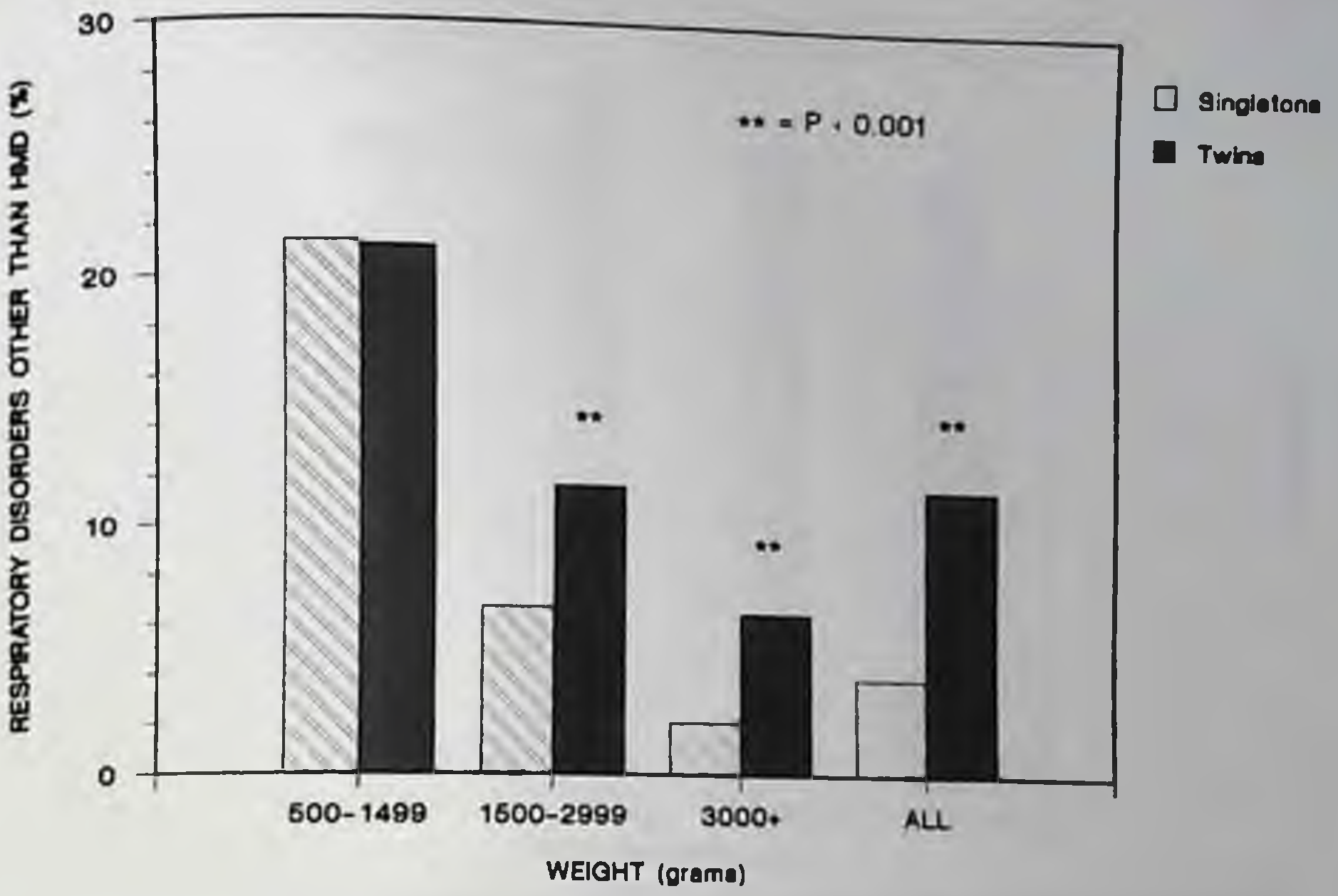


Figure 5. Incidence of respiratory disorder (other than HMD in twins and singletons (* = $p < 0.05$; ** = $p < 0.001$).

There were no differences found between the first- and second-born twins or between male and female twins. Our data indicated that the larger twins are more prone to develop respiratory disease in the neonatal period. It is a common experience that many of these disorders are either causally related to, or aggravated by, intrauterine stress and birth asphyxia. We speculate that this indicates a greater proneness of larger twins to *in utero* stress and birth asphyxia.

Neurologic Morbidity

Twins are known to have higher incidence of neurodevelopmental disorders as compared to singletons.[28] The incidence of twins in populations with cerebral palsy is higher than normal (5–10 per cent).[18, 53] The most common form of palsy in twins is spastic diplegia.[19, 33] Premature birth, growth retardation, birth trauma, and birth asphyxia are important antecedents to the neurologic problems of twins. It has been reported that, aside from these factors, twins are not any more prone to neurologic defects than are singletons.[28] However, in cases of intrauterine demise of one twin, there may be as much as 20 per cent incidence of neurologic sequelae in the surviving co-twin.[10, 11] Most of this morbidity is probably due to monozygotic twinning and sharing of placental vasculature.[10, 11, 61] Large birth weight differences in monozygous twins have been associated with lower IQ scores in the smaller twin of the pair.[26]

We looked at the incidence of seizures in the neonatal period as an index of neurologic morbidity in our population. Twins had a

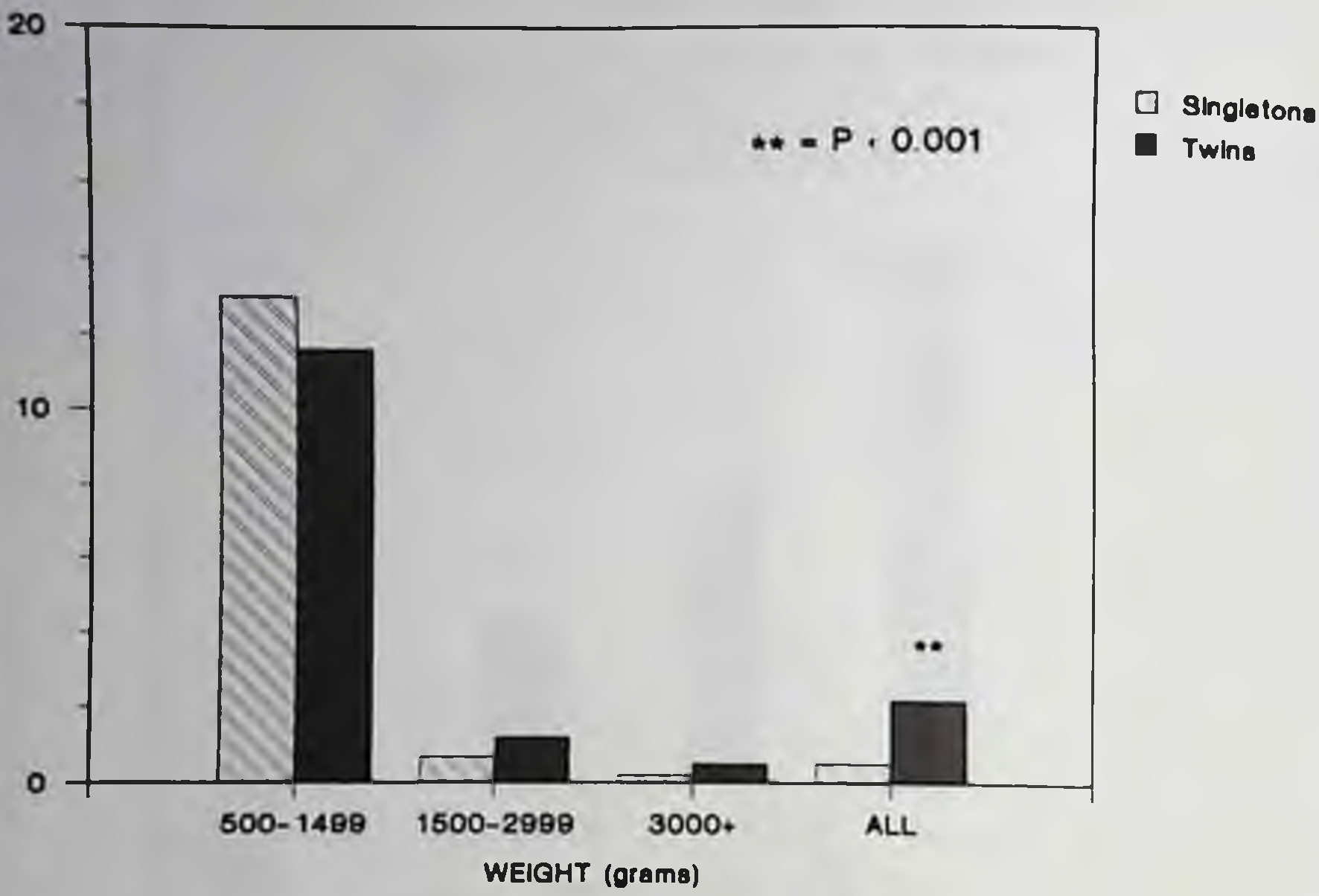


Figure 6. Incidence of neonatal seizures in twins and singletons (* = $p < 0.05$; ** = $p < 0.001$).

higher incidence of seizures when compared with singletons ($p < 0.001$, Fig. 6). When adjustment is made for birth weight, group II and III twins had a higher incidence of seizures (though owing to small numbers the difference was not statistically significant in group III). There was no difference between the first and second twins or between male and female twins.

