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RCOG GREEN-TOP GUIDELINES

Investigation and Care of a Small-for-Gestational-Age Fetus and a Growth Restricted Fetus (Green-top Guideline No. 31)

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This is the third edition of this guideline. It replaces the previous editions published in February 2013 and November 2002 under the same title.

Key recommendations

- All women should be assessed at booking (by 14 weeks) for risk factors for fetal growth restriction (FGR) to identify those who require increased surveillance using an agreed pathway [Grade GPP]. Findings at the midtrimester anomaly scan should be incorporated into the fetal growth risk assessment and the risk assessment updated throughout pregnancy. [Grade GPP]
- Reduce smoking in pregnancy by identifying women who smoke with the assistance of carbon monoxide (CO) testing and ensuring in-house treatment from a trained tobacco dependence advisor is offered to all pregnant women who smoke, using an opt-out referral process. [Grade GPP]
- Women at risk of pre-eclampsia and/or placental dysfunction should take aspirin 150 mg once daily at night from 12^{+0}–36^{+0} weeks of pregnancy to reduce their chance of small-for-gestational-age (SGA) and FGR. [Grade A]
- Uterine artery Dopplers should be carried out between 18^{+0} and 23^{+6} weeks for women at high risk of fetal growth disorders [Grade B]. In a woman with normal uterine artery Doppler and normal fetal biometry at the midtrimester scan, serial ultrasound scans for fetal biometry can commence at 32 weeks. Women with an abnormal uterine artery Doppler (mean pulsatility index > 95th centile) should commence ultrasound scans at 24^{+0}–28^{+6} weeks based on individual history. [Grade B]
- Women who are at low risk of FGR should have serial measurement of symphysis fundal height (SFH) at each antenatal appointment after 24^{+0} weeks of pregnancy (no more frequently than every 2 weeks). The first measurement should be carried out by 28^{+6} weeks. [Grade C]
- Women in the moderate risk category are at risk of late onset FGR so require serial ultrasound scan assessment of fetal growth commencing at 32^{+0} weeks. For the majority of women, a scan interval of four weeks until birth is appropriate. [Grade B]
- Maternity providers should ensure that they clearly identify the reference charts to plot SFH, individual biometry and estimated fetal weight (EFW) measurements to calculate centiles. For individual biometry measurements the method used for measurement should be the same as those used in the development of the individual biometry and fetal growth chart [Grade GPP]. For EFW the Hadlock three parameter model should be used. [Grade C]
- Maternity providers should ensure that they have guidance that promotes the use of standard planes of acquisition and calliper placement when performing ultrasound scanning for fetal growth assessment. Quality control of images and measurements should be undertaken. [Grade C]

- Ultrasound biometry should be carried out every 2 weeks in fetuses identified to be SGA [Grade C]. Umbilical artery Doppler is the primary surveillance tool and should be carried out at the point of diagnosis of SGA and during follow-up as a minimum every 2 weeks. [Grade B]
- In fetuses with an EFW between the 3rd and 10th centile, other features must be present for birth to be recommended prior to 39^{+0} weeks, either maternal (maternal medical conditions or concerns regarding fetal movements) or fetal compromise (a diagnosis of FGR based on Doppler assessment, fetal growth velocity or a concern on cardiotocography [CTG]) [Grade C]. For fetuses with an EFW or abdominal circumference less than the 10th centile where FGR has been excluded, birth or the initiation of induction of labour should be considered at 39^{+0} weeks after discussion with the woman and her partner/family/support network. Birth should occur by 39^{+6} weeks. [Grade B]
- Pregnancies with early FGR (prior to 32^{+0} weeks) should be monitored and managed with input from tertiary level units with the highest level neonatal care. Care should be multidisciplinary by neonatology and obstetricians with fetal medicine expertise, particularly when extremely preterm (before 28 weeks) [Grade GPP]. Fetal biometry in FGR should be repeated every 2 weeks [Grade B]. Assessment of fetal wellbeing can include multiple modalities but must include computerised CTG and/or ductus venous. [Grade B]
- In pregnancies with late FGR, birth should be initiated from 37^{+0} weeks to be completed by 37^{+6} weeks [Grade A]. Decisions for birth should be based on fetal wellbeing assessments or maternal indication. [Grade GPP]

1 | PURPOSE AND SCOPE

The purpose of this guideline is to provide advice, based on the best evidence available, to guide clinicians regarding the investigation and care of the small-for-gestational-age (SGA) fetus and growth restricted fetus. The guideline reviews the risk factors for these conditions and provides recommendations regarding surveillance, diagnosis, and management, including recommendations for fetal monitoring and birth. Large for gestational age (LGA) is outside the scope of this guidance.

This guideline is for healthcare professionals who care for women, non-binary and trans people with a SGA fetus or with fetal growth restriction (FGR). Within this document we use the terms woman and women's health. However, it is important to acknowledge that it is not only women for whom it is necessary to access women's health and reproductive services in order to maintain their gynaecological health and reproductive wellbeing. Gynaecological and obstetric services and delivery of care must therefore be appropriate, inclusive and sensitive to the needs of those individuals whose gender identity does not align with the sex they were assigned at birth.

1.1 | Population and setting

Women at low risk of fetal growth problems in community settings.Women at moderate or high risk of fetal growth problems (determined based on past obstetric history, current medical disorders, or ultrasound diagnosis) in hospital settings.The guideline does not address multiple pregnancies or pregnancies with fetal anomalies (chromosomal or structural).

1.2 | Interventions to be studied

Comparison of modalities for surveillance and diagnosis of a SGA fetus or FGR. Comparison of modalities to monitor fetuses with concerns regarding growth.

2 | DEFINITIONS

The most common definitions used and either agreed by consensus of experts or other national guidance

Terminology	Definition	Notes
Appropriate for gestational age	Fetal size between the 10th and 90th centile	
Small-for-gestational-age	Fetal size <10^{th} centile	
Fetal growth restriction	Fetal size or abdominal circumference <3rd centile or <10^{th} centile with Doppler abnormalities	• FGR can be described as early (detected before 31^{+6} weeks) or late (from 32^{+0} weeks) and are characterised by different clinical, ultrasound and pathological characteristics • FGR determined by sub-optimal fetal growth has varying definitions (see Section 7.3.2.)

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Terminology	Definition	Notes
Static growth	No forward growth velocity in EFW, or AC measured at least 14 days apart	

Abbreviations: AC, abdominal circumference; EFW, estimated fetal weight; FGR, fetal growth restriction.

Fetal size is measured at a single time point in pregnancy and assessed via individual biometric measurements (e.g. head circumference [HC], abdominal circumference [AC], and femur length [FL]) or measurements combined as estimated fetal weight (EFW) using different formulas. Fetal growth is a dynamic process occurring throughout the pregnancy requiring multiple assessments and a minimum of at least two assessments of fetal size. Additional information that can be considered includes maternal history and symptoms, amniotic fluid assessment and Doppler velocimetry. Any measurement obtained (biometry or EFW) can only be interpreted when plotted on a growth chart to determine both the centile of the measurement but also any change in growth trajectory. Growth charts are discussed further in section 7.2.1.

An appropriate for gestational age (AGA) fetus is one whose size is within a normal range for its gestational age. This is typically defined as between the 10th and 90th centiles. A fetus is considered SGA when individual biometric measurements or a combination of measurements used to estimate fetal weight fall below set parameters and requires accurate assessment of gestational age. Commonly, the definition of SGA refers to a fetus with a predicted weight or an AC measurement less than the 10th centile. SGA at birth is commonly diagnosed based on a birthweight below the 10th centile and often birthweight charts are adjusted for the sex of the baby.

FGR implies a pathological restriction of the genetic growth potential.[1-2] Some, but not all, growth restricted fetuses/infants are SGA. The likelihood of FGR is higher in fetuses that are smaller.[3] Growth restricted fetuses may manifest evidence of fetal compromise (abnormal Doppler studies, reduced liquor volume).

Defining FGR and thus diagnosing it in a current pregnancy is challenging because of the need to determine growth potential. Similarly, risk assessing whether FGR existed in a previous pregnancy presents a different challenge. There is a need to focus on those fetuses at risk of adverse outcome and thus those that are FGR rather than SGA using varying parameters such as sequential ultrasound measurements, Doppler assessments, and biomarkers. FGR can also be subdivided clinically into early and late depending on the gestational age, with variation in gestational thresholds between 32 and 37 weeks.

