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SMFM Special Statement: State of the science on multifetal gestations: unique considerations and importance

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We sought to review the state of the science for research on multiple gestations. A literature search was performed with the use of PubMed for studies to quantify the representation of multiple gestations for a sample period (2012–2016) that were limited to phase III and IV randomized controlled trials, that were written in English, and that addressed at least 1 of 4 major pregnancy complications: fetal growth restriction or small-for-gestational-age fetus, gestational diabetes mellitus, preeclampsia, and preterm delivery.

Of the 226 studies that are included in the analysis, multiple pregnancies were most represented in studies of preterm delivery: 17% of trials recruited both singleton and multiple pregnancies; another 18% of trials recruited only multiple pregnancies. For trials that studied preeclampsia, fetal growth restriction, and gestational diabetes mellitus, 17%, 8%, and 2%, respectively, recruited both singleton and multiple gestations. None of the trials on these 3 topics were limited to women with a multiple pregnancy.

Women with a multiple pregnancy are at risk for complications similar to those of women with singleton pregnancies, but their risk is usually higher. Also, the pathophysiologic condition for some complications differs in multiple gestations from those that occur in singleton gestations. Conditions that are unique to multiple pregnancies include excess placenta, placental crowding or inability of the uteroplacental unit to support the normal growth of multiple fetuses, or suboptimal placental implantation sites with an increased risk of abnormal placental location. Other adverse outcomes in multiple gestations are also influenced by twin-specific risk factors, most notably chorionicity.

Although twins have been well represented in many studies of preterm birth, these studies have failed to identify adequate predictive tests (short cervical length established over 2 decades ago remains the single best predictor), to establish effective interventions, and to differentiate the underlying pathophysiologic condition of twin preterm birth.

Questions about fetal growth also remain. Twin growth deviates from that of singleton gestations starting at approximately 32 weeks of gestation; however, research with long-term follow-up is needed to better distinguish pathologic and physiologic growth deviations, which include growth discordance among pairs (or more). There are virtually no clinical trials that are specific to twins for gestational diabetes mellitus or preeclampsia, and subgroups for multiple pregnancies in existing trials are not large enough to allow definite conclusions. Another important area is the determination of appropriate maternal nutrition or micronutrient supplementation to optimize pregnancy and child health.

There are also unique aspects to consider for research design in multiple gestations, such as designation and tracking of the correct fetus prenatally and through delivery. The correct statistical methods must be used to account for correlated data because multiple fetuses share the same mother and intrauterine environment.

In summary, multiple gestations often are excluded from research studies, despite a disproportionate contribution to national rates of perinatal morbidity, mortality, and health-care costs. It is important to consider the enrollment of multifetal pregnancies in studies that target mainly women with singleton gestations, even when sample size is inadequate, so that insights that are specific to multiple gestations can be obtained when results of smaller studies are pooled together. The care of pregnant women with multiple gestations presents unique challenges; unfortunately, evidence-based clinical management that includes the diagnosis and treatment of common obstetrics problems are not well-defined for this population.

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In 2016, the twin birth rate was 33.4 per 1000 total children born, and the triplet/higher-order birth rate was 101.4 per 100,000 total children born in the United States.[1] Collectively in the United States in 2016, there were 133,155 twin,

3871 triplet, and 252 quadruplet and higher-order multiple births. Until recently, multiple gestation births had been increasing, with approximately one-third of this increase associated with delayed maternal age at childbearing and two-thirds associated with an increase in the use of assisted reproductive technology (ART).[2,3]

Recent modest decreases in multiple births might be attributed to changes in ART practices, which includes the increasing use of single-embryo transfer in vitro fertilization.[4] Nonetheless, multiple gestations constitute a considerable percentage of pregnancies in the United States and contribute to a disproportionate degree to national rates of perinatal morbidity, mortality, and health-care costs.[5,6]

Given their high-risk status, our objective was to review the state of the science on women with multiple gestations. This review includes an estimation of how often multiple gestations are included in studies, whether we can translate findings from studies of singleton gestations to multiple gestations in instances in which data gaps exist, unique aspects of research on multiple gestations, and a call for future research. This article is not meant to be a comprehensive review of all data on multiple gestations; in most instances, we have limited the discussion to twins for illustration.

