
Title: Obstetrics & Gynecology Clinics of North America
ArticleTitle: Fetal Growth and Stillbirth
ArticleAuthor: Page, Jessica; Blue, Nathan; Silver, Robert
Vol: 48 No: 2 Date: 2021 Pages: 297-310
OCLC - 14091825; ISSN - 08898545;
Publisher: W.B. Saunders ©1987-
Copyright: CCG

Fetal Growth and Stillbirth

Jessica M. Page, MD, MSCI[a,*], Nathan R. Blue, MD[b], Robert M. Silver, MD[c]

KEYWORDS

• Stillbirth • Fetal death • Fetal growth restriction

KEY POINTS

- Fetal growth restriction is a strong risk factor for stillbirth.
- The interval between fetal death and recognition of the fetal death may exaggerate the association between fetal growth restriction and stillbirth.
- Further work is needed to identify those pregnancies at highest risk of placental insufficiency and stillbirth.
- Antenatal surveillance and early delivery may reduce the risk of stillbirth in pregnancies affected by fetal growth restriction.
- Stillbirths with fetal growth restriction should be evaluated with fetal autopsy, placental pathology, genetic testing, antiphospholipid antibody testing, and fetal-maternal hemorrhage testing.

INTRODUCTION

Stillbirth is one of the most devastating obstetric outcomes for both families and clinicians. In the United States, stillbirth is defined as fetal death at 20 weeks' gestation or later and occurs in approximately 1 per 160 deliveries.[1] The stillbirth rate has remained largely stable in the United States and exceeds that of many other high-resource countries.[2,3] At least one-quarter of US stillbirths are potentially preventable with many of these cases, including intrapartum losses, complications of maternal medical conditions, and placental insufficiency.[4] A large proportion of stillbirths is attributed to placental insufficiency and represents an important target for prevention. Placental causes of death were the most common cause of fetal death (28%) in US fetal death certificate reporting.[5] In a well-characterized multicenter US stillbirth study, placental causes of fetal death were also common, occurring in 23.6% of cases.[6] One of the

[a] Maternal-Fetal Medicine, Intermountain Healthcare, University of Utah, 5121 South Cottonwood Street, Suite 100, Murray, UT 84107, USA; [b] Maternal-Fetal Medicine, Intermountain Healthcare, University of Utah, 30 North 1900 East, 2A200, Salt Lake City, UT 84132, USA; [c] Maternal-Fetal Medicine, University of Utah, 30 North 1900 East, 2A200, Salt Lake City, UT 84132, USA
* Corresponding author.
E-mail address: jessica.page@hsc.utah.edu
Twitter: @Nateyblue (N.R.B.)

Obstet Gynecol Clin N Am 48 (2021) 297–310
https://doi.org/10.1016/j.ogc.2021.03.001
obgyn.theclinics.com

most common clinical manifestations of placental insufficiency is diminished fetal growth. Fetal growth restriction (FGR) is one of the best-characterized risk factors for stillbirth. Here the authors discuss FGR as it pertains to stillbirth.

FEATURES OF FETAL GROWTH RESTRICTION UNIQUE TO STILLBIRTH

FGR has been associated with stillbirth in many retrospective studies. Small-for-gestational-age (SGA) infants are more common following stillbirths as compared with livebirths, particularly at preterm gestational ages.[7] Also, the risk of fetal death is increased when FGR occurs as a result of placental insufficiency rather than as an association with maternal small stature or obstetric or medical comorbidities.[8] Poor fetal growth has also had a strong association with stillbirth in case control studies, with Frøen and colleagues[9] reporting an odds ratio (OR) of 7.0 (95% confidence interval [CI]: 3.3–15.1). The increased risk of stillbirth is more pronounced with increasing severity of FGR in population-based studies as well.[10] Prospective studies also demonstrate an increased risk of stillbirth, with Hirst and colleagues[11] reporting a hazard ratio of 4.6 (95% CI: 3.4–6.2). In an analysis of prospectively ascertained perinatal outcomes of SGA versus appropriately grown infants at term, the incidence of stillbirth was 3.5 per 1000 among SGA infants as compared with 0.9 per 1000 in non-SGA infants.[12] This association was also demonstrated when including preterm deliveries, with an adjusted OR of 3.98 (95% CI: 2.92–5.42).[13] In meta-analysis, SGA had a population attributable risk of 23% for stillbirth in high-income countries.[14]

Stillbirth can be associated with FGR and SGA via many pathophysiologic pathways. FGR is usually considered a marker for placental insufficiency. Placental insufficiency can occur when the placenta functions suboptimally because of abnormal development or damage during the pregnancy. FGR is also associated with placental insufficiency as a result of maternal medical or obstetric complications. The most common obstetric complications include chronic hypertension, renal disease, pregestational diabetes, and systemic lupus erythematosus. Exposures to tobacco or other illicit drugs can also result in placental insufficiency because of reduced uterine blood flow. Maternal infections, such as syphilis, cytomegalovirus, and malaria, can also cause placental damage through an inflammatory pathway. Obstetric complications that are associated with placental insufficiency include preeclampsia, abruption, and multiple gestation, particularly when monochorionicity is present. Placental insufficiency, regardless of the clinical scenario, results in reduced blood, oxygen, and nutrient passage to the fetus, which underlies the biologic association with stillbirth.

Determining the Timing of Stillbirth

Concern has been raised regarding the strength of the association of FGR with stillbirth given the difficulty of accurate determination of gestational age in the setting of fetal death. Often the exact gestational age at fetal death is not known and some time has elapsed from the time of death to the time of delivery. This delay in diagnosis can overestimate the gestational age of the fetus and incorrectly identify a fetus as growth restricted given that the birthweight is smaller than expected for the gestational age at delivery. Indeed, SGA is often used as a proxy for FGR in the setting of stillbirth, as there is not always a preceding clinical history of FGR that was well documented. This results in nearly a quarter of stillbirths being associated with poor fetal growth or SGA, which is substantially higher than other associations.[14,15]

Work has been done to address the discrepancy between the gestational age at the time of death compared with the assigned gestational age at the time of delivery. A prospective case-control study of stillbirths and live births at 5 clinical centers in the

United States determined the likely age of fetal death by taking into account several clinical criteria. First, the reliability of the estimated due date was evaluated. If the due date was well established by menstrual or ultrasound dating, it was taken into account. Second, the time interval from the last documented evidence of fetal viability to the time of documented fetal death was considered. Last, information regarding the degree of fetal maceration and the fetal foot length was used to provide additional insight into the likely date of death and interval before delivery.[16] These data points were integrated to determine an estimated date of death, which was considered precise in 47% of cases evaluated where reliable dating criteria and an interval of 1 week or less from the date of death had occurred.[16] This algorithm also had good correlation with fetal foot length with agreement within 2 weeks in 75% of cases.[17]

A series of 533 stillbirths with fetal autopsy investigated the relationship between the time interval from fetal death to delivery as well as from delivery to autopsy. Fetal tissue maceration is associated with longer in utero retention from the time of death to delivery. Man and colleagues[18] demonstrated that there was a higher proportion of fetal tissue maceration in the cohort that was classified as SGA with an artifactual reduction in birthweight of approximately −0.8 standard deviations. They also noted an additional decrease in weight from the time of delivery to the time of autopsy with an average 12% reduction. This was related to the length of time elapsed between delivery and postmortem examination, highlighting the importance of noting the delivery weight and accounting for the elapsed time in utero from fetal death to delivery.

