5 Multiple gestation

Isaac Blickstein

INTRODUCTION

The human female is clearly programmed to ovulate a single oocyte, to carry a singleton fetus, and to nurse one neonate at a time. Consequently, multiple pregnancies overwhelm the uterine (maternal) capacity to adequately nurture the fetuses as animal and human models have repeatedly confirmed the inverse relationship between birth weight and gestational age at delivery and litter size. This natural sequence is relatively rare (about 1 twin pair per 80–100 births) and is extremely rare in the case of high-order multiple pregnancies.

The infrequency of high-order multiple gestations might be understood from the quasi-mathematical relationship, known as the Hellin-Zellany rule for twins, triplets, and quadruplets (1). This rule states that if the frequency of twins in a given population is $1/N$, then the frequency of triplets will be $1/N^2$ and that of quadruplets $1/N^3$. The Hellin-Zellany relationship appears quite accurate as long as the population remained homogeneous and enjoyed natural procreation. However, deviations from the rule were observed already in the thirties of the 20th century mainly because of racial differences in the frequency of dizygotic (DZ) twinning. A second, and much more dramatic deviation from the Hellin-Zellany relationship, occurred during the emergence of effective treatment of infertility. Indeed, within a very small fraction in human history, the natural order of multiples has been profoundly changed. Physician-made (i.e., *iatrogenic*) multiple gestations are now seen in most developed countries with frequencies approaching 50% of twins and more than 75% of high-order sets.

Iatrogenic multiple gestations, the major contributors to the epidemic of multiple pregnancies, did not arise *ex vacuo*. Women nowadays are able to rely on efficient modern fertility treatment when deciding on postponing childbirth. Advanced maternal age, by itself an established risk for natural multiples, is thus a significant risk factor for age-related reduced fecundity and for the increased need for fertility treatment. It appears that social trends act in concert with available assisted procreation techniques to increase the risk of multiple pregnancy. Consequently, all developed countries exhibited a dramatic increase in multiple births. For example, the ratio of induced to spontaneous twins in the East Flanders (Belgium) over the last two decades changed dramatically from 1:46 into 1 in every 2–3 twin pairs (1). This population-based trend might be even more accentuated in hospital-based data.

Data from England and Wales and the United States demonstrate decreasing rates of higher order multiple births and represent a striking and optimistic change in trend when compared with the previous steep fourfold increase since the early 1980s (2). At the same time, however, the incidence of other and by far more frequent multiples—twins—continued to escalate on both sides of the Atlantic Ocean. Regardless of

the probable reasons for this change (2), twins are predictably associated with significantly increased likelihood of perinatal morbidity and mortality and, therefore, the implications of the ever-increasing multiple birth rates is a major public health issue. For example, the contribution of infertility treatment can be appreciated from as yet unpublished data of the Israel Neonatal Network on very low-birth weight (VLBW) infants (<1500 g). The data indicate that roughly one-third of all VLBW infants are from multiple pregnancies, three-fourth of which are iatrogenic multiples (i.e., about one-fourth of all VLBW infants are iatrogenic multiples). Interestingly, the proportion of iatrogenic twins conceived by assisted reproductive technology (ART) to those conceived by ovulation induction increased over the period 1996–2005, but at the same time, this proportion decreased for iatrogenic triplets.

BIOLOGY

Most human conceptions (>99.2%) result from a single zygote [i.e., monozygotic (MZ)] following the fertilization of a single egg by a single spermatozoon. In the remaining cases, more than one egg is ovulated and fertilized, resulting in polyzygotic conceptions [DZ, trizygotic, etc.]. The polyzygotic conception occurs more often in taller, older, parous, heavier, and black women, pointing to a genetic predisposition. However, the exact mechanism whereby the ovary is naturally stimulated to release more than one egg per cycle is basically unknown. By contrast, all infertility treatments are associated with ovarian stimulation, multiple ripe ovarian follicles, polyovulation, and multiple conceptions.

The vast majority of MZ conceptions result in singleton birth. In only a small fraction of the cases (0.4% of all natural conceptions), the zygote splits to form an MZ twin gestation. Available hypotheses proposed to explain the mechanism of zygotic splitting fail to explain why MZ twins are more prevalent after all methods of assisted reproduction (3) and which structure is likely to control this phenomenon. It was hypothesized (4) that a small proportion of oocytes might have an inborn propensity to undergo splitting upon fertilization leading to the constant prevalence of spontaneous MZ twins among different populations. Ovarian stimulation—the common denominator of all infertility treatments—would then predictably increase the number of available splitting-prone oocytes and as a result would increase the chance for such oocytes to develop upon fertilization into MZ twins. An intact zona pellucida seems to be required to control embryonic division into two distinct cell lines and to prevent ill-timed hatching. Human fertilized oocytes are able to undergo binary fissions, just as in the nine-banded armadillo (the only other mammal that produces MZ quadruplets), and to produce a variety of

Figure 1 Quadrophorionic quadruplets. This first-trimester scan demonstrates the thick inter-twin membranes (several lambda signs).

Figure 2 Monozygotic twins. At this stage, the twins are very close to each other and an inter-twin membrane is not visualized.

combinations of MZ pregnancies. Importantly, this hypothesis does not negate previous genetically sound hypotheses, but places them into a broader perspective in light of observations from modern infertility treatment (4).

The increased frequencies of iatrogenic multiples changed the proportion of DZ and MZ twinning. In a population comprising mainly spontaneous gestations, the usual quoted frequency of MZ twinning is about one-third of the twin population, whereas in a population comprising a large proportion of iatrogenic conceptions, the expected MZ rate is 1 in 10 to 14 twin gestations.

ZYGOSITY, CHORIONICITY, AND PLACENTATION

DZ twins have two placentas (separate or fused), each with its chorion and amnion, forming the so-called dichorionic (DC) placenta. The inter-twin membrane comprises four layers (one chorion and one amnion from each twin) and usually appears as a thick septum during the optimal time of sonographic diagnosis at 11 to 14 weeks of gestation (Fig. 1). However, the triangle of decidual tissue between the reflections of the membranes, known as the “lambda” sign, is more easily identified and is pathognomonic of poly-chorionicity (Fig. 1). After birth, a DC placenta is confirmed by simply counting the placental discs and/or the number of layers in the inter-twin membrane.