Our data indicate an increased risk for neurologic morbidity in larger twins. Seizures are generally a reflection of intracerebral hemorrhage, hypoxic–ischemic encephalopathy, or malformation. We speculate that the increased incidence of birth asphyxia in twins may be responsible for the seizures.

Congenital Anomalies

The incidence of congenital anomalies among twins (2.5 per cent) and singletons (2.5 per cent) was found to be similar in our study population. A higher incidence of congenital anomalies in twins has been reported[30] by some; other studies did not report the same.[30] It is thought that the higher incidence is confined to monozygotic twinning. In our study sample we could not ascertain zygosity with certainty. However, when we segregated the infants as like-sexed versus unlike-sexed twins, we still did not find any increase in the incidence of anomalies in twins. Congenital anomalies are more likely to be picked up if multiple sources of ascertainment (besides a routine newborn examination at birth) are used and also if there is a longer followup allowing for the anomalies to manifest. The risk for malformations as well as the risk for dizygotic twinning increases with

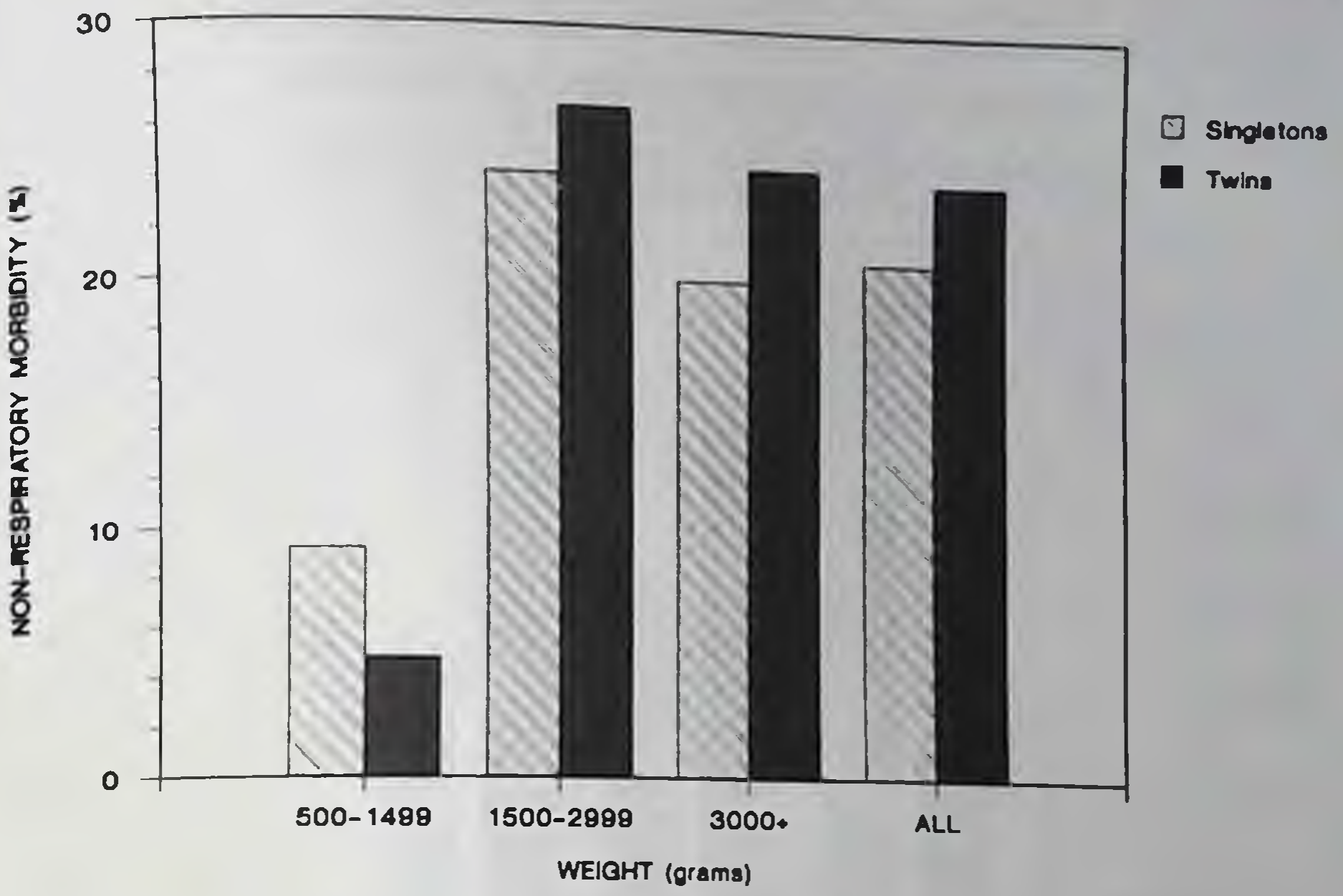
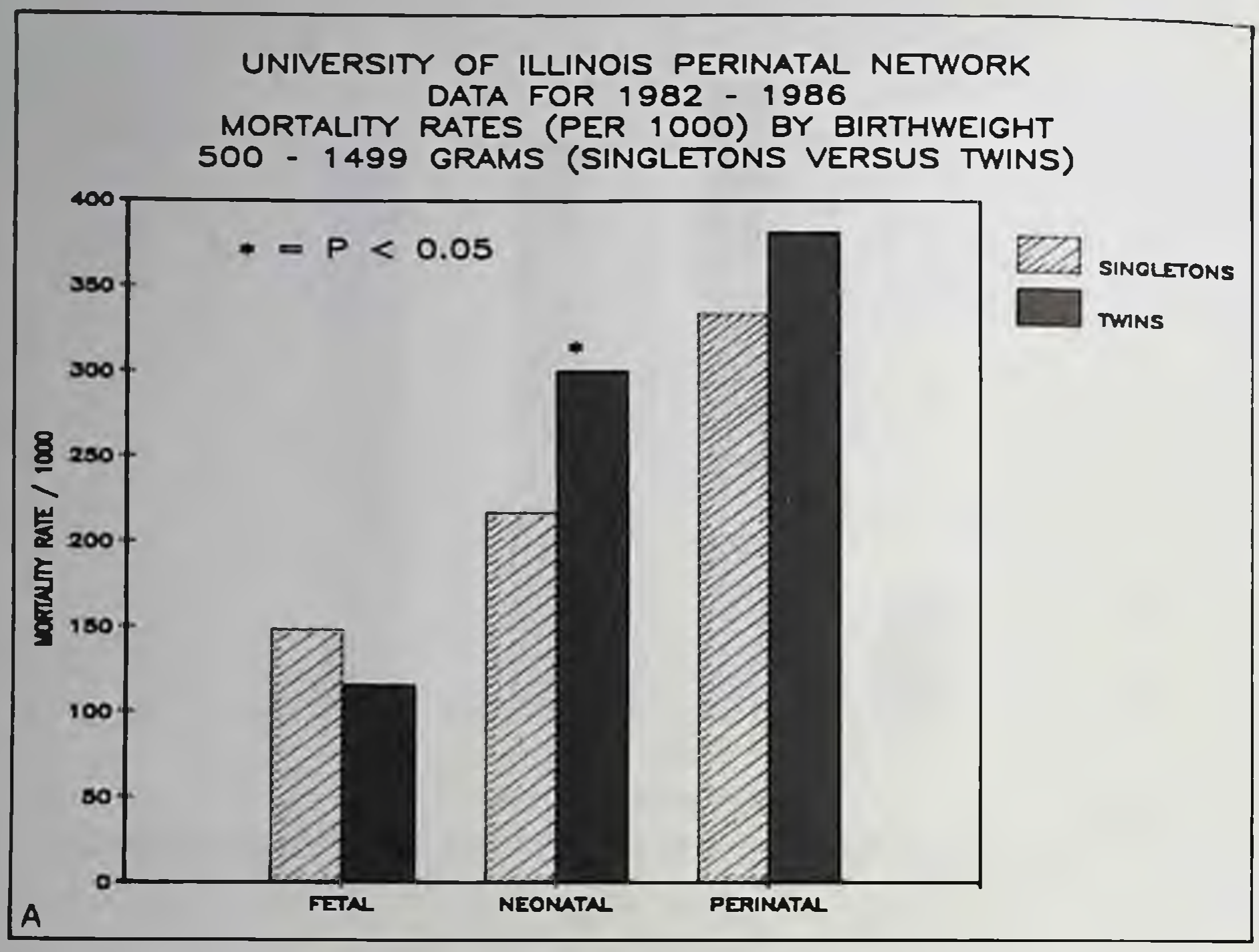


Figure 7. Incidence of nonrespiratory morbidity in twins and singletons (* = $p < 0.05$; ** = $p < 0.001$).

advanced maternal age; therefore, the increased malformation rate in twins is to be expected. Windham et al.[58] found no evidence of increased risk for malformations in twins after adjusting for maternal age.