A prospective study of stillbirths in the United States used the above referenced algorithm for determining the gestational age at fetal death, incorporating time of death interval, fetal autopsy findings, and reliability of dating criteria.[19] This study demonstrated that stillbirth was associated with SGA when evaluated with population (OR 3.0), ultrasound (OR 4.7), and individualized (OR 4.6) normative curves. This association persisted when adjusting for known prepregnancy stillbirth risk factors and in both preterm and term deliveries. This study demonstrated that the association of placental insufficiency and thus FGR with stillbirth persists even after accounting for the pitfalls of accurately diagnosing FGR in stillbirths.

STILLBIRTH RISK STRATIFICATION IN THE SETTING OF FETAL GROWTH RESTRICTION

It is important to note that FGR is a clinical indicator of placental insufficiency and is thus a risk factor for stillbirth rather than a cause. The underlying cause in this case would be placental insufficiency. Unfortunately, there are limited clinical tools with which to predict and detect placental insufficiency. Currently, tools for detection of placental insufficiency include ultrasound and biochemical markers.

A detailed discussion of routine ultrasonography for identification of FGR as well as the various growth standards by which to diagnose FGR is presented in Katherine L. Grantz's article, "Fetal Growth Curves: Is There a Universal Reference?"; Katie Stephens and colleagues' article, "Routine Third Trimester Sonogram: Friend or Foe," in this issue, and thus the authors briefly review the issues as they pertain to stillbirth here. Of particular interest is identifying those pregnancies at highest risk of stillbirth that do not have other risk factors and so will not have a standard indication for serial screening measures. This otherwise low-risk population is in need of an effective screening test that would identify those at a heightened risk of stillbirth and would benefit most from obstetric intervention. Fetal growth monitoring by way of fundal height measurement and fetal growth ultrasound is the most commonly used measure of placental function in current obstetric practice. Surveillance with fundal height

measurement is used essentially universally in practice, whereas, in contrast, serial ultrasound for fetal growth is generally reserved for pregnancies with medical or obstetric risk factors.[20] Randomized trials and meta-analysis of universal third-trimester ultrasound in otherwise low-risk pregnancies did not demonstrate maternal or fetal benefits to screening.[21,22] This may be due in part to lack of a standard definition of FGR and of a standard intervention. In addition, it is difficult to power a trial to show a reduction in stillbirth, as it is a relatively rare event, occurring in approximately 1 per 200 deliveries in high-resource settings.[23] Of course, identification of a small fetus is only the first step in assessing fetal status, as up to 70% of FGR fetuses are healthy and constitutionally small.[24]

Among fetuses diagnosed with FGR, additional sonographic tools are used to risk stratify them based on the likelihood of fetal death. One approach is evaluation of each biometric parameter, as adverse outcomes are best correlated with the fetal abdominal circumference measurement.[25,26] By this approach, a smaller abdominal circumference measurement would be interpreted as conferring a higher risk for placental insufficiency and thus fetal death. Physiologically, when placental insufficiency is present, reduced oxygen and nutrients are available, and the fetal circulation preferentially shunts blood flow to the fetal brain, heart, and adrenal glands, resulting in reduced fat and liver glycogen storage, leading to a small abdominal circumference despite normal fetal head measurements (biparietal diameter, head circumference).

Additional sonographic methods are used to further risk stratify growth-restricted fetuses to determine those at highest risk of fetal death. The first of these strategies is assessment of amniotic fluid volume. Placental insufficiency reduces blood flow to the fetus with subsequent cephalization of blood flow, as discussed above. Placental insufficiency reduces renal perfusion and thus urination and amniotic fluid volume. Low amniotic fluid volume is termed oligohydramnios and is defined as a single deepest vertical pocket measurement of less than 2 cm. The impact of oligohydramnios on outcomes in FGR pregnancies has not been extensively studied. The PORTO study prospectively studied 1100 FGR pregnancies and investigated characteristics associated with adverse perinatal outcomes.[27] They demonstrated that oligohydramnios was not predictive of adverse outcomes unless the fetus was also less than the third percentile. However, there is strong biologic plausibility that oligohydramnios in combination with FGR poses a higher risk for fetal death via either worsening placental insufficiency or cord compression. Thus, current guidelines recommend delivery between 34 weeks 0 days and 37 weeks 6 days for pregnancies affected with both FGR and oligohydramnios.[28,29]

Doppler velocimetry can also assist in further fetal death risk stratification. Umbilical artery Doppler measurement assesses the impedance of blood flow from the fetus to the placenta throughout the fetal cardiac cycle.[30] In the setting of placental insufficiency, placental impedance to blood flow increases, resulting in reduced return of deoxygenated blood to the placenta.[30] Increasing placental resistance results in an elevation in the pulsatility index, resistance index, and systolic-to-diastolic ratio. All of these measures have been used in various studies, and an abnormal value is defined as those above the 95%ile for gestational age or those with absent or reversed end-diastolic velocity.[29] Assessment of umbilical artery Doppler velocimetry can help to distinguish those fetuses with pathologic placental insufficiency from those who are healthy.[27] In fact, incorporating use of umbilical artery Doppler velocimetry reduces the risk of perinatal death, induction of labor, and cesarean delivery.[31,32] Deterioration in umbilical artery Doppler measurement is associated with an increased risk of stillbirth, with a risk of 6.8% for absent end diastolic flow (AEDF) and 19% for reversed end diastolic flow (REDF).[33] These risks for fetal death exceed the risks of severe infant

morbidity or mortality at 33 to 34 weeks for AEDF and 30 to 32 weeks for REDF, resulting in recent recommendations for delivery at these gestational ages for each of these groups.[29,34] Umbilical artery Doppler measurement is more predictive of adverse outcomes in cases of early-onset FGR rather than late-onset FGR.[35] Given this, it is important to use additional modalities to monitor fetal status when FGR develops at later gestational ages.

