# Evidence-based national guidelines for the management of suspected fetal growth restriction: comparison, consensus, and controversy

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Small for gestational age is usually defined as an infant with a birthweight <10th centile for a population or customized standard. Fetal growth restriction refers to a fetus that has failed to reach its biological growth potential because of placental dysfunction. Small-for-gestational-age babies make up 28-45% of nonanomalous stillbirths, and have a higher chance of neurodevelopmental delay, childhood and adult obesity, and metabolic disease. The majority of small-for-gestational-age babies are not recognized before birth. Improved identification, accompanied by surveillance and timely delivery, is associated with reduction in small-for-gestational-age stillbirths. Internationally and regionally, detection of small for gestational age and management of fetal growth problems vary considerably. The aim of this review is to: summarize areas of consensus and controversy between recently published national guidelines on small for gestational age or fetal growth restriction; highlight any recent evidence that should be incorporated into existing guidelines; and identify future research priorities in this field. A search of MEDLINE, Google, and the International Guideline Library identified 6 national guidelines on management of pregnancies complicated by fetal growth restriction/small for gestational age published from 2010 onwards. There is general consensus between guidelines (at least 4 of 6 guidelines in agreement) in early pregnancy risk selection, and use of low-dose aspirin for women with major risk factors for placental insufficiency. All highlight the importance of smoking cessation to prevent small for gestational age. While there is consensus in recommending fundal height measurement in the third trimester, 3 specify the use of a customized growth chart, while 2 recommend McDonald rule. Routine third-trimester scanning is not recommended for small-for-gestational-age screening, while women with major risk factors should have serial scanning in the third trimester. Umbilical artery Doppler studies in suspected small-for-gestational-age pregnancies are universally advised, however there is inconsistency in the recommended frequency for growth scans after diagnosis of small for gestational age/fetal growth restriction (2-4 weekly). In late-onset fetal growth restriction (≥32 weeks) general consensus is to use cerebral Doppler studies to influence surveillance and/or delivery timing. Fetal surveillance methods (most recommend cardiotocography) and recommended timing of delivery vary. There is universal agreement on the use of corticosteroids before birth at <34 weeks, and general consensus on the use of magnesium sulfate for neuroprotection in early-onset fetal growth restriction (<32 weeks). Most guidelines advise using cardiotocography surveillance to plan delivery in fetal growth restriction <32 weeks. The recommended gestation at delivery for fetal growth restriction with absent and reversed end-diastolic velocity varies from 32 to ≥34 weeks and 30 to ≥34 weeks, respectively. Overall, where there is high-quality evidence from randomized controlled trials and meta-analyses, eg, use of umbilical artery Doppler and corticosteroids for delivery <34 weeks, there is a high degree of consistency between national small-for-gestational-age guidelines. This review discusses areas where there is potential for convergence between small-for-gestational-age guidelines based on existing randomized controlled trials of management of small-for-gestational-age pregnancies, and areas of controversy. Research priorities include assessing the utility of late third-trimester scanning to prevent major morbidity and mortality and to investigate the optimum timing of delivery in fetuses with late-onset fetal growth restriction and abnormal Doppler parameters. Prospective studies are needed to compare new international population ultrasound standards with those in current use.

**Key words:** clinical management, fetal growth restriction, national guidelines, small for gestational age

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## Introduction

Small for gestational age (SGA) is usually defined as an infant with a birthweight for gestational age <10th centile for a population[1,2] or customized standard.[3,4] These definitions of SGA will include a proportion of babies (18-22%) who are constitutionally small but healthy.[4,5] Fetal growth restriction (FGR)

generally refers to a fetus that has failed to reach its biological growth potential because of placental dysfunction.[6] FGR has considerable overlap with SGA but is more difficult to define in practice, as not all FGR infants have a birthweight <10th centile.[7-9]

Suboptimal fetal growth is important as SGA babies comprise 28-45% of non-anomalous stillbirths.[10,11] Placental insufficiency is a major contributor to the pathophysiology in SGA pregnancies and contributes to the adverse perinatal outcomes.[12] Infants born SGA have higher rates of neurodevelopmental delay, poor school performance, childhood and adult obesity, as well as metabolic disease.[13-18] A limitation of current antenatal care is that the majority of SGA pregnancies are not identified before birth.[19-21] SGA infants recognized before birth who undergo surveillance and timely delivery have a 4- to 5-fold reduction in mortality and/or severe morbidity.[22,23] Therefore, many SGA stillbirths are preventable if detection could be improved and management optimized.

Internationally and regionally, detection of SGA and management approaches can vary considerably. Only 2 previous publications have compared SGA management guidelines between countries.[24,25] The first by Chauhan et al[24] compared the now obsolete 2000 American Congress of Obstetricians and Gynecologists (ACOG) guidelines with the 2002 Royal College of Obstetricians and Gynecologists (RCOG) United Kingdom guidelines and noted that there were considerable variations in content, references cited, and recommendations. More recently, Unterscheider et al[25] compared recommendations made in 4 national guidelines but did not include the New Zealand or the French guideline. The aim of this review is to summarize areas of consensus and controversy between recently published national guidelines on SGA or FGR; to highlight any recent evidence that should be incorporated into existing guidelines; and to identify future research priorities in this field.

## Materials and Methods

Searches through MEDLINE and Google were performed to identify national guidelines on management of pregnancies complicated by FGR/SGA. MEDLINE searches were undertaken using the terms: "fetal growth retardation/or fetal growth restriction," "small for gestational age," and "clinical practice guideline." The search was confined to articles published from 2010 and published in English. The last search was undertaken on Aug. 7, 2017. Four relevant national guidelines were identified through this process.

