Timing Delivery of the Growth-Restricted Fetus

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Intrauterine growth restriction (IUGR) is commonly defined as an estimated fetal weight of less than the 10th percentile. While 70% of these are small for normal reasons and not at risk, 30% are pathologically small at risk for numerous complications including fetal death. In the late preterm IUGR fetus (>34 weeks), prematurity risks less and the risk of fetal demise becomes the primary concern. Pulsed-wave Doppler interrogation of the umbilical and middle cerebral artery is useful in reducing perinatal mortality, however, Doppler changes in these vessels of the IUGR fetus may not occur after 34 weeks gestation. There are no randomized trials addressing the timing of delivery of the IUGR fetus in the late preterm or early-term period. However, retrospective reports show an increase risk of fetal demise. While timing the delivery of the late preterm/early-term IUGR fetus requires consideration of multiple factors (e.g. degree of growth restriction, etiology, amniotic fluid volume, and biophysical and Doppler testing), available data suggests that delivery should occur by 37 to 38 weeks for singleton IUGR fetuses. In twin pregnancies with a co-twin IUGR fetus, chorionicity also impacts timing of delivery, but delivery should occur by 34-36 weeks.

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Small for gestational age (SGA) and intrauterine growth restriction (IUGR) are terms frequently used to describe the small fetus. SGA was defined by neonatologists in 1967 to categorize a newborn with a birth weight less than the 10th percentile.1 Over time, SGA was adopted by obstetricians to broadly classify the under grown fetus regardless of etiology. Although the terms SGA, fetal growth restriction, and IUGR are often used interchangeably, the term IUGR will be used in this article because it reflects both the fetus and placenta and because it is the preferred term of both the American College of Obstetrics and Gynecology (ACOG).2 An estimated fetal weight (EFW) less than the 10th percentile has been most widely applied as the threshold to define IUGR and has been used by ACOG.3 Relative to the diagnosis, management and timing of delivery of the IUGR fetus, it is important to be mindful of 3 points regarding this definition. First, this definition, like many, is derived from population-based growth curves, and this does not take into account the individualized growth potential of individuals. As such, it will overdiagnose growth failure and will miss a small percentage of larger fetuses that have failed to achieve their growth potential and may be at risk.3 Second, Approximately 70% of infants with a birth weight less than the 10th percentile are small but normally grown (constitutionally small), and are not at risk for adverse perinatal outcomes, leaving 30% that are truly IUGR and at risk.4 Third, lower percentile cutoffs may be more highly associated with adverse perinatal outcomes.5 Despite the limitations of the 10th percentile based on population growth curves, this cutoff is more sensitive in the identification of fetuses at increased perinatal risk.6 Most evaluated neonatal complications are increased with decreasing birth weight percentile, even when addressed for pregnancies delivering at term. This is highlighted by a study of more than 137,000 deliveries at term from the North-West Thames regional database. The authors found increased rates of perinatal mortality, meconium staining, emergency cesarean delivery, transfer to the neonatal intensive care unit, as well as low Apgar scores and umbilical cord pH with reduced birth weight percentile (especially below 2 standard deviations).7

Although the focus of this article is on timing delivery of the late preterm and early-term IUGR fetus, most what we understand about the pathologic processes and timing of delivery for IUGR is based on studies that were performed on preterm (less than 34 weeks) fetuses. There are a limited
number of studies that address timing the delivery of the late preterm/early-term IUGR fetus, and it has historically been generally accepted that lower thresholds for delivery of the IUGR fetus should exist after 34 weeks of gestation. Whether the pregnancy is preterm, near term, or at term, several factors are important to consider that influence the management of and delivery timing of the IUGR fetus.