Ideally, a biochemical marker could be assessed in pregnancy that would identify high-risk gestations for placental insufficiency and thus stillbirth. Research efforts have focused primarily on placental proteins. Of these, pregnancy-associated plasma protein-A (PAPP-A) has been studied as an early biochemical marker of placental insufficiency.[36,37] Meta-analysis of PAPP-A as a predictor of fetal death also showed promise with PAPP-A level less than 0.4 multiples of the median (MoM) having a post-test probability of 1.75% for antepartum stillbirth because of placental abruption or growth restriction versus a value of 0.13% with a normal PAPP-A.[36] Patients with a PAPP-A level less than the fifth percentile have also been shown to have a higher chance of fetal death after 24 weeks' gestation (adjusted OR 2.15). However, the positive predictive value for stillbirth after 24 weeks' gestation was low at 58%.[38] A Cochrane Review examining 3 randomized controlled trials of biochemical markers for placental dysfunction (estrogen and human placental lactogen) demonstrated that there was no evidence that use of these biochemical markers was predictive of stillbirth or other adverse perinatal outcomes.[39] Maternal serum alpha-fetoprotein (AFP) has been identified as a second-trimester marker for placental insufficiency. A systematic review of 11 studies showed an increased risk of fetal death in patients with an elevated AFP level. An AFP level of greater than or equal to 2.5 MoM, corresponding to the 97th percentile, resulted in relative risks ranging from 4.4 to 21.0 for fetal death. Additional information on this topic is reviewed elsewhere.[40] There is ongoing investigation into new, novel biomarkers of placental insufficiency. Recently, Cleaton and colleagues[41] demonstrated that deltalike homolog 1, a growth factor involved in adipose homeostasis, is expressed in decreased amounts in maternal serum in the setting of FGR with abnormal umbilical artery Doppler flow. All things considered, there are no biomarkers currently available with sufficient test performance for predicting risk of stillbirth or placental insufficiency.

INTERVENTIONS TO PREVENT STILLBIRTH IN THE SETTING OF PLACENTAL INSUFFICIENCY

Given the lack of effective risk-stratification tools in low-risk pregnancies, use of stillbirth prevention interventions remains guided by maternal and obstetric risk factors. Interventions that have been studied for stillbirth risk reduction include medical treatment and antenatal surveillance. Use of these tools quickly becomes controversial, as clinicians and patients balance the desire to explore all options to ensure fetal safety with the cost, anxiety, and potential for iatrogenic harm inherent to these measures of (sometimes) unproven efficacy.

First, optimization of maternal medical conditions and modifiable risk factors should be addressed before conception, including encouragement of maternal weight loss, cessation of smoking, alcohol, and illicit substances, and appropriate interpregnancy interval. Pregestational diabetes, hypertension, and systemic lupus erythematosus are among the most crucial to maternal/fetal well-being. Finally, although multiple gestation is not a modifiable risk factor from a patient's perspective, efforts should be made to achieve singleton pregnancies when artificial reproductive technologies are used.

Medication treatment is aimed at improving placental function via either reduction in inflammation or enhanced blood flow. In some instances, data for these approaches have been extrapolated from treatment of antiphospholipid syndrome or preeclampsia prevention. Low-dose aspirin has been shown to reduce stillbirth risk, but benefit may be due to reductions in preeclampsia, spontaneous preterm birth, FGR, and placental insufficiency. A meta-analysis of 40 trials included 33,098 women treated with low-dose aspirin demonstrated a 14% reduction in fetal or neonatal deaths. These data points must be interpreted with caution, as preeclampsia was the primary outcome rather than fetal death.[42] Accordingly, the American College of Obstetrics and Gynecology does not recommend aspirin use for stillbirth prevention unless risk factors for preeclampsia are also present.[43] Recently, the US Preventive Services Task Force (USPSTF) evaluated the available randomized controlled trials of aspirin use for preeclampsia prevention. Their work demonstrated a 20% risk reduction in preterm birth, 18% reduction in SGA/FGR, and a 21% reduction in perinatal mortality.[44,45] The USPSTF states that more data are needed to define the populations that will benefit most from aspirin prophylaxis. Low-molecular-weight heparin (LMWH) has also been studied for the prevention of fetal death. One randomized clinical trial assessing treatment with LMWH resulted in a reduction in composite morbidity, including fetal death; however, it did not show a significant reduction in fetal death itself.[46] Subsequent trials have not demonstrated a mortality benefit, and thus, use of LMWH for stillbirth prevention is not recommended.[47] Additional medical treatments aimed at improving placental function have been considered, including phosphodiesterase inhibitors, hydroxychloroquine, and prednisolone. These treatments have primarily been studied in the setting of severe FGR, antiphospholipid syndrome, and severe placental pathologic condition, such as chronic histiocytic intervillositis.[48–50] There are no data to support their use for stillbirth prevention in an otherwise low-risk population without other clinical indications.

Antenatal Surveillance

Antenatal surveillance, such as nonstress tests (NSTs) and biophysical profiles (BPPs), is used as a clinical measure of fetal well-being. These tests rely on the premise that the fetal heart rate pattern and motor activity are influenced by fetal hypoxemia and acidemia.[51] Accordingly, these tests are best suited to identifying fetuses with an ongoing hypoxic insult owing to placental insufficiency rather than sudden or unexplained cases of fetal death. A reactive fetal heart rate tracing is defined as one having 2 fetal heart rate accelerations (increase by 15 beats per minute for 15 seconds) noted within a 20-minute period. The use of NSTs as a measure of fetal well-being depends on the neurologic development of the fetus, the presence of sleep-wake cycles, maternal medications, and other substances that cross the placenta. The reliability of NSTs improves with advancing gestational age, with nonreactive NSTs in up to 50% of patients tested between 24 and 28 weeks' gestation and 15% between 28 and 32 weeks' gestation. Hence, the criteria for a reactive NST before 32 weeks were adjusted to an acceleration threshold of 10 beats per minute for 10 seconds (rather than 15 beats per minute for 15 seconds), which improves the performance before 32 weeks.[51] The BPP builds on the NST with incorporation of fetal movement, tone, breathing, and amniotic fluid assessment. Each component is scored as 2 points, and a score of 8 or 10 is considered normal and reassuring. A score of 6 is equivocal, and a score $\leq$4 is abnormal. The stillbirth rate following a normal BPP is 0.8 per 1000. A modified BPP consists of an NST and amniotic fluid index and imparts a 0.8 per 1000 stillbirth risk in the following week.[52–54] The decision to proceed with

