INTERIM UPDATE

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INTERIM UPDATE: This Practice Bulletin is updated to reflect a limited, focused change in the gestational age at which to consider antenatal corticosteroids and rescue-course timing.

Multifetal Gestations: Twin, Triplet, and Higher-Order Multifetal Pregnancies

The incidence of multifetal gestations in the United States has increased dramatically over the past several decades. The rate of twin births increased 76% between 1980 and 2009, from 18.9 to 33.3 per 1,000 births (1). The rate of triplet and higher-order multifetal gestations increased more than 400% during the 1980s and 1990s, peaking at 193.5 per 100,000 births in 1998, followed by a modest decrease to 153.4 per 100,000 births by 2009 (2). The increased incidence in multifetal gestations has been attributed to two main factors: 1) a shift toward an older maternal age at conception, when multifetal gestations are more likely to occur naturally, and 2) an increased use of assisted reproductive technology (ART), which is more likely to result in a multifetal gestation (3).

The principal complication encountered with multifetal gestations is spontaneous preterm birth and the resultant infant morbidity and mortality. Although multiple interventions have been evaluated in the hope of prolonging these gestations and improving outcomes, none has been shown to be effective. The purpose of this document is to review the issues and complications associated with twin, triplet, and higher-order multifetal gestations and present an evidence-based approach to management.

Background

Fetal and Infant Morbidity and Mortality

Multifetal gestations are associated with increased risk of fetal and infant morbidity and mortality (Table 1). There is an approximate fivefold increased risk of stillbirth and a sevenfold increased risk of neonatal death, which primarily is due to complications of prematurity (4). Women with multifetal gestations are six times more likely to give birth preterm and 13 times more likely to give birth before 32 weeks of gestation than women with singleton gestations (2).

An increase in short-term and long-term neonatal and infant morbidity also is associated with multifetal gestations. Twins born preterm (less than 32 weeks of gestation) are at twice the risk of a high-grade intraventricular hemorrhage and periventricular leukomalacia when compared with singletons of the same gestational age (5). This, in part, explains the increased prevalence of cerebral palsy in multifetal gestations (6).

Multifetal gestations are associated with significantly higher costs, in the antenatal and neonatal periods, in large part because of the costs associated with prematurity (7). The average first-year medical costs, including inpatient and outpatient care, are up to 10 times greater for preterm infants than for term infants (8).

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Table 1. Morbidity and Mortality in Multifetal Gestations ⇦

Characteristic	Singleton	Twins	Triplets	Quadruplets
Mean birth weight*	3,296 g	2,336 g	1,660 g	1,291 g
Mean gestational age*	38.7 weeks	35.3 weeks	31.9 weeks	29.5 weeks
Percentage less than 32 weeks of gestation*	1.6	11.4	36.8	64.5
Percentage less than 37 weeks of gestation*	10.4	58.8	94.4	98.3
Rate of cerebral palsy (per 1,000 live births)†	1.6	7	28	—
Infant mortality rate‡ (per 1,000 live births)	5.4	23.6	52.5	96.3§

*Martin JA, Hamilton BE, Ventura SJ, Osterman MJ, Kirmeyer S, Mathews TJ, et al. Births: final data for 2009 Natl Vital Stat Rep, 2011, 60, 1, 1–70, United States.

†Petterson B, Nelson KB, Watson L, Stanley F. Twins, triplets and cerebral palsy in births in Western Australia in the 1980s. BMJ 1993;307:1239–43.

‡Luke B, Brown M. The changing risk of infant mortality by gestation, plurality, and race: 1989-1991 versus 1999-2001. Pediatrics, 2006;118:2488–97.

§Quadruplet and quintuplet data combined.

Chorionicity

Using clinical criteria alone to diagnose multifetal gestations is unreliable. A reliable method to diagnose multifetal gestations is by ultrasound assessment. In the Routine Antenatal Diagnostic Imaging With Ultrasound (RADIUS) trial, for 37% of women who did not have a screening ultrasound examination, their twin pregnancies were not diagnosed until 26 weeks of gestation, and in 13% of women their multifetal gestations were only diagnosed during their admission for delivery (9). Ultrasonography can be used to determine fetal number, estimated gestational age, chorionicity, and amnionicity. The determination of chorionicity in multifetal gestations is clinically important. Assessment of chorionicity is most accurate early in gestation, and its determination is optimal when ultrasonography is performed in the first trimester or early second trimester.