The Google searches for national guidelines on diagnosis and management of FGR or SGA identified 3 additional guidelines. The International Guideline Library web site was also searched for fetal growth guidelines, but no additional guidelines were identified from this source. Guidelines published before 2010 were not eligible for inclusion in this review as they did not incorporate recently published evidence.[26]

Each guideline was read by all authors. Summary tables were produced incorporating input from each guideline and included: process for guideline development; definitions, screening, and prevention of SGA; ultrasound surveillance and surveillance after diagnosis of SGA; and timing of delivery. Early-onset SGA (<32 weeks) and late-onset SGA were considered separately as management approaches are different. L.M.M. and N.H.A. developed the tables and checked the tables against the original guideline documents.

## Results

National guidelines from 6 countries were identified that met the above criteria. These were produced in the United States (ACOG[27] and Society for Maternal-Fetal Medicine[28]); the United Kingdom (RCOG[29]); Canada (Society of Obstetricians and Gynecologists of Canada[30]); New Zealand (New Zealand Maternal Fetal Medicine Network[31]); Ireland (Health Service Executive[32]); and France (French College of Gynecologists and Obstetricians[33]). The process for guideline development is summarized in Table 1.

All guidelines highlight the importance of an accurate assessment of gestational age to determine whether the pregnancy is complicated by FGR or is possibly misdated. The definitions of SGA and FGR, approaches to risk selection, and early screening and prevention are shown in Table 2. There is broad consensus on definitions of SGA and FGR, as birthweight or estimated fetal weight (EFW) <10th centile but 4 of 6 (67%) recommend using a customized EFW[29,31-33] and 2 (33%) recommend using a population reference for EFW.[27,30] Some require other evidence of severity such as abnormal Doppler studies or an EFW <3rd centile to confirm pathological FGR.[29,31-33]

All guidelines comment on the need for early pregnancy risk selection and 5 of 6 (83%) guidelines recommend low-dose aspirin treatment for women with major risk factors for placental insufficiency.[29-33] All guidelines highlight the importance of smoking cessation to prevent SGA and while all recommend that fundal height should be measured in the third trimester, 3 (50%) recommend using customized growth charts,[29,31,32] 2 (33%) recommend use of McDonald rule,[27,30,34] and 1 does not specify a reference.[33]

In Table 3, approaches to third-trimester ultrasound in low- and high-risk women are compared. Five of 6 (83%) agree that there is no current evidence to support routine third-trimester scanning[27,29-32] and 4 of 6 (67%) specify that women with major risk factors should have serial scans in the third trimester.[27,29,31,32] There is also unanimous agreement about the importance of undertaking umbilical artery (UA) Doppler studies in suspected SGA pregnancies as this has been shown to reduce perinatal mortality[35] and no guideline currently incorporates recommendations on utility of third-trimester biomarkers.

Approaches to surveillance and timing of birth in late-onset SGA/FGR (≥32 weeks) are summarized in Table 4. Four of 6 (83%) recommend undertaking cerebral Doppler studies[29-31,33] and using the information to influence management. There is considerable inconsistency in terms of recommended frequency for ongoing growth scans after diagnosis of SGA/FGR (2-4 weekly), fetal surveillance

methods (most recommend undertaking cardiotocography [CTG]), and timing of delivery. In late-onset FGR with abnormal Doppler studies (raised UA, uterine artery, or reduced cerebral Doppler indices) or EFW <3rd centile the majority (5 of 6, 83%) recommend delivery at 37-38 weeks.[27,29,31-33] When Doppler studies are normal the recommendation varies between delivery at 37[29]-40 weeks.[31]

Management approaches in early-onset SGA/FGR (<32 weeks) are described in Table 5. Not surprisingly there is universal agreement about use of corticosteroids before birth that is likely to occur at <34 weeks 0 days, however the RCOG alone recommends corticosteroids up to 35 weeks 6 days.[29] Four of 6 (67%) recommend use of magnesium sulfate for neuroprotection before very preterm delivery,[27,31-33] with gestation of administration varying from <30[31] to 32-33 weeks.[33] Regarding timing of delivery for preterm FGR with absent or reversed end-diastolic velocity the recommendations for timing of delivery vary from 32[29]-34 weeks[27,28,31-33] and 30[32]-34 weeks,[33] respectively, with the majority (4 of 6, 67%)[29,31-33] specifying that cesarean delivery should be undertaken with this severe Doppler abnormality. The commonest criterion for deciding when to deliver, based on fetal grounds, was a computerized antenatal CTG (3 of 6, 50%),[29,32,33] which includes a real-time automated assessment of short-term fetal heart rate variability (Table 5).

A summary of recommendations where >50% consensus between SGA guidelines is achieved is presented in Table 6.

## Comment

### Areas where there is potential for improved convergence between SGA guidelines

*Definitions of FGR.* All guidelines recommended that EFW <10th centile is an appropriate definition of FGR, with some requiring additional parameters to confirm pathological growth restriction. Incorporation of a measure of reduced growth velocity was inconsistent, included in 4 of 6 guidelines (67%),[29,31-33] but often without a specific definition. A recently published Delphi survey on