Monozygotic twins are most often discordant for anomalies,[15, 30] the concordance rate being only 9 to 18 per cent. Some anomalies, such as conjoined twins and acardia[30] are unique to twins. Other anomalies occur in both twins and singletons but with increased frequency in twins. Neural tube defects, hydrocephalus congenital heart disease, malformation of the urogenital sinus, chromosomal abnormalities, and single umbilical artery all occur more commonly[30] in twins. Twins are also more likely to be subject to deformational stresses in utero. Minor foot abnormalities and skull asymmetry are more prevalent in them.[30]

A majority of monozygotic twins have monochorionic placenta[25] and therefore have a high chance of vascular connections between the two twins. This common chorionic vasculature makes them prone to the twin transfusion syndrome with the associated discordant growth, abnormal blood volume, and cardiovascular function. It has recently been reported that at least some of the discordant structural defects in monozygous twins may be the result of vascular insults via this shared circulation.[24] Death of one twin *in utero* with possible reembolization and regional ischemia in the surviving twin may be responsible for defects such as aplasia cutis,[35] horseshoe kidney, hy-


UNIVERSITY OF ILLINOIS PERINATAL NETWORK
DATA FOR 1982 - 1986
MORTALITY RATES (PER 1000) BY BIRTHWEIGHT
500 - 1499 GRAMS (SINGLETONS VERSUS TWINS)
* = P < 0.05
MORTALITY RATE / 1000
400
350
300
250
200
150
100
50
0
*
*
SINGLETONS
TWINS
FETAL
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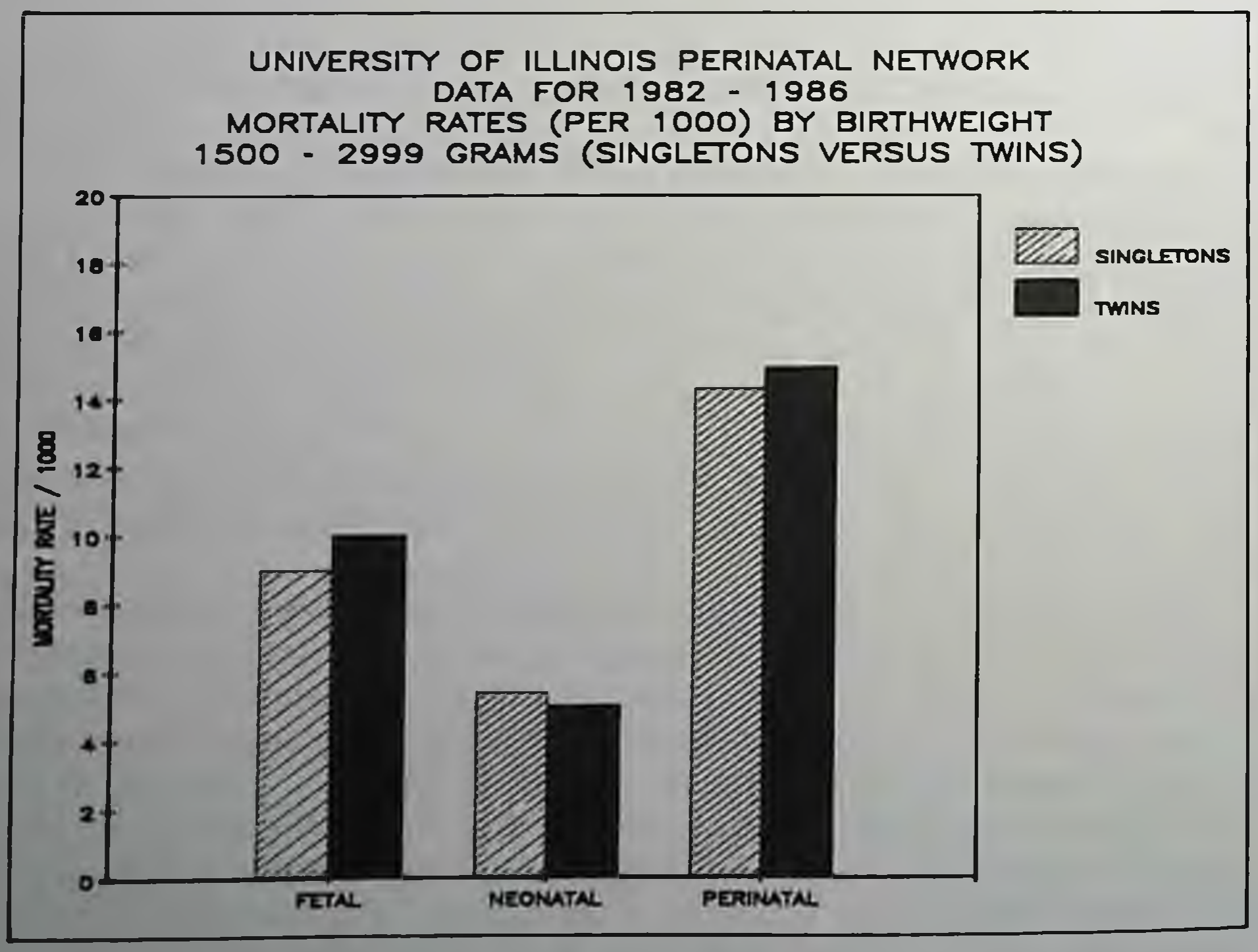
UNIVERSITY OF ILLINOIS PERINATAL NETWORK
DATA FOR 1982 - 1986
MORTALITY RATES (PER 1000) BY BIRTHWEIGHT
1500 - 2999 GRAMS (SINGLETONS VERSUS TWINS)
MORTALITY RATE / 1000
20
18
16
14
12
10
8
6
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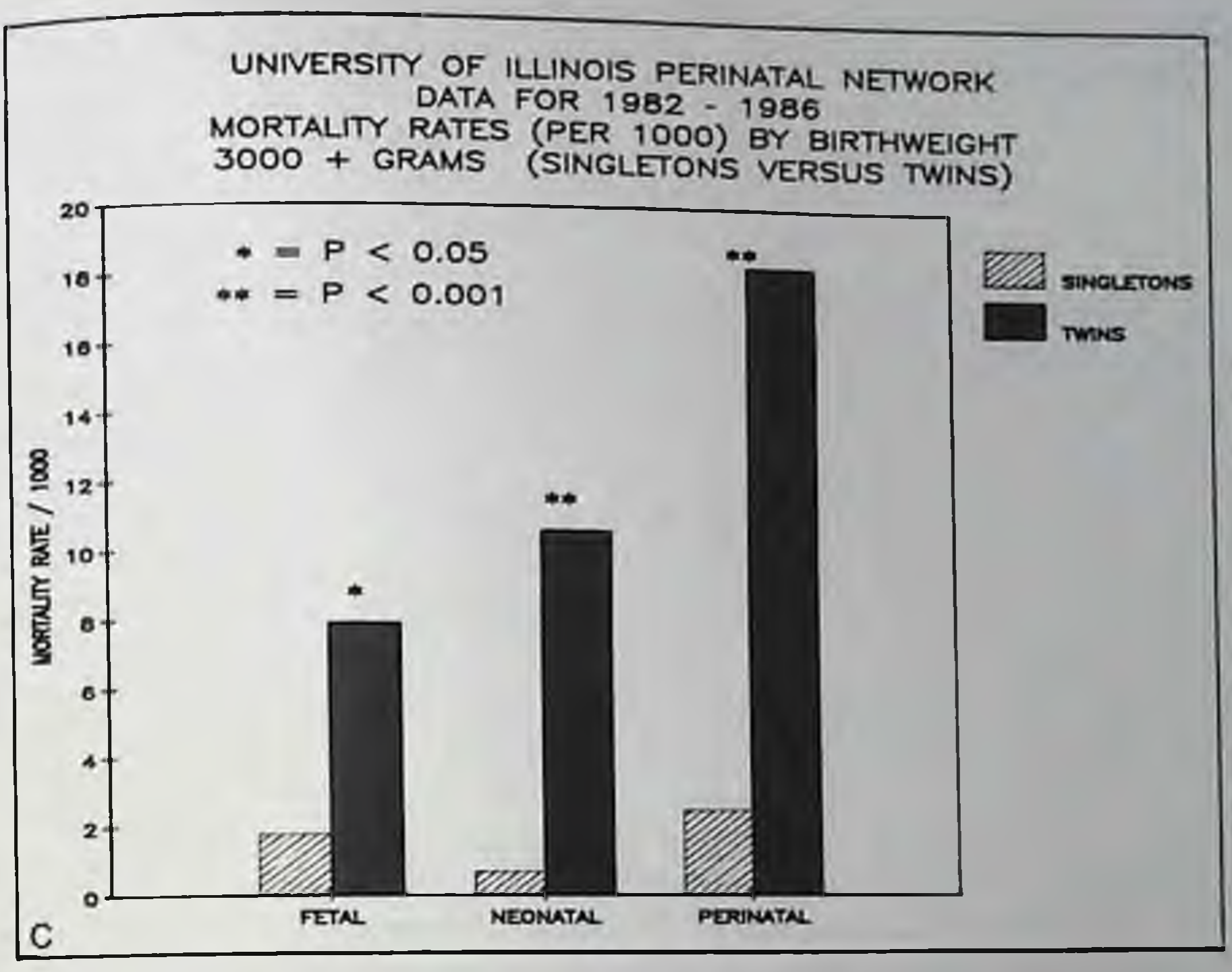
SINGLETONS
TWINS
FETAL
NEONATAL
PERINATAL