Compared with dichorionic twins, monochorionic twins have a higher frequency of fetal and neonatal mortality, as well as morbidities, such as fetal and congenital anomalies, prematurity, and fetal growth restriction (10, 11). This trend also is seen in higher-order multifetal gestations; for example, a triplet gestation that is fully monochorionic or has a monochorionic twin pair is at higher risk of complications than a triplet gestation that is trichorionic (12, 13). Because of the increased rate of complications associated with monochorionicity, determination of chorionicity by late first trimester or early second trimester in pregnancy is important for counseling and management of women with multifetal gestations.

Maternal Morbidity and Mortality

Medical complications are more common in women with multifetal gestations than with singleton gestations. These include hyperemesis, gestational diabetes mellitus, hypertension, anemia, hemorrhage, cesarean delivery, and postpartum depression (14–20). Although these complications are more common in women with multifetal gestations, the management of these complications follows the same strategies as with a singleton gestation.

Women with multifetal gestations have an increased incidence of hypertensive conditions associated with pregnancy. The occurrence of hypertensive complications is proportional to the total fetal number, with singletons at 6.5%, twins at 12.7%, and triplets at 20.0% (21). One study found that ART pregnancies were at increased risk (relative risk [RR], 2.1) of developing mild or severe preeclampsia, even after controlling for maternal age and parity (22).

Preeclampsia occurs more frequently in women with twin pregnancies than in women with singleton gestations, with a relative risk of 2.6, and it tends to occur earlier in pregnancy. This results in a higher likelihood of complications, such as preterm delivery at less than 35 weeks of gestation (34.5% twins versus 6.3% in singletons) and abruptio placentae (4.7% twins versus 0.7% singletons) (16). Women with higher-order multifetal gestations are more likely to develop preeclampsia but also to present in an atypical manner (23). If hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome develops before term, transfer to a tertiary care center may improve the outcome for the woman and her fetus (24).

The likelihood of a multifetal gestation increases with maternal age, even outside of ART use. The multiple birth ratio increases from 16.3 per 1,000 live births for women younger than 20 years to 71.1 per 1,000 live births for women 40 years and older (2). Older women also are more likely to have obstetric complications irrespective of fetal number, including gestational hypertension, gestational diabetes mellitus, and abruptio placentae.

Contribution of Assisted Reproductive Technology

Over the past several decades, the increased use of ART has led to a dramatic increase in the incidence of multifetal births. Only recently has there been a decrease in the higher-order multiple birth rate (1). This decrease is the result of a reduction in the number of embryos transferred

with each cycle of in vitro fertilization (IVF) and an increase in the number of multifetal pregnancy reduction procedures being performed.

The specific ART techniques that may have the most significant effect on the increase of multifetal pregnancies are IVF and controlled ovarian hyperstimulation with gonadotropins. According to the most recent data available from cycles completed in 2010, 26% of pregnancies after IVF are twin pregnancies and 1.3% are higher-order multifetal pregnancies (25).

Multifetal Reduction and Selective Fetal Termination

Multifetal reduction reduces the likelihood of spontaneous preterm delivery and other neonatal and obstetric complications by decreasing the number of fetuses. A Cochrane review found that women who underwent pregnancy reduction from triplets to twins, as compared with those who continued with triplets, were observed to have lower frequencies of pregnancy loss, antenatal complications, preterm birth, low-birth-weight infants, cesarean delivery, and neonatal deaths, with rates similar to those observed in women with spontaneously conceived twin gestations (26). Multifetal reduction may decrease the risk of preeclampsia in women with higher-order multifetal gestations. One study reported that only 14% of 59 women with twin pregnancies remaining after multifetal reduction developed preeclampsia compared with 30% of women with triplet pregnancies (27).

In multifetal pregnancy reduction, the fetus(es) to be reduced are chosen on the basis of technical considerations, such as which is most accessible to intervention and chorionicity. Monochorionicity can complicate the reduction procedure; if one fetus of a monochorionic twin pair is reduced, the negative effects on the development of the other are unknown. For this reason, it is usually recommended that both fetuses of a monochorionic pair be reduced.

Selective fetal termination is the application of the fetal reduction technique to an abnormal fetus that is part of a multifetal gestation. The risks of the procedure are higher than those associated with multifetal reduction, largely because of a later gestational age at the time of diagnosis of fetal anomaly (ie, 18–22 weeks of gestation compared with 10–12 weeks of gestation) (28). In particular, the unintended loss rate of healthy fetuses is increased when women with higher-order multifetal gestations undergo selective fetal termination in comparison with women with twin gestations who undergo the procedure (11.1 % versus 2.4%, respectively) (29). Despite the unintended loss rate, pregnancy prolongation also has been observed in women who undergo selective fetal termination (30, 31).

