OBSTETRICS

Intrauterine growth restriction: new concepts in antenatal surveillance, diagnosis, and management

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Intrauterine growth restriction (IUGR) remains one of the main challenges in maternity care. Improvements have to start from a better definition of IUGR, applying the concept of the fetal growth potential. Customized standards for fetal growth and birthweight improve the detection of IUGR by better distinction between physiological and pathological smallness and have led to internationally applicable norms. Such developments have resulted in new insights in the assessment of risk and surveillance during pregnancy. Serial fundal height measurement plotted on customized charts is a useful screening tool, whereas fetal biometry and Doppler flow are the mainstay for investigation and diagnosis of IUGR. Appropriate protocols based on available evidence as well as individualized clinical assessment are essential to ensure good management and timely delivery.

Key words: birthweight, customized charts, fetal growth, growth potential

Intrauterine growth restriction (IUGR) is associated with stillbirth, neonatal death, and perinatal morbidity as well as delayed effects including cerebral palsy (CP) and adult diseases.[1-3] In most cases, IUGR is due to placental insufficiency but may also be due to a number of other conditions such as congenital anomalies, infections, or drug and substance misuse.

However, the study of the natural history of IUGR or fetal growth restriction (FGR) has particular challenges. First, growth failure is often not detected antenatally, and in routine clinical practice, as many as three-quarters of babies at risk of IUGR are not recognized as such before delivery.[4] In low-risk pregnancy, with a lower threshold of suspicion, the detection rate is even lower, about 15%.[5] Second, when IUGR *is* recognized, the pregnancy is likely to be interrupted if the growth failure is considered severe and if the babies are mature enough to have a better chance ex utero. Therefore, most qualitative and quantitative evidence for the significance of IUGR comes from the retrospective assessment of the birthweight of live or stillborn babies.

Studies have been hampered by the widespread practice of using the terms small for gestational age (SGA) and IUGR synonymously. SGA simply refers to a weight for gestation below a given threshold, but a significant proportion of smallness is due to constitutional or physiological causes, which means that the association between pathological smallness and adverse outcome is blurred. However, such factors can now be adjusted for by the use of the customized growth potential, which improves the association between low birthweight and pathology, as explained in the next section.

Association between IUGR and outcome

New tools and new insights

In modern epidemiological research, the standard for birthweight for gestation has been refined to be able to assess birthweight not against the average of the population but against an individual growth potential calculated for each baby in each pregnancy.

This is based on 3 principles.[6,7] First, the standard is adjusted or customized for sex as well as maternal characteristics such as height, weight, parity, and ethnic origin on the principle that one size does not fit all.[8] The stepwise improvement of prediction through this method is illustrated in Figure 1.

Second, pathological factors such as smoking, hypertension, diabetes, and preterm delivery are excluded to predict the optimum weight that a baby can reach at the end of a normal pregnancy.

Third, the term *optimal weight* and associated normal range is projected backward for all gestational age points, using an ultrasound growth based proportionality curve; this avoids basing the standard on preterm neonatal weights, which by definition are derived from pregnancies with a pathological (preterm) outcome and hence do not represent the growth potential.[6,7]

Recent studies have shown that this principle is also internationally applicable, with striking similarities of the predicted birthweight of a baby born to a standard European mother in the United Kingdom, Australasia, and the United States.[9,10] In practice, the fetal growth potential, and the individually adjusted or customized normal limits (eg, the 10th and 90th centile), are calculated by computer software[11] because of the infinite number of possible variations.

Validation

The new standard has been applied to the research of birthweight as well as fetal weight and has helped to improve our understanding of the association between smallness and outcome.

In studies of birthweight databases, SGA based on the customized growth

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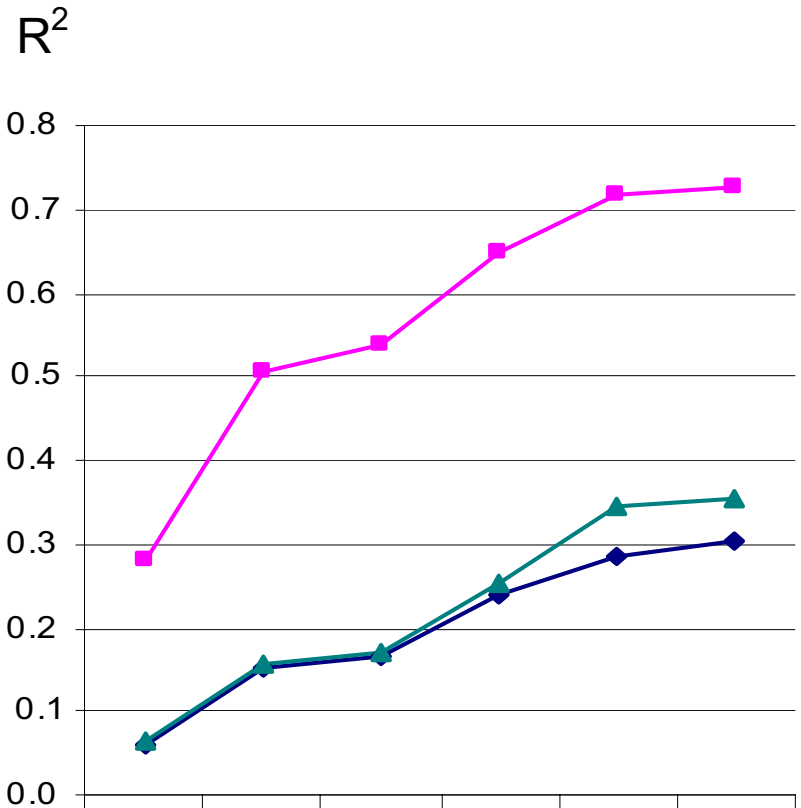
FIGURE 1
Accuracy of birthweight prediction and maternal characteristics (n = 313,285)



	sex	+parity	+ethnic	+mat height	+mat weight	+excl path
T1	0.06	0.15	0.17	0.24	0.28	0.30
T2	0.28	0.51	0.54	0.65	0.72	0.73
T3	0.06	0.16	0.17	0.25	0.35	0.35

Swedish births with gestational age-controlled residuals of birthweight; goodness of fit (R^2) is plotted against variables added. R^2 was best in the middle tertile (T2), rising from 0.28 with adjustment for sex only, to 0.73 with all variables included. Upper (T3) and lower tertiles (T1) are also shown.