A Delphi consensus-based definition of FGR (Table 1) has been suggested for use both in clinical practice and in research for early (defined in the Delphi consensus as before 32^{+0} weeks) and late onset FGR.[4-5]

Saving Babies Lives Care Bundle version 3 (SBLCBv3) suggests practical definitions for FGR in a previous pregnancy, FGR in the current pregnancy, and suboptimal growth.[6] It highlights that absent or reversed end diastolic flow in the umbilical artery is a feature of early onset FGR, but importantly that absence of this feature (for example, a normal umbilical artery Doppler) from 32^{+0} weeks of gestation does not mean that the fetus is not growth restricted and does not rule out the possibility of fetal compromise.

Definition of FGR in a previous pregnancy as a risk factor is defined as any of the following:

- Birthweight below 3rd centile in a previous pregnancy.
- Early onset pre-eclampsia or FGR necessitating birth before 34^{+0} weeks in a previous pregnancy.
- Birthweight below 10th centile with evidence of placental dysfunction (defined as below for current pregnancy).

Definition of FGR in a current pregnancy is defined as either of the following:

- EFW or AC below the 3rd centile
- EFW or AC below the 10th centile with evidence of placental dysfunction (either):
  - Abnormal uterine artery Doppler (mean pulsatility index [PI] above 95th centile[7]) and/or
  - Abnormal umbilical artery Doppler (absent or reversed end diastolic flow or PI above 95th centile).

TABLE 1 Consensus based definitions for early and late fetal growth restriction (FGR) in absence of congenital anomalies[5]

Early FGR: Gestational age < 32 weeks, in absence of congenital anomalies	Late FGR: Gestational age ≥ 32 weeks, in absence of congenital anomalies
AC/EFW < 3rd centile or UA-AEDF	AC/EFW < 3rd centile
Or	**Or at least two out of three of the following:**
AC/EFW <10th centile combined with either:	1. AC/EFW <10th centile
1. UtA-PI >95th centile and/or	2. AC/EFW crossing centiles >two quartiles on growth centiles*
2. UA-PI >95th centile	3. CPR <5th centile or UA-PI >95th centile

*Growth centiles are non-customised centiles. AC, fetal abdominal circumference; CPR, cerebroplacental ratio; EFW, estimated fetal weight; PI, pulsatility index; UA, umbilical artery; UtA, uterine artery.

Suboptimal fetal growth may also be indicative of FGR and can be diagnosed when a previously well-grown fetus (i.e. size 10th centile or above) fails to maintain adequate fetal growth during pregnancy. Suboptimal growth is difficult to define, with SBLCBv3 defining it as a pattern of slowing growth velocity (i.e. a downward trend in the centile).[6] The Delphi consensus defines it as AC/EFW crossing centiles greater than two quartiles on non-customised growth centiles ≥32^{+0} weeks (equivalent to 50 centiles).[5] Static growth can be defined as no forward growth velocity in EFW, or AC measured at least 14 days apart. Suboptimal fetal growth is further addressed in section 7.3.2.

Low birthweight (LBW) refers to an infant with a birthweight less than 2500 g regardless of gestation. This is no longer used in clinical practice as the majority of pregnancies have an early dating scan therefore birthweight can be adjusted for gestational age. This definition is included for interpretation of older research papers only. FGR has previously been described as symmetrical or asymmetrical and it has been proposed that it may help determine possible aetiology. However, this feature can vary and is not prognostic of outcome[8] so should no longer be used as a description of FGR.

3 | INTRODUCTION AND EPIDEMIOLOGY

Small fetuses are divided into normal (constitutionally small), non-placenta mediated growth restriction (e.g. structural, or chromosomal anomaly, inborn errors of metabolism and fetal infection), and placenta mediated growth restriction (placental dysfunction). Maternal factors such as low pre-pregnancy weight, undernutrition, substance misuse or severe anaemia can affect placental transfer of nutrients. Medical conditions can also affect placental implantation and vasculature and hence transfer (pre-eclampsia, autoimmune disease, thrombophilias, renal disease, diabetes, cardiac disease, and essential hypertension).

The underlying aetiology as well as timing of onset is important when considering the risk of adverse outcome in pregnancy. Early onset FGR is associated with significant and abnormal placentation that results in increased hypoxia and cardiovascular adaptions[9] and therefore carries an increased risk of adverse perinatal mortality and morbidity.[10] Early FGR also often coexists with maternal manifestations of placental dysfunction (hypertensive disorders of pregnancy) or maternal medical conditions and thus is easier to detect through screening pathways. In late onset FGR, the deficit in placentation is milder, with less cardiovascular adaption and a lower risk of adverse events. However, late FGR is more common, and it is more difficult to identify fetuses that may be at risk (on ultrasound scan [USS]) and thus detect, and therefore these pregnancies account for a significant proportion of adverse outcomes. They are, therefore, an important area for effective surveillance and management.

Serial symphysis fundal height (SFH) measurement is a method of surveillance for fetal size, however, it has a low sensitivity for detecting SGA/FGR fetuses.[11] Suspicion of a fetal growth disorder usually relies on ultrasound measurement of fetal AC or estimation of fetal weight. Care of the SGA/FGR fetus is directed at timely birth. Several surveillance tests are available, including cardiotocography (CTG), Doppler and USS to assess biophysical activity, but there is controversy about which test or combination of tests should be used to time birth in late onset FGR and SGA.

The NHS England SBLCB (a care bundle for reducing perinatal mortality) was first published in 2016 and focussed on detection and management of SGA (rather than FGR) and recommended birth at 37^{+0} to 37^{+6} weeks for SGA, as did the 2013 version of this RCOG guidance.[12] The SpiRE evaluation of the SBLCB version 1 demonstrated a measurable difference in antenatal detection of SGA babies across England.[13] The evaluation also demonstrated an increase in USS and inductions of labour at early term (37^{+0}–38^{+6} weeks). Thus, by seeking to capture all babies at risk, interventions increased in women who were only marginally at increased risk of FGR-related stillbirth, with risks to the babies of early term induction (namely increased risk of admission to the neonatal unit and potential long-term adverse effects, e.g. increased risk of special educational needs).[14-15] This was partly addressed in version 2 of the bundle (2019), with different management strategies for SGA and FGR to try and reduce unnecessary intervention in SGA babies not at risk of adverse outcome.[16] SBLCBv3, and this guideline, addresses this further with a focus on detecting FGR and targeting intervention (i.e. birth) for those at increased risk of perinatal death.[6]

4 | IDENTIFICATION AND ASSESSMENT OF EVIDENCE

The Cochrane Library and electronic databases (DARE, EMBASE, Trip, MEDLINE and PubMed) were searched using the relevant Medical Subject Headings (MeSH) terms, including all subheadings and synonyms, and this was combined with a keyword search and was limited to humans and English language; search terms included 'fetal growth retardation', 'fetal growth restriction' and 'infant, small for gestational age'. The search was restricted to articles published from 2011 until December 2022. The full search strategy is available to view online as supporting information (Appendix S1 and S2). Papers identified by peer reviewers and the developers which fall outside the literature searches and may be more recent have also been included in the evidence base for the guideline.

This guideline was developed using the standard methodology for Green-top Guidelines.[17] Where possible, recommendations are based on available evidence. In the absence of published evidence, these have been annotated as 'good practice points'. Further information about the assessment of evidence and the grading of recommendations may be found in Appendix I.

5 | WHAT ARE THE RISK FACTORS FOR FETAL GROWTH DISORDERS IN PREGNANCY?

Risk assessment is a fundamental part of care in the maternity pathway and should be a dynamic process with continual assessment throughout the pregnancy. Risk assessment must always consider previous medical history, obstetric history and current pregnancy history with information obtained from the woman, review of medical notes and contact with previous care providers as necessary.[18] All pregnant women should have a risk assessment for FGR carried out by 14 weeks of gestation using an agreed pathway.[6]

The likelihood of a FGR or FGR-related stillbirth occurring in a pregnancy is influenced by many factors. When considering risk assessment, the following are important: *a priori* risk (this is the probability of an event occurring that the woman has as she enters the pregnancy based on previous history); absence of risk factors (e.g. if a certain risk factor is not present does this reduce the risk overall and the influence of other risk factors that are present); if multiple risk factors are present how do these interplay and change the level of risk. This information is not known in sufficient detail for many conditions in pregnancy nor related to risk factors for FGR.