Clinical Considerations and Recommendations

▶ *How is chorionicity determined?*

Fetal risk is largely dependent on chorionicity. Therefore, the chorionicity of a multifetal pregnancy should be established as early in pregnancy as possible, and the optimal timing for determination of chorionicity by ultrasonography is in the late first trimester or early second trimester. In one series, the reported sensitivity, specificity, and positive and negative predictive values for prediction of chorionicity by ultrasonography at 14 weeks of gestation or less was shown to be 89.8%, 99.5%, 97.8%, and 97.5%, respectively (32). Overall, chorionicity was determined correctly in 95% of cases.

When ultrasound assessment clearly shows two placentas or differing fetal sex, the pregnancy is dichorionic. If only one placenta is visualized, the best ultrasonographic characteristic to distinguish chorionicity is the twin peak sign. The twin peak sign (also called the lambda or delta sign) is a triangular projection of tissue with the same echogenicity as the placenta that extends beyond the chorionic surface of the placenta and is indicative of a dichorionic gestation (33). The management of complications related to monochorionicity (eg, twin–twin transfusion syndrome, single fetal death, and monoamniotic gestation) and timing of delivery are discussed in "Clinical Considerations and Recommendations" later in this document.

▶ *Can adjunctive tests be used to predict spontaneous preterm birth in women with multifetal gestations?*

Asymptomatic Women

Several methods have been used in an attempt to further quantify the risk of spontaneous preterm birth when screening asymptomatic women with multifetal gestations, including transvaginal ultrasonographic cervical length, digital examination, fetal fibronectin screening, and home uterine monitoring. There are no interventions that have been shown to prevent spontaneous preterm delivery in asymptomatic women with multifetal gestations identified to be at risk based on these screening methods. The use of these screening methods in asymptomatic women with multifetal pregnancies is not recommended (34).

Symptomatic Women

In symptomatic women, the positive predictive value of a fetal fibronectin test result or of a short cervical length

alone is poor, and they should not be used exclusively to direct management in the setting of acute symptoms (35). Although several observational studies have suggested that knowledge of fetal fibronectin status or cervical length in women with singleton gestations who present with symptoms of preterm labor may help health care providers reduce the use of unnecessary resources, these findings have not been consistently confirmed by randomized trials for use in singleton or in multiple gestations (36–40).

▶ *Are there interventions that can prolong pregnancy in women with multifetal gestations?*

Interventions, such as prophylactic cerclage, routine hospitalization and bed rest, prophylactic tocolytics, and prophylactic pessary, have not been proved to decrease neonatal morbidity or mortality and, therefore, should not be used in women with multifetal gestations.

Prophylactic Cerclage

Prophylactic cerclage placement in women with a twin gestation or a triplet gestation without a history of cervical insufficiency has not been shown to be beneficial (41–43). Moreover, the placement of cerclage in women with a twin gestation with an ultrasonographically detected short cervical length has been observed to double the rate of spontaneous preterm birth (RR, 2.2; 95% confidence interval [CI], 1.2–4.0) (44, 45). Based on these findings, the placement of cerclage in women with multifetal gestations should be avoided.

Routine Hospitalization and Bed Rest

The use of bed rest with or without hospitalization has been commonly recommended to women with multifetal gestations. However, a Cochrane review demonstrated no benefit from routine hospitalization or bed rest for women with an uncomplicated twin pregnancy (46). Thus, bed rest with or without hospitalization in women with multifetal pregnancies is not recommended because of the lack of benefit and the risk of thrombosis and deconditioning associated with prolonged bed rest in pregnancy.

Prophylactic Tocolytics

There is no role for the prophylactic use of any tocolytic agent in women with multifetal gestations, including the prolonged use of betamimetics for this indication. The use of tocolytics to inhibit preterm labor in multifetal gestations has been associated with a greater risk of maternal complications, such as pulmonary edema (47, 48). In addition, prophylactic tocolytics have not been shown to reduce the risk of preterm birth or improve neonatal outcomes in women with multifetal gestations (49–51). The administration of oral betamimetics, specifically, did not reduce the incidence of preterm birth, low-birth-weight newborns, or neonatal mortality in women with multifetal gestations when compared with placebo (52). Oral betamimetics have been associated with increased maternal and fetal cardiac stress and gestational diabetes mellitus (53, 54). Recently, prolonged use of betamimetics also has been associated with increased adverse maternal cardiovascular events, including death (55). Based on the available evidence, prophylactic tocolysis in women with multifetal gestations is not recommended.