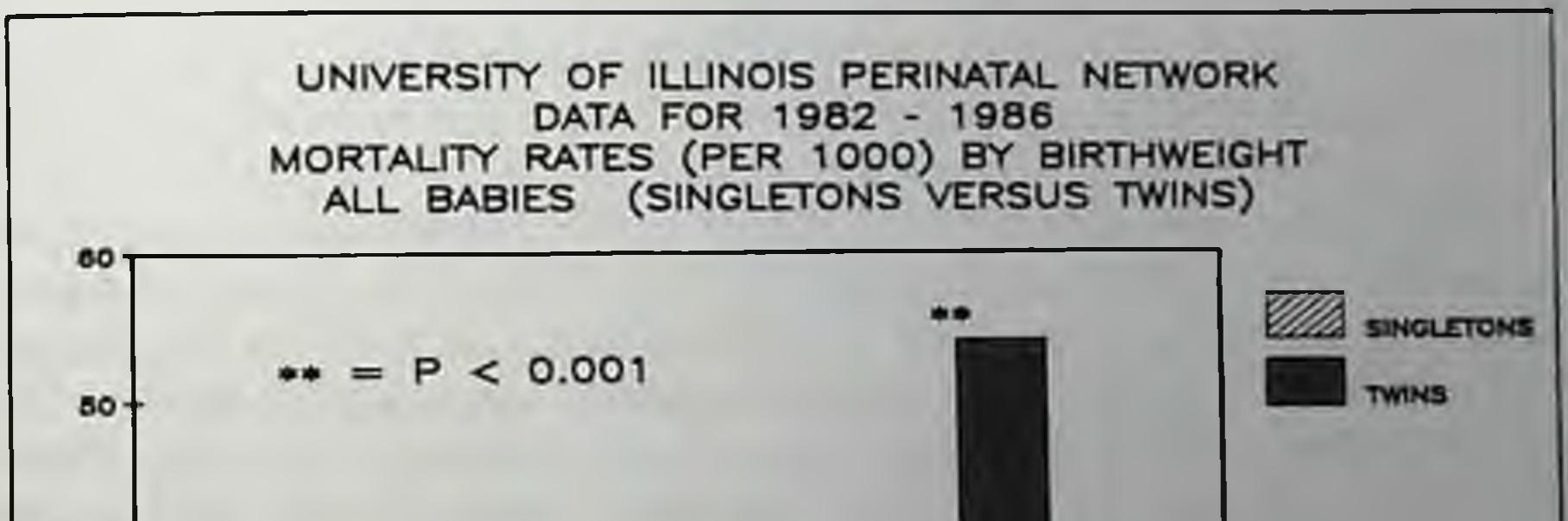


Figure 8. Fetal, neonatal, and perinatal mortality rates for twins and singletons (* = $p < 0.05$; ** = $p < 0.001$).

dranencephaly,[24] porencephaly, multicystic encephalomalacia,[61] intestinal atresia, limb amputation, and hemifacial microsomia.[30]

MORBIDITY

We studied the incidence of any significant diagnosis/morbidity (Table 1) in our study population. We found that 47 per cent of twins had some morbidity as compared to 26.6 per cent of singletons. However, when we excluded respiratory ailments, there were no significant differences between the two groups (Fig. 7). There were also no differences after adjusting for birth weight. Our data are consistent with those of Ho and Wu[23] who found a 50 per cent incidence of total morbidity in twins. We also found no differences in the incidence of morbidity between twins by birth order or by sex. Clarkson[9] also found excess morbidity in twins overall but no difference after adjusting for birth weight and gestation.

MORTALITY

Twins contribute disproportionately to perinatal mortality. It has been estimated that 10 per cent of the perinatal mortality rate is contributed by twins.[42] In our study twins accounted for 12.6 per cent of the perinatal mortality though they accounted for only 2.5 per cent of the population.

It is well known that twins have a 3 to 11 times higher perinatal mortality rate than do singletons.[9, 21, 23, 36, 44, 62] In our study the perinatal mortality rate (per 1000) was 54 for twins and 9.1 for singletons. The perinatal mortality of twins has remained significantly higher than for singletons over the last three decades even though the overall rates have declined and causes of the perinatal mortality have changed. Perinatal mortality rates in the early 1960s were 120 to 130 for twins and 30 to 35 for singletons.[41] In this period the major causes of death were chorioamnionitis, asphyxia, twin transfusion, placental infarcts, congenital anomalies, hydramnios, pneumonia, cord compression and birth trauma.[41] In more recent studies excess mortality rate in twins is thought to be the consequence of prematurity and low birth weight.[8, 23, 36, 44] Birth weight or gestational age adjusted mortality rates for twins have been reported to be no different for twins and singletons.[9, 23, 36]

We plotted the perinatal mortality rates by gestational age groups and found that twin mortality closely approximates singleton mortality till 37 weeks' gestation. At this point twin mortality far exceeded the mortality for singletons. We also analyzed the fetal, neonatal, and perinatal mortality rates by the birth weight groups (I, II, and III) previously described (Fig. 8). We found no difference in the mortality rates in groups I and II (besides a higher neonatal mortality rate in group I twins). In the largest birth weight twins (group III) fetal ($p <$

0.05), neonatal ($p < 0.001$), and perinatal ($p < 0.001$) mortality rates for twins were significantly higher than for singletons. The neonatal mortality rate for the larger twins (group III) was higher than in the preceding weight group (II) even though the difference was not statistically significant. Seventy-four per cent of the total perinatal mortality in twins was accounted for by twins with birth weight less than 1500 gm. It is evident that prematurity and the associated complications accounted for the bulk of the mortality in twins. It is also evident that more mature twins contributed disproportionately to perinatal mortality in twins. Some recent studies have reported an increased incidence of near-term fetal deaths[4, 52] in twins. MacGillivray ascribed the high incidence of near-term fetal deaths in twins to intrauterine growth retardation[33] and thought that if both babies were well grown, there was no increased risk. The high perinatal mortality in the more mature twins in our series cannot be ascribed to intrauterine growth retardation as the high mortality rate also was seen in twins with birth weight greater than 3000 gm. It has been suggested that postmaturity may be occurring 2 to 3 weeks earlier in twins.[48] That maturation may be occurring at an advanced rate in twin fetuses is also corroborated by evidence of advanced ultrasonic maturation of the placenta in twin pregnancy.[45] The findings of high neonatal mortality in larger twins has never been reported before to the best of our knowledge.