Pathophysiologic differences between multiple and singleton gestations

For many perinatal complications, including preeclampsia, gestational diabetes mellitus, preterm birth, growth restriction, perinatal death, operative delivery, and maternal morbidity, women with multiple gestations are at increased risk compared with women with singleton gestations.[5] Fetal growth in multiple gestations can be characterized additionally by the discrepancy in sizes or discordance.[7] Although many pregnancy complications are not unique to multiple gestations, it is likely that many have a different pathophysiologic condition, which includes excess placenta in some cases (eg, gestational diabetes mellitus[8] and preeclampsia[9]), placental crowding or inability of the uteroplacental unit to support the normal growth of multiple fetuses (eg, small for gestational age [SGA] or growth restriction),[10] or suboptimal placental implantation sites with increased risk of placenta previa, velamentous cord insertion, and vasa previa, than do singleton gestations.[11,12] In addition, excess carbohydrates and inadequate protein, iron, and other micronutrient deficiencies may all contribute to the higher rates of prematurity, growth restriction, preeclampsia, and possibly gestational diabetes mellitus that are observed in multiple gestations compared with singleton pregnancies.[13]

Spontaneous preterm birth of multiple gestations may also have unique predisposing factors. Multiple gestations have been hypothesized to be at higher risk of spontaneous preterm delivery because of uterine stretch, which is associated with increased expression of gap junctions, oxytocin receptors, and labor-associated signaling proteins in the myometrium.[14] Increased placental mass is associated with higher levels of corticotrophin-releasing hormone, which is correlated with the onset of parturition.[14] However, there is also likely to be some element of a shared cause for preterm birth, because women with a preterm birth of twins have an increased risk of preterm birth of a singleton in a subsequent pregnancy.[15,16]

Some adverse outcomes in twin gestations are due to twin-specific risk factors, most notably chorionicity. There are unique problems that pertain only to monochorionic twins, including twin-twin transfusion syndrome, certain congenital anomalies, disproportionate placental sharing, and a higher incidence of cord abnormalities, such as velamentous insertion.[17,18] Placental disease also demonstrates differences by chorionicity. Dichorionic placentas have been associated with more maternal vascular malperfusion lesions compared with monochorionic placentas, although monochorionic placentas have been associated with more fetal vascular malperfusion lesions compared with dichorionic placentas.[19] Monochorionicity (compared with dichorionicity) is also associated with a higher preterm birth risk and associated morbidity and death.[20] In monochorionic twins, increased rates of morbidity and mortality have been attributed primarily to the increased risk of twin-twin transfusion syndrome. In 1 study, the rates of hypertensive disease and preterm premature rupture of membranes were the same for monochorionic and dichorionic twins.[21]

Another risk factor that affects adverse outcomes in twin gestations is ART. Twin pregnancies that result from treatment with fertility drugs or ART are at higher risk of many adverse outcomes that include low birth weight, preterm delivery, and placental disorders such as bleeding, placental abruption, placenta previa and vasa previa, compared with twin pregnancies that are achieved without the use of fertility drugs or ART.[22,23]

Certain maternal characteristics independently affect outcomes in multiple pregnancies. These characteristics include race/ethnicity (increased risk of cesarean delivery and gestational diabetes mellitus in nonwhite vs white women with twins),[24] parity (increased risks of cesarean and preterm delivery in nulliparous vs multiparous women with twins),[25] maternal weight (increased risks of preterm delivery, gestational diabetes mellitus, gestational hypertension, and preeclampsia with increasing maternal body mass index [BMI] in women with twins),[26,27] and maternal height (increased risk of preterm delivery with shorter stature in women with twins).[26] However, the extent to which these factors differentially affect multiple vs singleton pregnancies is less clear. Another important factor is fetal sex; male and female fetuses in a dichorionic twin pregnancy benefit from a higher birth weight and longer gestation if they have an intrauterine female counterpart (ie, male-female pairs fare better than male-male, and female-female pairs fare better than female-male).[28]

One example of an important pathophysiologic question that remains unanswered is appropriate maternal nutrition in

multiple gestations. The 2009 Institute of Medicine (IOM) recommendations on BMI-specific weight gain in twins is provisional, and there are no recommendations for underweight women who are likely to be at the greatest risk.[29] These recommendations were formulated based on the weight gain patterns of almost 2500 women with twin pregnancies and optimal outcomes, which include normal fetal growth and birthweights, that was published by Luke et al[30] in 2003. Underweight women were excluded from the IOM recommendations because of a change in the definition of underweight BMI from <19.8 to <18.5 kg/m^2, which resulted in a smaller sample of underweight women.

Despite the provisional nature of the IOM recommendations, the impact of appropriate maternal weight gain on twin birth weight has been relatively well studied.[31] Two recent investigations noted higher rates of preterm birth and lower birthweights in women with twin gestations who failed to meet 2009 IOM weight gain recommendations.[32,33] Neither of these studies included underweight women or determined the impact of achieving weight gain goals on neonatal outcomes. Pettit et al[34] found that inadequate weight gain between 20 and 28 weeks of gestation was the strongest predictor of preterm birth at <32 weeks of gestation for multiple gestations. Women with inadequate weight gain also had increased rates of adverse neonatal outcomes that included admission to the neonatal intensive care unit, intraventricular hemorrhage, and necrotizing enterocolitis.