Risk assessment in FGR is also challenged by the fact that many analyses of risk factors for fetal growth disorders identify newborns with a birthweight less than the 10th centile as a proxy for FGR, with the majority of these births occurring at term and thus including a significant proportion of heathy smaller babies. Hence, studies using SGA as a proxy for FGR may underestimate the risk of adverse outcomes associated with FGR. This makes evidence assimilation difficult to identify which women should have increased surveillance.

There have been several risk assessment models designed for the prediction of pre-eclampsia that have been used for SGA prediction. There are data from the ASPRE randomised controlled trial (RCT; model for prediction of pre-eclampsia and aspirin administration) and SPREE study (prediction of pre-eclampsia) related to SGA prediction that identifies a high proportion of cases of preterm SGA that can be prevented by the prophylactic use of aspirin.[19] As these models are designed for pre-eclampsia prediction, they can be expected to have utility in prediction of FGR associated with placental dysfunction and pre-eclampsia but cannot assess all risk factors for FGR. These are discussed further in section 5.2.4.

Tools used to assess risk should provide a structured, consistent approach that can adapt throughout the pregnancy and support the pregnant woman and her clinician in making decisions about her care by making personalised care recommendations using clinically validated machine learning algorithms. Checklists for the presence of risk factors cannot weigh or assess this interaction between risk factors as described above, they also address risk as a binary function of present or absent and cannot consider all the information available from the presence and "level" of the risk. They also do not provide information in a way that can support decision making. Thus, it is imperative that future research addresses development of prediction models that are designed specifically for FGR and importantly FGR with adverse outcome, so that they can be incorporated into tools such as the Tommy's App,[20] a clinical decision tool being developed by Tommy's and the RCOG and other electronic patient record systems.

Within this section, the known risk factors for FGR and relevant evidence are discussed. A pathway for assessing risk and subsequent management is shown in Appendix II. It is recognised that this pathway has some of the limitations of the checklist approach as discussed above. However, this pathway attempts to incorporate all the risk factors detailed below for FGR and provide an assessment of level of risk in keeping with the National Institute for Health and Care Excellence (NICE) guideline [CG62] for pathways of care.[18] It is recognised that maternity providers may wish to use technology platforms and validated prediction models for pre-eclampsia and placental dysfunction prediction. Where this is the case, providers must ensure that risk assessment for other FGR risks not related to pre-eclampsia can be facilitated.

Women must also be assessed at booking for conditions where SFH measurements are not appropriate (e.g. raised body mass index [BMI] of 35 kg/m^2 or above at booking; presence of fibroids in uterus [based on clinical judgement]).

5.1 | Booking history

Recommendation	Evidence quality	Strength	Rationale for the recommendation
All women should be assessed at booking (by 14 weeks) for risk factors for FGR to identify those who require increased surveillance using an agreed pathway.	**3**	**GPP**	Risk assessment at the beginning of pregnancy allows women to make informed choices about their care and for planning of antenatal care.

Recommendation	Evidence quality	Strength	Rationale for the recommendation
The birthweight, gestation and birthweight centiles of all previous pregnancies should be recorded at the booking appointment.	**3**	**GPP**	This allows accurate risk assessment.
The proposed plan of assessment should be altered based on the specific combination of risk factors and this should inform further targeted tests (such as uterine artery Doppler when available) and/or serial ultrasonic surveillance (see section 7).	**3**	**GPP**	Plans should be modified in the presence of multiple risk factors.

5.1.1 | Previous FGR/SGA newborn

Determining the recurrence risk of a fetal growth disorder is limited by the definitions used to identify FGR and SGA within research studies. Women who had evidence of placental dysfunction in a previous pregnancy have a risk of recurrence and subsequent FGR affected pregnancy.[21] In a large cohort study evaluating the risk of recurrence of an SGA pregnancy (defined in this study as a newborn below 5th centile) there was an increased risk of a subsequent SGA below the 5th centile (adjusted odds ratio [aOR] 8.1, 95% CI 7.8–8.5).[22] *[Evidence level 2+]*

Therefore, a careful risk assessment must be carried out to identify women who had previous affected FGR pregnancies and need increased surveillance for early onset FGR. Where there is evidence of a previous SGA infant without identified FGR, early assessment of placental dysfunction and early onset growth restriction is not required.

5.1.2 | Previous stillbirth

A systematic review summarises the evidence evaluating the risk of adverse pregnancy outcomes following exposure to one of stillbirth, preterm birth (PTB) or SGA in a previous pregnancy.[23] Previous stillbirth is associated with an increased risk of SGA in a subsequent pregnancy, with the association greater when there was evidence of FGR in association with the stillbirth.[23] This observation is supported by other studies[24-25] with an increased risk of a SGA infant following a previous pregnancy with a placentally related stillbirth (OR 2.3, 95% CI 1.2–4.2).[25] *[Evidence level 2+]*

Stillbirth is a multifactorial condition and can occur because of a variety of reasons including maternal, fetal and placental factors. Where there is evidence of placental dysfunction, FGR or pre-eclampsia in association with a stillbirth, additional screening should be carried out.[26]

5.1.3 | Previous preterm birth

Women with a previous PTB (before 37^{+0} weeks) have an increased risk of SGA/FGR; this effect is greater after extreme PTB (20^{+0}–27^{+6} weeks). Most studies did not differentiate between iatrogenic or spontaneous PTB, thus it is possible that this association is secondary to birth for maternal medical conditions such as pre-eclampsia or indeed placental dysfunction leading to FGR, rather than an independent association with spontaneous PTB and subsequent SGA/FGR.[23] No evidence was identified that evaluated the risk of fetal growth disorders following a history of second trimester pregnancy loss. A retrospective cohort study of 133 136 women in Scotland demonstrated a risk of unexplained stillbirth in women with a previous PTB.[27] It is recommended in any women with a history of PTB or second trimester pregnancy loss that a detailed history is undertaken to determine whether placental dysfunction was implicated and thus whether ultrasound surveillance for FGR and aspirin is required. *[Evidence level 2++]*

5.1.4 | Previous pregnancy loss

The evidence regarding recurrent miscarriage is conflicting and comes mainly from retrospective cohort studies. The largest study to date demonstrated no increased risk of SGA (aOR 1.07, 95% CI 0.93–1.23).[28] As recurrent miscarriage can be caused by a heterogenous group of conditions and some of these are associated with pregnancy complications themselves, it is important to look at the group with unexplained recurrent miscarriage as these women may have underlying abnormal placentation.[29] Another retrospective study found an increased risk of SGA below 10th centile but this was not adjusted for other confounders (OR 2.82, 95% CI 1.32–6.04).[30] There is thus a need for further prospective research, to evaluate the relationship between unexplained recurrent miscarriage and SGA/FGR. *[Evidence level 2–]*

Second trimester medical termination of pregnancy (MTOP) is not a risk factor for an SGA infant, with this being explored in a large cohort study comparing the outcomes of PTB, LBW, SGA and placental complications in women undergoing first trimester versus second trimester MTOP.[31] *[Evidence level 2+]*

5.1.5 | Previous pregnancy with placenta-mediated complications

Women who have had a previous pregnancy affected by a placenta-mediated complication (e.g. hypertensive disorders of pregnancy, placental abruption or abnormal fetal growth) are at greater risk of recurrence of these complications in

subsequent pregnancies, with the risk increasing with each pregnancy affected.[32] *[Evidence level 2–]*

NICE recommends aspirin 75–150 mg daily from 12^{+0} weeks until the birth of the baby, to reduce the risk of hypertensive disorders of pregnancy related to placental dysfunction, particularly pre-eclampsia.[33] *[Evidence level 1++]*

In women with previous FGR (including those born preterm), clinicians should determine whether placental dysfunction may have been a contributory factor and, if so, advise low dose aspirin 150 mg from 12^{+0} weeks of gestation.[6-34] Aspirin may be more effective if taken at night.[35] *[Evidence level 4]*

In some circumstances this may not be appropriate and lower doses (60–75 mg) may be used (for example, women with hepatic or renal disease).