Condition	General Timing	Suggested Specific Timing
Placental/Uterine Conditions		
Placenta previa[b]	Late preterm/early term	36 0/7–37 6/7 weeks of gestation
Suspected accreta, increta, or percreta[b]	Late preterm	34 0/7–35 6/7 weeks of gestation
Vasa previa	Late preterm/early term	34 0/7–37 0/7 weeks of gestation
Prior classical cesarean	Late preterm/early term	36 0/7–37 0/7 weeks of gestation
Prior myomactomy requiring cesarean delivery[c]	Early term (individualize)	37 0/7–38 6/7 weeks of gestation
Previous uterine rupture	Late preterm/early term	36 0/7–37 0/7 weeks gestation
Fetal Conditions		
Oligohydramnios (isolated or otherwise uncomplicated [deepest vertical pocket less than 2 cm])	Late preterm/early term	36 0/7–37 6/7 weeks of gestation or at diagnosis if diagnosed later
Polyhydramnios (mild, idiopathic)[b]	Full term	39 0/7–39 6/7 weeks of gestation
Growth restriction (singleton)		
Otherwise uncomplicated, no concurrent findings, EFW between 3rd and 10th percentile	Early term/full term	38 0/7–39 0/7 weeks of gestation
Otherwise uncomplicated, no concurrent findings, EFW <3rd percentile	Early term	37 0/7 weeks of gestation or at diagnosis if diagnosed later
Abnormal umbilical artery dopplers: decreased end diastolic flow without absent end diastolic flow	Early term	37 0/7 weeks of gestation or at diagnosis if diagnosed later
Abnormal umbilical artery dopplers: absent end diastolic flow	Preterm/late preterm	33 0/7–34 0/7 weeks of gestation or at diagnosis if diagnosed later[d]
Abnormal umbilical artery dopplers: reversed end diastolic flow	Preterm	30 0/7–32 0/7 weeks of gestation[d] or at diagnosis if diagnosed later
Concurrent conditions (oligohydramnios, maternal co-morbidity [eg, preeclampsia, chronic hypertension])	Late preterm/early term	34 0/7–37 6/7 weeks of gestation
Multiple gestations—uncomplicated		
Dichorionic-diamniotic twins	Early term	38 0/7–38 6/7 weeks of gestation
Monochorionic-diamniotic twins	Late preterm/early term	34 0/7–37 6/7 weeks of gestation
Monochorionic-monoamniotic twins	Preterm/late preterm	32 0/7–34 0/7 weeks of gestation
Triplet and higher order multiples	Preterm/late preterm	Individualized
Alloimmunization		
At-risk pregnancy not requiring intrauterine transfusion	Early term	37 0/7–38 6/7 weeks of gestation
Requiring intrauterine transfusion	Late preterm or early term	Individualized
Maternal Conditions		
Hypertensive disorders of pregnancy		
Chronic hypertension: isolated, uncomplicated, controlled, not requiring medications	Early term/full term	38 0/7–39 6/7 weeks of gestation
Chronic hypertension: isolated, uncomplicated, controlled on medications	Early term/full term	37 0/7–39 6/7 weeks of gestation[e]
Chronic hypertension: difficult to control (requiring frequent medication adjustments)	Late preterm/early term	36 0/7–37 6/7 weeks of gestation
Gestational hypertension, without severe-range blood pressure	Early term	37 0/7 weeks or at diagnosis if diagnosed later
Gestational hypertension with severe-range blood pressures	Late preterm	34 0/7 weeks of gestation or at diagnosis if diagnosed later
Preeclampsia without severe features	Early term	37 0/7 weeks of gestation or at diagnosis if diagnosed later
Preeclampsia with severe features, stable maternal and fetal conditions, after fetal viability (includes superimposed)	Late preterm	34 0/7 weeks of gestation or at diagnosis if diagnosed later
Preeclampsia with severe features, unstable or complicated, after fetal viability (includes superimposed and HELLP)	Soon after maternal stabilization	Soon after maternal stabilization
Preeclampsia with severe features, before viability	Soon after maternal stabilization[f]	Soon after maternal stabilization[f]
Diabetes		
Pregestational diabetes well-controlled[b]	Full term	39 0/7–39 6/7 weeks of gestation
Pregestational diabetes with vascular complications, poor glucose control, or prior stillbirth	Late preterm/early term	36 0/7–38 6/7 weeks of gestation
Gestational: well controlled on diet and exercise	Full term	39 0/7–40 6/7 weeks of gestation
Gestational: well controlled on medications	Full term	39 0/7–39 6/7 weeks of gestation
Gestational: poorly controlled	Late preterm/early term	Individualized
HIV		
Intact membranes and viral load >1,000 copies/mL	Early-term cesarean delivery	38 0/7 weeks of gestation
Viral load ≤1,000 copies/mL with antiretroviral therapy	Full term (early term birth not indicated)	39 0/7 weeks of gestation or later
Intrahepatic cholestasis of pregnancy: total bile acid levels <100 micromol/L	Late preterm/early term	36 0/7–39 0/7 weeks of gestation[g] or at diagnosis if diagnosed later
Intrahepatic cholestasis of pregnancy: total bile acid levels ≥100 micromol/L	Late preterm	36 0/7 weeks of gestation or at[g] diagnosis if diagnosed later
Obstetric Conditions		
Preterm PROM	Late preterm	34 0/7 weeks of gestation or at diagnosis if diagnosed later
PROM (37 0/7 weeks of gestation and beyond)	Generally, at diagnosis	Generally, at diagnosis
Previous stillbirth	Full term (early term birth not routinely recommended)	Individualized[h]

Abbreviations: EFW, estimated fetal weight; HELLP, hemolysis, elevated liver enzymes, and low platelet count; PROM, prelabor rupture of membranes (also referred to as premature rupture of membranes).

[b]In situations in which there is a wide gestational age range for acceptable delivery thresholds, the lower range is not automatically preferable, and medical decision making for the upper or lower part of a range should depend on individual patient factors and risks and benefits.

[c]Uncomplicated, thus no fetal growth restriction, superimposed preeclampsia, or other complication. If these conditions are present, then the complicating conditions take precedence and earlier delivery may be indicated.