Prophylactic Pessary

There is at present no high-quality evidence that prophylactic cervical pessary use in unselected multifetal pregnancies reduces the frequency of spontaneous preterm birth or perinatal morbidity. In a recent multicenter randomized trial, 813 women with twins between 16 weeks and 20 weeks of gestation were randomized to an Arabin cervical pessary or no pessary (56). In the pessary group, at least one child of 53 women (13%) had poor perinatal outcome (defined as either stillbirth, periventricular leukomalacia, severe respiratory distress syndrome, bronchopulmonary dysplasia, intraventricular hemorrhage, necrotizing enterocolitis, proven sepsis, or neonatal death) compared with at least one child of 55 women (14%) in the control group (RR, 0.98; 95% CI, 0.69–1.39). Thus, based on available evidence, the use of prophylactic cervical pessary is not recommended in multifetal pregnancies (56).

▶ *Does progesterone treatment decrease the risk of preterm birth in women with multifetal gestations?*

Progesterone treatment does not reduce the incidence of spontaneous preterm birth in unselected women with twin or triplet gestations and, therefore, is not recommended (57–63). The administration of 17α-hydroxyprogesterone caproate to women with triplet gestations did not reduce neonatal morbidity or prolong gestation (61). In addition, another randomized trial found that its use in women with triplet gestations was associated with a significantly increased rate of midtrimester fetal loss (60). There are insufficient data to assess whether progesterone has any beneficial effect in women with multifetal gestations and short cervical length determined by transvaginal ultrasonography (64, 65). In a recent randomized trial of asymptomatic women with twin pregnancies and a short cervical length of 25 mm or less determined by transvaginal ultrasonography, no benefit was seen with the use of intramuscular 500-mg 17α-hydroxyprogesterone

caproate twice weekly in significantly prolonging gestation (66). In another recent randomized trial of women with twins, vaginal progesterone (200 mg and 400 mg) did not prolong the pregnancies (67).

▶ *How is preterm labor managed in women with multifetal gestations?*

Tocolytics

Tocolytic therapy may provide short-term prolongation of pregnancy, which enables the administration of antenatal corticosteroids as well as transport to a tertiary care facility, if indicated. The overall evidence suggests that when tocolysis is used for short-term pregnancy prolongation, calcium channel blockers or nonsteroidal antiinflammatory drugs should be first-line treatment. Although there is a dearth of large-scale randomized trials of multifetal gestations alone, data supporting these conclusions come from trials that have included singleton and multifetal gestations (68). Thus, in multifetal gestations a brief course of tocolysis may be considered for up to 48 hours in the setting of acute preterm labor, in order to allow corticosteroids to be administered. Maternal risks associated with tocolytic use include pulmonary edema.

Corticosteroids

Administration of antenatal corticosteroids to women with singleton gestations at risk of delivery between 24 weeks and 34 weeks of gestation has been shown to decrease the incidence of neonatal death, respiratory distress syndrome, intraventricular hemorrhage, and necrotizing enterocolitis (69). A Cochrane review concluded that although antenatal corticosteroids are beneficial in singleton gestations, further research is required to demonstrate an improvement in outcomes for multifetal gestations (69). However, based on the improved outcomes reported in singleton gestations, the National Institutes of Health recommends that, unless a contraindication exists, one course of antenatal corticosteroids should be administered to all patients who are between 24 weeks and 34 weeks of gestation and at risk of delivery within 7 days, irrespective of the fetal number (70). In the absence of data, it is reasonable to extend this so that antenatal corticosteroids may be administered for pregnant women starting at 23 weeks of gestation, regardless of fetal number. Administration of corticosteroids to pregnant women during the periviable period who are at risk of preterm delivery within 7 days is linked to a family's decision regarding resuscitation and should be considered in that context (71).

Regularly scheduled repeat courses or serial courses (more than two) are not recommended. A single repeat course of antenatal corticosteroids should be considered in women with a gestation of less than 34 weeks, who have an imminent risk of preterm delivery within the next 7 days, and whose prior course of antenatal corticosteroids was administered more than 14 days previously. Rescue-course corticosteroids could be provided as early as 7 days from the prior dose, if indicated by the clinical scenario.

Magnesium Sulfate for Fetal Neuroprotection

Several large studies have been performed to examine whether intravenous magnesium sulfate administered before preterm delivery would decrease the incidence of death and cerebral palsy (72–74). Although none of these studies showed improvement in the primary combined outcome, several meta-analyses of these randomized trials concluded that prenatal administration of magnesium sulfate reduced the occurrence of cerebral palsy (75–77). The accumulated available evidence suggests that magnesium sulfate reduces the severity and risk of cerebral palsy in surviving infants if administered when birth is anticipated before 32 weeks of gestation, regardless of fetal number. Hospitals that elect to use magnesium sulfate for fetal neuroprotection should develop uniform and specific guidelines for their departments regarding inclusion criteria, treatment regimens, concurrent tocolysis, and monitoring in accordance with one of the larger trials (72–74, 78).