**TABLE 1**
**Existing national small-for-gestational-age guidelines**

| Title | Investigation and management of small-for-gestational-age fetus | Guideline for management of suspected small-for-gestational-age singleton pregnancies and infants >34 wk' gestation | Intrauterine growth restriction: screening, diagnosis, and management | Fetal growth restriction—recognition, diagnosis, and management | ACOG Practice bulletin no. 134: fetal growth restriction; SMFM Clinical guideline: Doppler assessment of fetus with intrauterine growth restriction | Fetal growth restriction and intrauterine growth restriction: guideline for clinical practice from CNGOF |
|---|---|---|---|---|---|---|
| Sponsoring organization | RCOG | NZMFMN | SOGC | Institute of Obstetricians and Gynecologists Royal College of Physicians of Ireland and Health Service Executive | ACOG, SMFM | CNGOF |
| Year | 2013, Updated 2014 | 2013, Updated 2014 | 2013 | 2014, Updated 2017 | 2012 SMFM, 2013 ACOG | 2015 |
| Country | United Kingdom | New Zealand | Canada | Ireland | United States | France |
| Development process | Developed by committee peer reviewed by professional groups and experts | Developed by MFM specialists and neonatologists; endorsed by clinical directors of obstetrics and gynecology | Prepared by MFM committee; approved by SOGC Executive Council | Written by 3 experts in field, peer reviewed and endorsed by clinical advisory group | Developed by ACOG committee | Organizing committee for guideline development appointed by CNGOF |

*ACOG*, American Congress of Obstetricians and Gynecologists; *CNGOF*, French College of Gynecologists and Obstetricians; *MFM*, maternal fetal medicine; *NZMFMN*, New Zealand Maternal Fetal Medicine Network; *RCOG*, Royal College of Obstetricians and Gynecologists; *SMFM*, Society for Maternal-Fetal Medicine; *SOGC*, Society of Obstetricians and Gynecologists of Canada.

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**TABLE 2**
**Definitions, screening, and prevention for small-for-gestational-age pregnancies**

| Country | United Kingdom | New Zealand | Canada | Ireland | United States | France |
|---|---|---|---|---|---|---|
| Definition of SGA | Birthweight <10th customized centile | EFW or birthweight <10th customized centile | EFW <10th population centile | EFW <10th customized centile | Birthweight <10th population centile | EFW or birthweight <10th population centile |
| Definition of FGR on ultrasound | EFW <10th customized centile, or AC <10th population centile | EFW <10th customized centile or AC ≤5th population centile | EFW <10th or AC <10th population centiles | EFW <10th customized centile | EFW <10th population centile | EFW <10th customized centile |
| Definition of high-risk FGR/IUGR | EFW <3rd centile | EFW <3rd centile, abnormal UA, uterine artery, MCA or CPR Doppler | Not specified | EFW <3rd, abnormal UA Doppler, oligohydramnios or reduced interval growth | Not specified | Evidence of reduced/arresting of growth with or without abnormal UA or cerebral Doppler, oligohydramnios |
| Reduced growth velocity in definition of FGR | Change in AC of <5 mm over 14 d | AC or EFW crossing centiles: >30% reduction | Not mentioned | If EFW >10th centile with "poor interval growth" | Not mentioned | Inadequate growth without being SGA |
| Risk assessment at booking? | Yes | Yes | Yes | Yes | Yes | Yes |
| Early pregnancy biomarkers | PAPP-A <0.415 MoM —major risk; use of PAPP-A for population screening not recommended | If PAPP-A <0.2 MoM major risk factor; use of PAPP-A for population screening not recommended | If ≥2 serum parameters of aneuploidy screen abnormal (threshold unspecified) increased SGA risk | Low PAPP-A <0.4 MoM risk factor for FGR | No evidence for improved outcome | Not discussed |
| Uterine artery Doppler for high-risk women? | At 20 wk if ≥3 minor risk factors | At 20—24 wk in high-risk women | At 19—23 wk in women with risk factors | Not recommended | No evidence for improved outcome | Not discussed |
| Fundal height measurement | Serial fundal height on customized chart from 24 wk; ultrasound if <10th centile, slow or static growth | Serial fundal height on customized chart from 26 wk; ultrasound if reducing velocity or fundal height <10th centile | Serial fundal height—if less than gestation (wk) by >3 cm, ultrasound scan recommended | Serial fundal height on customized chart if available | Serial fundal height at every visit —ultrasound if >3 cm discrepancy with gestation | Serial fundal height screening from 22 wk leading to ultrasound if abnormal—reference chart not specified |
| Prevention: low-dose aspirin | Low-dose aspirin <16 wk in women with risk factors for preeclampsia | Women at high risk of growth restriction, consider low-dose aspirin 100 mg daily starting <20 wk | Low-dose aspirin for prior preeclampsia, growth restriction, or ≥2 SGA risk factors | Low-dose aspirin 75 mg daily for major SGA risk factors at <16 wk; consider heparin in individual cases | Insufficient evidence to recommend | Low-dose aspirin if previous: preeclampsia <34 wk or FGR <5th centile; 100—160 mg nocte start <16 wk |
| Prevention: smoking cessation and other interventions | Smoking cessation; no evidence for dietary measures | Smoking cessation in early pregnancy | Smoking cessation—any stage in pregnancy | Smoking cessation—any stage in pregnancy | Tobacco modifiable risk factor; no evidence for bed rest or dietary measures | Smoking cessation and support to become alcohol and drug free before pregnancy; limit multiple pregnancy in assisted reproductive technology; no evidence for bed rest |

*AC*, abdominal circumference; *CPR*, cerebroplacental ratio; *EFW*, estimated fetal weight; *FGR*, fetal growth restriction; *IUGR*, intrauterine growth restriction; *MCA*, middle cerebral artery; *MoM*, multiples of median; *PAPP*, pregnancy-associated plasma protein; *SGA*, small for gestational age; *UA*, umbilical artery.

*McCowan. Evidence-based national guidelines for management of suspected fetal growth restriction. Am J Obstet Gynecol 2018.*

definition of FGR, that incorporated responses from 45 experts, reached a consensus definition of early- and late-onset FGR diagnosed before birth.[6] For late FGR (≥32 weeks), 2 solitary parameters (abdominal circumference [AC] or EFW <3rd centile) and 4 contributory parameters (EFW or AC <10th centile, AC or EFW crossing centiles by >2 quartiles on growth charts, cerebroplacental ratio <5th centile, or UA pulsatility index [PI] >95th centile) were defined. For early-onset FGR (<32 weeks) 3 solitary parameters (AC <3rd centile, EFW <3rd centile, and absent end-diastolic velocity in the UA) and 4 contributory parameters (AC or EFW <10th centile with a PI >95th centile in either the UA or uterine artery) were agreed upon.[6] These definitions could be incorporated into existing and new SGA guidelines.