[c]Prior myomectomy may require earlier delivery similar to prior classical cesarean (36 0/7-37 0/7 weeks of gestation) in situations with more extensive or complicated myomectomy. Data are conflicting regarding specific timing of delivery. Furthermore, timing of delivery may be influenced by the degree and location of the prior uterine surgery, with the possibility of delivering as late as 38 6/7 weeks of gestation for a patient with a less extensive prior surgery. Timing of delivery should be individualized based on prior surgical details (if available) and the clinical situation.

[d]Consultation with maternal-fetal medicine subspecialist is recommended.

[e]Expectant management beyond 38 0/7 weeks of gestation should only be done after careful consideration of the risks and benefits and with appropriate surveillance.

[f]Management individualized to particulars of maternal-fetal condition and gestational age.

[g]Measurement of serum bile acid levels and liver transaminase is recommended in patients with suspected intrahepatic cholestasis of pregnancy. Delivery before 36 weeks of gestation occasionally may be indicated depending on laboratory and clinical circumstances.

[h]Deliveries before 39 weeks of gestation are associated with an increased risk of admission to neonatal special care units for respiratory complications and other neonatal morbidities; however, maternal anxiety with a history of stillbirth should be considered and may warrant an early term delivery (37 0/7 weeks to 38 6/7 weeks) in women who are educated regarding, and accept, the associated neonatal risks.

antenatal surveillance using NSTs depends on clinical circumstance, gestational age, and intended use of clinical interventions such as delivery and cesarean.

Of course, the ultimate stillbirth prevention strategy is delivery. However, the decision to proceed with delivery must take into account the gestational age and the risks to the infant following delivery, particularly if preterm or early term delivery is considered. The point at which the fetal death risk exceeds the predicted infant mortality risk is a reasonable time to consider delivery and has been studied in multiple obstetric contexts.[10,55–57] The Society for Maternal-Fetal Medicine and American College of Obstetricians and Gynecologists have developed a guideline to assist physicians with timing and indications for late preterm and early delivery, and this is shown in **Fig. 1**.[29,58]

EVALUATION OF STILLBIRTHS IN THE SETTING OF FETAL GROWTH RESTRICTION

If a fetal death occurs, the maternal medical history and obstetric history should be carefully assessed to determine potential risk factors for placental insufficiency. The date that the fetus was last documented to have cardiac activity, last time at which fetal movement was known to the mother, and the criteria by which the pregnancy is dated should be obtained. Following this, providers can perform fetal biometry to estimate the fetal weight. Taken together, these data points can help to inform whether FGR is suspected before delivery.

Of utmost importance to the evaluation of fetal death are fetal autopsy and placental histopathology. The fetal autopsy has been shown to assist in identifying a cause of death in an unselected stillbirth population in 42% of cases. However, in cases in which FGR is suspected, this yield increases to 79%[59] This is due to the ability of the fetal autopsy to assist in determining a time interval from death, and thus confirming or ruling out FGR as well as detecting fetal changes secondary to growth restriction, such as evidence of chronic hypoxic stress. Obtaining placental pathology is of paramount importance following a stillbirth in the setting of suspected FGR.

In pregnancies complicated by FGR, placental evaluation by histopathology contributes to the clarification of the cause of death in 89% of cases.[59] There are numerous studies examining pathologic placental lesions in cases of stillbirth and FGR. In general, the mechanism of placental insufficiency and thus fetal death in these cases is thought to be due to impaired placental circulation and gas exchange. This may occur via maternal or fetal vascular changes or through inflammatory changes, which can result in fibrin deposition and infarction.[60] Among the most common lesions are villous infarction, maternal vascular changes, and villous morphologic changes.[61] These findings vary according to gestational age, with more severe findings in early-onset (before 28–32 weeks) FGR as compared with late-onset FGR. In addition, severe placental lesions, such as maternal floor infarction and massive chronic intervillositis, carry a high recurrence risk and thus inform counseling regarding future pregnancies.[62] As with other factors, they should not be relied on in isolation, as they may also occur in uncomplicated pregnancies, and up to 25% of placentas affected by FGR lack histopathologic evidence of placental insufficiency.[61] **Fig. 2** demonstrates severe placental lesions associated with placental insufficiency.

Fig. 1. Recommendations for the timing of delivery when conditions complicate pregnancy. (*Reprinted* with permission from American College of Obstetricians and Gynecologists. Medically indicated late-preterm and early-term deliveries. ACOG Committee Opinion No. 818. American College of Obstetricians and Gynecologists. Obstet Gynecol 2021;137:e29–33.)

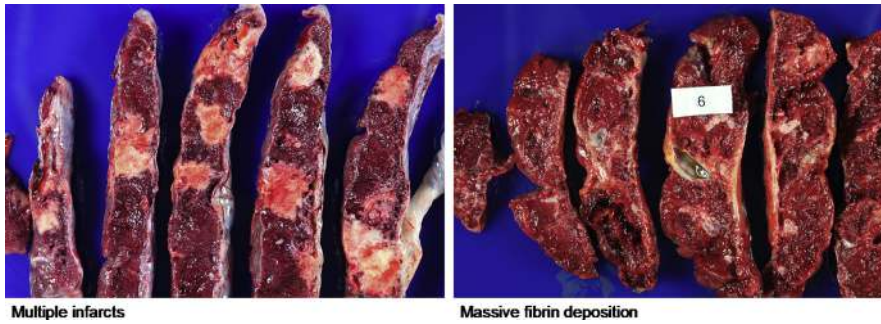

Fig. 2. Placental lesions associated with placental insufficiency and stillbirth.

Stillbirths in the setting of FGR should also have testing for antiphospholipid syndrome performed. Antiphospholipid antibodies are associated with thromboembolism and obstetric complications, including fetal death and early-onset (before 34 weeks) preeclampsia or placental insufficiency.[63–65] The antibodies most strongly associated with obstetric complications include lupus anticoagulant, anti-β2-glycoprotein-I, and anticardiolipin antibodies.[63,66] Adverse obstetric outcomes are suspected to be due to placental damage through either abnormal development or inflammation and thrombosis.[67] These placental insults increase the risk for FGR with a prevalence of 15% to 30% in most reports.[64,65,68,69] Antiphospholipid antibodies were assessed in a large cohort of stillbirths. There was a 3-fold increase in the chance of stillbirth when women tested positive for anticardiolipin or anti-β2-glycoprotein-I antibodies. Of these cases with positive antiphospholipid antibodies, 37% also were SGA.[70] In cases of FGR from the same cohort, testing for antiphospholipid antibodies helped to identify or refute a cause of death in 32% of cases.[59]