### Determinants of Delivery of the IUGR Fetus

Factors that influence whether the IUGR fetus should be delivered are listed in Table 1. Understanding the value that each of these determinants brings to the management and delivery of the IUGR fetus helps one understand the current health and developmental status of the fetus. Furthermore, these factors can assist the practitioner in determining whether continued intrauterine life or removal from a hostile intrauterine environment is more appropriate. These factors are reviewed as they pertain to the delivery indication, and in many circumstances are applicable to the preterm, near term and term IUGR fetus.

#### Classification and Etiology

IUGR can be classified as symmetric or asymmetric, with the latter characterized by a head-to-abdominal circumference ratio of greater than the 95th percentile. This categorization may be helpful in understanding the etiology and to stratify risk, but its clinical utility has not been clearly demonstrated. For example, IUGR because of a placental cause is typically asymmetric but may be symmetric if the insult occurs early in gestation. The underlying etiology is more important and may assist with determination of timing of delivery. For instance, fetal aneuploidy or congenital viral infection may not have outcomes altered by delaying delivery until term. More specifically, the presence of a lethal condition would result in maternal preference with safety taking precedence in timing the delivery. The fetus with IUGR because of uteroplacental disease is most amenable to management with biophysical testing and Doppler velocimetry studies. This diagnosis is usually one of exclusion. However, various phenotypic signs, especially in combination, are suggestive of a uteroplacental cause. These are delineated in Table 2.

#### Behavioral Responses

A number of methods for assessing fetal well-being, including the nonstress test (NST), biophysical profile (BPP), and maternal perception of fetal movement (FM), can be grouped under behavioral responses. The IUGR condition impacts the fetal response in these tests compared with controls. A decrease in maternal perception of FM has been reported to be a concerning sign for fetal health and helps physicians identify fetuses at increased risk for fetal distress in labor. However, FM assessment is more objectively performed by ultrasound and biophysical profile testing. Approximately 80% of normally developed fetuses at 32 weeks will demonstrate fetal heart rate reactivity and biophysical profile test scores of 8/8 or 8/10. However, IUGR fetuses resulting from uteroplacental dysfunction with secondary chronic hypoxia demonstrate slow maturation of the central nervous system that leads to a delay in all the behavioral responses of the biophysical profile and NST, most noticeably between 28 and 32 weeks gestation. Other findings seen with IUGR compared with normally developed fetuses include an elevated fetal heart rate (FHR) and lower short/long term variability. Although central nervous system maturation is delayed, centrally regulated responses to hypoxia remain preserved. With fetal hypoxemia, there will be a decrease in overall fetal activity, a progressive loss of individual biophysical profile components, and often a gradual decline in amniotic fluid volume. With persistent hypoxemia and developing acidemia, fetal breathing motions, body movements, and tone decrease and finally cease. IUGR fetuses delivered before 34 weeks generally receive betamethasone for fetal benefit if delivery is not emergent. Importantly, antenatal corticosteroids influence behavioral responses, including temporary reductions in FHR variability, fetal movements, and fetal breathing motions on days 2 and 3 after administration. A reactive NST reflects an absence of fetal acidemia and correlates well with a low risk of fetal demise. In contrast, a biophysical profile score of 4 or less, repetitive decelerations, or computerized FHR monitor showing a nonreactive tracing are asso-

### Table 1 Determinants of delivery timing for the IUGR fetus

<table>
<thead>
<tr>
<th>Classification and etiology</th>
<th>Behavioral responses</th>
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<tbody>
<tr>
<td>Nonstress testing</td>
<td>Biophysical profile</td>
</tr>
<tr>
<td>Fetal movement</td>
<td>Doppler velocimetry</td>
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<tr>
<td>Amniotic fluid volume</td>
<td>Interval growth</td>
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<tr>
<td>Gestational age</td>
<td>Maternal comorbidity</td>
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### Table 2 Phenotype of the IUGR Fetus with Uteroplacental Disease