It is known that acute and chronic uteroplacenta insufficiency is more prevalent in twin pregnancy.[47] Twins may be growing beyond the capacity of their uteroplacental reserves as they grow bigger. This may be responsible for the stress experienced by the large twin fetuses.[25] Placental and cord abnormalities are also more common in twins. Intrapartum problems like interlocking twins, cord prolapse. abnormal fetal position, difficult delivery, and birth trauma are all known to be more common in twins.[47] It can be well appreciated that in the larger infants these factors may assume greater importance. All these factors associated with the stress of labor and the marginal uteroplacental reserve can be important antecedents of birth asphyxia. This may present as low Apgar scores, respiratory distress, meconium aspiration syndrome, persistent pulmonary hypertension of the newborn or as fetal or neonatal demise depending on the time and severity of the asphyxial insult. That this line of reasoning is valid is supported by our finding of a high incidence of low Apgar scores, respiratory disorders, and even seizures in larger twins.

In our study there was no difference in mortality between the first- and second-born twins. This is contrary to what earlier authors had found,[13, 23, 60] but is consistent with more recent reports[6, 36] and is probably the result of better perinatal care. There was no observable difference in mortality between male and female twins.

SUMMARY

Some epidemiologic characteristics of twin pregnancies and twin infants have been reviewed. We found that twins are prone to be born

prematurely and have lower birth weights than their singleton counterparts after 30 to 34 weeks of gestation. Twins are also more prone to birth asphyxia, hyaline membrane disease, respiratory disorders, and seizures. Congenital anomalies and nonrespiratory morbidity were not found to be increased in twins. Twins have a six times higher perinatal mortality rate than do singletons. This is accounted for by prematurity in the main. A part of the excess mortality in twins is accounted for by a higher mortality in larger, near-term twins. Efforts should be directed toward decreasing the incidence of prematurity in twins and understanding and managing the problems of near-term twins better.

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Neonatal Problems in Twins

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> We are faced with the undeniable fact
> that the human species is not designed to
> carry more than a single fetus *in utero*
> with any degree of biologic grace.
>
> CHARLES H. HENDRICKS[40]

The higher incidence of neonatal problems in twins compared with infants born singly supports the notion that multiple gestation is a hazardous deviation from the human norm of singleton pregnancy. Intrauterine growth retardation, prematurity, congenital malformations, and perinatal mortality are all more common in twins than in singletons.[77] The frequency with which some of these problems occur among twins is affected by zygosity and by placentation. An understanding of the embryology of twinning aids in understanding the occurrence of some of its complications.

EMBRYOLOGY, ZYGOSITY, PLACENTATION

Dizygotic twinning is caused by the fertilization of two ova. The resulting blastocysts generate separate amnions, chorions, and placentas. If their implantation sites are proximate, the placentas may fuse; however, vascular communications do not occur between the two circulations, and the portion of placental tissue belonging to each twin is generally easy to determine by simple inspection. Monozygotic twinning is caused by the splitting of a single fertilized ovum sometime during the first 2 weeks after conception. Early division results in dichorionic twins. Later splitting produces monochorionic but diamniotic placentation, which is the type most commonly found among monozygotic twins. Still later division results in monochorionic monoamniotic twins. Splitting even later produces conjoined twins. Dichorionic monozygotic twins have different placentas, which can

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be separate or fused. As with the fused placentas of dizygotic twins, vascular anastomoses do not occur, and the part of the placenta belonging to each twin usually can be distinguished grossly. Monochorionic twins have a common placenta, which invariably has vascular communications between the two circulations.[4–6, 37, 47, 85]

It is evident from embryologic events that monochorionic twins should always be monozygotic. This is confirmed by studies showing that monochorionic twins are invariably of the same sex and have identical blood groups.[85] In the United States, about one third of twins are monozygotic and about two thirds are dizygotic.[44, 85] Sixty to seventy per cent of monozygotic twins (20–25 per cent of all twins) are monochorionic.[4, 20, 31, 69, 85] Studies comparing the incidence of various complications in monochorionic and dichorionic twins are fairly numerous because placentation can be determined relatively easily by pathologic examination of the placenta. Studies examining the effects of zygosity are fewer because the determination of zygosity in like-sex dichorionic twins has relied on red blood cell antigen and enzyme testing.[20, 31, 69, 85] Often a small group remains in which zygosity cannot be established definitely. Future studies using HLA typing may allow better zygosity determination.[101]

PERINATAL MORTALITY

Perinatal mortality in twins is more than four times higher than in singletons.[31, 41, 71, 81] The perinatal mortality in monochorionic twins is approximately two to three times higher than in dichorionic twins.[6, 37, 69, 71, 73] Nylander showed that the perinatal mortality rate in dichorionic monozygotic twins (186 per 1000) was only slightly higher than in dizygotic (thus, all dichorionic) twins (151 per 1000), whereas that in monochorionic monozygotic twins (310 per 1000) was more than twice as high as in dizygotic twins.[81] These data strongly implicate an effect of placentation, rather than zygosity, on perinatal mortality among twins. While accounting for only 1.5 per cent of all twins, monoamniotic monochorionic twins have a perinatal mortality of approximately 30 to 50 per cent.[6, 69] The high risk for perinatal loss of monoamniotic twins has been explained by cord problems, including entwinement, knotting, and wrapping around the co-twin. In cases of breech–vertex presentations, the twins may become locked, the head of the second twin descending before the head of the first, making vaginal delivery extremely difficult.[30, 66] D'Alton et al. reported two sets of diamniotic monochorionic twins with rupture of the dividing amniotic membranes resulting in cord complications (e.g., entanglement or knotting) similar to those seen in monoamniotic twins.[22]

PREMATURITY, LOW BIRTH WEIGHT, INTRAUTERINE DEVELOPMENT

In reviewing perinatal mortality in twins, Chaurasia noted that aproximately 80 per cent of deaths occurred at less than 37 weeks'

gestation and approximately 90 per cent were associated with low (<2500 gm) birth weight.[17] Prematurity and low birth weight are obviously covariant factors; however, intrauterine growth retardation also contributes to low birth weight.

Approximately 40 to 55 per cent of twin deliveries occur before 37 weeks' gestation.[14, 40, 51] The fact that birth weight specific mortality rates are similar or even somewhat lower for twins compared to singletons suggests that it is the high incidence of premature births that is largely responsible for the excess of neonatal deaths in twins.[18, 41, 62, 85]

The incidence of low birth weight in twins is approximately 50 to 60 per cent, a figure that is five to seven times higher than the incidence of low birth weight in singletons.[41, 51, 63] Birth weights, lengths, and head circumferences of twins born at various gestational ages have been used to construct intrauterine growth curves for twins. Acceptance of such data as normal standards presupposes that whatever factors result in premature birth are not also responsible for aberrations of growth. Twins show a normal growth pattern for length and head circumference, with values falling into the low normal range for singletons. However, weight begins to deviate from the singleton curve early in the third trimester. The weights of monochorionic twins are consistently lower than those of dichorionic twins.[27, 37, 40, 56, 72, 73] Corney et al. found that among survivors, the mean birth weights of dichorionic and monochorionic monozygotic twins were similar, both being markedly less than the mean birth weight of dizygotic twins. These data suggest an effect of zygosity, rather than placentation, on birth weight, at least among surviving twins.[20]

Greater degrees of intrapair variation in birth weight have been noted among monochorionic than among dichorionic twins.[28, 37, 73] Erkkola et al. reported that perinatal mortality is 2.5 times higher in twins showing intrapair birth weight differences greater than 25 per cent of the weight of the larger twin when compared with twins showing smaller intrapair birth weight discrepancies.[25]

In the population studied by Manlan et al., the incidence of intrauterine growth retardation, defined as a birth weight more than two standard deviations below the singleton mean for gestational age, was about ten times higher in twins than in singletons.[59] Intrauterine growth retardation was noted by Gruenwald to occur more frequently in monochorionic than in dichorionic twins.[37] Hendricks showed that, for both premature and term twins, perinatal mortality was increased in infants whose birth weights were lower than 1 standard deviation (SD) below the mean in comparison with infants whose birth weights were within 1 SD of the mean or greater than 1 SD above the mean.[40]

Consistent with the notion that multiple pregnancy is a deviation from the human norm, most workers use singleton rather than twin standards to evaluate intrauterine growth in twins. Marivate and Norman suggest that intrauterine growth retardation be diagnosed in a twin when the birth weight is less than the tenth percentile for gestational age on the singleton weight curve or when the birth weight

is less than 85 per cent of the birth weight of the co-twin, even if the smaller twin's birth weight is above the tenth percentile.[61]

Congenital anomalies are generally reported to be more common in twins than in singletons, the increase being entirely due to a higher incidence in monozygotic twins.[40, 57, 70] The anomaly rate, like perinatal mortality, was shown by Hendricks to be highest in association with birth weights lower than 1 SD below the mean in both premature and term twins.[40]

Because of the increased rates of mortality and anomalies, attempts have been made to detect intrapair size discrepancies and fetal growth retardation in twin pregnancies by antenatal ultrasound examinations. Erkkola et al. found that biparietal diameter measurements identified intrapair growth discordancy with a sensitivity of only 35 per cent.[25] Estimates of Secher et al. made by combining biparietal diameter and abdominal diameter measurements had a sensitivity of only 62 per cent in the detection of intrauterine growth retardation in twins.[95] Farmakides et al. measured umbilical artery flow velocity by continuous-wave Doppler ultrasound and found that intrapair differences in the ratio of systolic to diastolic velocities could identify intrapair weight differences of greater than or equal to 350 gm, with a sensitivity of 73 per cent.[26]

TWIN TRANSFUSION SYNDROME

The vascular anastomoses found exclusively and probably universally in monochorial placentas are responsible for much of the excess morbidity and mortality associated with monochorionic twins. The most common type of anastomoses are between arteries from the two circulations.[32, 96] When a cotyledon is supplied by an artery from one twin and drained by a vein from the other, the potential exists for transfer of significant quantities of blood from the twin on the arterial side (donor) to the twin on the venous side (recipient) of the connection. The effects of the fetofetal transfusion on each of the twins probably depends on the period over which the transfer of blood occurs.