A recent publication has demonstrated that fetuses with a >30% reduction in EFW with a birthweight in the normal range are more likely to be acidotic at birth, have abnormal cerebroplacental ratio, and have lower percentage body fat.[9] This report provides further support for adding reduced growth velocity to definitions of FGR in future guidelines.

### Low-dose aspirin

Low-dose aspirin is recommended for women at increased risk of preeclampsia.[36-38] Recent publications on low-dose aspirin have demonstrated a marked reduction in risk of early-onset preeclampsia in women who are identified as high risk during first-trimester screening using combinations of maternal history, uterine artery Doppler, blood pressure, serum pregnancy-associated plasma protein (PAPP)-A, and placental growth factor and treated with low-dose aspirin 150 mg in the evening.[39] A reduction in SGA has also been demonstrated with low-dose aspirin treatment[40] especially in high-risk women.[41] A recent systematic review of low-dose aspirin trials concluded that aspirin was more effective in preventing preeclampsia and FGR when started at ≤16 weeks and in a dose of 100 mg compared with 60 mg.[42]

**TABLE 3**
**Third-trimester ultrasound in low and high-risk women**

| Country | United Kingdom | New Zealand | Canada | Ireland | United States | France |
|---|---|---|---|---|---|---|
| Screening with routine third-trimester ultrasound in low-risk women | Not recommended | Not recommended | Not recommended | Not recommended | Not recommended | Recommended at 32 wk |
| Criteria for serial scanning | ≥1 Major risk factor, unsuitable for fundal height monitoring, abnormal uterine artery Doppler (including notching); scans from 26–28 wk | Major risk factor(s) or unsuitable for fundal height monitoring; gestation to start scanning depends on severity of risk factors | Not specified | Women with risk factors from 26 wk | Previous SGA, other risk factors or unsuitable for fundal height monitoring | Not specified |
| Recommended biometry charts | EFW customized chart; no evidence to recommend 1 specific method of measuring AC nor which centile chart to use | EFW customized chart; AC on Australasian Society for Ultrasound in Medicine population charts | EFW or AC on population chart; charts not specified | EFW customized chart; biometry—chart not specified | EFW and biometry; charts not specified | EFW customized, biometry using French population ultrasound charts |
| Umbilical artery Doppler? | Yes—from 26–28 wk in high risk | If fetus small on biometry, or reduced growth velocity | If fetus small on biometry | Yes—criteria not specified | Yes—criteria not specified | Yes—criteria not specified |
| Interval between scans in suspected SGA/FGR | 3 wk | 2–3 wk | 2 wk | 2–4 wk | 3–4 wk | 3 wk |

*AC*, abdominal circumference; *EFW*, estimated fetal weight; *FGR*, fetal growth restriction; *SGA*, small for gestational age.

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**TABLE 4**
**Surveillance and timing of birth in late-onset small for gestational age/fetal growth restriction (≥32 wk)**

| Country | United Kingdom | New Zealand | Canada | Ireland | United States | France |
|---|---|---|---|---|---|---|
| UA Doppler frequency | Every 2 wk if UA Doppler normal, twice weekly if abnormal UA Doppler | Every 2 wk if UA Doppler normal, at least weekly if abnormal UA Doppler | Every 2 wk | Every 2 wk if UA Doppler normal, at least weekly if abnormal UA Doppler | From gestational age where delivery considered for fetal benefit; every 1–2 wk to assess for deterioration[b] | 2–3 Weekly if Doppler studies normal, more frequent if severe FGR; weekly if UA Doppler abnormal |
| Cerebral Doppler studies | MCA Doppler >32 wk with normal UA Doppler | MCA Doppler and CPR every 2 wk ≥34 wk; if Doppler(s) abnormal repeat at least weekly | MCA and DV Doppler studies but gestation not specified | MCA optional if UA Doppler abnormal —should not be used to indicate delivery | Insufficient evidence to support use of MCA Doppler in clinical practice | Cerebral artery Doppler every 2–3 wk if normal UA Doppler; increase frequency if UA Doppler abnormal |
| CTG | Not as only form of surveillance | Not as only form of surveillance; at least weekly if abnormal UA, MCA, CPR, uterine artery Doppler or EFW <3rd centile | Not as only form of surveillance, consider if BPP abnormal | Not specified | Not as only form of surveillance; if abnormal UA Doppler, twice-weekly CTG and/or BPP[b] | "Essential element in assessment of SGA fetus," frequency not specified |
| BPP | Do not use | Not as only form of surveillance | Weekly | Not standard | Not as only form of surveillance; if abnormal UA Doppler, twice-weekly CTG and/or BPP[b] | Not discussed |
| Timing of birth Abnormal Doppler[a] | Deliver by 37 wk if MCA PI <5th centile or abnormal UA Doppler | Deliver by 38 wk if UA Doppler >95th, MCA <5th centile, CPR <5th centile, uterine artery >95th | Consider delivery >34 wk if Doppler studies (UA, MCA, DV) abnormal | Abnormal UA PI deliver at 37 wk or earlier if poor interval growth | Consider delivery >37 wk when decreased diastolic flow in UA | Birth from ≥37 wk depending on EFW, amniotic fluid, and Doppler measurements |
| Timing of birth normal Doppler | If >34 wk deliver if static growth over 3 wk; offer delivery by 37 wk with involvement of senior obstetrician | If EFW <3rd centile deliver by 38 wk; if EFW >3rd and <10th centile deliver at 40 wk unless other concern; if MCA and uterine Doppler studies not available, deliver at 38 wk | Discuss delivery vs ongoing monitoring >37 wk; if amniotic fluid volume or BPP abnormal, consider delivery | Isolated FGR (EFW <10th centile, normal UA Doppler, and AFI), delay delivery until 37 wk, no later than 40 wk | FGR with no additional abnormal parameters, deliver at 38+0 to 39+6 wk | Birth from ≥37 wk depending on EFW, amniotic fluid, and Doppler measurements |
| Mode of birth | If UA end-diastolic flow present, induction of labor with continuous CTG recommended | Individualize care; high risk of CS with abnormal CPR, MCA, or UA Doppler —continuous fetal monitoring from onset of labor | Not specified | Individualize care; consider CS <34 wk | FGR alone not indication for CS | Routine CS for FGR not recommended; CS recommended for very preterm FGR or severe UA Doppler abnormalities; continuous fetal monitoring in labor |