MZ placentation, however, is presumably depended on the stage of embryonic development at which the split occurs. Early splits (about one-third) would result in DC placentas, whereas later splits result in monozygotic (MC) placentas. Moreover, if the amnion has not yet differentiated, the MC placenta includes two amniotic sacs: the MC-diamniotic placenta (about two-thirds of the cases). If the split occurs after differentiation of the amnion (i.e., >8 days after fertilization), an MC-monoamniotic placenta develops. Finally, even later splits are believed to result in all varieties of conjoined twins.

The sonographic diagnosis of an MC placenta is usually initiated by the absence of sonographic signs of DC placentation. In such a case, one should look for the tau sign, i.e., reflection of a thin inter-twin membrane (Fig. 2). If a first-trimester sonographic diagnosis is not available, a subsequent

scan might become less accurate, but a methodical assessment of chorionicity is nevertheless required.

The early diagnosis of chorionicity does not require high-tech imaging and is of utmost clinical importance. At times, however, complex cases of high-order multiples and/or ill-defined chorionicity–amnioticity arrangements might be a diagnostic challenge.

A distinction should always be made between zygosity and chorionicity. Because MZ twins with a DC placenta cannot be differentiated clinically from same-sex DZ twins (half of all DZ pairs) who also have a DC placenta, zygosity can be determined with certainty only in the DC-unlike-sex twins (all must be DZ twins) and in twins with an MC placenta (all must be MZ pairs). Simple calculation reveals that we are blind to zygosity in about 45% of the cases, and zygosity determination must be performed by DNA testing. Importantly, nothing should be said about zygosity to parents of same-sex twins with a DC placenta.

THE FIRST-TRIMESTER SONOGRAPHY

As suggested in Figures 1 and 2, a “window of opportunity” exists between 10 and 14 weeks for the best sonographic assessment of chorionicity. Admittedly, not all first-trimester pregnancies are scanned and therefore early losses of one or more embryos of a multiple pregnancy are missed (the so-called vanishing twin syndrome, VTS) and the true incidence of multiples is thus underestimated. The first-trimester scan should count the number of gestational sacs, the number of embryos, and the chorionic and amniotic arrangements. Ideally, the relative position of each embryo should be noted in a general “map” of the pregnancy, designating each embryo/fetus as being right/left, upper/lower, etc. Such “mapping” seems useful to provide and enhance some form of in utero individualized follow-up of the multiples.

Although each member of the multiple gestations has the same maternal-age-dependent risk for chromosomal anomalies, pure probability calculations show that the risk for a mother that one of her twins will have trisomy 21 is greater than that of a mother of a singleton. Roughly, this risk is

increased by 5/3, thus a 32-year-old mother of twins has the same risk of one infant with trisomy 21 as a 35-year-old mother of a singleton (5–7).

Because multiples are more commonly seen in older mothers (5) and invasive cytogenetic procedures (amniocentesis or chorionic villus sampling) carry a greater risk of pregnancy loss when performed in multiples, there is a genuine utility to noninvasive screening of aneuploidy to minimize the need for invasive procedures in these premium pregnancies (7). Regrettably, screening tests like the triple test [second-trimester maternal serum human chorionic gonadotropin (hCG) or free beta-hCG, alpha-fetoprotein, and unconjugated estriol] have a significantly lower predictivity for trisomy 21 in multiples compared with singletons (7). Thus, sonographic screening by measuring nuchal translucency (NT) thickness in each fetus should be offered to women who require genetic counseling. Flow in the ductus venosus (DV) might be measured to reduce the false-positive rate associated with NT measurement.

MATERNAL CONSEQUENCES

The changes in women's role in Western societies witnessed after World War II were facilitated by effective contraception, allowing ample time to achieve education and a career. This, in turn, resulted in increased maternal age at first delivery. Regrettably, age and fecundity are inversely related and infertility treatment to achieve a pregnancy often becomes inevitable for the older woman. Because all infertility treatments carry an increased risk of multiple gestations, the end result of these socio-medical trends is an increased age of the cohort of mothers of multiples. U.S. data clearly show that the increase in maternal age is more marked in high-order multiple pregnancies than in twins and in twins than in singletons, with a net result of multiples being more often delivered to older mothers in whom chronic disease conditions have already accumulated (5).

It goes without saying that a multiple pregnancy overwhelms the maternal homeostasis. Considering that the average fetus has a similar birth weight until 28 weeks (around 1000 g) irrespective of plurality, it appears that by 28 weeks, the mother of twins and the mother of triplets has accumulated twice and three times the fetal mass of singletons, respectively. This excess of fetal mass comes from either existing maternal resources or from supplemental energy that must be added throughout early gestation. It is also clear why all maternal systems are overwhelmed and some may be only a step away from clinical insufficiency in the advanced multiple pregnancy.

The overwhelmed maternal homeostasis is vividly demonstrated by the increased frequency of clinically significant anemia as a result of either depleted maternal iron stores or inadequate iron supplementation. Also the increased cardiac output has been estimated to increase in certain clinical situations to as much as two to three times the normal value. It is therefore understandable why cardiac function so easily turns into dysfunction when additional load, such as beta-sympathomimetic tocolysis, fever, premature contractions, and so on, is created.

Regardless of the inherent changes in maternal physiology due to the multiple pregnancy, some maternal disease

conditions are more frequent in multiple gestations. The best example is the two to three times increased incidence of hypertensive disorders (8,9) and their most dangerous complication—eclampsia—is six times more frequent among mothers of multiple gestations (10). Moreover, pre-eclampsia occurs earlier in multiples than in singletons and often occurs in a more severe form. It appears that a plurality-dependent risk of pre-eclampsia exists. For example, with the current epidemic dimensions of multiple gestations, it has been shown that the risk of hypertensive disorders in triplets is higher than that in twins, and the risk in twins is higher than that in singletons (8). In addition, numerous reports exist on the resolution of severe pre-eclampsia following intrauterine demise of a twin. Interestingly, the reason for the increased risk of hypertensive disorders among multiples is still unclear, but data seem to support an association with the increased placental mass, that is, hyperplacentosis (8,11). At this point it is important to mention that several rare but potentially pre-eclampsia-related conditions such as acute fatty liver of pregnancy are also more frequent in multiple gestations and seem to demonstrate the plurality-dependent risk pattern.