Since the publication of the IOM guidelines, a retrospective cohort study was performed of twin gestations that were delivered at a single center from 2000–2010.[35] Women were grouped as either having met or not met weight gain guidelines established by Luke et al[30] for a given gestational age at delivery. Of 588 twin gestations with deliveries at >24 weeks of gestation, BMI-specific weight gain was within guidelines for 59.9% of women. This group had a 1.5-fold reduction in the rate of preterm birth at <32 weeks of gestation, had larger mean birthweights, and were significantly less likely to deliver either twin with a birth weight less than the <10th percentile for gestational age than the group who had weight gains below the guidelines. A composite of neonatal morbidity, days on the respirator, length of neonatal hospital stay, and rate of neonatal intensive care admission was decreased significantly in the guideline group. Furthermore, the timing of weight gain during pregnancy also appears to be important. Greater maternal weight gain from 14–20 and from 21–27 weeks of gestation has been found to be associated differentially with increases in multiple fetal biometric parameters that include abdominal circumference, biparietal diameter, and femur and humerus lengths.[36]

Additional research is needed to evaluate the impact of maternal weight gain goals on prematurity, fetal growth, and neonatal outcomes in multiple gestations. Determination of whether trimester-specific rates, as opposed to total weight gain recommendations, leads to better outcomes may also be more clinically useful given the increased risk of preterm delivery in twins and the potential importance of timing of weight gain. In the absence of randomized control trials (RCTs), future studies need to combine data from multiple institutions to ensure adequate sample sizes when stratifying by prepregnancy BMI, including underweight women, so that a stronger argument can be made for the IOM to revise their provisional and incomplete recommendations. More data regarding the potential consequences or benefits that are associated with overachieving the recommended maternal weight gain goals would also be informative.

In summary, important questions remain about the pathophysiologic conditions that are associated with twin pregnancy complications and potentially effective interventions. For multiple gestations, there are even more data gaps to consider than in the care of complicated singleton gestations.

Methods

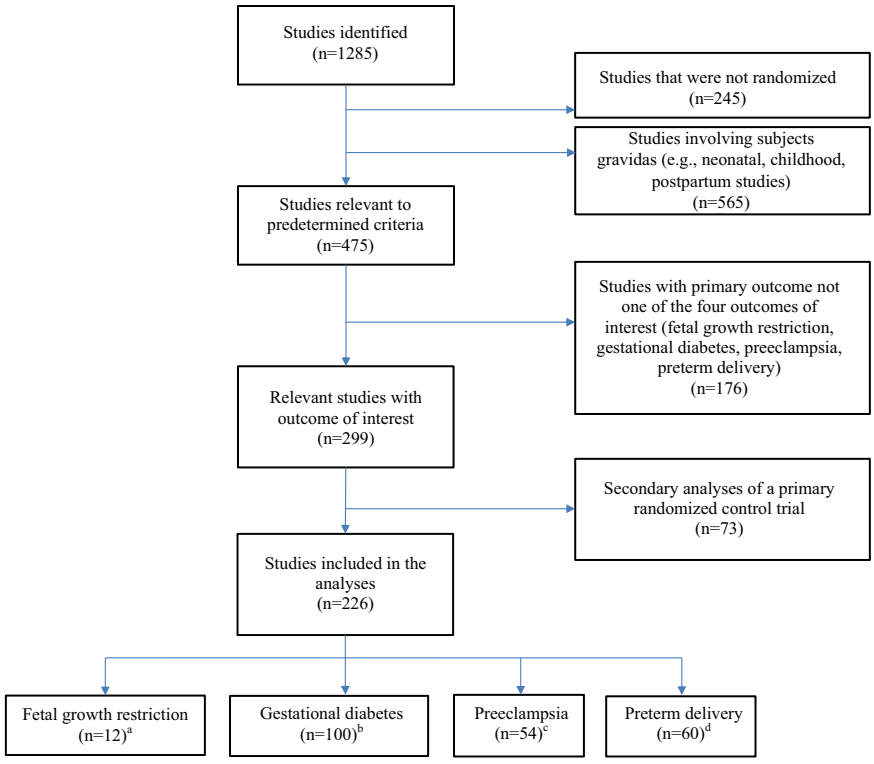
To quantify the representation of twins and multiple gestations, we performed a literature search in PubMed for a sample period (2012–2016) limited to phases III and IV RCTs that were written in English and that addressed at least 1 of 4 major pregnancy complications that were used for illustration: fetal growth restriction or SGA, gestational diabetes mellitus, preeclampsia, and preterm delivery. Search terms included controlled vocabulary terms (ie, medical subject headings) and variations of the following keywords: singleton, twin, triplet, and multiple births. See the Appendix for search details. Our search resulted in 1285 articles. Because some articles might have addressed multiple topics, this number includes double-count results (Figure 1). Articles from the search were reviewed individually and excluded if they had any of the following subjects: nonrandomized controlled trials; study subjects who were not pregnant women (eg, neonatal, childhood, or postpartum studies); the primary study outcome was not 1 of the 4 outcomes of interest; and studies that were secondary analyses of a primary RCT.