▶ *How is prenatal screening of women with multifetal gestations different than for singleton pregnancies?*

All women with multifetal gestations, regardless of age, are candidates for routine aneuploidy screening. In the presence of multiple fetuses, the mathematical probability that one or more fetuses will be affected with a trisomy increases and, thus, results in a higher overall risk to the pregnancy than attributed to maternal age alone. For example, in dizygotic twins, the maternal age-related risk of having one of the two fetuses affected with a trisomy is doubled compared with a maternal age-matched singleton gestation (79). This equates to a similar age-related risk of Down syndrome between a 33-year-old woman carrying twins and a 35-year-old woman carrying a singleton gestation (80).

However, several limitations must be considered when screening for aneuploidy in multifetal gestations. Serum screening tests are not as sensitive in women with twin or triplet gestations compared with singleton gestations, in part because analyte levels must be estimated by mathematical modeling. In addition, analytes from the

normal and the affected fetuses enter the maternal serum and are in effect averaged together, thus potentially masking the abnormal levels of the affected fetus. In a prospective study of second-trimester maternal serum marker screening, the mean detection rate for trisomy 21 was 63% in twin gestations (71% when both twins were affected and 60% when one was affected), with a false-positive rate of 10.8% (81). Furthermore, counseling is more complex because women must consider a different set of options in the event that only one of the fetuses is affected.

Nuchal translucency screening in the first trimester with the option of chorionic villus sampling (CVS) and earlier selective reduction may be desirable for some women. In women with twin gestations, first-trimester screening that combines maternal age, nuchal translucency, and biochemistry serum analytes identifies approximately 75–85% of pregnancies with Down syndrome and 66.7% of pregnancies with trisomy 18, with a 5% false-positive rate (82–85). Experience is limited with triplet gestations, but studies suggest that nuchal translucency measurement is feasible, and screening using only maternal age and nuchal translucency has been validated for the detection of Down syndrome and trisomy 18 (85). However, in one study of monochorionic twin pregnancies, a nuchal translucency value above the 95th percentile had a 38% positive predictive value for later development of severe twin–twin transfusion syndrome, further complicating first-trimester genetic screening in monochorionic gestations (86).

Noninvasive prenatal testing that uses cell free fetal DNA from the plasma of pregnant women offers potential as a screening tool for fetal aneuploidy. However, more information is needed before use of this test can be recommended in women with multifetal gestations (87).

▶ *What issues arise in prenatal diagnosis of aneuploidy in women with multifetal gestations?*

Amniocentesis and CVS can be performed in women with a multifetal gestation who desire definitive testing for genetic anomalies. The procedure-associated pregnancy loss rates for both tests are similar (reported at 1–1.8%) and are slightly increased compared with loss rates reported in women with singleton gestations (88–90). Chorionic villus sampling has the advantage that it can be performed earlier in gestation.

However, there are technical difficulties that may be encountered when performing amniocentesis and CVS in women with multifetal gestations. There is a risk of sampling error of approximately 1% in women with multifetal gestations who undergo CVS (91). Genetic amniocentesis, which typically is performed at 15 weeks of gestation or beyond, has a lower chance of this complication. To avoid sampling error in women with multifetal gestations, an amniocentesis is performed by sampling the first sac, then injecting indigo carmine into that sac before removing the needle. A second needle is then inserted into the second sac, and a clear sample obtained from the second sac ensures that two different sacs have been sampled. A complex counseling issue arises in the presence of a monochorionic twin gestation, in which case the likelihood of discordance in the karyotype is low, and patients may opt for having a karyotype analysis performed on a single fetus. In this situation, it is important to discuss the accuracy of determining chorionicity by ultrasonography.

When aneuploidy is diagnosed, counseling should include a discussion of options for pregnancy management if only one fetus is found to be affected. These options include terminating the entire pregnancy; selective reduction of the affected fetus; and continuing the pregnancy without any intervention, reduction, or termination.

▶ *Are multifetal gestations with discordant fetal growth at risk of adverse outcomes?*

Discordant fetal growth in women with multifetal gestations is most commonly defined as a 20% difference in estimated fetal weight between the larger and smaller fetus (92, 93). This growth discordance ratio is calculated by determining the difference in the estimated fetal weight between the two fetuses, divided by the weight of the larger fetus.

Whether growth-discordant multifetal gestations—without a structural anomaly, aneuploidy, discordant infection, oligohydramnios, or fetal growth restriction—are at increased risk of adverse outcomes is debatable. Several studies that examined this population have shown that multifetal gestations with discordant but appropriate-for-gestational-age growth are not at increased risk of fetal or neonatal morbidity and mortality (94–97). However, multifetal gestations with discordant growth and pregnancies with at least one growth-restricted fetus have been observed to be associated with a 7.7-fold increased risk of major neonatal morbidity (98). Moreover, growth-restricted twins have higher perinatal mortality and morbidity rates when compared with age-matched singletons (99). Thus, although there is no clear evidence of increased neonatal morbidity or mortality with twin discordance alone, fetal growth restriction (or other abnormalities, such as fetal anomalies or oligohydramnios) in the setting of discordance may be a risk factor for adverse perinatal outcomes.