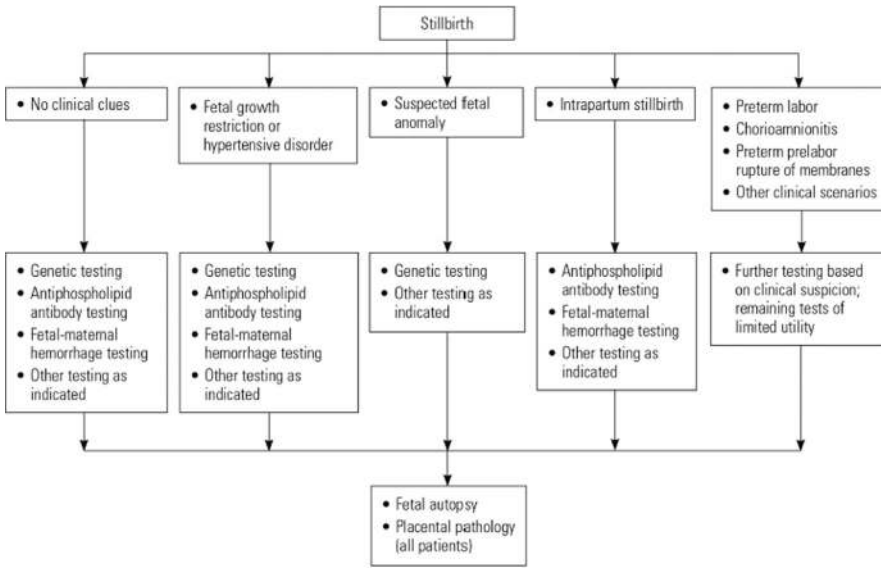

Fig. 3. Evaluation of stillbirth based on test utility in a variety of clinical scenarios. (*From* Management of Stillbirth: Obstetric Care Consensus No, 10. Obstet Gynecol. 2020 Mar;135(3):e110-e132, with permissions.)

Evaluating stillbirth cases affected by FGR for genetic abnormalities is also an important part of the stillbirth work-up. Genetic abnormalities in the placenta can lead to dysfunction resulting in placental insufficiency and FGR. While testing for genetic disorders, using chromosomal microarray is recommended following all stillbirths, as it confers increased diagnostic yield in FGR cases compared with cases without FGR (26% vs 12%, respectively).[40,59,71] In most cases, these abnormalities are coincident in the fetus and placenta but can also affect only the placenta as in confined placental mosaicism (CPM). Although CPM is an uncommon diagnosis in the general obstetric population, it has been identified in up to 15% of placentas from FGR pregnancies.[72]

Testing for fetal-maternal hemorrhage is also reasonable following diagnosis of a stillbirth, as this is a time-sensitive assay, and it is inexpensive.[71] Less common infection-related causes of placental insufficiency and stillbirth, such as cytomegalovirus and syphilis, should be tested for only when clinical evidence for infection is present. Stillbirth owing to these agents is rare, and if they are present with a severity to cause fetal death, there is typically evidence on placental pathology or fetal autopsy.[73] A suggested approach to evaluation of stillbirth in a variety of clinical circumstances, including suspected FGR, is shown in **Fig. 3**.

SUMMARY

FGR is one of the most readily identifiable clinical manifestations of placental insufficiency. Further work is needed to better risk stratify pregnancies at risk for placental insufficiency and thus stillbirth. The association of FGR with stillbirth has been demonstrated in many studies, but concern for an overestimated effect has been raised because of the possibility of a time lag from the time of death to diagnosis. Use of fetal autopsy and careful obstetric history can help to better estimate the gestational age at death and reduce the incorrect assignment of growth restriction. Studies have examined methods by which to account for this time lag, and when this is taken into account, the increased risk for stillbirth persists among FGR fetuses. For those pregnancies with recognized FGR, additional risk stratification by way of serial growth surveillance and umbilical artery Doppler monitoring is prudent. Antenatal testing in the form of NST or BPP and delivery timing should be tailored to the clinical circumstances. There is some benefit to medical treatment with low-dose aspirin in select populations, but other medical therapy for stillbirth prevention should be considered experimental. In stillbirths with FGR, evaluation with fetal autopsy, placental pathology, antiphospholipid antibodies, genetic evaluation, and fetal-maternal hemorrhage is recommended.

CLINICS CARE POINTS

- All pregnancies should undergo screening for fetal growth restriction by fundal height assessment, and when indicated, serial ultrasonographic examination.
- Fetal growth restriction is a major risk factor for stillbirth, and as such, pregnancies complicated by fetal growth restriction should undergo antenatal surveillance with delivery timed according to the clinical circumstance.
- In cases of fetal growth restriction and stillbirth, evaluation by fetal autopsy, placental pathology, antiphospholipid screening, genetic testing, and fetal-maternal hemorrhage testing are important to determining the underlying cause of the fetal death.

DISCLOSURE

The authors have nothing to disclose.