*AFI*, amniotic fluid index; *BPP*, biophysical profile; *CPR*, cerebroplacental ratio; *CS*, cesarean delivery; *CTG*, cardiotocography; *DV*, ductus venosus; *EFW*, estimated fetal weight; *FGR*, fetal growth restriction; *MCA*, middle cerebral artery; *PI*, pulsatility index; *SGA*, small for gestational age; *UA*, umbilical artery.

[a] Pregnancies with absent or reversed end-diastolic volume are considered in Table 5; [b] Society for Maternal-Fetal Medicine guideline.

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Five of 6 guidelines (83%) recommend low-dose aspirin for prevention of SGA[29-33] with 3 specifying that low-dose aspirin should be started by 16 weeks[29,32,33,41] and the New Zealand Maternal Fetal Medicine Network guideline recommending that low-dose aspirin can be commenced up to 20 weeks.[40] The French guideline specifies that low-dose aspirin should be taken in the evening to maximize efficacy[33] and this advice, which is based on randomized controlled trial (RCT) evidence,[43] should also be incorporated into the other guidelines.

### The role of heparin to prevent SGA

Consistent with an earlier meta-analysis,[44] the Canadian guideline recommends that heparin should be offered in selected women. The publication of an individual patient data meta-analysis,[45] along with findings from the Enoxaparin for the Prevention of Preeclampsia and Intrauterine Growth Restriction trial,[46] have demonstrated that enoxaparin is not effective in preventing FGR in women with previous severe or early-onset FGR, or in those with thrombophilia, and can therefore not be recommended for this purpose.

### Uterine artery Doppler velocimetry screening

Second-trimester uterine artery Doppler velocimetry screening in the general population has a modest ability to predict later-onset FGR. A 2008 meta-analysis showed abnormal second-trimester uterine PI in low-risk/unspecified-risk women gave a positive likelihood ratio FGR of 3.4, increasing to 9.1 with uterine artery notching, with low negative likelihood ratios (0.87 and 0.89, respectively).[47] However, a recent randomized study failed to show any benefit on perinatal outcomes of universal second-trimester screening by uterine artery Doppler at the time of the anatomy scan for risk stratification in an unselected population.[48] Much of the benefit of uterine artery Doppler screening for FGR is identifying women at risk for early-onset preeclampsia.[49] Three of the guidelines (50%) recommend second-trimester uterine Doppler

**TABLE 5**
**Management of early-onset small for gestational age/fetal growth restriction (<32 wk)**

| Country | United Kingdom | New Zealand | Canada | Ireland | United States | France |
|---|---|---|---|---|---|---|
| Corticosteroids | Up to 35+6 wk | Up to 34+0 wk | Up to 34+0 wk | Up to 34+0 wk | Up to 34+0 wk | Up to 34+0 wk |
| Magnesium sulfate | Not specified | <30 wk[b] | Not specified | <32 wk | <32 wk | <32–33 wk |
| Recommended timing of delivery with AEDV and REDV | AEDV by 32 wk; REDV by 32 wk | AEDV by 34 wk; REDV by 32 wk | AEDV not specified; REDV not specified; "Requires intervention and possibly delivery" | AEDV no later than 34 wk; REDV no later than 30 wk | AEDV ≥34 wk[a]; REDV ≥32 wk | AEDV ≥34 wk; REDV ≥34 wk |
| Indication for delivery | Abnormal computerized CTG or DV Doppler | Not applicable —NZMFMN guideline for SGA ≥34 wk | Abnormal BPP, CTG, or DV Doppler | Abnormal computerized CTG | Abnormal fetal surveillance (CTG, amniotic fluid, or BPP) | Abnormal computerized CTG or DV Doppler |
| Mode of delivery | CS for AEDV and REDV | CS for AEDV and REDV | Not specified | CS for AEDV and REDV | FGR alone not indication for CS | CS for AEDV and REDV |

Includes surveillance for AEDV as this usually occurs <32 wk' gestation, and >32 wk' gestation delivery is usual practice.

*AEDV*, absent end-diastolic volume; *BPP*, biophysical profile; *CS*, cesarean delivery; *CTG*, cardiotocograph; *DV*, ductus venosus; *FGR*, fetal growth restriction; *NZMFMN*, New Zealand Maternal Fetal Medicine Network; *REDV*, reversed end diastolic volume; *SGA*, small for gestational age.