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Figueras and Gardosi. Intrauterine growth restriction. Am J Obstet Gynecol 2010.

potential is more strongly associated with abnormal antenatal Doppler findings, fetal distress, cesarean section, admission, and prolonged stay in neonatal intensive care as well as stillbirths and neonatal deaths than centiles based on population standards.[12-16] In fact, SGA by population centiles but normal size by customized growth potential can be termed physiological smallness because it is not associated with adverse outcome. Importantly, the customized standard also detects a substantial number of additional, significantly at-risk cases that were not flagged up as SGA by the population norm.[12,13,16] This dual effect of identifying normal-small cases *not* at risk, and pathologically small cases that *are* at risk, is illustrated in Figure 2. Such findings lead to the useful conclusion that "SGA by customized growth potential" represents pathological smallness and can be used interchangeably with "IUGR" for retrospective research on pregnancy outcome.

Estimated fetal weight also varies with individual characteristics in low- as well as high-risk pregnancies.[17,18] An adjustable standard improves the association with pathology, while reducing false-positive assessments by adjusting for constitutional smallness.[19] This can have clinical relevance when seeking to reduce false-positive diagnoses of IUGR and unnecessary intervention.[20]

Recent work has shown that the length of growth deficit is linked with perinatal morbidity,[21] in that morbidity is worse the longer the slow growth has occurred in utero. A similar principle could be inferred from the findings of a case control study of birthweight and CP,[2] in which IUGR at term was highly associated with an increased risk of CP, whereas it did not increase the risk in early and late preterm gestations.

Stillbirth and IUGR

Such validation of the principles of the growth potential have allowed IUGR or FGR to be introduced as an additional category when classifying stillbirth and found that after excluding congenital anomalies, more than 50% of stillbirths had preceding IUGR (<10th customized centile). As a result, the proportion of unexplained stillbirths drops from 65-70% using the Wigglesworth classification to 15%.[22] This has since been confirmed in an independent comparative study.[23] While IUGR is usually the result of underlying placental pathology and not in itself the cause of the demise,[24] it is a clinically relevant condition. Awareness of this strong link allows a renewed focus of attention on the antenatal identification of IUGR as a first step toward prevention. Antenatal awareness that the fetus is not growing well is an essential quality indicator of maternity care.

Purpose of detection

First, detection informs the clinician and thence the mother that the pregnancy is at increased risk, allowing considerations on the optimal timing for delivery. Depending on severity, babies that are not fulfilling their growth potential have a 5- to 10-fold risk of dying in utero.[12]

Second, the information is important to prompt further investigation such as

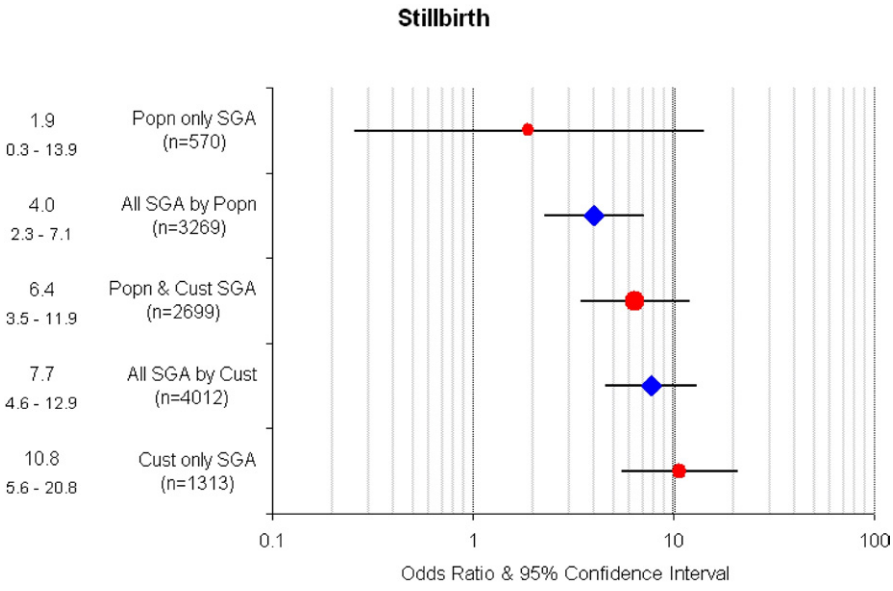
umbilical artery Doppler, which has been shown to reduce stillbirth and increase preterm delivery without increasing neonatal mortality.[25] In a large single-center retrospective study, Lindqvist and Molin[26] found that antenatal detection of SGA led to significantly improved outcome.

Screening for the at-risk fetus

History

Previous history of growth restriction or stillbirth. Women with a previous growth-restricted baby have a 50% increased risk of severe growth restriction in the current pregnancy,[27] and serial third-trimester assessment for this indication is common practice. A history of stillbirth is also an accepted indication for intensive antepartum surveillance because more than half of normally formed stillbirths are associated with IUGR.[22] Stillbirths before 32 weeks' gestation have a particularly strong association with IUGR.[28] Previous stillbirth would appear to be a significant risk factor, especially when associated with a diagnosis of hypertension or clinical IUGR.[29]

FIGURE 2
Stillbirth and SGA status by customized and population-based centiles



Small for gestational age was defined according to population-based centiles (Popn only SGA) and SGA by customized centiles (all SGA by Cust) (*blue markers*). Subgroups that are SGA by both methods (Pop and Cust SGA), by the population method only (SGA Pop only), or by the customized method only (Cust only SGA) (*red markers*) are shown. Odds ratios and 95% confidence intervals are shown.