REFERENCES

1. MacDorman MF, Gregory EC. Fetal and perinatal mortality: United States, 2013. Natl Vital Stat Rep 2015;64(8):1–24.
2. Gregory EC, MacDorman MF, Martin JA. Trends in fetal and perinatal mortality in the United States, 2006-2012. NCHS Data Brief 2014;(169):1–8.
3. Lawn JE, Blencowe H, Waiswa P, et al. Stillbirths: rates, risk factors, and acceleration towards 2030. Lancet 2016;387(10018):587–603.
4. Page JM, Thorsten V, Reddy UM, et al. Potentially preventable stillbirth in a diverse U.S. cohort. Obstet Gynecol 2018;131(2):336–43.
5. Hoyert DL GE. Cause-of-death data from the fetal death file, 2015-2017. 2020; No. 4. Located at: National Vital Statistics Reports, Hyattsville, MD.
6. Stillbirth Collaborative Research Network Writing Group. Causes of death among stillbirths. JAMA 2011;306(22):2459–68.
7. Gardosi J, Mul T, Mongelli M, et al. Analysis of birthweight and gestational age in antepartum stillbirths. Br J Obstet Gynaecol 1998;105(5):524–30.
8. Cnattingius S, Haglund B, Kramer MS. Differences in late fetal death rates in association with determinants of small for gestational age fetuses: population based cohort study. BMJ 1998;316(7143):1483–7.
9. Frøen JF, Gardosi JO, Thurmann A, et al. Restricted fetal growth in sudden intrauterine unexplained death. Acta Obstet Gynecol Scand 2004;83(9):801–7.
10. Pilliod RA, Cheng YW, Snowden JM, et al. The risk of intrauterine fetal death in the small-for-gestational-age fetus. Am J Obstet Gynecol 2012;207(4):318.e1-6.
11. Hirst JE, Villar J, Victora CG, et al. The antepartum stillbirth syndrome: risk factors and pregnancy conditions identified from the INTERGROWTH-21(st) Project. BJOG 2018;125(9):1145–53.
12. Mendez-Figueroa H, Truong VT, Pedroza C, et al. Morbidity and mortality in small-for-gestational-age infants: a secondary analysis of nine MFMU network studies. Am J Perinatol 2017;34(4):323–32.
13. Mendez-Figueroa H, Truong VT, Pedroza C, et al. Small-for-gestational-age infants among uncomplicated pregnancies at term: a secondary analysis of 9 maternal-fetal medicine units network studies. Am J Obstet Gynecol 2016; 215(5):628.e1-e7.
14. Flenady V, Koopmans L, Middleton P, et al. Major risk factors for stillbirth in high-income countries: a systematic review and meta-analysis. Lancet 2011; 377(9774):1331–40.
15. Smith GC, Fretts RC. Stillbirth. Lancet 2007;370(9600):1715–25.
16. Conway DL, Hansen NI, Dudley DJ, et al. An algorithm for the estimation of gestational age at the time of fetal death. Paediatric Perinatal Epidemiol 2013;27(2): 145–57.
17. Drey EA, Kang MS, McFarland W, et al. Improving the accuracy of fetal foot length to confirm gestational duration. Obstet Gynecol 2005;105(4):773–8.
18. Man J, Hutchinson JC, Ashworth M, et al. Effects of intrauterine retention and postmortem interval on body weight following intrauterine death: implications for assessment of fetal growth restriction at autopsy. Ultrasound Obstet Gynecol 2016;48(5):574–8.
19. Bukowski R, Hansen NI, Willinger M, et al. Fetal growth and risk of stillbirth: a population-based case-control study. PLoS Med 2014;11(4):e1001633.

20. Practice Bulletin No. 175: Ultrasound in pregnancy. Obstet Gynecol 2016;128(6): e241–56.
21. Bricker L, Medley N, Pratt JJ. Routine ultrasound in late pregnancy (after 24 weeks' gestation). Cochrane Database Syst Rev 2015;(6):CD001451.
22. Henrichs J, Verfaille V, Jellema P, et al. Effectiveness of routine third trimester ultrasonography to reduce adverse perinatal outcomes in low risk pregnancy (the IRIS study): nationwide, pragmatic, multicentre, stepped wedge cluster randomised trial. BMJ 2019;367:l5517.
23. Smith GC. Screening and prevention of stillbirth. Best Pract Res Clin Obstet Gynaecol 2017;38:71–82.
24. Ott WJ. The diagnosis of altered fetal growth. Obstet Gynecol Clin North Am 1988;15(2):237–63.
25. Dudley NJ. A systematic review of the ultrasound estimation of fetal weight. Ultrasound Obstet Gynecol 2005;25(1):80–9.
26. Ott WJ. Diagnosis of intrauterine growth restriction: comparison of ultrasound parameters. Am J Perinatol 2002;19(3):133–7.
27. Unterscheider J, Daly S, Geary MP, et al. Optimizing the definition of intrauterine growth restriction: the multicenter prospective PORTO Study. Am J Obstet Gynecol 2013;208(4):290.e1-6.
28. Spong CY, Mercer BM, D'Alton M, et al. Timing of indicated late-preterm and early-term birth. Obstet Gynecol 2011;118(2 Pt 1):323–33.
29. Martins JG, Biggio JR, Abuhamad A. Society for Maternal-Fetal Medicine (SMFM) consult series #52: diagnosis and management of fetal growth restriction. Am J Obstet Gynecol 2020;223(4):B2–17.
30. Trudinger BJ. Doppler ultrasonography and fetal well-being. In: Albert Reece JCH E, Mahoney MJ, Petrie RH, editors. Medicine of the fetus & mother. Philadelphia (PA): JB Lippincott Co; 1992.
31. Alfirevic Z, Stampalija T, Dowswell T. Fetal and umbilical Doppler ultrasound in high-risk pregnancies. Cochrane Database Syst Rev 2017;6:CD007529.
32. McCowan LM, Harding JE, Roberts AB, et al. A pilot randomized controlled trial of two regimens of fetal surveillance for small-for-gestational-age fetuses with normal results of umbilical artery doppler velocimetry. Am J Obstet Gynecol 2000;182(1 Pt 1):81–6.
33. Caradeux J, Martinez-Portilla RJ, Basuki TR, et al. Risk of fetal death in growth-restricted fetuses with umbilical and/or ductus venosus absent or reversed end-diastolic velocities before 34 weeks of gestation: a systematic review and meta-analysis. Am J Obstet Gynecol 2018;218(2s):774–82.e1.
34. Lees C, Marlow N, Arabin B, et al. Perinatal morbidity and mortality in early-onset fetal growth restriction: cohort outcomes of the trial of randomized umbilical and fetal flow in Europe (TRUFFLE). Ultrasound Obstet Gynecol 2013;42(4):400–8.
35. Oros D, Figueras F, Cruz-Martinez R, et al. Longitudinal changes in uterine, umbilical and fetal cerebral Doppler indices in late-onset small-for-gestational age fetuses. Ultrasound Obstet Gynecol 2011;37(2):191–5.
36. Conde-Agudelo A, Bird S, Kennedy SH, et al. First- and second-trimester tests to predict stillbirth in unselected pregnant women: a systematic review and meta-analysis. BJOG 2015;122(1):41–55.
37. Lamont K, Scott NW, Jones GT, et al. Risk of recurrent stillbirth: systematic review and meta-analysis. BMJ 2015;350:h3080.
38. Dugoff L, Hobbins JC, Malone FD, et al. First-trimester maternal serum PAPP-A and free-beta subunit human chorionic gonadotropin concentrations and nuchal