▶ *How is the death of one fetus managed?*

In the first trimester, a substantial number of women with multifetal gestations undergo spontaneous reduction of one or more fetuses, commonly referred to as the "vanishing twin" (100). The probability of this reduction increases with the number of gestational sacs: 36% for twins, 53% for triplets, and 65% for quadruplets (101).

In the second trimester and third trimester, up to 5% of twins and 17% of triplets undergo death of one or more fetuses (102). Chorionicity influences the rate of loss, predicts outcome in the survivor, and guides management. Monochorionic–diamniotic twins have an increased risk of stillbirth compared with dichorionic–diamniotic twins (103–105). Subsequent to the demise of one twin after 14 weeks of gestation, the risk of death in the co-twin is 15% in monochorionic gestations and 3% for dichorionic gestations (105). The risk of neurologic abnormality in the surviving twin is greater in monochorionic gestations (18%) versus dichorionic gestations (1%) (106, 107). Although death of a co-twin in a monochorionic pregnancy in the late second trimester or early third trimester is associated with significant morbidity and mortality in the other fetus, immediate delivery of the co-twin has not been demonstrated to be of benefit (108). Therefore, in monochorionic twin gestations in which death of one fetus is identified before 34 weeks of gestation, management should be based on the condition of the mother or surviving fetus. In the absence of another indication, delivery before 34 weeks of gestation is not recommended (109). Care should be individualized for each patient, and consultation with a physician with advanced training in maternal–fetal medicine is recommended. In the event that a twin pregnancy is diagnosed late enough that chorionicity cannot be established, management should be guided by individualized assessment of fetal growth, growth discordance, and other indicators of fetal well-being.

▶ *What is the role of antepartum fetal surveillance in dichorionic pregnancies?*

Once chorionicity has been established in the first or early second trimester, ultrasound examination between 18 weeks and 22 weeks of gestation allows for a survey of fetal anatomy, amniotic fluid, placentation, and growth. Fetal growth in uncomplicated twin pregnancies occurs at a similar rate as singletons until approximately 28–32 weeks of gestation, when the growth rate of twins slows (110). For women with dichorionic twin gestations, there are no evidence-based recommendations on the frequency of fetal growth scans after 20 weeks of gestation; however, it seems reasonable that serial ultrasonographic surveillance be performed every 4–6 weeks in the absence of evidence of fetal growth restriction or other pregnancy complications.

The use of antepartum testing or umbilical artery Doppler ultrasonography in women with uncomplicated dichorionic multifetal gestations is not associated with improved perinatal outcomes (111). Antenatal fetal surveillance generally is reserved for women with dichorionic twin gestations complicated by maternal or fetal disorders that require antepartum testing, such as fetal growth restriction.

▶ *How are the complications caused by monochorionic placentation managed?*

Women with monochorionic pregnancies are followed more closely than those with dichorionic pregnancies because of the higher risk of developing complications in pregnancy, including twin–twin transfusion syndrome (112). This disorder occurs in approximately 10–15% of monochorionic–diamniotic pregnancies and results from the presence of arteriovenous anastomoses in a monochorionic placenta. In the affected pregnancy, there is an imbalance in the fetal–placental circulations, whereby one twin transfuses the other. It usually presents in the second trimester, and serial ultrasonographic evaluation approximately every 2 weeks beginning at approximately 16 weeks of gestation should be considered (113–115).

The criterion for diagnosis of twin–twin transfusion syndrome with ultrasonography is a monochorionic–diamniotic twin gestation with oligohydramnios (maximum vertical pocket less than 2 cm) in one sac and polyhydramnios (maximum vertical pocket greater than 8 cm) in the other sac. It is essential to rule out other etiologies, such as selective fetal growth restriction or fetal discordance for structural, genetic, or infectious disorders. There is no evidence that routine assessment with umbilical artery Doppler is beneficial in the absence of growth or fluid discordance. Once the diagnosis of twin–twin transfusion syndrome has been made, the prognosis depends on gestational age and severity of the syndrome. Staging is commonly performed via the Quintero staging system (Box 1), and treatment commonly is done by laser coagulation or amnioreduction, often in collaboration with a clinician with expertise in twin–twin transfusion syndrome diagnosis and management (112, 116).