5.1.6 | Maternal characteristics and medical history

Maternal medical conditions associated with an increased risk of a fetal growth disorder include diabetes with vascular disease,[36] moderate and severe renal impairment (especially when associated with hypertension),[37] antiphospholipid syndrome,[38] chronic hypertension[39] and systemic lupus erythematosus (SLE).[40] *[Evidence level 2– to 2++]*

Maternal congenital heart disease (CHD) has a varying association with SGA, and the largest prospective series to date demonstrated that SGA was mainly seen in women with complex CHD (OR 2.29, 95% CI 1.49–3.51) and symptomatic patients (New York Heart Association class III–IV) (OR 2.39, 95% CI 0.72–7.95). Multivariable analysis revealed that women with valvular disease, stenotic lesions (OR 2.31, 95% CI 1.33–4.03) and anticoagulant use (OR 2.16, 95% CI 1.24–3.78) had an increased risk of SGA. Thus, women with complex CHD and/or ventricular dysfunction should be offered fetal monitoring by ultrasound.[41] *[Evidence level 2+]*

A significant number of women with cardiac disease in pregnancy will be taking multiple medications with the most common being beta-blockers. The mechanism underpinning the relationship between cardiac dysfunction and FGR is complex and concomitant use of medicines, especially beta-blockers may play a role. Thus, medication use should also be considered when assessing the need for growth scans.[42] *[Evidence level 2+]*

The associations with asthma, anaemia, inflammatory bowel disease and depression are less strong. Meta-analyses of observational studies have demonstrated weak or no associations with SGA (less than 50% increase in risk) for asthma,[43] inflammatory bowel disease[44], anaemia[45] and depression.[46,47] Therefore, if uncomplicated and adequately treated, these are not considered important risk factors for an SGA fetus.[48,49] *[Evidence level 2++]*

Advanced maternal age of 40 years or more is associated with increased risk of SGA and FGR although this is smaller than previously thought (SGA OR 1.20, 95% CI 1.07–1.33; FGR birthweight below 5th centile OR 1.53, 95% CI 1.07–2.20).[50] *[Evidence level 1–]*

Maternal pre-pregnancy BMI and gestational weight gain have been evaluated in an individual patient data (IPD) meta-analysis of 265 270 singleton pregnancies.[51] Maternal pre-pregnancy BMI of 20–30 kg/m^2 was associated with a lower risk of SGA ($P < 0.05$) (reference group 20.0–22.4 kg/m^2). Women with excessive weight gain had a lower risk for SGA (OR 0.62, 95% CI 0.60–0.65). Women with a BMI lower than 18.5 kg/m^2 and low gestational weight gain (Z scores of −1.1SD or less Institute of Medicine Guidelines) had the highest risk for SGA birth (OR 3.12, 95% CI 2.75–3.54).[51] NICE guideline [CG62] recommends that women are offered a height and weight measurement at booking and BMI calculated,[18] but they are not routinely, repeatedly weighed during pregnancy.[52] Therefore, women with a low BMI at booking (below 18.5 kg/m^2) and who have features which indicate that the maternal stature is not physiological, e.g. those with eating disorders or medical disorders affecting nutrition, should be considered at increased risk and serial USS undertaken.[53] *[Evidence level 2++]*

Bariatric surgery appears to increase the risk of SGA independent of BMI associated risks, with gastric bypass (malabsorptive) associated with a higher risk compared with gastric bands (restrictive) (gastric bypass: OR 2.39, 95% CI 1.94–2.94; gastric bands: OR 1.38, 95% CI 0.90–2.10).[54-56] Hence, women who have undergone gastric bypass surgery should be considered at moderate risk of fetal growth disorders regardless of their BMI, whereas women with a gastric band should not. *[Evidence level 2++]*

Ethnicity, specifically Southeast Asian, African and Black African Caribbean, have been reported to be associated with an increased risk of SGA.[57-59] The relationship between ethnicity and adverse pregnancy outcomes is complex and multifaceted. The evidence base is limited because of its observational nature, lack of relevant classification, and lack of adjustment for confounders, e.g. geographical location, healthcare system, coexisting disease, malnutrition, inequality, etc. However, perinatal mortality and adverse outcomes are higher in some groups, such as women who are Black and Asian. A national cohort study in England demonstrated that socioeconomic and ethnic inequalities were responsible for a substantial proportion of stillbirths, PTBs, and births with FGR. Population attributable fractions indicated that 23.6% (95% CI 16.7–29.8) of stillbirths, 18.5% (16.9–20.2) of PTBs, and 31.1% (28.3–33.8) of births with FGR could be attributed to socioeconomic inequality, and these fractions were substantially reduced when adjusted for ethnic group, smoking, and BMI (11.6% for stillbirths, 11.9% for PTBs, and 16.4% for births with FGR). The largest inequalities were in Black and South Asian Women in the most socioeconomically deprived quintile (FGR 71.7% in South Asian Women and 55% in Black women).[60]

One recommendation is for high-quality research addressing health inequality, racial bias, and ethnic disparities and for maternity providers to use local data to understand their populations and the health inequalities they face. This need for understanding local populations is further highlighted by one of the secondary findings of the DESiGN trial

which demonstrated that unidentified SGA (in women with no ultrasound surveillance) was more common among white women than Asian women (aOR 0.58, 95% CI 0.69–0.93).[61] Local maternity and neonatal systems and trusts should report data on the distribution of fetal growth outcomes with relation to maternal reported ethnicity and use this data to determine whether ethnicity should be included in local risk assessment pathways. *[Evidence level 4]*

Maternity services and healthcare providers have an important role to play in ensuring that all women are provided with a risk assessment at booking for fetal growth disorders and all modifiable contributory factors are addressed. *[Evidence level 2+]*

Nulliparity, social deprivation, unmarried status, maternal SGA, a short (less than 6 months) or long (over 60 months) inter-pregnancy interval have all been shown to have minor associations with SGA.[62-66] The effect of some of these risk factors is reduced once adjusted for other factors. *[Evidence level 2++]*

An IPD meta-analysis did not support an association between moderate to vigorous physical activity and the risk of SGA.[67] *[Evidence level 2++]*

Congenital uterine anomalies are associated with adverse pregnancy outcomes, which include an increased risk of FGR (OR 3.75, 95% CI 1.88–7.46). The level of risk is associated with the categorisation and severity of the defect, with the greatest risk being for women with septate and bicorporeal uteri.[68] These women are high risk for other adverse outcomes in particular PTB and the uterine circulation can often be affected by the anomaly, making uterine artery Doppler assessment and interpretation more challenging. These women should thus be considered outside the context of the management guidance in section 7.3. It is however reasonable to offer these women growth scans from 28^{+0} weeks. *[Evidence 2++]*

The interaction of multiple maternal risk factors is unknown and is an important area for further research.

5.1.7 | Antenatal risk factors

Several maternal exposures have a seemingly causative relationship with fetal growth disorders. A systematic review from 2011 reported a dose–response relationship with maternal alcohol consumption and SGA, with no association with low levels of alcohol consumption, a small association with one drink per day and a doubling of risk at approximately 4 drinks per day.[69] A more recent systematic review concluded that there is limited evidence on the effects of drinking 32 g/week or less (two UK units up to twice per week). There was some evidence that light prenatal alcohol consumption was associated with the risk of having an SGA infant (OR 1.08, 95% CI 1.02–1.14) but there is a lack of evidence about the effect of alcohol consumption at different stages of conception and pregnancy. It was concluded that guidance could advise abstention as a precautionary principle, but clinicians should explain this is based on limited evidence.[70] *[Evidence level 2++]*

Drug misuse is associated with being born SGA, specifically cocaine use (OR 3.23, 95% CI 2.43–4.30) with crack cocaine use increasing the risk further (OR 4.00, 95% CI 1.74–9.18).[71-72] Data regarding fetal growth with marijuana exposure demonstrates an association with all placental dysfunction conditions and therefore as a principle should be avoided.[73] It must be noted that often studies of marijuana use are hampered by inadequate reporting of usage and concomitant tobacco use.[73] *[Evidence level 2++]*

Smoking increases the risk of SGA and the effects of smoking are dose dependent and greater in older women.[74-75] Multiple cohort studies have demonstrated that smoking throughout pregnancy approximately doubles the risk of SGA.[76-78] The risk of preterm SGA which is more strongly associated with FGR is also increased (OR 1.39, 95% CI 1.35–1.42).[78] Women who are able to stop smoking can reduce their risk of SGA. If able to stop by 15 weeks of gestation, they can return to the pregnancy risk status of similar non-smoking women of preterm and term SGA. Less is known about the impact of secondhand smoke on SGA rates.[75,76,79] *[Evidence level 2+]*