SGA, small for gestational age.
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Diabetes. Women with diabetes are at increased risk of having a baby with macrosomia as well as FGR, with increased risk of perinatal morbidity and mortality.[30] Preeclampsia is observed in 15-20% of pregnancies complicated by type 1 diabetes mellitus without nephropathy and approximately 50% in the presence of nephropathy.[31] Preeclampsia is also more likely in women with hypertension and poor glucose control.[32] When assessed by customized standards, 15% of women with type 2 diabetes are found to have an SGA baby.[33]

Regular monitoring of fetal growth is recommended in diabetic pregnancies.[34] Umbilical artery Doppler seems to be more effective than biophysical profile or cardiotocography,[35-37] but its use should be limited to women with additional risk factors for placental insufficiency, such as SGA or preeclampsia.

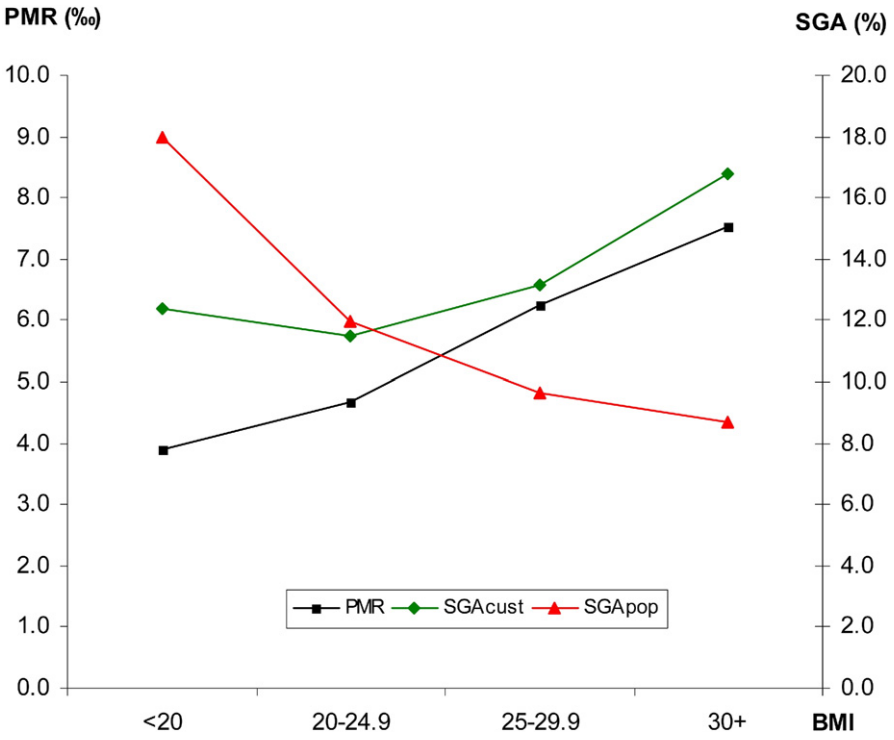
Obesity. Obesity has been considered a protective factor for growth restriction,[38,39] but such findings are likely to be artifactual because of the use of unadjusted population standards. When SGA is defined by customized centiles, obesity increases the risk of SGA by 50%.[15] Such relative smallness is pathological: a large population-based study[40] reported that in obese women, higher perinatal mortality is associated with higher rates of SGA but only when SGA is defined by customized growth potential (Figure 3). Although obesity affects the accuracy of ultrasound biometry, it makes palpation and fundal height measurement even more difficult. A small series including 42 obese women showed that ultrasound estimation of fetal weight was more accurate than abdominal palpation in predicting birthweight.[41]

Multiple pregnancy. Compared with singletons, twin pregnancies have increased risk of mortality and morbidity.[42] Because growth restriction and weight discordance are responsible for a large part of this higher risk of mortality and morbidity,[43] optimal monitoring of fetal growth is essential. Clinical assessment does not allow individual fetal evaluation, and therefore, serial fetal weight estimation by ultrasound from 28 weeks is considered best practice. Growth standards for multiple pregnancies have been published,[44] but singleton nomograms are more commonly used with good accuracy.[45]

Customized charts for estimated fetal weight (EFW) can also be used for twins because the growth potential up to 37 weeks is similar to that in singleton pregnancy.[46] There is no consensus on the best definition of weight discordance and its correlation to clinical events,[43] but discordance greater than 20-25% is certainly considered significant.

In addition, the clinical meaning of growth discordance may differ greatly between monochorionic and dichorionic pregnancies.[42] Although it may seem reasonable to incorporate umbilical artery Doppler for an earlier detection of growth restriction, there is insufficient evidence to support its use in dichorionic multiple pregnancies not complicated by growth restriction.[47,48]

FIGURE 3
Perinatal mortality rate and SGA by customized and population-based centiles



Perinatal mortality rate (PMR) and SGA by customized (SGAcust) and population-based centiles (SGApop), according to maternal body mass index (BMI). Comparison test for difference of slopes: PMR vs SGAcust: $P = .753$; PMR vs SGApop: $P = .007$.

SGA, small for gestational age.
Reproduced, with permission, from Gardosi et al.[40]

Figueras and Gardosi. Intrauterine growth restriction. Am J Obstet Gynecol 2010.

Screening in early pregnancy

Biochemical markers. In the first trimester, an unexplained low pregnancy-associated plasma protein A or human chorionic gonadotropin (hCG) is associated with an increased risk of placental-related diseases such as IUGR or preeclampsia.[49,50] In the second trimester, an unexplained elevation of serum alpha-fetoprotein, hCG, or inhibin-A is also associated with these adverse outcomes.[51-54]

In general, the association is more marked for early-onset IUGR or preeclampsia.[55] Despite these associations, the performance in terms of sensitivity/specificity and predictive values of these markers individually or combined does not support their use. Moreover, no clear benefit of intensive surveillance[56] or prophylactic strategies[57] in women with abnormal biochemical markers has been demonstrated.