Clinically the twin transfusion syndrome is diagnosed when twins exhibit a hemoglobin difference of more than 5 gm per 100 ml.[100] It may be suspected when one twin appears plethoric and the other pale at the time of birth. In some cases, there also will be discordance in birth weight, the recipient twin always being larger, which indicates that chronic intrauterine transfer of blood has resulted in significant growth retardation of the donor twin. Such pregnancies are often complicated by hydramnios in the amniotic sac of the recipient and oligohydramnios in that of the donor.[74] When the intrapair birth weight difference is small (≤300 gm), either the donor or the recipient can be the larger and the transfer of blood is thought to have occurred acutely, perhaps from early and late clamping of the umbilical cords of the donor and recipient, respectively.[53]

Hydramnios associated with the recipient twin in chronic fetofetal

transfusion can be severe and lead to preterm labor.[107] Deaths among twins with transfusion syndrome are usually due to prematurity with respiratory distress.[74] Postmortem studies on pairs of twins who have died with transfusion syndrome have provided the basis for speculation on the pathophysiology underlying its clinical features.[74–76] Cardiac weights are above normal for recipient twins and subnormal for donors, presumably resulting from longstanding hypervolemia and hypovolemia, respectively. Medial smooth muscle in small systemic and pulmonary arteries is increased in recipients and decreased in donors, indicating the antenatal presence of hypertension in the former and hypotension in the latter. The kidneys of the recipients show glomerular enlargement and a greater proportion of mature glomeruli when compared with the donors. The combined effects of hypervolemia, hypertension, and increased urine output could explain the common finding of polyhydramnios in the amniotic sacs of recipient twins. Conversely, the oligohydramnios often associated with donors may result from a combination of hypovolemia, hypotension, and oliguria. Body length and weight are not significantly lower in donor twins when compared with recipients; however, heart, liver, kidney, pancreas, and fetal adrenal cortex are significantly smaller in the donors. The pattern of body and organ size seen in donor twins is similar to that seen in infants who have growth retardation associated with placental insufficiency.[76] This suggests that donor twins experience intrauterine malnutrition, probably from the shunting of nutrients to the recipients. A report of twins with evidence of twin transfusion syndrome (birth weights, 2.7 and 1.56 kg; hemoglobins, 21.5 and 7.9 gm per 100 ml, respectively) in which values for total protein, albumin, transferrin, alpha-1 antitrypsin, and IgG were markedly lower in the donor than in the recipient is consistent with one-way transfer of plasma proteins in this syndrome.[12] Some of the problems encountered in infants with growth retardation due to placental insufficiency, especially neonatal hypoglycemia,[29] can be anticipated in small donor twins following chronic fetofetal transfusion.

Two cases of twin transfusion syndrome have been described in which the donor twins had "blueberry muffin" skin lesions, which showed dermal erythropoiesis on histologic examination.[94] Neither infant showed evidence of intrauterine infection and the persistence of cutaneous hematopoiesis was thought to be an unusual response to severe longstanding anemia. Hydrops fetalis can complicate fetofetal transfusion. It is usually seen in the donor, but it also has been described in the recipient only,[108] and in both members of a pair.[58]

In addition to the transfer of blood from a living donor to a living recipient, vascular anastomoses between monochorionic twins can serve as channels for the passage of thromboplastic substances to a living recipient following the intrauterine demise of a co-twin. The transferred material can initiate widespread intravascular coagulation, with resultant thrombosis, infarction, and necrosis in the organs of the recipient.[6, 68] This sequence of events may produce intrauterine death,

severe anemia, renal cortical necrosis,[87] encephalomalacia,[22] and disruptive structural defects.[93]

The most devastating effect of vascular connections in a monochorionic placenta is the formation of an acardiac or amorphous fetus.[5, 93, 102] This occurs in association with large artery–artery and vein–vein anastomoses between the anomalous fetus and its usually normal co-twin. Early in gestation the pressure in the artery of the normal twin exceeds that in the artery of the other. The circulation in the recipient twin thus is reversed. Blood enters the recipient through an umbilical artery and leaves through the umbilical vein to drain into a large placental vein–vein anastomosis. Low perfusion pressure, desaturation, and circulatory reversal in the recipient lead to multiple severe structural defects, producing an acardiac or amorphous fetus. The initially normal donor twin must perfuse both fetal circulations and thus may develop cardiac hypertrophy, congestive heart failure,[98] or hydrops fetalis.[42, 54]

In recent years, the availability of diagnostic ultrasound has made antenatal detection of chronic fetofetal transfusion possible. Sonographic evidence of twin transfusion syndrome includes identification of a twin gestation with a single placenta and like-sex fetuses; biometric assessments indicating significant fetal size differences; intrapair discrepancies in estimates of amniotic fluid volume and fetal activity; and possibly the presence of fetal edema, serous effusions, cardiac enlargement, and hepatomegaly, suggesting congestive heart failure and hydrops fetalis.[10, 107, 108] Using continuous-wave Doppler ultrasound to measure umbilical artery flow velocities, Farmakides et al. noted the presence of one unusually high and one unusually low systolic/diastolic ratio in the respective members of two pairs of twins with fetofetal transfusion.[26]

Management of the twin transfusion syndrome is determined by the clinical presentation of the twins at birth.[97, 100] In cases of acute fetofetal transfusion, the recipient and the donor may show signs of volume overload and shock, respectively. Partial exchange transfusion using fresh frozen plasma is the treatment of choice for the recipient.[8] Rapid volume expansion with crystalloid or colloid solutions followed by simple transfusion with packed red blood cells is appropriate treatment for the donor. In cases of chronic fetofetal transfusion, significant growth retardation may be seen in the donor, and hypoglycemia may occur. If such an infant is vigorous and stable, it may be possible to avoid this complication by early and frequent enteral feedings and frequent estimations of blood glucose values.[100] When a donor twin with significant growth retardation is unstable or has a history of perinatal hypoxemia or hypotension, it may be necessary to withhold enteral feedings for a time; instead, continuous infusion of dextrose solutions, initially calculated to provide 5 mg per kg per min of glucose, should be administered. The infusion rate can be adjusted subsequently based on blood glucose measurements. In both acute and chronic fetofetal transfusions, increased red blood cell mass in the recipient can result in increased bilirubin production. Tan et al. found

that hyperbilirubinemia in recipient twins is the most common complication of fetofetal transfusions.[100] Frequent serum bilirubin measurements and appropriate use of phototherapy may prevent the need for exchange transfusion. Rarely, either or both of the twins involved in a fetofetal transfusion may present with hydrops fetalis. Hydropic infants are difficult to manage and mortality is high. Affected infants usually show severe depression at birth.[45] They require vigorous resuscitation and may need immediate drainage of serous effusions to reduce respiratory or cardiac embarrassment. Neonatal management includes estimation of intravascular volume by aortic and central venous pressure monitoring[83, 84] and administration of diuretics and fluids accordingly; measurements of total serum protein, albumin,[67] and hemoglobin, as well as administration of blood components to correct low levels; and, of course, the supportive measures usually employed to maintain adequate ventilation, blood pressure, glucose,[99] and electrolyte levels, and an optimal thermal environment. When one of twins is a macerated stillborn or fetus papyraceus, the living twin must be evaluated carefully for disseminated intravascular coagulation, signs of renal cortical necrosis, cystic encephalomalacia, and structural malformations. In the rare event of the delivery of an acardiac or amorphous fetus, the surviving co-twin should be assessed for signs of cardiac decompensation and congestive heart failure.