[a] Society for Maternal-Fetal Medicine Doppler guideline[28]; [b] New Zealand magnesium sulfate guidelines.[101]

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**TABLE 6**
**Recommendations from small-for-gestational-age guidelines where >50% consensus is achieved**

| Country | United Kingdom | New Zealand | Canada | Ireland | United States | France |
|---|---|---|---|---|---|---|
| Definition of FGR on ultrasound | EFW <10th customized centile, or AC <10th population centile | EFW <10th customized centile or AC ≤5th population centile | EFW <10th or AC <10th population centiles | EFW <10th customized centile | EFW <10th population centile | EFW <10th customized centile |
| Risk assessment at booking? | Yes | Yes | Yes | Yes | Yes | Yes |
| Fundal height measurement | Serial fundal height on customized chart from 24 wk; ultrasound if <10th centile, slow or static growth | Serial fundal height on customized chart from 26 wk; ultrasound if reducing velocity or fundal height <10th centile | Serial fundal height —if less than gestation (wk) by >3 cm, ultrasound scan recommended | Serial fundal height on customized chart if available | Serial fundal height at every visit—ultrasound if >3 cm discrepancy with gestation | Serial fundal height screening from 22 wk leading to ultrasound if abnormal—reference chart not specified |
| Prevention: low-dose aspirin | Low-dose aspirin <16 wk in women with risk factors for preeclampsia | Women at high risk of growth restriction, consider low-dose aspirin 100 mg daily starting <20 wk | Low-dose aspirin for prior preeclampsia, growth restriction, or ≥2 SGA risk factors | Low-dose aspirin 75 mg daily for major SGA risk factors at <16 wk; consider heparin in individual cases | Insufficient evidence to recommend | Low-dose aspirin if previous: preeclampsia <34 wk or FGR <5th centile; 100—160 mg nocte start <16 wk |
| Prevention: smoking cessation and other interventions | Smoking cessation; no evidence for dietary measures | Smoking cessation in early pregnancy | Smoking cessation —any stage in pregnancy | Smoking cessation—any stage in pregnancy | Tobacco modifiable risk factor; no evidence for bed rest or dietary measures | Smoking cessation and support to become alcohol and drug free before pregnancy; limit multiple pregnancy in assisted reproductive technology; no evidence for bed rest |
| Screening with routine third-trimester ultrasound in low-risk women | Not recommended | Not recommended | Not recommended | Not recommended | Not recommended | Recommended at 32 wk |
| UA Doppler? | Yes—from 26—28 wk in high risk | If fetus small on biometry, or reduced growth velocity | If fetus small on biometry | Yes—criteria not specified | Yes—criteria not specified | Yes—criteria not specified |
| UA Doppler frequency | Every 2 wk if UA Doppler normal, twice weekly if abnormal UA Doppler | Every 2 wk if UA Doppler normal, at least weekly if abnormal UA Doppler | Every 2 wk | Every 2 wk if UA Doppler normal, at least weekly if abnormal UA Doppler | From gestational age where delivery considered for fetal benefit; every 1—2 wk to assess for deterioration[a] | 2—3 Weekly if Doppler studies normal, more frequent if severe FGR; weekly if UA Doppler abnormal |

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(continued)

**TABLE 6**
**Recommendations from small-for-gestational-age guidelines where >50% consensus is achieved** *(continued)*

| Country | United Kingdom | New Zealand | Canada | Ireland | United States | France |
|---|---|---|---|---|---|---|
| Cerebral Doppler studies | MCA Doppler >32 wk with normal UA Doppler | MCA Doppler and CPR every 2 wk ≥34 wk; if Doppler(s) abnormal repeat at least weekly | MCA and DV Doppler studies but gestation not specified | MCA optional if UA Doppler abnormal —should not be used to indicate delivery | Insufficient evidence to support use of MCA Doppler in clinical practice | Cerebral artery Doppler every 2—3 wk if normal UA Doppler; increase frequency if UA Doppler abnormal |
| CTG | Not as only form of surveillance | Not as only form of surveillance; at least weekly if abnormal UA, MCA, CPR, uterine artery Doppler, or EFW <3rd centile | Not as only form of surveillance, consider if biophysical profile abnormal | Not specified | Not as only form of surveillance; if abnormal UA Doppler, twice-weekly CTG and/or biophysical profile[a] | "Essential element in assessment of SGA fetus," frequency not specified |
| Corticosteroids | Up to 35+6 wk | Up to 34+0 wk | Up to 34+0 wk | Up to 34+0 wk | Up to 34+0 wk | Up to 34+0 wk |
| Mode of delivery | CS for AEDV and REDV | CS for AEDV and REDV | Not specified | CS for AEDV and REDV | FGR alone not indication for CS | CS for AEDV and REDV |

*AC*, abdominal circumference; *AEDV*, absent end-diastolic volume; *CPR*, cerebroplacental ratio; *CS*, cesarean delivery; *CTG*, cardiotocography; *DV*, ductus venosus; *EFW*, estimated fetal weight; *FGR*, fetal growth restriction; *MCA*, middle cerebral artery; *REDV*, reversed end-diastolic volume; *SGA*, small for gestational age; *UA*, umbilical artery.

[a] SMFM guideline.

*McCowan. Evidence-based national guidelines for management of suspected fetal growth restriction. Am J Obstet Gynecol 2018.*

in high-risk women.[29-31] Although the predictive value of abnormal uterine Doppler is limited, a normal test may allow ruling out FGR in women with a baseline increase in risk.