Early growth restriction. Low first-trimester measurement of crown-rump length in pregnancies dated by the last menstrual period is also linked with FGR.[58,59] However, practical applicability is limited in spontaneously conceived pregnancies because the exact date of conception is usually not known, and a crown-rump length measurement cannot be used simultaneously for establishing gestational age and for assessing fetal size for gestation.

More recently, it has been demonstrated that slow growth between the first and second trimester is able to identify a subgroup of slow-growing babies that are at increased risk of perinatal death before 34 weeks' gestation, in most cases with growth restriction.[60] An early indication of an increased risk would allow more intensive fetal assessment and surveillance. Therefore, serial ultrasound evaluation of fetal growth in the third trimester seems justified in these cases.

Uterine artery. Uterine Doppler evaluation in the second or first trimester has been proposed as a screening tool for early-onset IUGR, with detection rates of about 75% and 25%, respectively, for a false-positive rate of 5-10%.[61,62] These sensitivities are higher for predicting early IUGR associated with preeclampsia and lower for late IUGR. Different strategies combining maternal risk factors, blood pressure, and biochemical markers have been published with detection rates greater than 90% for early-onset preeclampsia,[63,64] and associated IUGR.

A metaanalysis[65] of 5 randomized studies including 1052 women with abnormal uterine Doppler in the second trimester treated with aspirin showed a 20% reduction in the incidence of preeclampsia, without reaching statistical significance (relative risk, 0.8; 95% confidence interval, 0.61–1.06). Only 2 randomized studies (n = 225) have evaluated the efficacy of aspirin in women with abnormal uterine Doppler in the first trimester,[66,67] showing a pooled 71% reduction in the incidence of preeclampsia. The limited number of cases included a high incidence of preeclampsia in the control group, and there is uncertainty whether the standard of care could be extrapolated between countries to draw reliable conclusions.

Thus, so far, there is no evidence in favor of any prophylactic strategy in cases of abnormal uterine artery Doppler. However, it could be useful in defining the standard of prenatal care by assessing the woman's risk at the beginning of the pregnancy. This is in agreement with the recommendations made by the UK National Institute on Clinical Excellence for risk-adjusted prenatal care.[68]

Screening in the third trimester

Serial fundal height measurement. The first fundal height plot represents the ini-

tial assessment as well as the baseline for subsequent measurements, which are interpreted on the basis of the slope or velocity of growth. Indications for referral for further investigations include cases in which the first fundal height measurement is below the 10th centile or consecutive measurements suggest static or slow growth, meaning that the serial measurements do not follow the expected slope of the growth curve. An audit on the population in the catchment area of a referral hospital in the West Midlands (UK) showed that the detection rates for SGA fetuses are improved if referral recommendations are fully adhered to, highlighting the need for a continuous program of education and training.[69]

Not all pregnancies are suitable for primary surveillance by fundal height measurement and require ultrasound biometry instead. In most instances, these pregnancies fall into the following categories: (1) fundal height measurement unsuitable (eg, due to fibroids, high maternal body mass index) or (2) pregnancy considered high risk (eg, due to previous history of SGA).

Fundal height measurement is more of a surveillance than a screening tool because its strength lies in serial assessment. However, most clinicians are not formally taught how to measure fundal height and use a variety of different methods. This reduces accuracy and increases interobserver variation. Not surprisingly, the evidence on fundal height assessment is mixed, with some studies reporting that it is a good predictor for IUGR,[70-73] whereas others fail to find much benefit.[74-78]

A recent review has summarized the efforts being made to standardize this tool to improve its reliability and effectiveness.[79] The name *symphysis-fundus height* is in fact misleading because the preferred direction of measurement is from the variable (the fundus) to the fixed point (the top of the symphysis). The measurement should be along the fetal axis, with no correction of the fundus to the midline, using a nonelastic tape.

One of the main problems has been the assumption that has crept into common clinical practice, without any good evidence, that 1 cm fundal height should equal 1 week of gestation and the definition of normal as fundal height ± 2 or ± 3 cm of gestational age. But as with birthweight and ultrasound growth, one size does not fit all, and different-sized mothers have different normal fundal height growth curves.[80] As a serial assessment, the emphasis with fundal height measurement is on the slope of the curve. Referral guidelines for further investigation by ultrasound biometry and Doppler include a single fundal height measurement which plots below the 10th customized centile, and serial measurements which cross centiles (ie, are slower than the predicted growth velocity).[79]

A controlled study of 1200 patients compared measurement and plotting of fundal height on customized growth charts against routine clinical assessment by palpation and found that it resulted in a significant increase in antenatal detection of SGA babies from 29% to 54%.[81] Furthermore, there was a significant reduction of false-positive rates (ie, small-normal babies being referred unnecessarily for investigation). The study was not powered to assess the effect on perinatal mortality, and there is a paucity of prospective trials large enough to be able to assess the effect on hard outcome measures. However, the antenatal identification of IUGR is already of proven benefit in itself and allows further investigations and interventions that are known to improve outcome. Serial measurement of fundal height and plotting on customized growth charts are recommended by the Royal College of Obstetricians and Gynaecologists guidelines.[82]

Routine/intermittent third-trimester ultrasound biometry. The effectiveness of third-trimester ultrasound biometry for the diagnosis of growth restriction and its impact on perinatal outcome is uncertain. Sensitivity of abdominal circumference for detecting a birthweight less than the 10th centile ranges from 48% to 87%, with specificity from 69% to 85%.[83-88] For estimated fetal weight, sensitivities of 25-100% have been reported, with a specificity of 69-97%.[84,87-89]