The relationship between use of e-cigarettes and the risk of fetal growth disorders is complex, pregnancy is unique in that women are motivated to alter behaviour to reduce risk to the fetus. Women may completely or partially substitute cigarettes in pregnancy for e-cigarettes. In women who used e-cigarettes prior to pregnancy and can stop tobacco use during pregnancy, the risk of SGA has been shown to return towards background risk. The continued use of e-cigarettes in pregnancy, in prior users, is associated with an increased risk of SGA compared with non-users in one large study, but there was also evidence that women who exclusively smoke cigarettes and change to e-cigarettes lower their risk of fetal growth disorders.[80] *[Evidence level 2+]*

For women who use nicotine replacement therapy (NRT), the evidence from a systematic review and meta-analysis suggests that most of the harmful effects of smoking on birthweight are not related to the nicotine and that any risk from using NRT are much lower than those of smoking.[81,82] These available studies do not currently provide enough evidence to say that there are no harmful effects from NRT for the fetus. *[Evidence level 1]*

However, evidence from an RCT where women who smoked in pregnancy were randomised to e-cigarettes or NRT found that e-cigarettes were more effective than NRT for smoking cessation and the infants born to women in the e-cigarette group were less likely to be of LBW than those randomised to NRT (14.8% versus 9.6% relative risk [RR] 0.65, 95% CI 0.47–0.90, $P = 0.01$).[82] *[Evidence level 1+]*

Women who use e-cigarettes or NRT who have carbon monoxide test > 4 ppm should be offered scan assessment on the moderate risk pathway as for smokers. *[Evidence level 4]*

More evidence is required on the short- and long-term benefits and risks of e-cigarettes and NRT as discussed in the NICE guideline [NG209].[83] Section 6.1 discusses support for women who smoke or use e-cigarettes in pregnancy.

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Maternal caffeine consumption of 300 mg/day or more in the third trimester has been associated with SGA, with evidence suggesting that even lower consumption has an association with SGA (OR 1.9, 95% CI 1.3–2.8).[84-85] The current recommended daily maximum caffeine intake in pregnancy is 200 mg/day (two mugs of instant coffee).[86] *[Evidence level 2+]*

A systematic review assessing in vitro fertilisation (IVF) and intracytoplasmic sperm injection (ICSI) has shown an association with these techniques and SGA (RR 1.39, 95% CI 1.27–1.53).[87] However, the underlying reason for fertility treatment, maternal and paternal (sperm donor) health and the techniques used all alter the risk of fetal growth disorders, and therefore currently it is difficult to determine accurate risk assessments. *[Evidence level 2++]*

There is increasing interest on the paternal influence on adverse pregnancy outcomes.[88] A systematic review of 36 studies on paternal factors and birth outcomes concluded that extreme paternal ages (below 20 and above 40 years), height and paternal birthweight had no association with SGA.[88,89] Changing paternity has been associated with an increased risk of a SGA infant (aOR 2.25, 95% CI 1.13–1.47) and pre-eclampsia even after taking into account confounders related to changing paternity such as social and behavioural changes.[90] Further research is needed to evaluate the potential mechanism between paternity change and SGA/pre-eclampsia.[90] *[Evidence level 2++]*

5.2 | Current pregnancy risk factors

5.2.1 | Biochemical markers used for aneuploidy screening

Recommendation	Evidence quality	Strength	Rationale for the recommendation
When low pregnancy-associated plasma protein A (PAPP–A) levels or raised alpha fetoprotein (AFP) levels and/or raised inhibin A are incidentally detected following first or second trimester screening for aneuploidy, it is recommended women should be offered additional ultrasound surveillance for SGA/FGR.	**2+**	**B**	Low PAPP-A, raised AFP and raised inhibin are risk factors for SGA and FGR.
Women with a low PAPP-A or raised beta-hCG level should be offered aspirin as per section 6.2	**4**	**GPP**	There are no studies assessing the effectiveness of aspirin for this indication. However, as these are placental biomarkers and associated with adverse outcomes related to placental mediated disease it is appropriate to offer women low dose aspirin.

Low (below 5th centile or below 0.415 Multiples of Median [MoM] if local data reference data unavailable) pregnancy associated plasma protein A (PAPP-A) levels are an independent risk factor for SGA, with the odds of SGA decreasing as PAPP-A increases.[91] Low PAPP-A levels are also strongly associated with stillbirth owing to placental dysfunction, defined as abruption or unexplained stillbirth associated with growth restriction (incidence rate: 11.7 versus 0.3 per 10 000 women per week, respectively; hazard ratio 46.0, 95% CI, 11.9–178.0).[92] A large meta-analysis of 32 studies (175 240 pregnancies) demonstrated that low PAPP-A is associated with SGA below 10th centile (OR 2.08, 95% CI 1.8–2.29), SGA below 5th centile (OR 2.83, 95%CI 2.52–3.18).[93] Raised alpha fetoprotein (AFP) (above 2 MoM) and raised inhibin A (above 2 MoM) are also associated with SGA/FGR.[94] A large UK observational study of 1079 women, which included women with low PAPP-A or raised AFP and/or raised inhibin A, confirmed the increased risk of SGA (24.5%) and FGR (10.3%) and demonstrated that most of the increased risk is FGR after 34^{+0} weeks of gestation with only 2.3% (27/1079) requiring birth before this gestation.[95] 90.6% of cases of early FGR were identified by performing uterine artery Doppler assessment and ultrasound EFW in the early third trimester (LR-0.14; 0.06–0.35) supporting earlier studies.[96] Risks of SGA and FGR were similar in low PAPP-A, raised AFP and raised inhibin A populations and risks increased as levels deviated further from the median. This finding is supported by other observational studies and as a result additional surveillance for FGR should be offered if abnormal levels of any of these biochemical markers are detected.[95,97] Information on low estriol levels (below 0.5 MoM) is too limited to draw firm conclusions because of rarity in chromosomally typical fetuses. Raised human chorionic gonadotrophin (beta-hCG; above 4 MoM) is not reliably associated with SGA/FGR and does not need to precipitate additional monitoring in isolation, although if it occurs in association with other raised midtrimester markers (AFP and/or inhibin A) then this may indicate even higher risk of SGA and FGR.[98] *[Evidence level 2++]*

Low PAPP-A, raised AFP and/or inhibin A thus should initiate uterine artery Doppler screening and serial growth

scans with frequency dependent upon the result.[99] *[Evidence level 2+]*

Although when incidentally detected, low PAPP-A or raised AFP and/or raised inhibin A are strongly associated with SGA and FGR, systematic reviews and observational studies have not supported their use in isolation as primary detection tools for FGR because of their low sensitivity.[94-101] Thus their use as a screening tool in isolation is not currently recommended. *[Evidence level 2++]*

A prospective, observational study of 60 875 women with a singleton pregnancy, undergoing first trimester ultrasound and PAPP-A measurement, assessed the predictive performance of a model using maternal characteristics and PAPP-A measurements. The analysis used a Bayesian approach and variables and outcomes as continuous factors rather than an arbitrary categorisation. External validation of this model is required but presents an opportunity for maximising the information available in each pregnancy in a personalised approach.[102]

There are no prospective studies demonstrating the effectiveness of the use of aspirin in women with an isolated low PAPP-A or raised beta-hCG. However, as these are placental biomarkers and associated with adverse outcomes related to placental mediated disease it is appropriate to offer women low dose aspirin.[103-104] *[Evidence level 4]*

Anomalous screening results can be used to contribute to risk assessment for that pregnancy and help determine surveillance pathways for fetal growth.[104] *[Evidence level 2+]*

5.2.2 | Findings at midtrimester anomaly scan

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Findings at the midtrimester anomaly scan should be incorporated into the fetal growth risk assessment at the next planned review.	**4**	**GPP**	The review following the anomaly scan appointment presents an opportunity to review maternal medical conditions, fetal condition and size and thus reassess risk for a fetal growth disorder.
Uterine artery Dopplers should be carried out between 18^{+0} and 23^{+6} weeks for women at high risk of fetal growth disorders: • **Previous FGR** • **Previous pre-eclampsia** • **Previous SGA stillbirth** • **Maternal medical conditions** • **Abnormal biomarkers (PAPP-A, AFP, inhibin A)**	**2++**	**B**	In high-risk populations uterine artery Doppler has a moderate predictive value for early onset SGA. Please see section 7.3.1
When the following are identified on midtrimester anomaly scan, uterine artery Dopplers should be carried out to assess the risk of early onset FGR:			
• **Echogenic bowel**	**2+**	**C**	Fetal echogenic bowel is associated with an increased risk of SGA.
• **Single umbilical artery**	**2–**	**C**	Studies have demonstrated an association between isolated single umbilical artery and the risk of growth restricted stillbirths
• **Fetal biometry if EFW < 10th centile**	**4**	**GPP**	A uterine artery Doppler should be carried out to assess for placental dysfunction and risk of early onset FGR

At the time of the midtrimester fetal anomaly scan, certain normal variants and incidental findings may be observed as well as fetal anomalies detected. The Fetal Anomaly Screening Programme (FASP) provides guidance as to how these findings should be classified and whether referral for further assessment as for other suspected fetal anomalies should occur.[105] The guidance below discusses the association of these with fetal growth disorders and stillbirth and thus consideration as to whether the surveillance pathway for fetal growth should be amended.