This process resulted in 226 articles for analysis. The 226 articles were further reviewed and coded by 3 reviewers (A.C., T.K,. and R.N. with adjudication by K.L.G.), based on subject inclusion of singleton gestations, twins, or both. In cases in which singleton or multiple births were not stated, we contacted the authors for clarification. If there was no response, the study was placed in the unidentified category.

Representation of multiple gestations in research

Figure 2 presents the percentages of RCTs for singleton gestation, twin or multiple gestation only, both singleton and multiple gestations, or unidentified pregnancies from 2012–2016 for the 4 major outcomes. Most studies were performed in only singleton gestations for all 4 outcomes. Of the 226 studies that were included in the analysis, multiple pregnancies were most represented in RCTs studying preterm delivery: 17% of trials recruited both singleton and multiple pregnancies, and another 18% of trials recruited only multiple pregnancies. For trials studying preeclampsia, fetal

FIGURE 1
Flow diagram for study selection



[a] Total includes three papers that overlap with preeclampsia and preterm delivery for primary outcome
[b] Total includes two papers that overlap with preeclampsia for primary outcome
[c] Total includes three papers that overlap with fetal growth restriction and gestational diabetes for primary outcome
[d] Total includes two papers that overlap with fetal growth restriction for primary outcome

Literature search was performed in PubMed to quantify the representation of twins and multiple gestations for a sample period (2012—2016) and limited to phases III and IV randomized control trials that addressed 4 major pregnancy complications for illustration: fetal growth restriction or small for gestational age (fetal growth restriction), gestational diabetes mellitus, preeclampsia, and preterm delivery. Search terms included controlled vocabulary terms (ie, medical subject headings) and variations of the following keywords: singleton, twin, triplet, and multiple births. [a]Total includes 3 papers that overlap with preeclampsia and preterm delivery for primary outcome; [b]Total includes 2 papers that overlap with preeclampsia for primary outcome; [c]Total includes 3 papers that overlap with fetal growth restriction and gestational diabetes mellitus for primary outcome; [d]Total includes 2 papers that overlap with fetal growth restriction for primary outcome.

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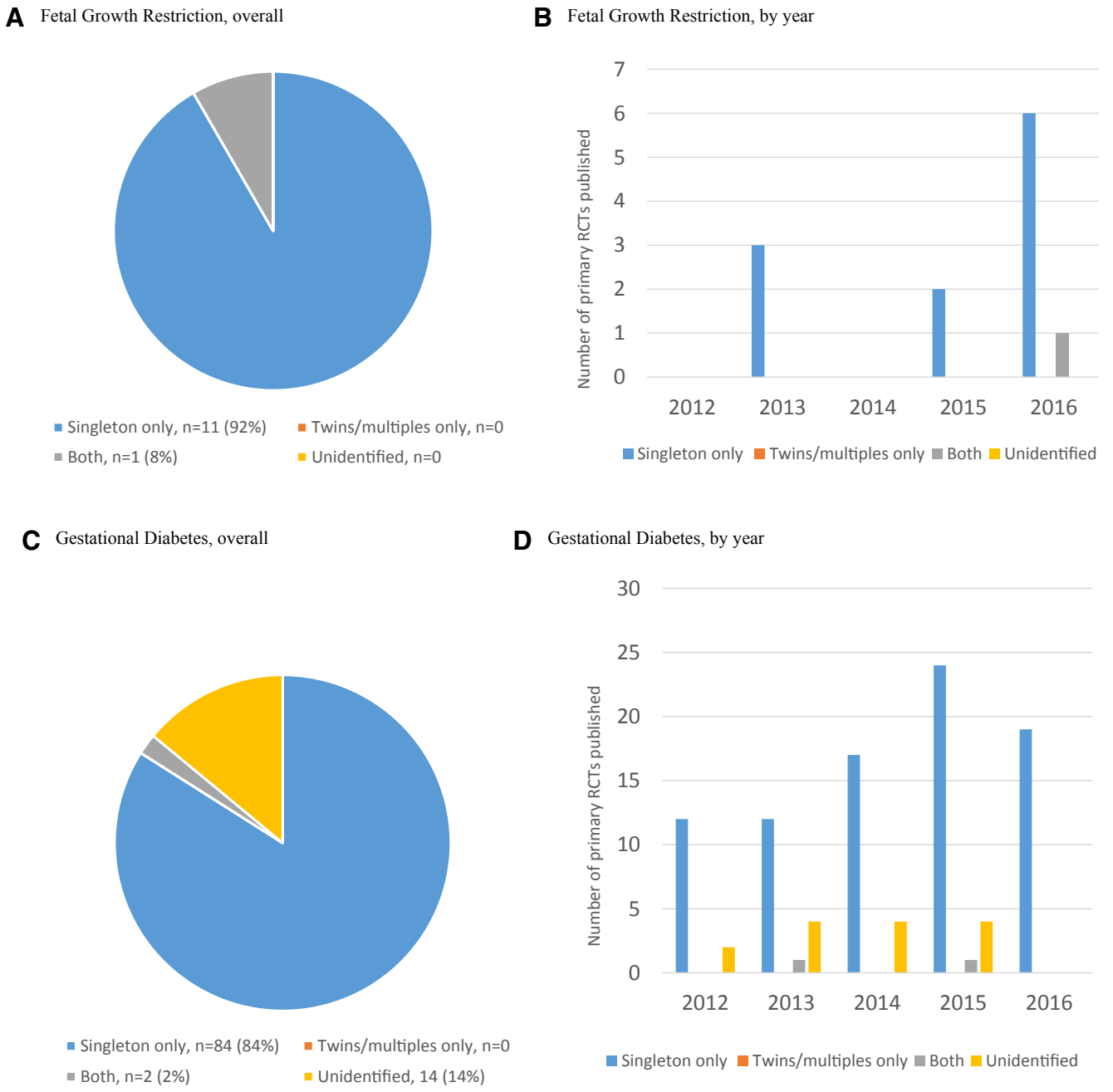
growth restriction, and gestational diabetes mellitus, 17%, 8%, and 2% recruited both singleton and multiple gestations, respectively. None of the trials on these 3 topics included only women with a multiple pregnancy. There did not appear to be a trend towards increasing or decreasing inclusion of multiple gestations over time.