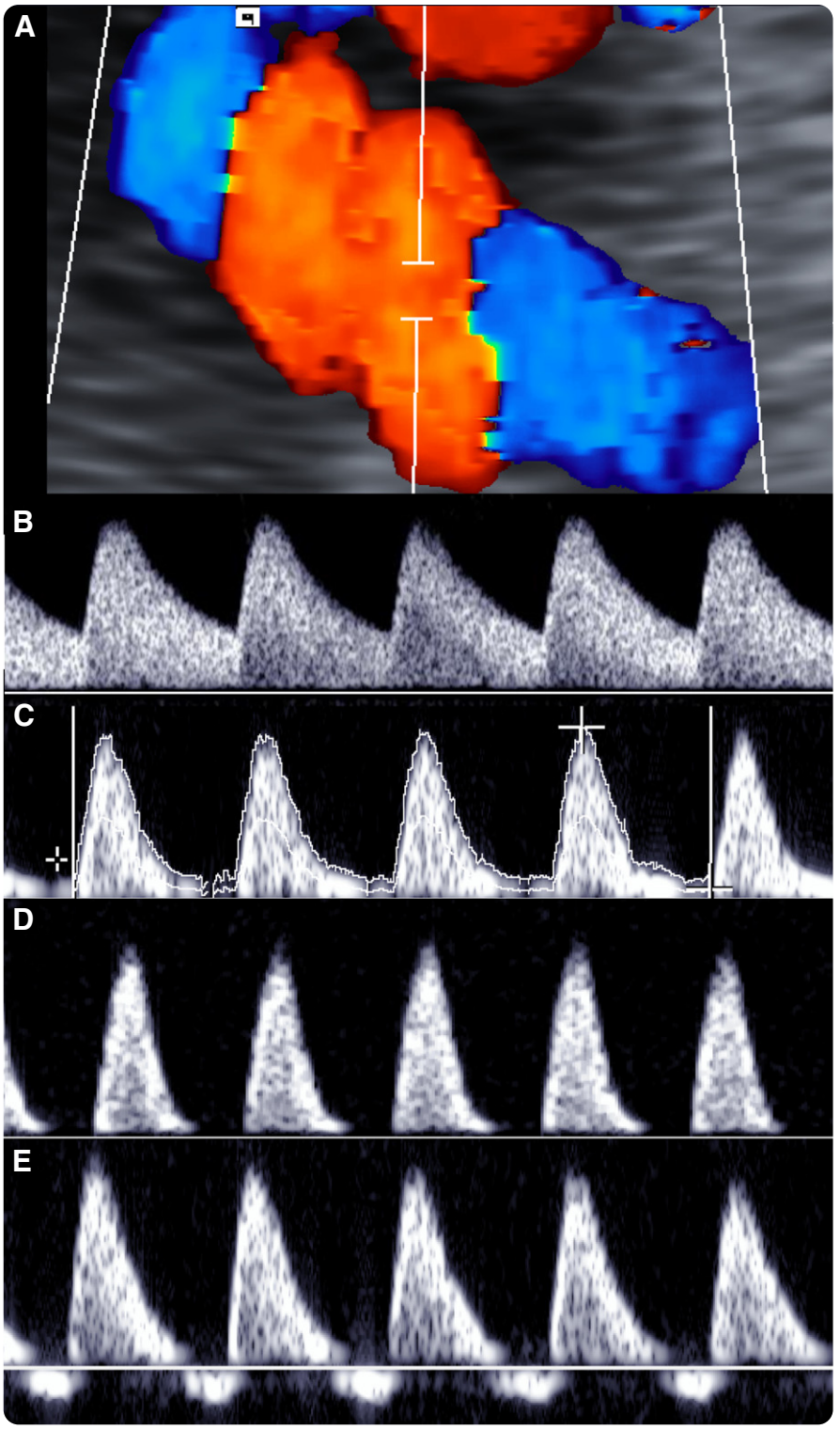
The high heterogeneity between studies does not allow the calculation of pooled values. The largest study,[88] from the United Kingdom, included 3616 low-risk women on whom a third-trimester (28-36 weeks) ultrasound was performed with abdominal circumference measurement. Sensitivity for birthweight less than the 10th centile was 48%, with a false-positive rate of 7%. Lindqvist and Molin[26] introduced a policy of a routine scan at 32 weeks and observed a detection rate of 54% for SGA (defined as birthweight deviation of at least 22% from the mean, equivalent to the third centile). Hedriana and Moore[89] compared serial vs single scan in low-risk women between 28 and 42 weeks and found that multiple ultrasonographic examinations provided little improvement in the prediction of birthweight compared with a single observation. McKenna et al[90] tested randomly a policy of 2 scans at 30 and 36 weeks and observed that fewer babies were born SGA as a result of increased intervention in the study group, although no data were given on actual detection rates.

The impact of routine third-trimester ultrasound on perinatal outcome is also unclear. Seven trials[83,85,86,91-94] have been included in a recently updated metaanalysis[95] that showed that routine late pregnancy ultrasound in low-risk or unselected populations does not confer benefit on mother or baby. Furthermore, it may be associated with a small increase in cesarean section rates.

However, it could be argued that the results of this metaanalysis have limited validity for contemporary practice because it included studies that used outdated surrogates of fetal growth such as biparietal diameter measurement[83] or protocols in which the diagnosis of IUGR was not followed by a change in management. A Swedish population-based study[96] compared the perinatal outcome of 56,371 unselected women in whom routine third-trimester ultrasound was performed with the outcome of 153,355 women with no such screening. No differences in perinatal mortality or early neonatal morbidity were found.

There is currently therefore insufficient evidence to support routine third-

FIGURE 4
Insonation of the umbilical artery Doppler



A, Site of insonation of the umbilical artery Doppler. Progressive waveform patterns with advancing severity were: **B,** normal umbilical artery waveform, **C,** increased impedance to flow, **D,** absent end-diastolic flow, and **E,** reversed end-diastolic flow.