The other hyperplacentosis-related condition—gestational diabetes—seems also to be increased among mothers of multiples. Critical reading of the literature suggests that most stimulation tests to detect glucose intolerance of various degrees showed a diabetogenic effect of multiple gestations, whereas demographic analyses failed to show increased rates of gestational diabetes (12).

However, the latter studies were conducted in the era before the epidemic of iatrogenic multiples and before the effect of older maternal age could be documented (12). It is also possible that in the multiple gestations, an equilibrium is created between the increased glucose levels produced by hyperplacentosis and the glucose pumping effect created by the growing mass of the multiples. It has been shown that the risk of gestational diabetes is also plurality dependent, as is the case for hypertensive disorders (13).

All mothers of multiples are at considerably greater risk of preterm labor and delivery. Quite often, preterm contractions with or without cervical changes necessitate tocolytic treatment. Many prophylactic measures, including progesterone, cervical sutures (cerclage), beta-sympathomimetics, bed rest, and hospitalization, were proposed to reduce the preterm birth rates, but failed to demonstrate a significant reduction of this common complication of multiple pregnancy. Nevertheless, expecting mothers of multiples are frequently asked to leave work and to conduct a more sedentary lifestyle. Two promising prophylactic measures are at an empirical stage: early maternal weight gain (14,15) and further studies on progesterone derivatives (16). The former approach is based on the contention that multiple pregnancy is a state of magnified nutritional requirements (14). An adequate amount and pattern of gestational weight gain, including BMI-specific weight gain goals by 20 and 28 weeks of gestation, as well as other nutritional interventions, has been associated with significantly better fetal growth and longer gestations in twin pregnancies (14). In this context, it is unknown how many of normal or overweight woman will turn obese at the end of pregnancy and remain obese thereafter, and if the beneficial

effect of weight gain is equally important in women with high-compared with low pre-gravid BMI (15). Although the results of earlier trials were disappointing (16), many randomized controlled trials are currently ongoing to find the usefulness of progesterone and progestogens as prophylactic measures against preterm birth in multiples. This interest seems to suggest that many researchers believe that progesterone might have an effect on multiples as it has on singletons, but the best derivative, route of administration, and dose are still unknown. Table 1 lists the most common maternal complications during multiple gestations (17).

FETAL NEONATAL CONSEQUENCES

All animals, including the *Homo sapiens*, demonstrate an inverse relationship between litter size and both gestational age and birth weight. In the human, the average gestational age at

birth is around 40 weeks for singletons, 36 weeks for twins, 32 weeks for triplets, and 29 weeks for quadruplets. Although multiple pregnancies exhibit many specific complications, the consequences of prematurity are by far the most common and are the most important public health concern.

Malformations

It is customary to cite a two- to threefold increased risk of malformations among multiples. Arguments against this view suggest that twins are more closely examined and therefore a selection bias exists when describing malformations in a twin population. Regardless, the increased risk seems to be primarily related to MZ twinning whereas the malformation rates of DZs are similar to that of singletons (18). The higher malformation rate among MZs is hypothetically related to a common teratogen: the one that causes the split of the zygote is also responsible for the malformation.

Malformations among multiples are commonly grouped into four types (Table 2) (18). The first includes malformations that are more frequent among multiples, in particularly those affecting the central nervous and cardiovascular systems. The second type involves malformations related to MZ twinning such as twin reverse arterial perfusion (TRAP) sequence and the various forms of conjoined twins. The third type relates to consequences of placental malformations, in particular the MC placenta, resulting in twin–twin transfusion syndrome (TTTS) and/or selective severe discordance. Finally, the fourth type involves skeletal (postural) deformities such as clubfoot and dolichocephaly that are caused by intrauterine fetal crowding.

Certain malformations might have a major impact on the normal co-twin. For instance, in the TRAP sequence, the circulation of the severely anomalous acardiac–acephalic twin is entirely supported by the normal (pump) twin. Sooner or later, this cardiac overload will lead to cardiac insufficiency. Similarly, both twins in the TTTS are completely normal but the anomalous transplacental shunt of blood might cause serious morbidity in both twins. The most striking example is the case of single fetal demise in MC twins, whereby the surviving fetus frequently dies or becomes seriously damaged in utero soon after the death of the first twin.

Most structural anomalies can be detected by a comprehensive sonographic scan aided by echocardiography and Doppler velocimetry. Once a serious anomaly is detected, the patient might be counseled and offered selective reduction of the anomalous twin. In multichorionic multiples, selective reduction is accomplished by ultrasound-guided intracardiac injection of potassium chloride. However, because of the risk to the survivor in MC sets, highly invasive procedures (selective cord occlusion) are used to interrupt the umbilical circulation of the anomalous twin. When indicated and permitted, selective termination of an anomalous twin in an MC set is best accomplished by bipolar cord occlusion. At times, the umbilical cord of the twin affected by the TRAP sequence is too edematous and an intrafetal radiofrequency technique might be used.

Because of the increased frequency of fetal malformations, all MC twins, and ideally all twins, should undergo a detailed anatomical scan at 18 to 22 weeks of gestation. If the cardiac assessment shows a normal “four-chamber” view and outflow

Table 1 Maternal Complications More Frequently Seen in Multiple Pregnancies	
Hypertensive diseases	
• Pre-eclamptic toxemia	
• HELLP syndrome	
• Acute fatty liver	
• Pregnancy-induced hypertension	
• Chronic hypertension	
• Eclampsia	
Anemia	
Gestational diabetes mellitus (?)	
Premature contractions and labor	
• Complications associated with tocolysis	
Delivery-associated complications	
• Cesarean section	
• Operative delivery	
• Premature rupture of membranes	
• Postpartum endometritis	
• Placental abruption	
Abbreviation: HELLP, hemolysis, elevated liver enzymes, low platelets.	