### Measurement of fundal height

All guidelines recommend fundal height measurement with a tape measure, of which 3 (50%) recommend plotting on a customized chart[29,31,32] and 2 (33%) diagnose suboptimal fetal growth by McDonald rule, when fundal height measurement is >3 cm less than gestational age in weeks.[27,30] Given the increase in maternal weight since these charts were produced in the 1980s they may not be applicable in current practice.[50,51] A single randomized trial[52] did not show any difference in detection of SGA infants between palpation and fundal height measurement and plotting on a population chart.[53] Staff training in fundal height measurement is not discussed in this article.[52] Additionally, a meta-analysis of fundal height measurement to predict low birthweight and SGA found that fundal height when plotted on a population chart was not a good primary screening tool.[53] Four guidelines (67%) recommend that ultrasound scans should be considered in women with obesity and/or a fibroid uterus as fundal height measurements are not reliable.[27,29,31]

The Growth Assessment Protocol (GAP), a United Kingdom initiative that incorporates training in standardized measurement of fundal height and plotting this on customized growth charts, has been designed to improve detection of SGA infants before birth and to optimize management.[54] GAP is recommended by the National Health Service in the United Kingdom as part of a bundle of care designed to reduce stillbirth.[55] This program has been associated with increased detection of SGA babies and an associated reduction in stillbirth.[56] The Detection of Small for Gestational Age Fetus trial, a cluster RCT of implementation of GAP, will provide further evidence as to whether this initiative improves important clinical outcomes (ISRCTN67698474).

### Routine third-trimester ultrasound in low-risk women

Five of the 6 guidelines (83%) recommend that there is no role for a routine third-trimester scans in low-risk women.[27,29-32,57] Several of the randomized trials included in the Cochrane review of routine ultrasound >24 weeks in low-risk women (8 trials n = 27,024 women) performed the third-trimester scan too early for optimum detection of late onset of FGR.[58,59] A recent prospective cohort study, in 3977 nulliparous women from Cambridge, United Kingdom, demonstrated that a research scan at 36 weeks correctly identified 57% of women who delivered SGA babies, whereas selective use of scanning identified 20% of SGA.[60] As clinicians were blinded to the results of the 36-week scan it was not possible to evaluate the impact on clinical outcomes. Fetuses that were SGA, and had reduced growth velocity of the AC between the 20- and 36-week scans, had the highest morbidity. Consideration is now being given to whether a large RCT of late pregnancy ultrasound is feasible as the studies included in the Cochrane review to date are underpowered to demonstrate an effect on stillbirth.

### Timing of delivery in late-onset FGR

In FGR with abnormal Doppler studies (raised UA, uterine artery, or reduced cerebral Doppler indices) or EFW <3rd centile the majority of guidelines (5 of 6, 83%) recommend delivery at 37-38 weeks,[28,29,31-33] with some (3 of 6, 33%) recommending a more conservative approach when Doppler studies are normal and the FGR is not severe (ie, EFW not <3rd centile).[27,28,31,32] These recommendations are likely based on the findings of the Disproportionate Intrauterine Growth Intervention Trial at Term study[26] in which 650 women with suspected FGR >36 weeks were randomized to induction or expectant management with twice-weekly surveillance. There was no difference in the primary outcome of severe neonatal morbidity or in cesarean delivery. Women who were expectantly managed had a 2-fold increase in risk of developing preeclampsia (7.9% vs 3.7%, $P < .05$) and were more likely to have a baby with birthweight <3rd centile (30% vs 13%, $P < .001$). The recommendation was that "it is rational to choose induction to prevent possible neonatal morbidity and stillbirth." A strength of Disproportionate Intrauterine Growth Intervention Trial at Term study is that additional data were published on outcomes in the children. There was no difference overall in neonatal morbidity between induction of labor and expectant management groups, but induction at <38 weeks was associated with increased neonatal unit admission.[61] It was recommended that, where possible, delivery should be delayed until 38 weeks with watchful monitoring. At 2 years an Ages and Stages questionnaire was administered. Severe FGR (birthweight <2.3 centile), more common with expectant management, was the most important predictor of abnormal Ages and Stages scores.[62] A health economics analysis demonstrated that costs were lower with induction at 38 weeks compared to earlier gestations.[63] These findings suggest that delivery at 38 weeks in the fetus with suspected FGR may be optimum, unless there are earlier concerns about fetal well-being, and are consistent with findings from population-based studies that show a marked increase in stillbirth from 38 weeks in the SGA baby.[64]

### Timing of delivery in early-onset FGR

The Trial of Randomized Umbilical and Fetal Flow in Europe (TRUFFLE) of management of preterm FGR between 26-32 weeks has been published since these SGA guidelines were submitted or published.[65] TRUFFLE was a study of early FGR where mothers were allocated to 1 of 3 monitoring strategies to indicate timing of delivery: (1) reduced fetal heart rate short-term variability on CTG; (2) early changes in fetal ductus venosus (DV) waveform; or (3) late changes in fetal DV waveform. Many infants were delivered because of safety-net criteria for maternal or other fetal indications, or >32 weeks of gestation when the protocol was no longer applied. TRUFFLE now provides evidence that waiting until late changes occur in the DV or abnormal CTG is associated with improved outcomes at 2 years of age. The recommendations from TRUFFLE should now be considered for incorporation into national SGA/FGR guidelines. As approximately 80% of cases in TRUFFLE delivered because of CTG abnormalities had late decelerations, this trial is unable to determine whether computerized CTG is superior to regular CTG for surveillance in FGR.

### Areas of controversy

*Customized or population birthweight centiles.* There is considerable controversy as to whether SGA at birth should be defined using customized, population, or ethnic-specific standards, and which population standard is better suited for international comparisons. Traditional population birthweight references are generated from regional/national databases and report average birthweight for gestational age, without accounting for maternal characteristics (or other factors) that contribute to infant birthweight.[66,67]

To overcome the limitations of multiple regional population standards, the INTERGROWTH-21st international standards for newborn size[1] proposed a universal birthweight standard compatible with the World Health Organization (WHO) child growth standards.[2] This was a prospective, multinational fetal growth and birthweight study that pooled data from 8 countries with diverse populations. While this approach is appealing in its simplicity, concerns over the appropriateness of combining data and the risks of overdiagnosing or underdiagnosing SGA in local populations have been raised.[68-71]

Within multiethnic populations, birthweight differences are observed between ethnic groups, even in low-risk populations.[72-74] Significant differences in fetal growth and birthweight have been reported in low-risk pregnancies between 4 ethnic groups in the United States by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) fetal growth studies,[74] which also illustrated the overdiagnosis of SGA in non-white populations using a white reference.