CONGENITAL MALFORMATIONS

Estimates of the frequency of anomalies in twins vary among studies because of differences in defining and ascertaining congenital defects.[57] Several large series have demonstrated an increased prevalence of anomalies at birth in twins when compared with singletons.[40, 70] The effect of zygosity on the incidence of malformations can be inferred by comparing incidences in like-sex (approximately half of whom are monozygotic) and unlike-sex (all dizygotic) twins.[39, 55] In other studies, zygosity actually is established for most pairs by placental and blood group studies.[70] Both methods consistently have shown that any excess of malformations found in twins is due entirely to a highly significant increase among infants from monozygotic pairs; twins known to be dizygotic have rates similar to singletons. Comparing the frequencies of specific types of anomalies, twins usually are found to have the greatest increases in central nervous system (CNS), cardiovascular system, and gastrointestinal tract defects.[39, 55, 70] Melnick and Myrianthopoulos showed that among twins who were known to be monozygotic, those with dichorial placentas had an incidence of congenital anomalies similar to those with monochorial placentas.[65] Thus, the occurrence of congenital malformations shows a significant association with zygosity but not with placentation.

Structural Defects

Schinzel et al. categorized structural defects in monozygotic twins based on three presumed etiologies: deformations imposed late in

gestation by the constraint of limited intrauterine space, disruption of normal blood flow due to placental vascular communications, and early, localized defects in morphogenesis.[93]

Late deformations are the result of mechanical pressure on normally formed structures. Plagiocephaly, facial asymmetry, torticollis, and positional foot defects are all possible effects of growing fetuses vying for space.[13, 48] Regardless of zygosity, it appears that "two is a crowd" after 34 weeks of intrauterine togetherness. Hay and Wehrung found that the incidence of positional foot defects was similar in like-sex and unlike-sex twins, both being higher than in singletons.[39] Presumably, the occurrence rates of other structural deformations also are similar for monozygotic and dizygotic twins.

Some of the effects of abnormal blood flow due to vascular communications in monochorial placentas already were mentioned in the discussion of twin transfusion syndrome. The anomalies found in acardiac fetuses probably result from very early reversal of flow through placental anastomoses. Recent transfer of thromboplastic material from a macerated fetus by way of vascular connections can cause disseminated intravascular coagulation to be present at birth in the surviving monochorionic co-twin.[68] In multiple gestation with earlier fetal demise, the end results of prior thrombosis or embolization of necrotic material can be seen after birth in the survivor. Occlusion of the carotid or middle cerebral arteries may lead to hydrancephaly and porencephaly, respectively, probably secondary to the resorption of previously necrotic brain tissue.[48] Diffuse involvement of smaller cerebral arteries can result in multicystic encephalomalacia.[109] Melnick reported cerebellar necrosis in an infant born 5 weeks after the death of a co-twin.[64] Affected infants may present with seizures soon after birth and subsequently show microcephaly, mental retardation, and cerebral palsy.[24, 43, 64] Saier et al. reported a case of ileal atresia in association with a fetus papyraceus and monochorionic placentation.[90] It is postulated that mesenteric arterial occlusion early in pregnancy can lead to infarction, resorption, and atresia of the portion of bowel supplied by the occluded artery.[48] Two infants, both products of monochorionic twin pregnancies in which the co-twin was a fetus papyraceus, were noted by Mannino et al. to have symmetric trunk and limb skin defects resembling the lesions of aplasia cutis congenita that are sometimes seen on the scalp. It was proposed that these unusually distributed defects were the result of degeneration due to vascular occlusion by emboli transferred from the dead co-twin early in gestation through placental anastomoses.[60] Other structural anomalies that have been reported in monochorionic twins with intrauterine demise of a co-twin include spinal cord transection, horseshoe kidney, hemifacial microsomia, and terminal limb defects.[43, 48, 93]

Since vascular anastomoses are found only with monochorionic placentation, a higher incidence of disruptive defects would be expected in monochorionic than in dichorionic monozygotic twins. The fact that Melnick and Myrianthopoulos found no such increase for all congenital anomalies in monozygotic twins suggests that disruptive

lesions represent a very small portion of total malformations.[65] Nevertheless, in cases of multiple gestation with intrauterine demise of one fetus, the surviving twin should be evaluated carefully for disruptive structural defects. Conversely, when an infant is noted to have one of the anomalies that have been described in single survivors of monochorionic gestations, the placenta should be examined closely for a fetus papyraceus. Because vascular accidents are random events, the recurrence risk is minimal, and parents can be counseled accordingly.[43, 48, 93]

The third category of structural malformations comprises early defects of morphogenesis. The etiology of such anomalies is believed to be closely related to the monozygotic twinning process itself. The most obvious example of such a relationship is seen in conjoined twinning—an anomaly that is probably due to incomplete division of the blastocyst.[7] The fact that conjoined twins also have an extremely high incidence of structural anomalies presumably due to defective morphogenesis[48, 57] supports an association between the twinning process and this type of structural defect. Because blastocyst fission probably is not a normal event, monozygotic twinning itself might be considered a congenital malformation.[43] The factor that initiates zygotic division might persist to inflict further developmental damage during embryogenesis.[93] An alternate explanation is that monozygotic twinning interrupts the normal progression of developmental events, producing in these fetuses an increased susceptibility to environmental factors whose teratogenic potential is too low to cause damage in nondisrupted embryos.[65] Malformations in this group include neural tube defects, holoprosencephaly, the VATERR association (vertebral anomalies, imperforate anus, tracheoesophageal fistula, renal anomalies and radial anomalies), congenital heart disease, extrophy of the cloaca, gonadal dysgenesis, and sirenomelia.[48, 93]

Conjoined Twins

When monozygotic twinning occurs late in the second week after conception, incomplete division of the embryos may occur, resulting in conjoined twins.[110] As would be expected from a review of embryonic events, conjoined twins are always monoamniotic and monochorionic.[88] The twins are always joined at identical points and are classified according to the site of union: approximately 40 per cent are joined at the chest (thoracopagus), approximately 34 per cent at the anterior abdominal wall (xiphopagus or omphalopagus), approximately 18 per cent at the buttocks (pygopagus), approximately 6 per cent at the ischium (ischiopagus), and approximately 2 per cent at the head (craniopagus).[103] About 70 per cent of affected pairs are females.[7] Mirror imaging (i.e., situs inversus in one of the twins) occurs commonly,[21] and organs that are normally asymmetric appear more symmetric in conjoined twins.[79] Most of these infants are stillborn.[38, 88] In liveborn infants, prognosis depends on the extent of union especially with respect to shared organs. For example, successful separation of thoracopagus twins largely depends on the type of cardio-

vascular connections. Infants with pericardial or atrial connections are potentially salvageable, whereas those with ventricular connection usually have multiple cardiac defects and are nonviable.[46, 78, 79] Use of diagnostic ultrasound allows detection of this anomaly prior to delivery.[33, 49] Antenatal diagnosis of potentially viable conjoined twins gives the obstetric, neonatal, and surgical teams the opportunity to plan optimal care for both mother and infants.

Concordance

Heritability of an abnormality can be inferred when the concordancy rate in monozygotic twins exceeds the sibling recurrence risk or the concordancy rate in dizygotic twins.[7, 106] For a disorder like Down's syndrome, with a well-defined genetic etiology, the concordance in monozygotic pairs approaches 100 per cent. Twins are usually discordant for congenital malformations; however, the concordance rates for monozygotic twins are consistently higher than for dizygotic twins.[28, 70] This suggests that both genetic and environmental factors contribute to the occurrence of congenital defects in twins.

OTHER NEONATAL PROBLEMS

Premature infants are at higher risk for hyaline membrane disease (HMD), retinopathy of prematurity (formerly called retrolental fibroplasia or RLF), group B streptococcal septicemia, and necrotizing enterocolitis (NEC). The high incidence of prematurity and low birth weight in twins increases their risk for all of these complications.