Table 2 Categories of Structural Defects in Twins	
Category	Defect
Malformations more common in twins than in singletons	Neural tube defects
	Hydrocephaly
	Congenital heart disease
	Esophageal and anorectal atresias
	Intersex
	Genitourinary tract anomalies
Malformations unique to monozygotic twins	Amniotic band syndrome
	TRAP sequence
	Conjoined twins
Placental malformations	Twin embolization syndrome
	Single umbilical artery
	Twin–twin transfusion syndrome
	Velamentous cord insertion
Deformations due to intrauterine crowding	Skeletal (postural) abnormalities
Abbreviation: TRAP, twin reverse arterial perfusion. Source: Adapted from Ref. 18.	

tract, it is believed that an anatomical echocardiography seems unnecessary.

All invasive procedures in multiple pregnancies (amniocentesis, chorionic villus sampling, and the reduction methods) are associated with the risk of 5% to 10% of membrane rupture and loss of the entire pregnancy. When an invasive procedure is considered during the second trimester, the risk of extremely preterm birth of the normal twin is apparent. Thus when one twin has a lethal anomaly such as anencephaly, the risk of reducing this twin should be weighed against the risk of endangering the normal fetus by preterm birth. Conversely, the risk of preterm delivery because of a large polyhydramnios surrounding an anomalous twin might be reduced after selective reduction.

Embryonic and Fetal Demise

From the early days of ultrasound, it was apparent that there are more twin pregnancies than twin deliveries. The early loss of one twin, the VTS, is considered by many as the natural equivalent of intentional multifetal pregnancy (numerical) reduction (MFPR). Obviously, the true frequency of VTS is unknown, as many twin pregnancies are unnoticed unless first-trimester sonography is performed (19). One estimate of VTS frequency comes from iatrogenic conceptions. Spontaneous reduction of one or more gestational sacs or embryos occurred before the 12th week of gestation in 36% of twin, 53% of triplet, and 65% of quadruplet pregnancies (20). Dickey also pointed out that spontaneous reduction of multiple gestational sacs occurs less frequently in iatrogenic pregnancies compared with spontaneously conceived multiples (21). La Sala and his co-workers (22) as well as Matias and her associates (23) demonstrate that loss rates of twin pregnancies after assisted reproduction have a two to five times lower miscarriage rate of the entire pregnancy compared with singletons. The source of this advantage of ART twins is unknown. Importantly, Pinborg et al. found that 1 in 10 in vitro fertilization (IVF) singletons originates from a twin gestation and is one reason for the higher risk of adverse obstetric outcome in IVF singletons (24).

Single fetal death beyond the first trimester is also said to be more common in multiples. In DC twins, it is believed that the risk to the surviving twin is extremely low and present only when an external insult such as maternal disease is the cause of death. By contrast, fetal death in MC twins is entirely different. In the past, some ill-defined thromboplastin-like material was assumed to be transfused from the dead to the live fetus—leading to the so-called twin embolization syndrome. The theory was that these emboli might either cause fetal death or result in end-organ damage, such as brain and kidney lesions. In the early 1990s, and following painstaking postmortem examinations of brains of survivors of the twin embolization syndrome, the embolic theory was abandoned because no emboli were found and the lesions were rather ischemic in nature.

The embolic theory was soon replaced by the ischemic theory, which postulates that blood is acutely shunted from the live twin to the low-resistance circulation of the demised fetus, causing acute hypovolemia, ischemia, and end-organ damage in the survivor. A meta-analysis found that 12% of the co-twins die very soon after death of a twin, 18% survive but with

a significant damage, and 70% enjoy an intact survival (25). Death of a co-twin in an MC pair is rarely noticed in real time. However, when single fetal death is a recent event (e.g., after laser photocoagulation), the peak systolic velocity of the middle cerebral artery (PSV-MCA) might demonstrate acute fetal anemia (associated with other signs of fetal anemia). In such a case, prompt delivery is a valid option when gestational age permits. Alternatively, percutaneous umbilical cord (rescue) blood transfusion can be offered. However, it is unknown whether rescue transfusion actually decreases brain damage because not enough evidence exists to suggest improving outcomes after such procedures. When the timing of fetal death is unknown, as is more often the case, the diagnosis of single fetal death is made some time after the event. Data indicate that acute blood loss probably occurs just before the time of death of the surviving twin, and therefore it is unlikely that immediate delivery of the surviving twin could decrease the associated high mortality and morbidity rates associated with severe premature birth (26). It is therefore prudent to suggest conservative management in such cases, especially remote from term, and to use ultrasound and magnetic resonance imaging (MRI) to exclude brain lesions. The latter is ideally performed after the end of neuromigration at 30 to 32 weeks, unless diffusion weighted MRI, where available, might demonstrate white matter lesions earlier after the event.

Twin–Twin Transfusion

One of the most interesting consequences of MC twinning is the TTTS. TTTS is seen mainly (or only) in the diamniotic variety. The extensive literature on TTTS may lead to the erroneous impression that the syndrome is very frequent. In fact, TTTS occurs in about 10% of MC twins, and about half are of mild severity. Nonetheless, early onset (before 20 weeks of gestation) severe TTTS, unless intensively treated, is associated with 100% mortality of both twins.

It is a transplacental arteriovenous anastomosis that enables blood shunting from one twin (the donor) to the other (the recipient). Since all MC placentas have inert-twin anastomoses, the syndrome probably occurs because of fewer compensating veno-venous and arterio-arterial connections. The hypovolemia of the donor is manifested by poor micturition (absent bladder and oligohydramnios on sonographic scan). Conversely, the hypervolemic recipient is surrounded by polyhydramnios and manifests signs of cardiac overload ranging from tricuspid regurgitation to cardiac insufficiency and hydrops fetalis (27).