- Asymmetric biometric growth
- Exclusion of structural abnormalities
- Evidence of brain-sparing effect
  - Head size maintained
  - Reduced MCA Doppler index or CPR
- Oligohydramnios
- Abnormal umbilical artery Doppler velocimetry
  - Elevated Doppler index
  - Absent (AEDF) or reversed (REDF) end-diastolic flow
- Abnormal venous Doppler velocimetry
  - Increased venous Doppler indexes
  - Umbilical venous pulsation
- Abnormal biophysical testing
  - Spontaneous recurrent late decelerations
  - Abnormal biophysical profile score (≤4)

CPR, cerebral-placental ratio; MCA, middle cerebral artery.
cated with increased rates of fetal hypoxemia/acidemia, and umbilical cord compression because of oligohydramnios. These findings also have been associated with increased perinatal mortality and are indicators for delivery. However, even in the face of BPP score or FHR abnormalities, gestational age may temper the desire to immediately deliver a very preterm IUGR fetus.

Amniotic Fluid Volume

Amniotic fluid volume reflects the degree of fetal renal perfusion and is thus an indirect measure of fetal vascular status. Oligohydramnios itself is a poor screening tool for IUGR, but may be the first sign of a growth-restricted fetus. Manning et al showed that up to 96% of fetuses with fluid pockets <1 cm in-depth may be IUGR. In general, progressive reduction in amniotic fluid volume is thought to be attributable to redistribution of blood flow favoring the fetal heart, brain, and adrenal glands and away from lungs, digestive tract, kidneys, and torso; it has been well described with hypoxia in lambs. This so-called “brain-sparing” effect has been described in human IUGR pregnancies and the reduction in renal blood flow is thought to account for the oligohydramnios. With progressive redistribution and deterioration of fetal vascular status, oligohydramnios becomes more likely. More specifically, there has been a well-described association between oligohydramnios and progressive worsening of both arterial and venous Doppler velocimetry findings. There are no randomized trials of delivery with oligohydramnios in IUGR pregnancies. However, data associating IUGR and oligohydramnios with fetal hypoxia, abnormal Doppler studies and biophysical testing, and with increased rates of fetal distress in labor and perinatal mortality have lead to expert opinion that delivery should occur after 34 weeks’ gestation in the setting of IUGR with oligohydramnios.

Doppler Velocimetry

The use of Doppler velocimetry has been studied extensively in the IUGR fetus and is considered a primary tool for assessment of vascular status and managing the pregnancy complicated by IUGR. Most of this work has been done in preterm pregnancies, with a focus on the umbilical and middle cerebral arteries and venous system. Absent or reverse flow in the umbilical artery is associated with approximately 60%-70% obliteration of placental arteries, rates of 50%-80% of intrauterine hypoxemia, and an 80-fold increased risk of perinatal mortality. Several meta-analyses have demonstrated that use of umbilical artery Doppler velocimetry in conjunction with standard antenatal testing significantly reduces the rate of fetal demise. During the past 2 decades, interrogation of the fetal venous structures has gained significant attention. Through studies, such as those by and Rizzo et al and Hecher et al, it has become apparent that reverse venous flow in the ductus venosus and inferior vena cava during atrial contraction is most reflective of fetal metabolic acidemia. Several studies that investigated longitudinal venous Doppler changes and biophysical testing in severely growth-restricted fetuses found that venous Doppler changes (especially ductus venosus) precede biophysical profile and FHR monitor abnormalities. Thus, it has been proposed that abnormal venous Doppler findings should be used to trigger delivery of the IUGR fetus. Work by Hecher and colleagues depicted the close relationship between ductus venosus flow abnormalities and decreased short-term variability in the IUGR fetus (Fig. 1).

Doppler triggers for delivery, like other determinants of delivery, need to be reconciled with the gestational age because the latter is the strongest predictor of intact survival at least until 29 weeks’ gestation. Unfortunately, data regarding Doppler blood flow in pregnancies beyond 34-weeks gestation are limited for 2 primary reasons: (1) the overwhelming majority of fetal vascular Doppler studies have been performed on fetuses <34 weeks of gestation, and (2) umbilical artery Doppler interrogation is less reliable after 34 weeks.