Hyaline Membrane Disease

De la Torre Verduzco et al. reported that among infants born at less than 35 weeks' gestation, twins were twice as likely to develop HMD than were singletons. The incidence of HMD was twice as high in monozygotic as in dizygotic twins but was not significantly different in monochorionic than in dichorionic twins. The concordancy rate for HMD in monozygotic twins (80 per cent) was significantly higher than that in dizygotic twins (25 per cent). The authors postulated that the higher incidence and concordancy in monozygotic twins was due to a greater degree of prematurity; however, their study did not actually document such a difference.[23] Lung maturity can be assessed prenatally by amniotic fluid analysis for phospholipids. Norman et al. obtained amniotic fluid from the sacs of each member of 30 twin pairs at the time of cesarean delivery. They showed that prior to the onset of labor, there were no significant intrapair differences in phospholipid profiles, even in the presence of intrauterine growth retardation in one of the twins. However, when fluid was obtained during labor, some of the values for the first twin were significantly higher than those for the second.[80] Use of ultrasonic guidance and dye injection following removal of fluid from the first amniotic sac has made an-

tenatal double amniocentesis feasible in twin pregnancies.[2,9] In addition to phospholipid evaluation and prenatal diagnosis of genetic disorders, this technique should prove valuable for following amniotic fluid optical densities and performing intrauterine transfusions in Rh-sensitized twin pregnancies because it is known that there can be intrapair variations in the degree of hemolytic disease.[3]

Retinopathy of Prematurity

In a report of results of the Cooperative Study of Retrolental Fibroplasia and the Use of Oxygen, Kinsey noted striking increases in the incidence of RLF (now called retinopathy of prematurity or ROP) in infant of multiple births when compared with singletons. Active stages of ROP occurred 1.25 times more frequently. The incidence of cicatricial disease was three times higher. These differences were seen despite the fact that mean number of days in oxygen was lower, and mean birth weight and gestational age at birth were higher in infants of multiple births than in singletons.[52]

Group B Streptococcal Disease

Pass et al. looked at maternal and neonatal group B streptococcal colonization and infection in over 5000 singleton and twin pregnancies. Colonization rates were similar for both mothers and infants; however, the rate of early-onset group B streptococcal infection in low (<2500 gm) birth weight infants was nearly five times higher in twins than in singletons.[82]

Necrotizing Enterocolitis

In comparing the incidence of necrotizing enterocolitis in multiple gestation and singleton infants, Samm et al. found it to be three times higher in twins and triplets. Only one infant from each multiple-birth case was affected. Mean gestational age was significantly higher for the singleton infants, but mortality was similar.[92]

Subsequent Growth and Development

The common occurrence of prematurity, low birth weight, and intrauterine growth retardation in twins already has been discussed. In most cases, initial postnatal growth is rapid and twins progressively attain higher weight-for-age percentiles over the first year of life.[59, 76] Chamberlain and Davey compared measurements of twins and a random sample of singletons at a postnatal age of 22 months. They found that, although twins showed greater weight gain with respect to birth weight, mean weight remained slightly but significantly lower than mean weight in singletons. Mean height was also slightly lower in twins, but weight for height (body "build") was similar to singletons. Mean head circumferences were not significantly different.[16] Comparing the same groups of infants at 3½ years of age, Chamberlain and Simpson noted that mean weight and mean height were more significantly lower in twins compared to singletons than they had been at 22 months of age. At 3½ years, mean head circumference was slightly

but significantly lower in twins than in singletons. The authors concluded that most growth compensation in twins occurred during the first 2 years, then appeared to stop in the third.[15] Walther and Ramaekers followed postnatal growth for 3 years in normally grown term singleton infants and in term singleton infants with disproportionate (low weight for height) growth retardation. They found it useful to identify and follow growth retarded infants by calculating a ponderal index ([100 × weight in gm]/[length^3 in cm]). The mean ponderal index at birth was significantly lower in the infants with disproportionate growth retardation than in the normally grown controls. Differences in mean ponderal indices gradually decreased during the first year of life, and mean ponderal indices were similar in the two groups at 12 months of age. Subsequently, mean ponderal indices again diverged, and at 3 years of age mean ponderal index was again significantly lower in the growth-retarded infants than in the controls.[104] This pattern of relative growth for disproportionately growth-retarded singleton infants is very similar to that seen by Chamberlain and coworkers in twins who were followed for 3½ years after birth.

Among twins with large intrapair birth weight discrepancies, initial rapid postnatal growth of the smaller twin progressively reduces the percentage weight difference during the first few months of life.[73] Keet et al. followed postnatal growth for 3 to 9 years in 14 pairs of monozygotic twins who were discordant for birth weight. They noted that growth rates were normal for twin pairs who had birth weights greater than the tenth percentile (using monochorionic twin standards[76]) and birth weight differences of less than 20 per cent. In infants whose birth weights were less than the tenth percentile, a normal ponderal index (proportionate growth retardation) was associated with poorer postnatal growth than was a low ponderal index.[50] Babson and Phillips followed eight pairs of monozygotic twins who had intrapair birth weight differences of more than 25 per cent for 18 years postnatally. They noted that mean weight, height, head circumference, and standardized aptitude test scores remained significantly lower for the smaller twins of the pairs even into adulthood.[1] Record et al. showed an appreciably lower mean verbal reasoning score at 11 years of age in the smaller members of twin pairs who had birth weight differences of more than 700 gm when compared with the larger twins.[86] Thus it appears that among twins with large intrapair birth weight differences, the smaller members show persistently poorer growth and intellectual achievement than their co-twins.

Record et al. used verbal reasoning scores in the 11-plus examination as an index of intelligence. They found that mean scores in twins were lower than in singletons even when allowances were made for maternal age, previous siblings, birth weight, and gestational age. Score differences between twins and singletons amounted to about 4 points.[86] Unfortunately, twins may suffer severer deviations in both mental and physical outcome. The incidence of twins among persons with cerebral palsy is about four times higher than in the general population.[24, 35] Among twins with cerebral palsy, approximately 80

per cent had birth weights less than 2500 gm[35, 89] and more than 40 per cent were growth retarded by singleton standards.[24]

Thus studies indicate that despite initial rapid postnatal growth, twins never really catch up. Furthermore, it appears that twins, especially those with low birth weights and intrauterine growth retardation, are at increased risk for postnatal developmental morbidity.

PARENTING

Caring for a small infant is time-consuming and exhausting. Attempting to satisfy the needs of two infants of the same age stretches the limits of the human capacity for parenting. Goshen-Gottstein used an observational method to study the ways in which mothers cope with the unusual demands of multiple birth. She noted that expressions of ambivalence about mothering twins were common. In rare instances, ambivalent feelings led mothers to attribute negative qualities to one of the twins and positive qualities to the other. In most cases, initial expressions of despair or apprehension were transient steps toward eventual affectionate relationships with both infants. A few mothers appeared to thrive on the extra attention they received as mothers of twins; conversely, others never seemed able to view their situation except as a burden to be borne. Although mothers usually attempted to be equally responsive to each of their infants, meeting the demands of both necessitated many shortcuts. For example, they invariably chose to bottle feed viewing simultaneous nursing as physically difficult and believing that breastfeeding would be more time-consuming.[34] In fact, it is possible to breastfeed twins fully or partially, and it has been shown that milk production in such mothers is approximately double that of mothers who are breastfeeding singletons.[91]

Record et al. noted that mean verbal reasoning scores at 11 years of age were appreciably higher for twins whose co-twins had died than for twins with surviving co-twins. The authors concluded that this difference pointed out the importance of postnatal environmental factors in intellectual development.[86] Lower scores in twins raised together may reflect the inability to provide adequate parental nurturing to meet the developmental needs of both children.

Because perinatal mortality rates are higher in twins, perinatal loss of one twin with survival of the other is not infrequent. Because parents regard their twins as separate persons and desire to give equally to both,[34] they cannot be expected to deal with their loss by focusing more intensely on the needs of the surviving twin.[11] Wilson et al. found that among parents experiencing neonatal death, the grieving process was as intense for a twin whose co-twin survived as for a singleton infant.[105]

The emotional and physical demands of caring for twin infants are potentially overwhelming. Groothuis et al. noted that the incidence of child abuse was approximately eight times higher in families

with twins than in matched control families. The authors believe that the additional burden of caring for twins may have added intolerably to preexisting family difficulties. Accurate assessment of family functioning and provision of support systems may avert abusive behavior.[36]

SUMMARY

Twins have higher rates of perinatal mortality, prematurity and its complications, low birth weight, intrauterine growth retardation, congenital anomalies, and long-term developmental morbidity. Monozygotic twins have lower birth weights and higher rates of congenital anomalies than dizygotic twins, which suggests that the etiology of these problems may be related to the monozygotic twinning process. Monochorionic twins have higher rates of perinatal mortality, intrapair birth weight discrepancies, and intrauterine growth retardation than dichorionic twins, which suggests that these complications may be related to placental vascular anastomoses. Monochorial vascular communications also can be responsible for twin transfusion syndrome, disseminated intravascular coagulation at birth and disruptive structural defects. Followup studies indicate that twins remain at a disadvantage for subsequent physical growth and intellectual achievement. The management of twins is challenging and fascinating because of the wide range of perinatal, neonatal, developmental, and parenting problems that can occur.

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