Figueras and Gardosi. Intrauterine growth restriction. Am J Obstet Gynecol 2010.

trimester ultrasound in all pregnancies. A management trial to investigate the impact of third-trimester ultrasound would be feasible in terms of maternal willingness to participate[97] but will require a large sample size to test effect on hard outcomes such as perinatal mortality. Further trials will also need to include growth scans in the late third trimester because most cases of IUGR deliver at term.[98]

Serial ultrasound biometry. For pregnancies at risk, serial assessment of estimated fetal weight or abdominal circumference is the best predictor of FGR as assessed by neonatal morphometry.[99] Therefore, serial biometry is the recommended gold standard for assessing pregnancies that are high risk,[82] either on the basis of past history or because of complications that arose during the current pregnancy. In the absence of clear evidence and consensus about the frequency and timing of scans, protocols and individual management plans are often limited by the resources available. However, more than fortnightly scans are not indicated because the scan error is likely to exceed the increment in size because of growth during the interval.[82]

Diagnosis of IUGR

Current thinking on the natural history of growth restriction differentiates between early-onset and late-onset forms,[100] which have different biochemical, histological, and clinical features.[101] Whereas the former is usually diagnosed with an abnormal umbilical artery Doppler and is frequently associated with preeclampsia, the latter is more prevalent, shows less change in umbilical flow pattern, and has a weaker association with preeclampsia.[101]

Umbilical artery Doppler

Most instances of growth restriction correspond with cases of placental insufficiency.[102] Evaluation of placental function by umbilical artery Doppler is a clinical standard to distinguish between SGA and IUGR.[103-105] The pathophysiological progression of this parameter is illustrated in Figure 4. As suggested by animal[106] and mathematical[107] models

of chronic placental embolization, the obliteration of more than 50% of the placental vessels is required before absent or reversed end-diastolic velocities appear. There is good evidence that umbilical Doppler ultrasound use in these pregnancies improves a number of obstetric care outcomes and reduces perinatal deaths.[108]

Whereas abnormal umbilical artery Doppler is associated with adverse perinatal and neurodevelopmental outcome,[109-112] small fetuses with normal umbilical artery Doppler are considered to represent one end of the normal-size spectrum, and the importance of managing them as completely differently from true IUGR babies has been stressed.[113,114] This may not be true for late-onset cases, in which a substantial proportion of cases with a normal umbilical artery may have true growth restriction, and are at risk of adverse perinatal outcome.[109,110,115,116]

Other Doppler parameters

Because the identification of late-onset SGA fetuses with mild forms of growth restriction cannot only be relied on by umbilical artery Doppler, other vascular territories have been proposed. Abnormal uterine artery Doppler is comparable with umbilical artery Doppler as a predictor of adverse outcome in growth-restricted fetuses.[116-118] Up to 20% of SGA fetuses have reduced resistance in the middle cerebral artery (MCA), and this sign is also associated with poorer perinatal outcome[116-119] and suboptimal neurodevelopmental development at 2 years of age.[120] Umbilical and cerebral Doppler can be combined in the cerebroplacental ratio. This ratio has been demonstrated in animal[121] and clinical[122] models to be more sensitive to hypoxia than its individual components and correlates better with adverse outcome.[123]

Assessment of the IUGR fetus

Because no treatment has been demonstrated to be of benefit for FGR,[124-127] the assessment of fetal well-being and timely delivery remains as the main strategy for management. Fetal well-being tests could be classified as chronic or acute. Whereas, the former becomes progressively abnormal because of increasing hypoxemia and/or hypoxia, the latter correlates with acute changes occurring in advanced stages of fetal compromise, characterized by severe hypoxia and metabolic acidosis, and usually precedes fetal death by a few days. Because a fixed sequence of fetal deterioration does not exist, integration of several well-being tests into comprehensive management protocols is required.

Chronic tests

Umbilical artery. Absent or reversed end-diastolic velocities are mostly found in early-onset IUGR, and these patterns have been reported to be present on average 1 week before the acute deterioration.[128] Up to 40% of fetuses with acidosis show this umbilical flow pattern.[128] Despite the fact that an association exists between the presence of reversed end-diastolic flow in the umbilical artery and adverse perinatal outcome (with a sensitivity and specificity of about 60%), it is not clear whether this association is confounded by prematurity. More recent series[129] of severely compromised IUGR fetuses suggest that such a finding has value independently of gestational age in the prediction of perinatal morbidity and mortality.

Middle cerebral artery. Longitudinal studies on deteriorating early-onset IUGR fetuses have reported that the pulsatility index in the MCA progressively becomes abnormal.[130] Figure 5 shows the progression of this parameter. Up to 80% of fetuses have vasodilatation 2 weeks before the acute deterioration,[128] although other series have found this figure to be less than 50%.[129] Preliminary findings of an acute loss of the MCA vasodilatation in advanced stages of fetal compromise have not been confirmed in more recent series,[128-131] and therefore this sign does not seems to be clinically relevant for management purposes in early-onset cases. In late-onset IUGR, there is observational evidence[116,119] that MCA vasodilatation is associated with adverse outcome independently of the umbilical artery. This suggests a role of MCA Doppler for fetal monitoring in late-onset IUGR cases, which needs further investigation in randomized trials.

Amniotic fluid. A metaanalysis[132] of 18 randomized studies demonstrated that an amniotic fluid index of less than 5 is associated with abnormal 5 minute Apgar score but failed to demonstrate an association with acidosis.