Recent publication of WHO fetal growth charts in low-risk pregnancies from 10 countries in Africa, Asia, Europe, and South America also showed considerable variation in both fetal ultrasound parameters and birthweight between countries,[75] and described these differences as "adaptive," ie, physiological. Further, the application of ethnic-specific birthweight standards better assesses the risk of adverse neonatal and obstetric outcomes among SGA infants in multiethnic populations.[76,77] Evidence seems to be accumulating that ethnic-specific birthweight standards not only improve the detection of at-risk SGA infants, but also reduce the overdiagnosis of SGA among some ethnic groups.

Population birthweight references do not account for the well-established association between preterm birth and FGR, leading to potential underdiagnosis of preterm SGA.[78-80] Birthweight customization as described by Gardosi et al,[81] used in the United Kingdom, New Zealand, and Ireland, utilizes an ultrasound fetal weight reference[82] to overcome the systematic bias of preterm birth on birthweight, and also adjusts for maternal height, weight, parity, ethnicity, and infant sex. Infants classified as SGA by customized birthweight standards are at higher risk of perinatal morbidity and mortality than infants SGA by population birthweight standards.[5,83] Between 18-22% of infants SGA by population standards are reclassified as normally grown by customized standards and as the perinatal mortality of these reclassified babies is similar to those who are normally grown they can be considered to be "constitutionally small."[5,84,85] Importantly, the inclusion of maternal characteristics in the customization model increases the detection of SGA infants at risk of perinatal death over and above use of the ultrasound reference alone.[3,4]

As there is currently no consensus on the appropriate birthweight standard to use (although accounting for ethnicity seems appropriate), it is important that local validation of the chosen standard is undertaken, to ensure its use is appropriate in a given setting.

### First-trimester biomarkers

While 3 of 6 guidelines (50%) recommend that PAPP-A should be considered a major risk factor for SGA,[29,31,32] no guidelines recommend PAPP-A as a stand-alone screening test for SGA. In the general population, low PAPP-A in the first trimester has a poor predictive ability (positive likelihood ratio of SGA 1.96; negative likelihood ratio 0.93), however the high specificity (0.96; multiples of the median <0.3) means that an abnormal value reported as part of first-trimester anomaly screening has value.[86]

While first-trimester screening for FGR has been the focus of much research, biomarkers have not performed well enough to date to be offered as stand-alone screening tests. Multiple biomarkers have been investigated, with commonly researched analytes including PAPP-A, human chorionic gonadotropin, placental growth factor, and soluble fms-like tyrosine kinase-1.[49,87] FGR biomarker prediction is improved by the addition of maternal characteristics and uterine artery Doppler studies at the 12-week scan, with detection rates for early and late FGR as high as 86% and 66%, respectively, for a 10% false-positive rate.[49] This increased detection, however, is mainly due to the increased prediction of FGR cases associated with preeclampsia.

### Research priorities

*Routine late third-trimester ultrasound?.* A meta-analysis of randomized trials failed to demonstrate benefit from routine third-trimester scan[57] but is underpowered to detect and impact on stillbirth. Most included studies were relatively old. The most recent[88] published in 2003 reported a 30% reduction in SGA. Furthermore, most studies involved no change in management if SGA was diagnosed, which does not reflect current practice. Thus, the contemporary benefit of routine late third-trimester ultrasound on severe morbidity and mortality is unknown.

*When should late-onset SGA pregnancies with abnormal middle cerebral artery/cerebroplacental ratio Doppler indices be delivered?.* Because of the association with adverse outcomes, 3 guidelines recommend early delivery generally at 37 weeks in pregnancies with abnormal middle cerebral artery/cerebroplacental ratio. Although earlier birth may prevent stillbirth, it also has the potential to cause harm by adding the effects of premature birth to the existing problems of growth restriction. Randomized trials to address this question would need to be huge and may not be feasible.

*What ultrasound population charts should be used?.* Population ultrasound references in common use tend to be older,[89-93] and are frequently limited by inaccurate or incomplete information on pregnancy dating.[94] Methodological limitations include the use of routine, hospital-based data and many studies do not account for pathological influences on fetal growth such as preeclampsia or gestational diabetes.[94,95] Rarely do ultrasound references account for maternal ethnicity, despite multiple studies showing variations in fetal biometric measurements between countries/ethnicities.[71,74,96] As fetal growth references are descriptive of whole populations, including pathology, they are specific to the population they are generated in and are not generalizable.

In contrast to references, fetal growth standards are developed under optimal conditions, excluding pathology, and are intended for general use. Customized fetal biometry standards accounting for individual maternal characteristics have been created,[97-99] but may have limited applicability in low-resource settings. Recent longitudinal studies in healthy pregnancies have been undertaken by the NICHD in the United States,[74] WHO,[75] and INTERGROWTH-21st,[100] with the aim of developing population fetal growth standards for international use. Prospective studies are required to assess the impact of using these new charts compared with existing local charts.

### Conclusions

This review has confirmed that where there is high-quality evidence from RCT and meta-analyses to guide management such as use of UA Doppler in SGA pregnancies and corticosteroids for

delivery <34 weeks, there is a high degree of consistency between national SGA guidelines. Recommendations from the limited existing RCTs of management of SGA pregnancies should also be incorporated into current and future SGA guidelines.[26,65] Currently, with a lack of RCT evidence to guide management of SGA pregnancies in many areas, existing guidelines incorporate evidence from observational studies and expert opinion. ■

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