TTTS should be excluded on each antenatal visit of an MC pregnancy by demonstrating adequate amount of amniotic fluid. By definition, the first sign of TTTS is the twin oligo-polyhydramnios sequence (TOPS) corresponding to combination of largest pocket >8 cm and <2 cm in the respective sacs before 20 weeks and >10 cm and <2 cm after 20 weeks. TOPS in MC twins is defined a Quintero's stage I and should initiate a series of targeted sonographic evaluations, including Doppler velocimetry of the umbilical artery, DV, and middle cerebral artery (MCA-PSV).

In general, TTTS means serious morbidity, but the specific outcome is related to the gestational age when TTTS developed and to the severity of the syndrome. Quintero's stages are

useful in comparing management of TTTS. At present, selective laser photocoagulation of the inter-twin anastomoses is the preferable treatment modality and should be performed in TTTS occurring between 16 and 28 weeks of gestation. A decision of “no treatment” after 28 weeks would thus invariably lead to very preterm delivery of affected twins and it seems just logical that preterm delivery of treated TTTS might be better than delivering an untreated pair with TTTS. However, laser interventions after 28 weeks are still at an investigational stage. Selective laser photocoagulation, when available, is indicated in Quintero’s stage II (invisible urinary bladder), stage III (pathologic umbilical artery Doppler values), and stage IV (*hydrops fetalis*). Selective laser photocoagulation might also be indicated in “symptomatic” stage I (TOPS, with uterine contractions and/or short cervix). Alternatively, Quintero’s stage I might be followed very closely, because a proportion of stage I cases do not progress and remain asymptomatic. Induction of labor is reasonable in cases with Quintero’s stage V and a double fetal death, whereas follow-up of the survivor seems appropriate after a single fetal demise.

Cervical length before selective laser photocoagulation bears a negative correlation with outcome following the procedure and should be considered during preoperative counseling.

Amnioreduction (amniodrainage), that is, removal of a large quantity of amniotic fluid, was used to treat symptomatic mothers suffering from respiratory problems related to TOPS. The best technique regarding how fast should the amniotic fluid be drained, how much fluid should be removed, and how frequent should the technique be repeated is not established.

Since it is currently unknown how amnioreduction works, many hold that this procedure should be reserved to symptomatic patients only and for indications such as refusal or when laser photocoagulation is not available, when laser photocoagulation is contraindicated or technically difficult to perform, or after 28 weeks of gestation in order to buy time to increase gestational age. Amnioreduction might impede laser photocoagulation thus decreasing success rates and should not be performed as an interval procedure. Other treatment methods such as creating a hole in the inter-twin septum (septostomy) are not indicated for the treatment of TTTS.

Discordance in MC Twins

In the classic definition of TTTS (28), the twins are supposed to be discordant in size (at least 20–25%) and in hemoglobin levels (at least 5 g/dL). This concept changed over time, and at present, neither hemoglobin difference nor size discordance is part of the definition of TTTS. At times, however, a difference in hemoglobin is present—the so-called twin anemia-polycythemia sequence. The anemic twin can manifest all signs of anemia, especially by measuring the MCA-PSV. At birth, the donor is usually pale and anemic, whereas the recipient is polycythemic. The donor twin might be acutely distressed, with severe anemia and hypovolemic shock necessitating transfusion or exchange of blood products, or both. The recipient occasionally requires partial dilution exchange and support for cardiac failure.

Size discordance, however, seems to develop more slowly. When a significant size disparity exists, the smaller twin is at

risk of intrauterine death. At present, follow-up with serial Doppler velocimetry of the umbilical artery is indicated. Three patterns are recognized: type I, normal (positive diastolic) Doppler flow; type II, absent/reversed-end diastolic flow; and type III, intermittent absent/reversed-end diastolic flow—in the same or in the subsequent sessions (29,30). Deterioration of the growth-restricted fetus occurred in 90% of type II cases, significantly higher compared with 0% and 10.8% of types I and III, respectively. Unexpected intrauterine fetal death of the smaller twin occurred in 15.4% of type III cases, significantly higher compared with 2.6% and 0% of types I and II respectively. And finally, parenchymal brain lesions in the larger twin were observed in 19.7% of type III cases and significantly less than 5% in the other groups (30).

Fetal Growth

As noted earlier, multiples grow in utero to the same extent as singletons until about 28 weeks. Thereafter, during the third trimester, a decelerating trend of the growth curves of multiples is clearly seen. Not surprisingly, the limited uterine capacity to nurture multiples leads to growth aberrations (31). The higher risk of delivering low-birth weight (LBW) infants in a multiple birth is well known, as is the advantage for the multiparous patient. For instance, analysis of population-based data related to 12,567 live-born twin pairs found that, overall, the risk of having at least one very LBW (VLBW, <1500 g) infant was 1:5 among nulliparous women and 1:12 among multiparous women. The risk of having two VLBW twins among nulliparas (1:11) was double that of multiparas (1:22) (32). A similar trend and similar frequencies, but for extremely LBW (<1000 g) babies, were found in the analysis of triplets (33).

The most common growth aberration in multiples is birth weight discordance, defined as a difference between the larger and the smaller infant of a multiple pregnancy set. In fact, it is quite rare to find that all members of the set have the same birth weight, and it is quite normal to find some variation between siblings. Discordance is usually defined by the percent difference, whereby the birth weight disparity is calculated as a percentage of the larger infant. However, this definition does not refer to the actual size of the twins, and the same degree of discordance (e.g., 20%) can be found in a twin pair weighing 1500 and 1200 g as well as in a pair weighing 3000 and 2400 g. The cumulative frequency (34) suggests that about 75% of twins exhibit less than 15% discordance, about 20% are 15% to 25% discordant, and about 5% are more than 25% discordant.

Birth weight discordance is even more complex in triplets. In a new approach, in which the relative birth weight of the middle triplet was defined, the set was considered symmetrical, low, or high skew (35). The frequencies of different types of triplet discordance (average values: 57%, 30%, and 13%, respectively) did not change with gestational age, suggesting three distinct types of discordant growth in triplets that are independent of gestational age (35).