Fetal echogenic bowel

Fetal echogenic bowel has been shown to be independently associated with a SGA newborn (aOR 2.1, 95% CI 1.5–2.9) and intrauterine fetal death (aOR 9.6, 95% CI 5.8–15.9).[106] A prospective study of 22 000 women with ultrasound findings of unknown significance at the 20-week anomaly scan included 50 cases of isolated echogenic bowel. There was an association with an increased risk of stillbirth but when restricted to live births with birthweight below 3rd centile no conclusion could be made.[107] *[Evidence level 2+]*

Single umbilical artery

A meta-analysis of 11 observational studies including 1731 pregnancies demonstrated an almost three-fold risk of SGA associated with isolated single umbilical artery.[108-109] Further studies have also demonstrated an association between isolated single umbilical artery and the risk of growth restricted stillbirths.[110-111] Finally, a retrospective analysis of over 200 000 pregnancies, excluding those with structural or chromosomal anomalies, reported an odds ratio of 8.1 for stillbirth with isolated single umbilical artery.[112] *[Evidence level 2–]*

Fetal biometry

At the time of the midtrimester scan fetal biometry is measured and an EFW calculated. Where the EFW is <10th centile, uterine artery Doppler should be performed to assess for placental dysfunction and risk of early onset FGR. If the uterine artery Doppler is normal re-scan in 3–4 weeks and if the uterine artery Doppler is abnormal arrange obstetric review for individualised care plan. *[Evidence level 4]*

The FASP guidance suggests that fetuses with measurements significantly less than the 5th centile at the midtrimester anomaly scan should be referred for further assessment.[113] This may include fetal medicine assessment for fetal anomaly or medical assessment for review of risk of fetal growth disorders and change of surveillance pathway (see section 8).

5.2.3 | Risk factors developing in pregnancy

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Women should be reassessed for their risk of a fetal growth disorder throughout pregnancy and after any antenatal admission.	**4**	**GPP**	Risk assessment should be a continuous process. The 28-week appointment presents a universal opportunity to review the pregnancy (and thus risk assessment) at the start of the third trimester. Antenatal admissions will be prompted by a change in maternal or fetal condition and thus should prompt a reassessment of the fetal growth monitoring plan.
Women with hypertensive disorders of pregnancy need to be assessed in line with the NICE guideline *Hypertension in Pregnancy* [NG133] to determine if growth scans and pathways need to be applied.	**2+**	**C**	Women with hypertensive disorders of pregnancy can be at increased risk of fetal growth disorders. The nature and severity of the hypertensive disorder determines the risk.
Women who have been seriously or critically unwell from COVID-19 should be offered an ultrasound scan to assess the fetal biometry. It seems reasonable to arrange the first scan within the first 14 days following recovery and to consider further ultrasound monitoring on an individual basis.	**4**	**GPP**	For women who have been acutely unwell with COVID-19 there is a risk that the severity of the illness may affect fetal growth.

Bleeding in the first trimester is common and a systematic review demonstrated an association with threatened miscarriage and growth restriction (OR 1.54, 95% CI 1.18–2.0), but with no consistent definition of the outcome and significant heterogeneity in results.[114] *[Evidence level 2++]*

Previous evidence regarding association between bleeding in the second half of pregnancy and fetal growth disorders has been conflicting with heterogeneity in definitions of bleeding and outcomes with the need for large, prospective studies able to adjust for confounders.[115] *[Evidence level 2–]*

Current RCOG guidance for care of women following an antepartum haemorrhage (APH) recommends serial scans for fetal growth stating *"Following APH from placental abruption or unexplained APH, the pregnancy should be reclassified as 'high risk' and antenatal care should be consultant-led. Serial ultrasound for fetal growth should be performed"*. It is not possible to determine whether there needs to be a certain amount of bleeding to confer a risk of FGR and thus a pragmatic definition is an APH that requires hospitalisation or repeated episodes of bleeding (i.e. bleeding on more than one occasion). Placenta praevia not complicated by APH is not a significant risk factor for SGA.[116]

A population-based study assessed the risk of SGA in women with hypertensive disorders of pregnancy. Women who develop hypertensive disorders of pregnancy had an increased risk of an SGA newborn compared with normotensive women (gestational hypertension no proteinuria RR 1.5, 95% CI 1.47–1.6, $P<0.001$; gestational hypertension with proteinuria RR 3.3, 95% CI 3.0–3.9, $P<0.001$; pre-existing hypertension were RR 2.5, 95% CI 2.1–2.9, $P<0.001$).[117] There is a dose–response relationship between SGA and hypertension with increases in diastolic blood pressure in women with non-proteinuric hypertension in pregnancy associated with an increased risk of SGA (severe pregnancy induced hypertension diastolic ≥110mHg RR 2.5, 95% CI 2.3–2.8).[117-119] NICE guideline [NG133] recommends that women with chronic hypertension, severe gestational hypertension (BP≥160/110 mmHg) and pre-eclampsia have ultrasound assessment for fetal growth and for women with mild hypertension if clinically indicated.[33] *[Evidence level 2+]*

Maternal COVID-19 infection probably increases the risk of FGR. A published systematic review of 42 studies reported an increased risk of LBW (OR 1.89, 95% CI 1.14–3.12)[120] associated with maternal COVID-19 infection, and a large multinational study also reported a higher LBW rate (RR 1.58, 95% CI 1.29–1.94) among women with COVID-19 infection but no effect on SGA probably reflecting the high prematurity rate.[121] RCOG COVID-19 guidance recommends that women who have been seriously or critically unwell from COVID-19 should be offered an ultrasound scan to assess the fetal biometry. It seems reasonable to arrange the first scan within the first 14 days following recovery and to consider further ultrasound monitoring on an individual basis.[122]

5.2.4 | Risk stratification for FGR and prediction models

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Prediction models should not be used as the only method for determining ultrasound surveillance.	**2+**	**C**	Despite moderate predictive ability, these models have not been shown to have sufficient clinical utility to determine which women should have ultrasound surveillance.
Multiparameter competing risk models for pre-eclampsia and placental dysfunction can be used to help reduce the risk of preterm SGA and identify those who can benefit from a prescription of aspirin.	**1–**	**B**	Pre-eclampsia prediction models can identify a high proportion of cases of preterm SGA that can be prevented using aspirin.
Implementation of these models requires sufficient local resources, training, and quality control to support implementation.	**4**	**GPP**	

There are several published prediction models for SGA based on combinations of maternal characteristics, biomarkers and ultrasound features.[123-128] However further analysis has demonstrated that while the models have moderate predictive value for SGA below the 5th centile, the clinical utility is limited because of the heterogeneous aetiology of fetal growth disorders.[129]

Data from the ASPRE RCT and SPREE study using pre-eclampsia prediction models demonstrated that these models identify a high proportion of cases of preterm SGA that can be prevented by the prophylactic use of aspirin.[19]

A competing risks model for SGA based on a combination of maternal risk factors, EFW and uterine artery pulsatility index was compared with a stillbirth specific risk model and the risk factors within the previous version of this guideline to predict placental dysfunction related stillbirth. This was a prospective observational study in 131 514 women at 19–24 weeks. At a screen positive rate of 21.8% (defined in RCOG 2013) the competing risks model predicted 71% (at any gestation), 76% (<37 weeks) and 79% (<32 weeks) of placental dysfunction related stillbirths compared with 40%, 44% and 42%. [130] *[Evidence level 1–]*

As these models were developed primarily for placental dysfunction and pre-eclampsia, they do not encompass all the known risk factors for FGR and in particular late FGR. Thus, at present these models are not sufficient to be used as the sole method of determining which women should have ultrasound surveillance. *[Evidence level 2+]*

However, where local resources, training and quality control can support their implementation, the use of multiparameter competing risk models for pre-eclampsia and placental dysfunction can be used to help reduce the risk of preterm SGA and identify those who can benefit from a prescription of aspirin *[Evidence level 4]*

6 | HOW CAN THE RISK OF FETAL GROWTH DISORDERS IN PREGNANCY BE REDUCED?