These findings indicate that twin and multiple gestations sometimes are included in studies with singleton gestations; however, in studies of twin or multiple gestations alone, they were well represented in trials of preterm delivery but underrepresented in studies of fetal growth restriction, gestational diabetes mellitus, and preeclampsia over the past 5 years.

Major advances in improving pregnancy outcomes for twin and multiple gestations in most areas are wanting. Much of the existing research has focused on preterm birth interventions, which have not proved effective. 17 Alpha-hydroxyprogesterone caproate has not been shown to decrease preterm birth in unselected women with twin and triplet gestations.[37–42] Progesterone gel has also been found to be ineffective in trials of unselected twin gestations.[43,44] An individual participant data meta-analysis reviewed 13 trials of progestogens in twin pregnancies and concluded that 17 alpha-hydroxyprogesterone caproate and vaginal progesterone are ineffective at the prevention of preterm birth or improvement of perinatal outcomes in unselected pregnancies.[45]

Of concern, 17 alpha-hydroxyprogesterone caproate was found to be associated with potential risks that included an

FIGURE 2
Representation of twins or multiple gestations in research



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(continued)

increased risk of midtrimester fetal loss in triplets[40] and with an increased risk of a composite adverse outcome and perinatal death.[46] A meta-analysis that used individual participant data noted a similar trend.[45] Two meta-analyses performed subgroup analyses and found that vaginal progesterone might decrease the risk of preterm birth in women with a short cervical length.[46,47] Based on these data, the American College of Obstetricians and Gynecologists does not recommend intramuscular progesterone in unselected twin or triplet gestations and cites insufficient data to make recommendations for vaginal progesterone in twin and triplet pregnancies with a short cervical length.[5]

Approaches to prevention of preterm birth in multiple gestations with the use of mechanical means have included

FIGURE 2
Representation of twins or multiple gestations in research *(continued)*

A, Fetal growth restriction, overall. **B,** Fetal growth restriction, by year. The percent of randomized controlled trials for singleton; twin or multiple only; both twin and singleton or unidentified pregnancies from 2012—2016 are presented for the 4 major outcomes overall (**A, C, E, G**) and by year (**B, D, F, H**; no statistical testing performed).

RCTs, randomized controlled trials.

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both cerclage and cervical pessary. Neither of these interventions is effective in women with unselected twin or triplet gestations.[48–52] Cerclage in selected twin pregnancies with a short cervix has been found potentially to be associated with an increased risk of spontaneous preterm birth.[53,54] In a subgroup analysis from a randomized trial of prophylactic Arabin pessary placement between 16 and 20 weeks of gestation, women with a short cervix had a

BOX

Examples of clinical questions in twin gestations that remain unanswered or have been addressed only partially[a]

- Corticosteroids for <34 weeks of gestation, 34–36 weeks of gestation
- Magnesium for neuroprotection
- Preterm birth prevention: role of cerclage, pessary, and/or vaginal progesterone
- Use of singleton vs twin fetal growth reference
- Monitoring and management of fetal growth discordance among twin pairs (in absence of fetal growth restriction of 1 or both fetuses)
- Aspirin for prevention of preeclampsia
- Management of severe preeclampsia remote from term
- Diagnosis and management of gestational diabetes mellitus
- Maternal and neonatal morbidity associated with gestational diabetes mellitus
- Benefits of focused nutritional intervention or micronutrient supplementation
- Trimester and chorionicity-specific maternal weight gain recommendations
- How to date (eg, use biometric measurements of larger twin, smaller twin, or average)
- Ultrasound scanning intervals for fetal growth assessment
- Antenatal testing in uncomplicated monochorionic and dichorionic twins
- Timing of delivery for uncomplicated monochorionic and dichorionic twins
- Clinical treatment of surviving twin after death of 1 twin
- Optimal delivery route for higher-order multifetal gestations

[a] Note that randomized controlled trials have been performed for some of these questions; however, questions remain, and clinical guidelines call for additional data.