Several important related issues should be considered. First, it has been determined that at lower levels of discordance, either twin can be the smaller but the likelihood of the second-born twin being the smaller increases with increasing discordance levels (36). At discordance levels greater than

25%, the smaller twin was three to six times more often the second born (36). Data also suggest that there are three levels of discordance whereby in the lowest levels (probably at less than 25%), discordance seems to be related to the normal variation expected from the natural dissimilarities between siblings whereas in the highest level (probably greater than 35%), discordance seems to be related to the exhausted uterine environment and reflects growth restriction (37). Consequently, observation or intervention is indicated for the lowest and highest degrees of discordance, respectively.

Mortality is 11 times higher among highly discordant smaller twins (>30%) compared with nondiscordant smaller twins. Risk estimates ranged from 1.1 among 15% to 19% discordant twins to 2.0 among highly discordant twins. After accounting for the association between fetal growth and discordance, mortality risk was substantially higher among smaller and larger twins who were highly discordant (30% or more) (38). After controlling for fetal growth, smaller and larger twins affected by higher levels of birth weight discordance (>25%) remain at disproportionate risk for neonatal mortality (38). Finally, when neonatal mortality rates were compared among three groups of discordant twins (>25%), distinguished by the birth weight of the smaller twin being in the lowest 10th percentile [i.e., small for gestational age (SGA), 62.4%], in the 10th to 50th percentile (32.9%), or above the 50th percentile (4.7%), the rate was significantly higher among pairs in which the smaller twin's birth weight was in the lowest 10th percentile (29% vs. 11.1% and 11/1000) (39). This difference results from the higher mortality rates among the smaller but not among the larger twins. Thus, in severely discordant twin pairs, about 40% do not comprise a growth-restricted fetus and identification of this group is an imperative step in the management of birth weight discordance in twin gestations and in avoiding unnecessary interventions that may lead to iatrogenic prematurity.

Controversy exists as to whether to use singleton or twin growth curves for assessing multiple pregnancies. Because most multiple pregnancies weigh less than singletons of the same gestational age, it seems that multiples grow differently than singletons do and therefore are frequently and erroneously defined as SGA by singleton standards. Before birth, sonographic assessment of individual fetal growth cannot establish a pattern of growth restriction unless the pregnancy is longitudinally followed by repeated scans. In addition, despite the relative accuracy of sonographic estimations of the individual fetal weight, the "plus or minus" situation that exists for each estimation can cause significant under- and overestimation of the weight difference between fetuses and to low positive predictive values of discordance (40).

Growth restriction in twins—genuine or relative—is usually managed conservatively unless signs of fetal compromise are seen. At times, especially with higher levels, discordant growth and discordant fetal well-being go hand in hand. Remote from term, a decision to save the ailing fetus is in clear conflict with the potential risks of extreme preterm birth imposed on the healthy fetus. Thus, whenever the clinical circumstance of one twin jeopardizes the other, care should be exercised to select a management plan that would optimize the outcome of both fetuses. The pregnant woman should be involved in such decision making. Obviously, when the risk for the unaffected

neonates is lower than the expected risk for the affected fetus, delivery is a clear option, as would be the case at greater than 32 weeks.

FETAL ASSESSMENT

Fetal surveillance before and during labor should be carried out on all fetuses. It follows that each fetus should be adequately and appropriately monitored. In fact, assessment in multiples is no different from assessment in singletons, although it might be more complicated. For instance, fetal heart rate should be traced for both twins at the same time and intrapartum dual tracing is as important as during pregnancy. Once the membranes are ruptured, the presenting twin might be traced with a scalp electrode while the nonpresenting twin is followed with an external Doppler electrode. The fetal biophysical profile is similarly assessed individually although the amniotic fluid volume is sometimes difficult to assess. Sophisticated technology, like Doppler velocimetry of the umbilical artery, DV, and MCA, three-dimensional or four-dimensional ultrasound, and MRI of the fetal brain should be reserved for special indications.

DELIVERY CONSIDERATIONS

Most twins and practically all high-order multiple pregnancies go into spontaneous labor before 38 weeks of gestation. Circumstantial evidence suggests that, at least for twins, delivery after 37 completed weeks might carry an increased risk of neonatal mortality (41) and morbidity (42), and that fetal systems of the multiple pregnancy are mature by this date.

Many reasons for a cesarean section could be indicated in most twins and all high-order multiple pregnancies (43). Because twin gestations often involve some complications and are considered "premium" pregnancies, many clinicians would deliver twins by cesarean section for many subtle reasons other than clear-cut, evidence-based indications. Vaginal birth is allowed in twins whenever the first twin is in vertex presentation. Breech delivery of the second twin or internal podalic version of a transverse-lying second twin is still permitted and clinicians await a Canadian randomized trial initiated in 2004, to evaluate the safety of such births. Otherwise, all pairs with a nonvertex presenting twin are likely to undergo a cesarean section. Nuances on this construct consider fetal size, discordance, prior uterine surgery, and—mainly—the experience and dexterity of the obstetrician. Delivery considerations should include the welfare of all fetuses and the mode of delivery should be based on medical considerations pertaining to each fetus, as well as on maternal health and preferences. Delivery of multiples should ideally take place in a center that is equipped with neonatal intensive care facilities available simultaneously for each infant, where a medical care provider certified in neonatal resuscitation is present for each neonate, and with facilities for a high-risk delivery (such as availability of an experienced obstetrician, 24-hour anesthesia coverage, blood availability, etc.). If this is not possible, in utero transfer may be preferable to postpartum transfer.

When a multiple birth is expected, the main neonatal problem is logistic, rather than medical, because immediate neonatal treatment of an infant of a multiple pregnancy is not significantly different from treating a singleton, except that

twins come in pairs, and triplets come in sets of three. In practical terms, this means more staff in the delivery suite, more cribs available in the nursery, and more stations ready in the neonatal intensive care unit (NICU). At times, delivery of several very preterm sets in a short period may occupy the entire NICU for a relatively long period. It is clear that if the availability of NICU cribs lags behind the increased production of multiples, a serious public health situation may be created.