6.1 | General population

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Reduce smoking in pregnancy by identifying women who smoke with the assistance of carbon monoxide (CO) testing and ensuring in-house treatment from a trained tobacco dependence advisor is offered to all pregnant women who smoke, using an opt-out referral process.	**4**	**GPP**	Smoking increases the risk of SGA and women who can stop smoking can reduce their risk of SGA.
All women should continue to take the recommended 10 micrograms/day of vitamin D (throughout pregnancy) and 400 micrograms/day of folic acid (preconception and for the first 3 months of pregnancy).	**1–**	**B**	The benefit of vitamin D and folic acid supplementation in pregnancy to reduce the risk of pre-eclampsia, SGA or FGR remains uncertain and thus all women should follow general pregnancy guidance to prevent other pregnancy complications.

6.1.1 | Dietary modification

Balanced energy/protein supplementation has been associated with a reduction of SGA (RR 0.79, 95% CI 0.69–0.90) and an increase in mean birthweight (+40.96 g, 95% CI 4.66–77.26; 11 trials, 5385 women).[131] The same meta-analysis examined whether high protein supplementation alone was beneficial. Only one study of 1051 women was included and appeared to show an increase in SGA (RR 1.58, 95% CI 1.03–2.41). However,

the evidence was of low quality, therefore high protein supplementation is not recommended.[131] *[Evidence level 1–]*

A single-centre Spanish RCT investigated whether structured interventions based on a Mediterranean diet or mindfulness-based stress reduction in high-risk pregnancies can reduce the percentage of newborns who were born SGA and other adverse pregnancy outcomes. Primary endpoint was SGA at birth and demonstrated that SGA occurred in 88 newborns (21.9%) in the control group, 55 (14.0%) in the Mediterranean diet group (OR, 0.58, 95% CI, 0.40–0.84; risk difference −7.9, 95% CI, −13.6 to −2.6; $P=0.004$). However, there were significant limitations and confounders within this study and so neither intervention should be recommended routinely.[132] [*Evidence level 1–]*

6.1.2 | Dietary supplements, minerals, micronutrients, and vitamins

Supplementation with omega-3 long chain polyunsaturated fatty acids has not been shown to reduce SGA or intrauterine growth restriction (RR 1.01, 95% CI 0.90–1.13; eight RCTs, 6907 participants).[133] Multiple micronutrient supplementation in pregnancy has been addressed in a Cochrane review of 21 trials involving 142 496 women. Micronutrient supplementation appeared to reduce the risk of SGA (RR 0.92, 95% CI 0.88–0.97).[134] However, all but one of these studies was conducted in low or middle income countries and the only UK study failed to demonstrate any significant effect.[135] *[Evidence level 1–]*

High dose folic acid supplementation has been previously suggested to reduce the risk of SGA, but the FACT study did not demonstrate any reduction in SGA or FGR rates over the standard preconceptual dose (400 microgram/day).[136] Calcium supplementation has been suggested to reduce the incidence of pre-eclampsia although a Cochrane review reported a modest 8% reduction at best and a high quality RCT did not demonstrate an effect.[137-139] The Cochrane review did not re-consider the effect of calcium on reducing the prevalence of SGA.[137] An NIHR funded RCT in the UK commenced in 2022 (CaPE NIHR27325) and is considering maternal and fetal outcomes. Magnesium supplementation to reduce the incidence of SGA has been extensively investigated, but a Cochrane review (10 trials, 9090 women) concluded there was no effect.[140] *[Evidence level 1–]*

6.1.3 | Vitamin D supplementation

The benefit of vitamin D supplementation to reduce the risk of pre-eclampsia, SGA or FGR in pregnancy remains uncertain. Several systematic reviews have not found evidence of a reduced pre-eclampsia or stillbirth risk, but have found some evidence of a reduced risk of LBW (below 2500 g) and/or SGA.[141-143] Another systematic review suggested that vitamin D supplementation may be useful in preventing pre-eclampsia.[144] At present therefore, there is insufficient evidence to recommend high dose supplementation for pregnant women at risk of FGR and women should continue to take the 10 microgram/day recommended for all UK pregnant women,[18] unless there are other reasons to increase daily dose independent of pregnancy, e.g. cultural skin coverage, in which case dose should be determined by local prescribing policy. *[Evidence level 1–]*

6.1.4 | Tobacco dependency treatment

Smoking increases the risk of SGA and women who can stop smoking can reduce their risk of SGA. If able to quit by 15 weeks of gestation, they can return to the pregnancy risk status of similar non-smoking women of preterm and term SGA.[75-145] *[Evidence level 1–]*

The NICE guideline [CG62] has detailed recommendations for treating tobacco dependence in pregnant women including behavioural support and nicotine replacement therapy. There is insufficient evidence for the effectiveness of e-cigarettes to help stop smoking in pregnancy or whether they have potential harm for the fetus or child after birth.[18] However, the risk is very likely to be less than for cigarettes. Thus, while women should be advised to try and avoid use of e-cigarettes in pregnancy, it is appreciated that for some women they will not be able to maintain a smoke-free pregnancy without e-cigarettes and these women should be supported to use e-cigarettes.[81,146]

SBLCBv3 Element 1 supports maternity care providers to reduce smoking in pregnancy.[6] Smoking is the most important modifiable risk factor for poor pregnancy outcomes. Ideally, women would be supported to stop smoking and provide a smoke-free environment prior to pregnancy via pre-pregnancy counselling.

6.2 | Women at risk of fetal growth disorders

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Taking folic acid and vitamin D doses above the recommended dose does not appear to provide any additional benefit to women at risk of FGR.	**1–**	**B**	Dietary modification/ supplement interventions for the prevention of FGR in an at-risk population have yielded conflicting results, but have consistently failed to show benefit when tested with adequately powered RCTs.
Women at risk of pre-eclampsia and/or placental dysfunction should take aspirin 150 mg once daily at night from 12^{+0}–36^{+6} weeks of pregnancy to reduce their chance of SGA and FGR.	**1++**	**A**	There is good evidence of aspirin safety and efficacy at 150 mg and doses below 100 mg should only be considered in the presence of other relative contraindications to prescription.

Recommendation	Evidence quality	Strength	Rationale for the recommendation
LMWH should not be prescribed to reduce the risk of SGA or FGR in at-risk women.	**1+**	**A**	RCT evidence has failed to demonstrate a reduction in FGR in any at-risk group including those with inherited thrombophilias.

6.2.1 | Maternal micronutrients

A Cochrane review published in 2003 and updated in 2010 reported four studies of 165 women and did not find evidence of improved outcomes or enhanced fetal growth.[147] *[Evidence level 1–]*

6.2.2 | Antiplatelet agents

Antiplatelet agents have been extensively investigated in women at varying levels of risk for pre-eclampsia, with SGA and/or FGR as outcomes, in multiple meta-analyses.[148,149] These studies have suggested a reduction in SGA and FGR birth with the use of aspirin in women at risk of pre-eclampsia, driven by a reduction in the incidence of pre-eclampsia in treated women.[19] Prevention of pre-eclampsia with aspirin is most effective when aspirin is initiated between 11^{+0} weeks and 16^{+6} weeks of gestation.[150] A meta-analysis demonstrated administration before 16 weeks was associated with a reduction in SGA (RR 0.76, 95% CI 0.61–0.94; 13 trials, 6393 women), where after 16 weeks there was no significant effect (RR 0.95, 95% CI 0.84–1.08; 18 trials, 14 996 women).[151] Meta-analysis supported the concept of a dose–response relationship for SGA prevention favouring a dose of 100–150 mg/day.[152] There is good evidence of aspirin safety and efficacy at 150 mg.[34] Thus, doses below 100 mg should only be considered in the presence of other relative contraindications. Two RCTs have demonstrated that administration of aspirin in the evening or night is more effective at lowering ambulatory blood pressure and reducing the risk of pre-eclampsia, than in the morning or day.[34,153] *[Evidence level 1++]*