Interval Growth

As a consequence of redistribution of blood flow towards “vital” structures and away from “nonvital” structures with uteroplacental insufficiency, somatic growth of the fetus is hindered. This has lead to the suggestion that cessation of growth, especially after 34 weeks, should be an indicator for delivery. However, before 34 weeks, consideration of gestational age should enter the decision-making process regarding delivery because this is a critical factor in overall and intact survival.

Gestational Age

There is a well-known inverse relationship between gestational age and perinatal morbidity and mortality. IUGR complicates matters more when it occurs before 34 weeks because the IUGR fetus appears to deteriorate more quickly and has greater prematurity-related morbidity. Studies by Baschat et al and Mari et al have shown that time gained in utero for IUGR pregnancies improves survival. Baschat and colleagues showed in severe IUGR pregnancies that the primary predictors for overall and intact survival were gestational ages of 26 6/7 weeks and 29 2/7 weeks, respectively. Bernstein et al found that each additional day in utero brought an estimated 2% benefit in neonatal survival until 29 weeks in IUGR pregnancies. Furthermore, 2 studies have suggested that delivery of the preterm IUGR fetus appears to increase perinatal morbidity and mortality. Both fetal growth and gestational age are important factors that are inversely related to newborn morbidities. This is underscored by the work of McIntyre and colleagues, who demonstrated a prominent reduction in respiratory distress syndrome (RDS) with both advancing gestational age and increasing birth weight (Fig. 2). The incidence of RDS at 35-36 weeks for neonates with birth weight below the 10th percentile was approximately 5% and decreased with increasing birth weight percentile.

Maternal Comorbidities

Chronic hypertension and pre-eclampsia are common conditions that are associated with increased rates of IUGR. Sev-
eral reports have suggested that women with severe pre-eclampsia remote from term, and who meet specific criteria, can be managed conservatively until 32-34 weeks’ gestation to gain time for fetal maturation.\textsuperscript{51,52} Recent reports have shown that in the face of severe pre-eclampsia, severe IUGR is associated with increased risk for perinatal death, but that it does not increase the risk of adverse outcome to the mother.\textsuperscript{53} Alternatively, in severe pre-eclampsia, it has also been shown more recently by some of the same authors that at longer than 32 weeks’ gestation, there is increased maternal morbidity with little benefit seen for the neonate.\textsuperscript{55} Thus, it seems reasonable for patients with severe pre-eclampsia or any maternal medical condition complicated by IUGR, that delivery should be pursued when maternal benefit from delivery outweighs the fetal benefit of pregnancy continuation.

Collectively, these studies suggest maternal thresholds for delivery should be considered for pregnancies complicated by IUGR in the late preterm and early-term period, and that concerns about newborn risks with delivery are less critical.\textsuperscript{8,9,55} Nevertheless, the morbidity and mortality associated with late preterm and early-term delivery of normal pregnancies with normal birth weights highlights the need for similar attention for the IUGR fetus in the same gestational age epoch.

### Timing Delivery of the Late Preterm or Early-Term IUGR Fetus

Delivery of the IUGR fetus before 34 weeks’ gestation is associated with high rates of newborn morbidity and mortality. In the absence of clear indications for delivery, the emphasis...
should be on safely prolonging pregnancy. Although the IUGR fetus at or after 34 weeks’ gestation poses less of a dilemma relative to the threshold for delivery, it is also reasonable to attempt to increase fetal maturity in utero. However, placental disease, fetal behavior, and Doppler velocimetry findings with IUGR after 34 weeks’ gestation are different from that seen in early gestation. This poses different challenges for management and timing of delivery.

Doppler Findings in the Late Preterm/Early-Term IUGR Fetus

IUGR at 34 or more weeks’ gestation (late onset) is typically characterized by milder placental dysfunction and often may not produce an elevation in the umbilical artery Doppler resistance indexes. Supporting this are studies showing that the cerebroplacental Doppler ratio loses its predictive accuracy after 34 weeks’ gestation. 