OUTCOME

Given the much-increased risk of maternal and fetal complications during a multiple pregnancy, the overall outcome for multiples is worse compared with the outcome for singletons. For example, the increased risk of cerebral palsy among multiples is clear: 28 to 45 for triplets, 7.3 to 12.6 for twins, and 1.6 to 2.3 for singletons per 1000 survivors, indicating that the greater the number of fetuses, the greater the prevalence of cerebral palsy. Moreover, the increase in cerebral palsy with the number of fetuses seems to be exponential (44). It is however unclear whether outcomes of multiples are poorer than outcomes of singletons matched for birth weight or gestational age. For example, the usual prophylactic dose of corticosteroids given to singletons does not have the same effect in multiples in terms of prevention of neonatal respiratory distress syndrome and intraventricular hemorrhage (45,46). A multivariate logistic regression analysis of a cohort of VLBW infants with similar background characteristics was done on 3717 singletons, 1394 twins, and 483 triplets. Respiratory distress syndrome was significantly more common in twins and triplets despite increased exposure to antenatal steroids (47). In addition, VLBW triplets were at increased risk of death, but VLBW twins and triplets had no increased risk of chronic lung disease or adverse neurologic findings compared with matched singletons (47).

PREVENTION VS. CURE

The epidemic dimensions of multiple births, and especially of high-order multiple pregnancies, became evident toward the end of the 1980s as an aftershock of effective infertility treatment. To amend this untoward consequence of infertility treatment, clinicians proposed to reduce the number of embryos during pregnancy (MFPR) (48). MFPR, considered by many as the ultimate paradox of medicine, soon became a popular "cure" of the side effects of infertility treatment. This procedure, performed during the early second trimester via the transvaginal or transabdominal route, carries a risk of about 5% to 8% total loss. However, MFPR is certainly associated with better outcomes simply because a lower plurality will always do better than a higher plurality pregnancy.

Interestingly, and somewhat disturbingly, clinicians were more busy in refining and mastering the technique of MFPR than in trying to reduce the number of iatrogenic high-order multiples. At present, it is believed that MFPR should be seriously considered with quadruplets or more and should rarely be considered with twins. The controversy remains regarding MFPR of triplets (49).

As always in medicine, prevention is better than cure. In terms of infertility treatment, this means transferring only one embryo in ART and canceling ovulation induction cycles

when more than one ripe follicle is visualized. Such preventive measures might somewhat reduce the overall success rates, although it is rarely debatable if a multiple pregnancy with three or four severely premature infants constitutes success. Put differently, the author of this chapter truly believes that if single-embryo transfer would have been the standard from the outset, it would never be possible to obtain ethical approval of a randomized trial for more than one embryo transfer.

REFERENCES

1. Blickstein I, Keith LG. Iatrogenic multiple pregnancy. *Semin Neonatol* 2002; 7: 169–76.
2. Blickstein I, Keith LG. The decreased rates of triplet births: temporal trends and biologic speculations. *Am J Obstet Gynecol* 2005; 193: 327–31.
3. Blickstein I, Jones C, Keith LG. Zygotic splitting rates following single embryo transfers in in-vitro fertilization. *N Engl J Med* 2003; 348: 2366–7.
4. Blickstein I, Keith LG. On the possible cause of monozygotic twinning: lessons from the 9-banded armadillo and from assisted reproduction. *Twin Res Hum Genet* 2007; 10: 394–9.
5. Blickstein I. Motherhood at or beyond the edge of reproductive age. *Int J Fertil Womens Med* 2003; 48: 17–24.
6. Meyers C, Adam R, Dungan J, Prenger V. Aneuploidy in twin gestations: when is maternal age advanced? *Obstet Gynecol* 1997; 89: 248–51.
7. Matias A, Montenegro N, Blickstein I. Down syndrome screening in multiple pregnancies. *Obstet Gynecol Clin North Am* 2005; 32: 81–96.
8. Skupski DW, Nelson S, Kowalik A, et al. Multiple gestations from in vitro fertilization: successful implantation alone is not associated with subsequent preeclampsia. *Am J Obstet Gynecol* 1996; 175: 1029–32.
9. Sibai BM, Hauth J, Caritis S, et al. Hypertensive disorders in twin versus singleton gestations. National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units. *Am J Obstet Gynecol* 2000; 182: 938–42.
10. Knight M, UKOSS. Eclampsia in the United Kingdom 2005. *BJOG* 2007; 114: 1072–8.
11. Bdolah Y, Lam C, Rajakumar A, et al. Twin pregnancy and the risk of preeclampsia: bigger placenta or relative ischemia? *Am J Obstet Gynecol* 2008; 198: 428.e1–6.
12. Hazan Y, Blickstein I. Diabetes and multiple pregnancies. In: Hod M, Jovanovic L, Di Renzo GC, De Leiva A, Langer O, eds. *Textbook of Diabetes and Pregnancy*, 2nd edn. London: Martin Dunitz, 2009: 338–42.
13. Sivan E, Maman E, Homko CJ, et al. Impact of fetal reduction on the incidence of gestational diabetes. *Obstet Gynecol* 2002; 99: 91–4.
14. Luke B. Nutrition and multiple gestation. *Semin Perinatol* 2005; 29: 349–54.
15. Flidel-Rimon O, Rhea DJ, Shinwell ES, Keith LG, Blickstein I. Early weight gain does not decrease the incidence of low birth weight and small for gestational age triplets in mothers with normal pre-gestational body mass index. *J Perinat Med* 2006; 34: 404–8.
16. Rouse DJ, Caritis SN, Peaceman AM, et al.; National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. A trial of 17 alpha-hydroxyprogesterone caproate to prevent prematurity in twins. *N Engl J Med* 2007; 357: 454–61.
17. Blickstein I, Keith LG. Multi-fetal gestations. In: Gronowski A, ed. *Handbook of Clinical Laboratory Testing During Pregnancy*. Totowa, NJ: Humana Press, 2004: 351–8.
18. Blickstein I, Smith-Levitin M. Multifetal pregnancy. In: Petrikovsky BM, ed. *Fetal disorders: diagnosis and management*. New York: John Wiley and Sons, 1998: 223–47.
19. Landy HJ, Keith LG. The vanishing twin: a review. *Hum Reprod Update* 1998; 4: 177–83.
20. Dickey RP, Taylor SN, Lu PY, et al. Spontaneous reduction of multiple pregnancy: incidence and effect on outcome. *Am J Obstet Gynecol* 2002; 186: 77–83.
21. Dickey RP. Embryonic loss in iatrogenic multiples. *Obstet Gynecol Clin North Am* 2005; 32: 17–27.