Monoamniotic Twins

The "natural" incidence of monoamniotic twins is 1 in 10,000. However, the incidence may be increased for women who undergo in vitro fertilization using zona manipulation (117). This type of twinning is at particularly high risk, with the historic perinatal mortality quoted at up to 80%, primarily related to cord entanglement (118).

Box 1. Staging for Twin–Twin Transfusion Syndrome

Stage 1	Monochorionic–diamniotic gestation with oligohydramnios (MVP less than 2 cm) and polyhydramnios (MVP greater than 8 cm)
Stage 2	Absent (empty) bladder in donor
Stage 3	Abnormal Doppler ultrasonography findings*
Stage 4	Hydrops
Stage 5	Death of one or both twins

Abbreviation: MVP, maximum vertical pocket.

*Defined as the presence of one or more of the following: umbilical artery absent or reversed diastolic flow; ductus venosus absent or reversed diastolic flow; or umbilical vein pulsatile flow.

Data from Quintero RA, Morales WJ, Allen MH, et al. Staging of twin-twin transfusion syndrome. J Perinatol 1999;19:550–5.

Although many clinicians offer early inpatient management (beginning at 24–28 weeks of gestation) with daily fetal surveillance, regular assessment of fetal growth, and delivery between 32 weeks and 34 weeks of gestation, the optimal management of these patients remains uncertain (118–120).

Rare Complications

Acardiac twin pregnancy is a complication unique to a monochorionic gestation that is characterized by a fetus lacking a normally developed heart and head. It occurs in approximately 1% of monochorionic twins (121). The acardiac fetus is able to survive in utero because of placental anastomoses shunting blood flow from the "pump twin." The pump twin can develop a high cardiac output state and subsequent cardiac failure, which results in intrauterine or neonatal demise in approximately 50% of cases (122). These rare conditions can be managed in collaboration with a clinician with expertise in complicated twin gestation management, such as a maternal–fetal medicine specialist.

Conjoined twinning is a rare anomaly, with an incidence of 1 in 50,000 to 1 in 100,000 births (123). Once the diagnosis is reached, it is imperative that a complete workup be undertaken to determine shared anatomy, which guides management and determines prognosis (124). Even with many reports in the lay press of successful separations, of those conjoined twinning cases diagnosed in utero, there is only an 18% survival rate of one twin from ultrasonographic diagnosis to successful separation (125).

▶ *Are there special considerations for timing and route of delivery in women with multifetal gestations?*

Although, on average, women with twin pregnancies give birth at approximately 36 weeks of gestation, preterm fetuses remain at significant risk of complications of prematurity (126). The risk of perinatal mortality begins to increase again in twin pregnancies at approximately 38 weeks of gestation (127). Based on these data, and in the absence of large randomized trials that demonstrate a clearly optimal time for delivery, the following recommendations for timing of delivery seem reasonable for women with uncomplicated twin gestations (108):

- Women with uncomplicated dichorionic–diamniotic twin gestations can undergo delivery at 38 weeks of gestation.
- Women with uncomplicated monochorionic–diamniotic twin gestations can undergo delivery between 34 weeks and 37 6/7 weeks of gestation.
- Women with uncomplicated monochorionic–monoamniotic twin gestations can undergo delivery at 32–34 weeks of gestation.

The optimal route of delivery in women with twin gestations depends on the type of twins, fetal presentations, gestational age, and experience of the clinician performing the delivery. A twin gestation in and of itself is not an indication for cesarean delivery. Women with monoamniotic twin gestations should undergo cesarean delivery to avoid an umbilical cord complication of the nonpresenting twin at the time of the initial twin's delivery (118).

Women with diamniotic twin gestations whose presenting fetus is in a vertex position are candidates for a vaginal birth (128). A recent randomized trial of women with uncomplicated diamniotic twin pregnancies between 32 0/7 weeks and 38 6/7 weeks of gestation with a vertex presenting fetus demonstrated that planned cesarean delivery did not significantly decrease the risk of fetal or neonatal death or serious neonatal morbidity, as compared with planned vaginal delivery (2.2% and 1.9%, respectively; OR [with planned cesarean delivery], 1.16; 95% CI, 0.77–1.74; P=.49) (129). Therefore, in diamniotic twin pregnancies at 32 0/7 weeks of gestation or later with a presenting fetus that is vertex, regardless of the presentation of the second twin, vaginal delivery is a reasonable option and should be considered, provided that an obstetrician with experience in internal podalic version and vaginal breech delivery is available (130).

The optimal route of delivery for women with higher-order multifetal gestations remains unknown. Small observational studies have suggested that similar perinatal outcomes can be obtained for women (with uncomplicated triplet pregnancies and a presenting fetus that is vertex) who undergo planned trial of labor compared with those who undergo planned cesarean delivery. Thus, in the presence of obstetricians with experience in vaginal delivery of multiple gestations, a planned vaginal delivery of triplets can be considered (131–133).