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potential benefit of decreased preterm delivery with more effect at earlier gestational ages (<28 weeks of gestation relative risk ([RR], 0.79; 95% confidence interval [CI], 0.50-1.27) and <32 weeks RR, 0.86; 95% CI, 0.65-1.15). In a subsequent randomized trial of 137 women with twin pregnancies and cervical length ≤25 mm, the Arabin pessary was associated with a decreased risk of spontaneous preterm birth at <34 weeks of gestation (16.2%) compared with 39.4% in the expectant treatement group (RR, 0.41; 95% CI, 0.22–0.76).[55] Among singleton gestations with a short cervix, 2 randomized trials found use of a pessary to be effective[56,57]; 2 trials did not.[58,59]

A recent meta-analysis compared progesterone (intramuscular and vaginal), pessary, or cerclage in unselected twin pregnancies and concluded that no intervention was beneficial in the prevention of preterm birth compared with no intervention or placebo. However, vaginal progesterone was associated with a decreased risk of some secondary neonatal outcomes, such as very low birth weight <1500 g (RR, 0.71; 95% CI, 0.52–0.98; 4 studies, I^2 46%) and mechanical ventilation (RR, 0.61; 95% CI, 0.45–0.82; 4 studies, I^2 22%).[60] In the subgroup of women with a short cervix, none of the interventions were associated with a reduction in preterm birth (the primary outcome), although the comparison groups varied across the studies and not all were placebo-controlled. Vaginal progesterone and pessary were associated with the secondary outcome of increased gestational age at delivery. Vaginal progesterone was also associated with a decreased risk of very low birth weight, neonatal mechanical ventilation, and neonatal death among twins delivered by women with a short cervix. An accompanying editorial called for additional intervention trials in high-risk twin gestations.[61] However, even the identification of high-risk groups remains challenging. In 1996, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Maternal-Fetal Medicine Units Network Preterm Prediction Study in twins established that short cervical length was the best predictor of preterm birth.[62] Almost 2 decades later, a review of 19 biophysical and biochemical tests to predict preterm birth (primarily in asymptomatic women) did not find any new preterm birth predictors in twin gestations. A single cervical length measurement at 20–24 weeks of gestation was the best available test, with sensitivity and specificity ranging from 21–64% and 93–97%, respectively, for different selected secondary outcomes: preterm birth <28, 32, 34, and 37 weeks of gestation and different cutoffs that included 20 or 25 mm.[63] Tests for improved prediction are essential to target interventions.[64]

Clinical management of pregnancies with threatened preterm birth have been evaluated primarily in studies of singleton gestations, including betamethasone, magnesium sulfate for neuroprotection, and tocolysis.[5] For example, a recent Cochrane review that included 30 RCTs (singleton or multiple gestations) that evaluated antenatal corticosteroids found that only 4 studies evaluated outcomes in multiple gestations.[65] Authors concluded that data are limited in multiple gestations; there are emerging data that singleton or multiple gestations had different outcomes after antenatal corticosteroids. In the absence of data, the American College of Obstetricians and Gynecologists recommends antenatal corticosteroids for women with multiple gestations at risk for preterm delivery within 7 days. Although prospective studies have not evaluated whether steroid dosages should differ for women with multiple gestations, betamethasone concentrations in umbilical cord serum are similar in twin and singleton gestations.[66]

Systematic evaluation and estimation of growth trajectories in twins require ultrasound measurements across gestation, performed in controlled clinical settings. Until recently, there were few such data for contemporary populations. The NICHD Fetal Growth Studies–Twins empirically defined the trajectory of fetal growth in 171 dichorionic twins and compared the fetal growth trajectories for dichorionic twins with those based on a growth standard that has been developed for singleton gestations.[67] Beginning at 32 weeks of gestation, the median