22. La Sala GB, Nucera G, Gallinelli A, et al. Spontaneous embryonic loss following in vitro fertilization: incidence and effect on outcomes. *Am J Obstet Gynecol* 2004; 191: 741–6.
23. Matias A, La Sala GB, Blickstein I. Early loss rates of entire pregnancies after assisted reproduction are lower in twin than in singleton pregnancies. *Fertil Steril* 2007; 88: 1452–4.
24. Pinborg A, Lidegaard O, la Cour Freiesleben N, Andersen AN. Consequences of vanishing twins in IVF/ICSI pregnancies. *Hum Reprod* 2005; 20: 2821–9.
25. Ong SS, Zamora J, Khan KS, Kilby MD. Prognosis for the co-twin following single-twin death: a systematic review. *BJOG* 2006; 113: 992–8.
26. Nicolini U, Pisoni MP, Cela E, Roberts A. Fetal blood sampling immediately before and within 24 hours of death in monochorionic twin pregnancies complicated by single intrauterine death. *Am J Obstet Gynecol* 1998; 179: 800–3.
27. Wee LY, Fisk NM. The twin-twin transfusion syndrome. *Semin Neonatol* 2002; 7: 187–202.
28. Blickstein I. The twin-twin transfusion syndrome. *Obstet Gynecol* 1990; 76: 714–22.
29. Lewi L, Cannie M, Blickstein I, et al. Placental sharing, birthweight discordance, and vascular anastomoses in monochorionic diamniotic twin placentas. *Am J Obstet Gynecol* 2007; 197: 587.e1–8.
30. Gratacós E, Lewi L, Muñoz B, et al. A classification system for selective intrauterine growth restriction in monochorionic pregnancies according to umbilical artery Doppler flow in the smaller twin. *Ultrasound Obstet Gynecol* 2007; 30: 28–34.
31. Blickstein I. Normal and abnormal growth of multiples. *Semin Neonatol* 2002; 7: 177–85.
32. Blickstein I, Goldman RD, Mazkereth R. Risk for one or two very low birth weight twins: a population study. *Obstet Gynecol* 2000; 96: 400–2.
33. Blickstein I, Jacques DL, Keith LG. The odds of delivering one, two or three extremely low birth weight (<1000 g) triplet infants: a study of 3288 sets. *J Perinat Med* 2002; 30: 359–63.
34. Blickstein I, Kalish RB. Birth weight discordance in multiple pregnancy. *Twin Res* 2003; 6: 526–31.
35. Blickstein I, Jacques DL, Keith LG. A novel approach to intertriplet birth weight discordance. *Am J Obstet Gynecol* 2003; 188: 1026–30.
36. Blickstein I, Goldman RD, Smith-Levitin M, et al. The relation between intertwin birth weight discordance and total twin birth weight. *Obstet Gynecol* 1999; 93: 113–16.
37. Blickstein I, Goldman RD, Mazkereth R. Adaptive growth restriction as a pattern of birth weight discordance in twin gestations. *Obstet Gynecol* 2000; 96: 986–90.
38. Branum AM, Schoendorf KC. The effect of birth weight discordance on twin neonatal mortality. *Obstet Gynecol* 2003; 101: 570–4.
39. Blickstein I, Keith LG. Neonatal mortality rates among growth discordant twins, classified according to the birth weight of the smaller twin. *Am J Obstet Gynecol* 2004; 190: 170–4.
40. Blickstein I, Manor M, Levi R, Goldchmit R. Is intertwin birth weight discordance predictable? *Gynecol Obstet Invest* 1996; 42: 105–8.
41. Minakami H, Sato I. Reestimating date of delivery in multifetal pregnancies. *JAMA* 1996; 275: 1432–4.
42. Luke B, Bigger HR, Leurgans S, Sietsema D. The cost of prematurity: a case-control study of twins vs singletons. *Am J Public Health* 1996; 86: 809–14.
43. Blickstein I. Cesarean section for all twins? *J Perinatol* 2000; 28: 169–74.
44. Blickstein I. Fetal brain injury and multiple pregnancies. In: Levene MI, Chervenak FA, eds. *Fetal and neonatal neurology and neurosurgery*, 4th edn. Edinburgh: Churchill Livingstone, 2009: 375–84.
45. Blickstein I, Shinwell ES, Lusky A, Reichman B, Israel Neonatal Network. Plurality-dependent risk of respiratory distress syndrome among very-low-birth-weight infants and antepartum corticosteroid treatment. *Am J Obstet Gynecol* 2005; 192: 360–4.
46. Blickstein I, Reichman B, Lusky A, Shinwell ES, Israel Neonatal Network. Plurality-dependent risk of severe intraventricular hemorrhage among very low birth weight infants and antepartum corticosteroid treatment. *Am J Obstet Gynecol* 2006; 194: 1329–33.
47. Shinwell ES, Blickstein I, Lusky A, Reichman B. Excess risk of mortality in very low birth weight triplets: a national, population-based study. *Arch Dis Child Fetal Neonatal Ed* 2003; 88: F36–40.
48. Evans MI, Hume RF Jr, Yaron Y, Kramer RL, Johnson MP. Multifetal pregnancy reduction. *Baillieres Clin Obstet Gynaecol* 1998; 12: 147–59.
49. Blickstein I, Keith LG. Outcome of triplets and higher order multiple pregnancies. *Curr Opin Obstet Gynecol* 2003; 15: 113–17.