The only sign of placental dysfunction and insufficiency of oxygen transfer may be Doppler changes in the middle cerebral artery with an increase in diastolic flow velocity or the so-called “brain sparing” effect and these pregnancies may still be at risk.

Late Preterm and Early-Term IUGR Delivery Studies

There are no randomized clinical trials addressing the optimal time for delivery of the IUGR fetus in the late preterm or early-term gestational period. A study by Vergani et al sought to identify independent predictors of adverse neonatal outcome in 481 cases of fetal growth restriction after 34 weeks and to determine the optimal timing of delivery. Logistic regression analysis revealed that gestational age at delivery (odds ratio [OR] 0.59; 95% confidence interval [95% CI] 0.50-0.70), abdominal circumference percentile (OR 0.69; 95% CI 0.59-0.81) and umbilical artery pulsatility index percentile (OR 1.02; 95% CI 1.01-1.04) correlated significantly with adverse neonatal outcomes. Using this information, they calculated a score of adverse neonatal outcome expressed by the formula: (umbilical artery – pulsatility index centile/3) – (10 × abdominal circumference centile) + [10 × (40 – gestational age at delivery in weeks)]. When receiver-operator curve analyses were used, a score of ≥25 optimally predicted adverse neonatal outcomes. Importantly, gestational age no longer had an independent impact on outcome beyond 37.5 weeks.

Risk of Fetal Death in Late Preterm and Early-Term IUGR

Because major complications of prematurity wane considerably after 34 weeks of gestation (eg, RDS; Fig. 2), a primary factor that should be considered regarding delivery after 34 weeks gestational age is the risk of fetal death. Late-onset IUGR contributes to more than 50% of unanticipated stillbirths at term. 

Concomitantly, twin gestations result in high rates of morbidity, mortality, and long-term sequelae. Reports of outcomes in twin gestations are confounded by lack of consid-

Timing Delivery of Late Preterm and Early-Term Twins with IUGR

Although only 2%-3% of live births in the United States result from twin pregnancies, these result in 10%-15% of adverse neonatal outcomes because of preterm delivery and low birth weight. Concomitantly, twin gestations result in high rates of morbidity, mortality, and long-term sequelae. Reports of outcomes in twin gestations are confounded by lack of consid-
eration of chorionicity. The same etiologies for IUGR described previously in this article can affect either monochorionic or diamniotic twin pregnancies. However, the monochorionic pregnancy presents a special situation because IUGR, twin discordancy, and twin-twin transfusion syndrome can result from an imbalance of vascular anastomoses characteristic of the single placenta. In addition, umbilical cord insertion abnormalities (eg, marginal or velamentous insertion) are more common in twin pregnancies.

IUGR in monochorionic pregnancies, also referred to as selective IUGR (sIUGR), results from unequal vascular sharing and is distinguished from twin-twin transfusion syndrome by the presence of normal fluid in the small twin. This is in contrast to the oligohydramnios of the growth-restricted “stuck twin” and polyhydramnios in the normally grown co-twin. The specific condition of sIUGR complicates approximately 11%-14% of monochorionic pregnancies. Several factors separate and complicate the sIUGR fetus compared with that observed in singleton or dichorionic twin pregnancies: (1) with single-twin demise, the remaining twin is at risk for neurologic injury or death related to thromboembolism, hypotension, or exsanguination because of vascular anastomoses; (2) umbilical artery Doppler absent end-diastolic flow (AEDF) may not reflect the same pathology as in singleton IUGR because it may reflect the bidirectional waveforms described with large arterioarterial anastomoses; and (3) there is a high risk of fetal demise in sIUGR, especially when seen with intermittent or persistently abnormal umbilical artery Doppler studies.