Women with one previous low transverse cesarean delivery, who are otherwise appropriate candidates for twin vaginal delivery, may be considered candidates for trial of labor after cesarean delivery (134–138). Delivery may be complicated by the need for internal fetal manipulation or emergent cesarean delivery. Women with multifetal gestations also are at increased risk of uterine atony, postpartum hemorrhage, and emergent hysterectomy (139). The administration of neuraxial analgesia in women with multifetal gestations facilitates operative vaginal delivery, external or internal cephalic version, and total breech extraction, if necessary, and can be converted to general anesthesia if the need for an emergent cesarean delivery arises (130).

Summary of Recommendations and Conclusions

The following recommendations and conclusions are based on good and consistent scientific evidence (Level A):

- There is no role for the prophylactic use of any tocolytic agent in women with multifetal gestations, including the prolonged use of betamimetics for this indication.
- Progesterone treatment does not reduce the incidence of spontaneous preterm birth in unselected women with twin or triplet gestations and, therefore, is not recommended.

The following recommendations and conclusions are based on limited or inconsistent scientific evidence (Level B):

- Because of the increased rate of complications associated with monochorionicity, determination of chorionicity by late first trimester or early second trimester in pregnancy is important for counseling and management of women with multifetal gestations.
- Interventions, such as prophylactic cerclage, prophylactic tocolytics, prophylactic pessary, routine hospitalization, and bed rest, have not been proved to decrease neonatal morbidity or mortality and, therefore, should not be used in women with multifetal gestations.
- Magnesium sulfate reduces the severity and risk of cerebral palsy in surviving infants if administered when birth is anticipated before 32 weeks of gestation, regardless of fetal number.
- Women with one previous low transverse cesarean delivery, who are otherwise appropriate candidates for twin vaginal delivery, may be considered candidates for trial of labor after cesarean delivery.
- Women who underwent pregnancy reduction from triplets to twins, as compared with those who continued with triplets, were observed to have lower frequencies of pregnancy loss, antenatal complications, preterm birth, low-birth-weight infants, cesarean delivery, and neonatal deaths, with rates similar to those observed in women with spontaneously conceived twin gestations.
- Unless a contraindication exists, one course of antenatal corticosteroids should be administered to all patients who are between 24 weeks and 34 weeks of gestation and at risk of delivery within 7 days, irrespective of the fetal number.

The following recommendations and conclusions are based primarily on consensus and expert opinion (Level C):

- Women with uncomplicated monochorionic–monoamniotic twin gestations can undergo delivery at 32–34 weeks of gestation.
- In diamniotic twin pregnancies at 32 0/7 weeks of gestation or later with a presenting fetus that is vertex, regardless of the presentation of the second twin, vaginal delivery is a reasonable option and should be considered, provided that an obstetrician with experience in internal podalic version and vaginal breech delivery is available.
- All women with multifetal gestations, regardless of age, are candidates for routine aneuploidy screening.
- The administration of neuraxial analgesia in women with multifetal gestations facilitates operative vaginal delivery, external or internal cephalic version, and total breech extraction.
- Women with monoamniotic twin gestations should be delivered via cesarean.

Performance Measure

Proportion of women with twin gestations who present for prenatal care before 16 weeks of gestation who have chorionicity determined

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The MEDLINE database, the Cochrane Library, and the American College of Obstetricians and Gynecologists' own internal resources and documents were used to conduct a literature search to locate relevant articles published between January 1990–October 2013. The search was restricted to articles published in the English language. Priority was given to articles reporting results of original research, although review articles and commentaries also were consulted. Abstracts of research presented at symposia and scientific conferences were not considered adequate for inclusion in this document. Guidelines published by organizations or institutions such as the National Institutes of Health and the American College of Obstetricians and Gynecologists were reviewed, and additional studies were located by reviewing bibliographies of identified articles. When reliable research was not available, expert opinions from obstetrician–gynecologists were used.

Studies were reviewed and evaluated for quality according to the method outlined by the U.S. Preventive Services Task Force:

- I Evidence obtained from at least one properly designed randomized controlled trial.
- II-1 Evidence obtained from well-designed controlled trials without randomization.
- II-2 Evidence obtained from well-designed cohort or case–control analytic studies, preferably from more than one center or research group.
- II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence.
- III Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Based on the highest level of evidence found in the data, recommendations are provided and graded according to the following categories:

Level A—Recommendations are based on good and consistent scientific evidence.

Level B—Recommendations are based on limited or inconsistent scientific evidence.

Level C—Recommendations are based primarily on consensus and expert opinion.

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