abdominal circumference and estimated fetal weight trajectories of twin fetuses diverged significantly from that of singleton gestations; there were no differences in head circumference or femur length. At 32 weeks of gestation, 34% of twins would be classified as SGA with the use of the NICHD singleton, non-Hispanic white standard cutoff of <10th percentile. This finding is important because the Hadlock et al[68] reference, which is used commonly in the United States, is based on white women only. By 35 weeks of gestation, 38% of twins were classified as SGA. The comparatively asymmetric growth pattern in twin gestations, initially evident at 32 weeks of gestation, is consistent with a pattern of constrained intrauterine growth for multiple fetuses.[69] It is unclear whether an ultrasound reference that is specific for twins should be used. Although SGA might be part of a normal adaptive process in multiple gestations, it is also possible that it represents pathologic fetal growth restriction that is associated with increased morbidity and death. In another study of twin growth with childhood follow-up, fetuses with a head circumference, abdominal circumference, or femur length below the 10th percentile at 28 weeks of gestation were shorter at age 3 years. Those with abdominal circumference or femur length below the 10th percentile had lower weight-for-age percentiles and z-scores compared with twin fetuses of normal growth.[70] Mental and motor development did not differ between the groups. Future studies with long-term follow-up are needed to determine whether twin neonates that are born smaller than gestational age–matched singleton gestations, but within a normal reference range of birth weight, experience long-term consequences.

Growth of twins can be characterized additionally by a relational discrepancy in sizes or discordance between the twins. The discordance percentile (eg, 15%, 18%, 20%) that may be the optimal threshold, independent of individual fetal growth restriction, is uncertain for increased clinical surveillance and interventions that include delivery.

In summary, these examples illustrate that clinical management, including diagnosis and treatment of common obstetric problems, is not well-defined for twin gestations. Data are limited regarding preterm birth in twins and fetal growth restriction, and there are virtually no clinical trials that are specific to twins for gestational diabetes mellitus or preeclampsia. Moreover, there may be significant physiologic differences between singleton and twin gestations. Findings from studies that were limited to singleton gestations should be applied to twin pregnancies with caution. Examples of important questions that remain unanswered about the optimal management of multiple gestations to maximize maternal, fetal, and child health are outlined in the Box.

Unique research opportunities

A significant body of literature addresses the variable incidence of numerous adult disease states among monozygotic and dizygotic twins. Discordance in disease states between monozygotic twins suggests the primacy of environmental influences, especially when they are reared separately, although differences in dizygotic twins raised together suggest a potential genetic predisposition to disease.[71,72] If the concordance rate of a particular disease in monozygotic pairs is greater than that of dizygotic pairs, a genetic cause can be inferred. For example, our knowledge about the genetic susceptibility for risk of death from early-onset (before age 55 years) coronary heart disease comes from a study of 3655 monozygotic and 6847 dizygotic twin pairs. This study found that the risk of death was much greater in individuals with a monozygotic twin who died of early-onset coronary heart disease than in individuals with a dizygotic twin who died of early-onset coronary heart disease, which suggests genetic susceptibility.[73] Most of these studies have been done in older children and adults. Perinatal research on twin gestations provides unique opportunities to study the environmental vs genetic cause of disease and epigenetic variation that arises during the fetal and newborn periods.[72] Shared factors include maternal lifestyle and gestational age, and nonshared factors include those that are individual to each twin (eg, individual growth, chorionicity, and zygosity). Studies of twin pregnancies may be used to advance research under the developmental origins of health and disease hypothesis that early life exposures can "program" an individual for health and chronic disease risk through cellular adaptations to biologic processes.[74]

Research designs for multiple gestations

There are specific aspects to consider when designing research studies of women with multiple gestations. Chorionicity should be established with ultrasound scanning in the first trimester and confirmed with placental pathologic findings (rate of confirmation, 77–100% in 1 review).[75] Procedures to maintain twin designation are necessary if in utero factors are an important variable. For example, the NICHD Fetal Growth Studies–Twins developed a protocol in which a series of identifying information was collated at each follow-up visit. This information included fetal sex, identification of markers or abnormalities (eg, intracardiac echogenic focus or anomaly), placental location, placental cord insertion, fetal position relative to the cervical os, relative size of individual fetal biometrics and estimated fetal weight, maximum vertical pocket, fetal location (noted as maternal left or right, inferior or superior, and anterior or posterior), and fetal presentation and lie.[67] At the time of delivery, care must be taken to match same-sex twins with their antenatal designation with the use of an established protocol.

Because data that are specific to multiple gestations are lacking, it remains a challenge to know whether new clinical management strategies and treatments in singleton gestations should be offered to multiple gestations. Women and their partners need to be counseled appropriately about such limitations.

The data gaps in the management of twin pregnancies are well-known, yet incorporation of multiple gestations into clinical studies remains challenging. When a study is designed, it is important to note when multiple gestations should be studied separately to answer a question, such as when the pathophysiologic condition of the disease process or the effect of the intervention in the case of a randomized controlled trial is expected to differ in multiple gestations compared with singleton gestations.

Sample size calculations need to be performed separately for singleton gestations and twin gestations in these instances. However, it is still important to enroll twin gestations, even if the sample size is small, so that insights that are specific to multiple gestations can be obtained. Although the number of twins is much lower than singleton gestations, the rates of various complications are higher (frequently much higher); with 2 fetuses experiencing neonatal outcomes, statistical power is increased. For studies that cannot recruit an adequate number of multifetal gestations to reach targeted sample sizes, researchers can consider whether the study design can be modified so that data are relevant to multiple gestations.