translucency are associated with obstetric complications: a population-based screening study (the FASTER Trial). Am J Obstet Gynecol 2004;191(4):1446–51.
39. Heazell AE, Whitworth M, Duley L, et al. Use of biochemical tests of placental function for improving pregnancy outcome. Cochrane Database Syst Rev 2015;(11):Cd011202.
40. Reddy UM. Prediction and prevention of recurrent stillbirth. Obstet Gynecol 2007; 110(5):1151–64.
41. Cleaton MA, Dent CL, Howard M, et al. Fetus-derived DLK1 is required for maternal metabolic adaptations to pregnancy and is associated with fetal growth restriction. Nat Genet 2016;48(12):1473–80.
42. Duley L, Meher S, Hunter KE, et al. Antiplatelet agents for preventing pre-eclampsia and its complications. Cochrane Database Syst Rev 2019;2019(10).
43. ACOG Committee Opinion No. 743: low-dose aspirin use during pregnancy. Obstet Gynecol 2018;132(1):e44–52.
44. Jillian T, Henderson P, Vesco KK, et al. Draft of aspirin use to prevent preeclampsia and related morbidity and mortality: an evidence update for the U.S. Preventive Services Task Force. U.S. Preventive Services Task Force. 2021. Available at: file:///C:/Users/u6019768/Downloads/aspirin-preeclampsia-prevention-draft-evidence-review.pdf. Accessed February 25, 2021.
45. LeFevre ML, U.S. Preventive Services Task Force. Low-dose aspirin use for the prevention of morbidity and mortality from preeclampsia: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2014;161(11): 819–26.
46. Rey E, Garneau P, David M, et al. Dalteparin for the prevention of recurrence of placental-mediated complications of pregnancy in women without thrombophilia: a pilot randomized controlled trial. J Thromb Haemost 2009;7(1):58–64.
47. Rodger MA, Gris J-C, De Vries JIP, et al. Low-molecular-weight heparin and recurrent placenta-mediated pregnancy complications: a meta-analysis of individual patient data from randomised controlled trials. Lancet 2016;388(10060): 2629–41.
48. Groom K, McCowan L, Mackay L, et al. STRIDER NZAus: a multicentre randomised controlled trial of sildenafil therapy in early-onset fetal growth restriction. BJOG 2019;126(8):997–1006.
49. Mekinian A, Costedoat-Chalumeau N, Masseau A, et al. Chronic histiocytic intervillositis: outcome, associated diseases and treatment in a multicenter prospective study. Autoimmunity 2015;48(1):40–5.
50. Pels A, Derks J, Elvan-Taspinar A, et al. Maternal sildenafil vs placebo in pregnant women with severe early-onset fetal growth restriction. JAMA Netw Open 2020;3(6):e205323.
51. Practice bulletin no. 145: antepartum fetal surveillance. Obstet Gynecol 2014; 124(1):182–92.
52. Freeman RK, Anderson G, Dorchester W. A prospective multi-institutional study of antepartum fetal heart rate monitoring. I. Risk of perinatal mortality and morbidity according to antepartum fetal heart rate test results. Am J Obstet Gynecol 1982; 143(7):771–7.
53. Manning FA, Morrison I, Harman CR, et al. Fetal assessment based on fetal biophysical profile scoring: experience in 19,221 referred high-risk pregnancies. II. An analysis of false-negative fetal deaths. Am J Obstet Gynecol 1987;157(4 Pt 1): 880–4.
54. Miller DA, Rabello YA, Paul RH. The modified biophysical profile: antepartum testing in the 1990s. Am J Obstet Gynecol 1996;174(3):812–7.

55. Page JM, Pilliod RA, Snowden JM, et al. The risk of stillbirth and infant death by each additional week of expectant management in twin pregnancies. Am J Obstet Gynecol 2015;212(5):630.e1-7.
56. Puljic A, Kim E, Page J, et al. The risk of infant and fetal death by each additional week of expectant management in intrahepatic cholestasis of pregnancy by gestational age. Am J Obstet Gynecol 2015;212(5):667.e1-5.
57. Rosenstein MG, Cheng YW, Snowden JM, et al. Risk of stillbirth and infant death stratified by gestational age. Obstet Gynecol 2012;120(1):76–82.
58. Medically indicated late-preterm and early-term deliveries: ACOG Committee Opinion, Number 818. Obstet Gynecol 2021;137(2):e29–33.
59. Page JM, Christiansen-Lindquist L, Thorsten V, et al. Diagnostic tests for evaluation of stillbirth: results from the stillbirth collaborative research network. Obstet Gynecol 2017;129(4):699–706.
60. Roberts JM. Pathophysiology of ischemic placental disease. Semin Perinatol 2014;38(3):139–45.
61. Mifsud W, Sebire NJ. Placental pathology in early-onset and late-onset fetal growth restriction. Fetal Diagn Ther 2014;36(2):117–28.
62. Roberts DJ. Placental pathology, a survival guide. Arch Pathol Lab Med 2008;132(4):641–51.
63. Practice Bulletin No. 132: antiphospholipid syndrome. Obstet Gynecol 2012;120(6):1514–21.
64. Branch DW, Silver RM, Blackwell JL, et al. Outcome of treated pregnancies in women with antiphospholipid syndrome: an update of the Utah experience. Obstet Gynecol 1992;80(4):614–20.
65. Lima F, Khamashta MA, Buchanan NM, et al. A study of sixty pregnancies in patients with the antiphospholipid syndrome. Clin Exp Rheumatol 1996;14(2):131–6.
66. Miyakis S, Lockshin MD, Atsumi T, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost 2006;4(2):295–306.
67. Meroni PL, Tedesco F, Locati M, et al. Anti-phospholipid antibody mediated fetal loss: still an open question from a pathogenic point of view. Lupus 2010;19(4):453–6.
68. Caruso A, De Carolis S, Ferrazzani S, et al. Pregnancy outcome in relation to uterine artery flow velocity waveforms and clinical characteristics in women with antiphospholipid syndrome. Obstet Gynecol 1993;82(6):970–7.
69. Kutteh WH. Antiphospholipid antibody-associated recurrent pregnancy loss: treatment with heparin and low-dose aspirin is superior to low-dose aspirin alone. Am J Obstet Gynecol 1996;174(5):1584–9.
70. Silver RM, Parker CB, Reddy UM, et al. Antiphospholipid antibodies in stillbirth. Obstet Gynecol 2013;122(3):641–57.
71. Metz TD, Berry RS, Fretts RC, et al. Obstetric care consensus #10: management of stillbirth: (replaces practice bulletin number 102, March 2009). Am J Obstet Gynecol 2020;222(3):B2–20.
72. Rajcan-Separovic E, Diego-Alvarez D, Robinson WP, et al. Identification of copy number variants in miscarriages from couples with idiopathic recurrent pregnancy loss. Hum Reprod 2010;25(11):2913–22.
73. Page JM, Bardsley T, Thorsten V, et al. Stillbirth associated with infection in a diverse U.S. cohort. Obstet Gynecol 2019;134(6):1187–96.