**Delivery of IUGR in Dichorionic Twins**

It has been recommended that IUGR in dichorionic pregnancies be managed similarly to IUGR in singleton pregnancies. Given the estimate that the risk of fetal death for twin pregnancies approximates the risk of fetal death for postterm singletons by approximately 36-37 weeks, it seems reasonable to recommend delivery of the dichorionic twin gestation affected with IUGR by 36 weeks’ gestation in the absence of additional triggers for delivery. However, there are no randomized clinical trials that identify the optimal timing for delivery of either dichorionic or monochorionic twins affected by IUGR.

**Delivery of sIUGR in Monochorionic Twins**

The study of Kahn et al did not take chorionicity into consideration. A recent report regarding 236 monochorionic twin pairs suggested a low rate of fetal demise with ongoing pregnancies at 34-weeks gestation and suggested delivery at 36-37 weeks. This finding is in contrast to 2 other studies that reported fetal demise rates of 3.3% and 2% in normal monochorionic twin pregnancies at 34 weeks. To prevent one fetal demise after 34 weeks, Barigye and colleagues reported that delivery of 30 twin pairs would be needed, and similarly, Lee et al reported that delivery of 50 twin pairs would be required.

Several investigators report a poor prognosis for one or both fetuses in monochorionic pregnancies complicated by sIUGR. Type II sIUGR (sIUGR with persistent AEDF in the umbilical artery) has been associated with in utero deterioration rates of 70%-90% and mortality rates as high as 50%. Type III sIUGR (sIUGR with intermittent AEDF in the umbilical artery) has been reported to have an unexpected fetal demise rate of 15% and brain lesion rate in the surviving co-twin of 20%. In contrast, type I sIUGR (IUGR with normal umbilical artery Dopplers) twin pregnancies carries a more favorable prognosis. Thus, it seems reasonable to consider delivering the monochorionic twin pregnancy with sIUGR at 34-35 weeks of gestation in the absence of other complicating factor, such as oligohydramnios or AEDF in Doppler flow studies of the umbilical artery.

**Conclusions**

In summary, there are no randomized clinical trials for timing delivery of the IUGR singleton or twin pregnancy in the late preterm or early-term period. In general, the threshold

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**Table 3 Outcomes of >72,000 Live-Born Singleton Term Infants Born at ≥37 Weeks of Gestation in Relation to Birth-Weight Percentile**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Birth-Weight Percentile</th>
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<tbody>
<tr>
<td></td>
<td>≤3rd (n = 3184)</td>
</tr>
<tr>
<td>Apgar score ≥3 at 5 min</td>
<td>7 (0.2)*</td>
</tr>
<tr>
<td>Umbilical-artery blood pH ≤7.0</td>
<td>28 (0.9)*</td>
</tr>
<tr>
<td>Intubation in delivery room</td>
<td>70 (2.2)*</td>
</tr>
<tr>
<td>Seizures during first 24 h after birth</td>
<td>14 (0.4)*</td>
</tr>
<tr>
<td>Sepsis (positive blood culture)</td>
<td>15 (0.5)*</td>
</tr>
<tr>
<td>Death in first 28 days</td>
<td>9 (0.3)*</td>
</tr>
</tbody>
</table>

Values are n (%).

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*P < 0.05 for the comparison with the infants with birth weights in the 26th through 75th percentiles for gestational age.
for delivering an IUGR fetus in this epoch in pregnancy should be low. After 34 weeks, the IUGR fetus in a singleton or twin pregnancy who develops either oligohydramnios or AEDF in the umbilical artery should be delivered proximate to the diagnosis of these complications. In singleton pregnancies in which the IUGR fetus has normal amniotic fluid volume, Doppler studies, and biophysical testing, the fetus is likely constitutionally small and may be managed expectantly until 38-39 weeks. If Doppler testing becomes abnormal indicating a placental etiology, delivery by 36-37 weeks is reasonable. In any of these scenarios, biophysical (weekly BPP or twice weekly modified BPP) and Doppler testing is warranted until delivery.

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