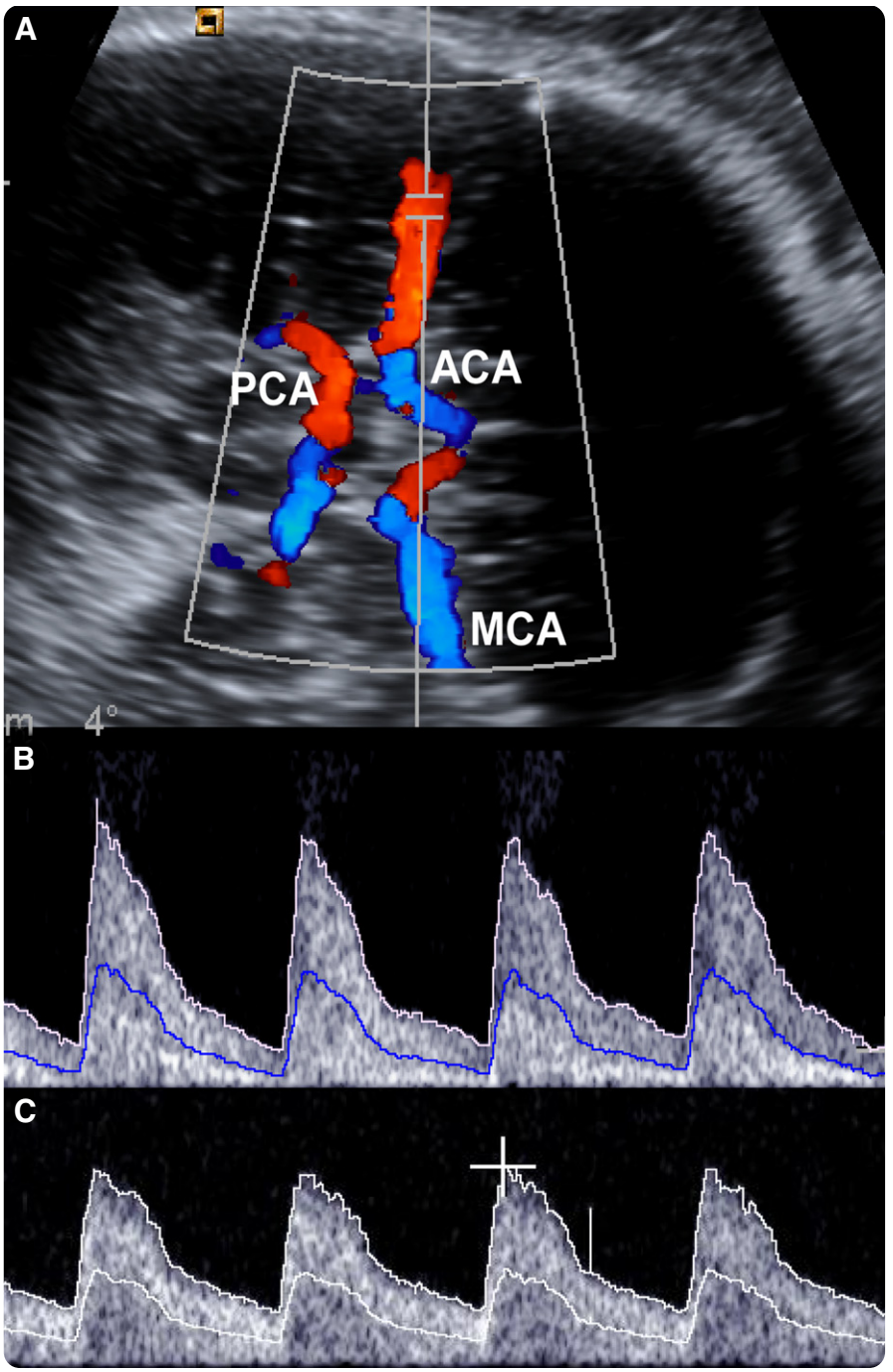
Longitudinal studies in early-onset IUGR fetuses have shown that the amniotic fluid index progressively decreases.[129,130] Amniotic fluid volume is believed to be a chronic parameter. In fact, among the components of biophysical profile, it is the only one that is not considered acute. One week before acute deterioration, 20-30% of cases have oligohydramnios.[129,130]

Acute markers

Ductus venosus (DV). Early studies on IUGR fetuses demonstrated a good correlation of abnormal DV waveform with acidemia at cordocentesis,[133] and this Doppler sign is considered a surrogate parameter of the fetal base-acid status. The progression of this parameter is shown in Figure 6. Absent-reversed velocities during atrial contraction are associated with perinatal mortality independently of the gestational age at delivery,[134] with a risk ranging from 60% to 100% in fetuses with early-onset IUGR.[135] However, its sensitivity for perinatal death is still 40-70%.[134,136,137]

Longitudinal studies have demonstrated that DV flow waveforms become abnormal only in advanced stages of fetal compromise.[128-131] Whereas in about 50% of cases abnormal DV precedes the loss of short-term variability in the fetal heart rate,[130] in about 90% of cases it becomes abnormal only 48-72 hours before the biophysical profile.[131] Debate exists regarding the advantages of DV Doppler investigation over biophysical profile. However, observational studies[138] suggest the integration of both DV Doppler investigation and biophysical profile in the management of preterm IUGR because these strategies seem to stratify IUGR fetuses into risk categories more effectively. An ongoing randomized clinical trial (Trial of umbilical and fetal flow in Europe, TRUFFLE) is aimed

FIGURE 5
Color Doppler assessment of the middle cerebral artery



A, Color Doppler assessment of the MCA at the level of the circle of Willis. **B,** Normal and abnormal (high diastolic velocities and decreased pulsatility index) **C,** waveforms are shown.

ACA, anterior cerebral artery; *MCA*, middle cerebral artery; *PCA*, posterior cerebral artery.