Studies with multiple gestations also need to use appropriate statistical considerations of correlated data. Because twins have the same mother, they share an environment that needs to be considered with statistical analyses. Gates and Brocklehurst[76] compared 4 analytic methods: (1) assuming independence among babies, (2) analyzing outcomes per woman (including a woman if any of her offspring had an adverse outcome), (3) randomly selecting 1 offspring for analysis, and (4) adjusting for nonindependence and noting the disadvantages of not including outcomes for all of the offspring in a trial. Yelland et al[77] found that adverse neonatal outcomes were correlated moderately to strongly among offspring from twin gestations, although the correlation varied considerably by outcome. They proposed including the correlation of outcomes into the sample size calculation when designing a trial. Analytic methods should be chosen based on the primary outcome and reported in the clinical trial. Consultation with a statistician or researcher experienced in this area is recommended.

Future

In summary, many important questions remain to be answered in the management and study of multiple gestations. Although multiple gestations represent a small proportion of deliveries in the United States, they have a disproportionately high population-attributable risk of perinatal morbidity and death. Therefore, multiple gestations should be included in as many studies as possible, and the likelihood of profound physiologic differences and differences in pathophysiologic conditions relative to singleton gestations, and factors such as chorionicity and mode of conception should be accounted for. It is unclear whether the epidemiologic condition of multiple gestations will change in the coming decade; however, trends towards later childbearing and increasing use of ART suggest that the rate of multiple gestations may increase as well.

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APPENDIX
Terms used in the literature search

Fetal growth restriction: ((("clinical trial, phase iii"[pt] OR "clinical trial, phase iv"[pt] OR "controlled clinical trial"[pt] OR "randomized controlled trial"[pt] OR "Double-Blind Method"[Mesh]) NOT "review"[pt:noexp]) AND Clinical Trial[ptyp] AND ("2012/01/01"[PDAT] : "2016/12/31"[PDAT])) AND ((("fetal growth retardation"[MeSH Terms] OR ("fetal"[TIAB] AND "growth"[TIAB] AND "retardation"[TIAB]) OR "fetal growth retardation"[TIAB] OR ("intrauterine"[TIAB] AND "growth"[TIAB] AND "retardation"[TIAB]) OR "intrauterine growth retardation"[TIAB]) AND English[Language] AND "humans"[MeSH Terms])

Premature birth: ((("clinical trial, phase iii"[pt] OR "clinical trial, phase iv"[pt] OR "controlled clinical trial"[pt] OR "randomized controlled trial"[pt] OR "Double-Blind Method"[Mesh]) NOT "review"[pt:noexp]) AND Clinical Trial[ptyp] AND ("2012/01/01"[PDAT] : "2016/12/31"[PDAT])) AND (("premature birth"[MeSH Terms] OR ("premature"[TIAB] AND "birth"[TIAB]) OR "premature birth"[TIAB] OR ("preterm"[TIAB] AND "birth"[TIAB]) OR "preterm birth"[TIAB]) AND English[Language] AND "humans"[MeSH Terms])

Preeclampsia: ((("clinical trial, phase iii"[pt] OR "clinical trial, phase iv"[pt] OR "controlled clinical trial"[pt] OR "randomized controlled trial"[pt] OR "Double-Blind Method"[Mesh]) NOT "review"[pt:noexp]) AND Clinical Trial[ptyp] AND ("2012/01/01"[PDAT] : "2016/12/31"[PDAT])) AND (("pre-eclampsia"[MeSH Terms] OR "pre-eclampsia"[TIAB] OR ("pre"[TIAB] AND "eclampsia"[TIAB]) OR "preeclampsia"[TIAB]) OR ("hypertension, pregnancy-induced"[MeSH Terms] OR ("hypertension"[TIAB] AND "pregnancy-induced"[TIAB]) OR "pregnancy-induced hypertension"[TIAB] OR ("gestational"[TIAB] AND "hypertension"[TIAB]) OR "gestational hypertension"[TIAB]) AND English[Language] AND "humans"[MeSH Terms])

Gestational diabetes mellitus: ((("clinical trial, phase iii"[pt] OR "clinical trial, phase iv"[pt] OR "controlled clinical trial"[pt] OR "randomized controlled trial"[pt] OR "Double-Blind Method"[Mesh]) NOT "review"[pt:noexp]) AND Clinical Trial[ptyp] AND ("2012/01/01"[PDAT] : "2016/12/31"[PDAT])) AND (("diabetes, gestational"[MeSH Terms] OR ("diabetes"[TIAB] AND "gestational"[TIAB]) OR "gestational diabetes"[TIAB] OR ("gestational"[TIAB] AND "diabetes"[TIAB])) AND English[Language] AND "humans"[MeSH Terms])

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