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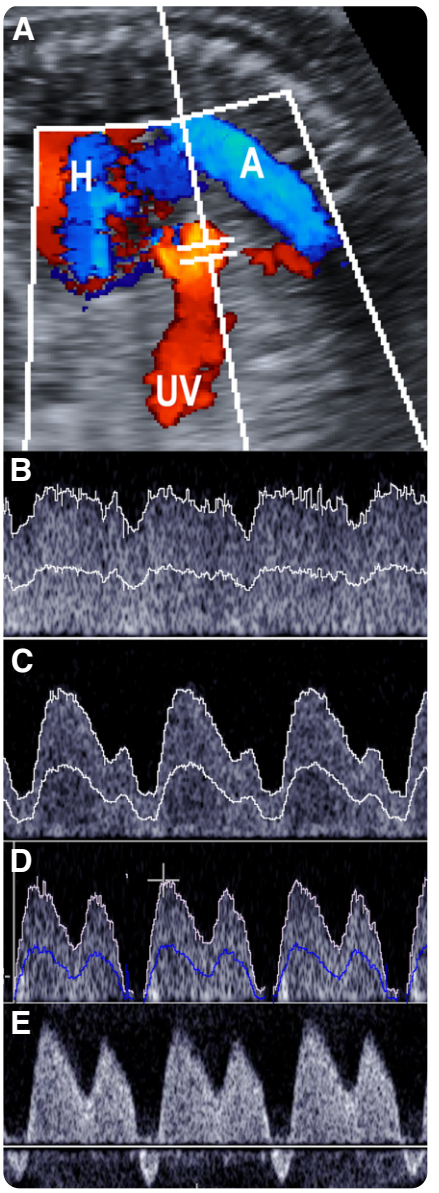
FIGURE 6
Insonation of the ductus venosus with color Doppler



A, Site of insonation of the DV with color Doppler. Progressive waveform patterns with advancing severity are shown: **B,** normal DV waveform, **C,** increased impedance to flow, **D,** absent end-diastolic flow, and **E,** reversed end-diastolic flow.

A, descendent aorta; *DV*, ductus venosus; *H*, heart; *UV*, umbilical vein.

Figueras and Gardosi. Intrauterine growth restriction. Am J Obstet Gynecol 2010.

at evaluating the role of DV assessment over standard management based on cardiotocography for timely delivering early-onset IUGR cases.

Fetal heart rate (FHR) analysis. Early studies on high-risk pregnancies showed that, although highly sensitive, cardiotocography has a 50% rate of false positives for the prediction of adverse outcome.[139] In addition, a metaanalysis[140] of its application in high-risk pregnancies failed to demonstrate any beneficial effect in reducing perinatal mortality. Hence,

there is no evidence to support the use of traditional fetal heart rate monitoring or nonstress tests in IUGR fetuses. However, these studies were conducted in the early 1980s, and the control group had no fetal well-being assessment or outdated techniques such as biochemical tests.

Computerized FHR has provided new insight into the pathophysiology of IUGR. Short-term variability closely correlates with acidosis and severe hypoxia as demonstrated by cord blood sampling at the time of a cesarean section.[141] Whereas Bracero et al[142] demonstrated no significant differences in perinatal outcome between visual and computerized FHR, more recent longitudinal series have pointed to a potential role as an acute marker.[130] Short-term variability becomes abnormal, coinciding with the DV: whereas in about half of the cases, abnormal DV precedes the loss of short-term FHR variability, the latter is the first to become abnormal in the other cases.[130] Both parameters are considered acute responses to fetal acidosis.

Biophysical profile. Some observational studies show an association between abnormal biophysical profile (BPP) and perinatal mortality and cerebral palsy,[143] whereas others fail to demonstrate this association.[129] In IUGR infants, BBP was not predictive of cognitive function at 2 years.[144] Similarly, whereas some studies with cordocentesis demonstrated a correlation with acidosis,[145] with fetal tone and gross motor movements the best correlated components, others have not found this correlation.[146]

As with FHR , a high false-positive rate (50%) limits the clinical usefulness of the biophysical profile.[147] A recent study[148] has shown that BPP alone in fetuses weighting more than 1000 g is not a reliable test in the treatment of preterm IUGR fetuses because of high false-positive and -negative results. A metaanalysis[149] showed no significant benefit of a biophysical profile in high-risk pregnancies, although more recent series[150,151] on IUGR have suggested that both Doppler and biophysical profile effectively stratify IUGR fetuses into risk categories. Because fetal deterioration appears to be independently reflected by both tests, further studies are required to prove the usefulness of combining both testing modalities.

Longitudinal series[131] have demonstrated that except for amniotic fluid volume and the fetal heart rate, the other components (tone, breathing, and body movements) of the biophysical profile become abnormal only in advanced stages of fetal compromise. In fact, in about 90% of cases, the biophysical profile becomes abnormal only 48-72 hours after the ductus venosus.[131]

Timing of delivery

IUGR is one of the most common pregnancy complications and substantially increases the prospective risk of adverse outcome. Yet according to pregnancy audits, most instances of IUGR are not detected as such antenatally. Modern obstetric care needs to raise the level of awareness of the importance of this condition, and establish evidence-based protocols for improved surveillance.

Because the only current treatment for IUGR is delivery, the main consideration needs to be appropriate timing, balancing the risk of potential iatrogenic morbidity and continued exposure to an unfavorable intrauterine environment. Studies are now in progress with regard to late-onset IUGR to evaluate whether elective induction beyond 36 weeks' gestation is of benefit. To date, prospective trials have not been able to throw much light and are often underpowered or flawed.

Regarding early-onset IUGR, the multicentre Growth Restriction Intervention Trial[153] compared outcome after randomization with early or delayed delivery and concluded that it was safe to wait, especially at preterm gestations. However, the study design has been criticized because it did not account for the cases that were not randomized and which were estimated to represent the majority of all eligible cases:[154] clinical selection bias may have preferentially included the less severe cases, in which it would be safe to wait anyway. Therefore, such results cannot be extrapolated to all cases with IUGR.

Improved definition of the intrauterine standard for IUGR by the use of the fetal growth potential allows a more discerning assessment. A baby with an EFW below the 10th customized centile has a significantly elevated risk of morbidity, even in the absence of an abnormal umbilical artery Doppler.[110] Added into the equation is the awareness that leaving pregnancies with IUGR to deliver at term may also lead to perinatal morbidity and delayed effects such as cerebral palsy.[2]

Therefore, current best practice would indicate that from the time fetal pulmonary maturity can be inferred, there is little to be gained by allowing a pregnancy to continue if good fetal growth cannot be demonstrated. However, each case needs to be carefully assessed and individually considered, in consultation with the parents. ■

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