NICE guideline *Hypertension in Pregnancy* [NG133] recommends that aspirin is continued until birth for prevention of hypertensive disorders, while other international guidelines recommend stopping at 36 weeks.[33] Aspirin may be associated with an increased risk of postpartum haemorrhage and thus the suggestion that aspirin should be stopped at 36 weeks, or even at the end of the second trimester.[148,154] However, it is not clear whether stopping aspirin earlier at 36 weeks reduces the risk of bleeding. Thus, in the context of this guideline aspirin should be ideally commenced at 12–16 weeks and continued until at least 36 weeks.[155] *[Evidence level 4]*

6.2.3 | Antithrombotic therapy

Antithrombotic therapy using low-molecular-weight heparin (LMWH) has been trialled repeatedly in women at risk of FGR, usually in association with pre-eclampsia, with or without coexistent thrombophilias. Previous systematic reviews have suggested a potential benefit in reducing the risk of SGA with the use of LMWH and aspirin (RR 0.41, 95% CI 0.27–0.61; seven studies, 710 women; RR 0.41, 95% CI 0.20–0.93).[156,157] However, prospective studies have failed to identify any benefit in reducing placental mediated disease. In the HEPEPE trial, 257 women with a previous history of early onset (before 34 weeks) severe pre-eclampsia were randomised to aspirin 100 mg with or without enoxaparin 4000 iu/day from early pregnancy.[158] There was no difference in the rate of SGA (RR 0.78, 95% CI 0.50–1.22) or FGR (defined below the 5th centile; RR 0.65, 95% CI 0.36–1.18). The EPPI study randomised 156 women with a history of either early onset pre-eclampsia (before 36 weeks) or early onset SGA (before 36 weeks) to aspirin 100 mg with or without enoxaparin 4000 iu/day.[159] There was no difference in the rate of SGA (aOR 1.17, 95%CI 0.56–2.47) or FGR (defined <3rd centile; aOR 1.19, 95% CI 0.40–3.52). Martinelli et al. randomised 135 women with a previous history of pre-eclampsia and showed no difference in the incidence of FGR (16%, $P=0.3$).[160] A secondary analysis of the FRUIT-RCT which examined the risk of SGA in women with a history of previous pre-eclampsia and an inherited thrombophilia, treated with or without enoxaparin, could also find no reduction in risks.[161] Finally, an IPD meta-analysis of 963 women from eight eligible studies (published prior to HEPEPE and EPPI and therefore not including their participants) failed to find any reduction in any placentally mediated outcome (RR 0.64, 95% CI 0.36–1.11).[162] *[Evidence level 1+]*

In summary, evidence does not support the use of LMWH as an effective treatment to prevent SGA or FGR, even in the presence of heritable thrombophilia.

6.2.4 | Progesterone

Secondary outcome analyses of studies on progesterone to prevent PTB have shown no effect on the risk of pre-eclampsia or FGR.[163-165] *[Evidence level 1+]*

6.2.5 | Hydroxychloroquine

Studies examining the effects of hydroxychloroquine on the risk of FGR are small and of low quality and meta-analysis failed to show significant benefit.[166] Hydroxychloroquine has also been suggested as treatment for women with previous placental chronic histiocytic intervillositis, but no prospective RCT data are currently available and therefore is not recommended outside a research setting.[167,168] *[Evidence level 1–]*

6.2.6 | Antihypertensive use

Antihypertensive drug therapy for hypertension in pregnancy does not seem to increase the risk of having an SGA newborn (aRR 0.96, 95% CI 0.78–1.18; 21 trials, 2686 women).[169] The evidence regarding the association of SGA and beta-blockers in women who are hypertensive is inconclusive. While some studies identify a significant association, others suggest that the SGA is associated with the maternal hypertensive disease regardless of the treatment. There does appear to be an increased risk of SGA in pregnant women who use beta-blockers in pregnancy for an

indication other than hypertension, again this may relate to the underlying condition rather than the drug.[170] *[Evidence level 1–]*

7 | WHAT IS THE OPTIMUM SURVEILLANCE PATHWAY FOR WOMEN ACCORDING TO THEIR RISK FOR FGR AND HOW TO DIAGNOSE FETAL GROWTH DISORDERS?

The risks of a pregnant woman developing early or late onset FGR are strongly linked to concurrent pregnancy risk factors. As a result of this, the prevalence of FGR varies dramatically in different pregnant populations directly influencing the performance of prediction and detection methods. Early onset FGR is a relatively uncommon condition (~0.3%) with late onset FGR being more common.

7.1 | Low risk of FGR

Women who are assessed as being at a low risk for FGR should have serial assessment of fetal growth using antenatal SFH measurements performed by healthcare professionals trained in their use and plotted on appropriate charts.[6] All staff performing these measurements should be competent in measuring, plotting, interpreting appropriately and referring when indicated, and measurements should be performed as per NICE guidelines.[6-18] *[Evidence level 2+]*

7.1.1 | Clinical examination and fundal height measurement

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Abdominal palpation has limited accuracy for the prediction of an SGA newborn and thus should not be routinely carried out in this context.	2+	C	Studies in both low and high-risk populations have consistently shown abdominal palpation to be of limited accuracy in the detection of an SGA newborn.
Serial measurement of SFH is recommended at each antenatal appointment after 24^{+0} weeks of pregnancy (no more frequently than every 2 weeks). The first measurement should be carried out by 28^{+6} weeks.	2+	C	SFH remains a valuable, although limited tool for the detection of SGA. Serial measurement may improve predictive accuracy.
Women with a single SFH which plots below the 10th centile or serial measurements which demonstrate suboptimal fetal growth (no apparent fetal growth over 2 weeks) should be referred for ultrasound measurement of fetal size.	4	GPP	Owing to the limited accuracy of SFH, abnormal SFH measurements should prompt assessment of the fetus with ultrasound.
Women in whom measurement of SFH is less accurate (e.g. BMI of 35 kg/m^2 or above, large fibroids, polyhydramnios) should be referred for serial assessment of fetal size using ultrasound.	4	GPP	Maternal obesity, abnormal fetal lie, large fibroids, hydramnios and the extent of fetal head engagement contribute to the limited predictive accuracy of SFH measurement
Providers should determine which charts they are going to use antenatally to record SFH and staff should be trained in the use of these. Charts should be able to be incorporated within electronic maternity records.	4	GPP	There is insufficient evidence to recommend a particular chart for recording SFH.

Studies in low risk populations have consistently shown abdominal palpation to be of limited accuracy in the detection of a SGA newborn (sensitivity 19–21%, specificity 98%) and severely SGA newborn (less than 2.3rd centile, sensitivity 28%).[171,172] In mixed risk populations, the sensitivity increases to 32–44%.[173,174] In high risk populations sensitivity is reported as 37% for a SGA newborn and 53% for severe SGA.[175] A Cochrane meta-analysis in 2015 did not find evidence that measurement of SFH was superior to abdominal palpation, but only included one study of 1639 women.[176] A large retrospective cohort study of 42 018 women in Sweden found improved overall sensitivity (47%) for SGA.[177] Thus, SFH measurement would seem superior to palpation in detecting fetuses at risk, although both methods have significant limitations. The Swedish study also demonstrated that SFH performs best nearer term.

NICE reviewed the evidence for SFH and fetal biometry using ultrasound to predict birthweight at term in unselected or low-risk pregnancies to inform the NICE guideline [CG62].[18] They included 19 studies (cohort and case–control) and concluded that for SFH carried out more than 7 days before birth

had very poor sensitivity for SGA (one study, high quality evidence) and moderate specificity for SGA (one study, high quality evidence). It was noted that there was very little evidence available on the accuracy of SFH measurements (one small study looking at SGA) and particularly on the accuracy of repeated measurements as opposed to a one-off assessment. While USS was noted to be more sensitive than SFH and when carried out close to birth it still was not very sensitive for SGA. They concluded that while SFH measurement is not very sensitive, SFH measurement is easily performed, with little resource implications and essentially no adverse effects (in terms of the test itself, inaccurate results will still have adverse effects). If SFH measurement was not undertaken routinely, it would make the selective choice of who should receive a USS more challenging. Thus, SFH remains a reasonable tool for monitoring growth in low-risk pregnancies.[18] *[Evidence level 2+]*

Charts for recording of SFH commence at 24^{+0} weeks and thus measurements can be taken and recorded from this gestation. It is recognised that performing measurements routinely between 24^{+0} and 26^{+7} weeks will result in a high rate of referral for USS assessment because of the relationship of the centiles at these earlier gestations. Thus, while in some circumstances measurement would be appropriate, e.g. as part of assessment of fetal growth due to maternal condition or concerns regarding fetal movement, routine assessment for surveillance of fetal growth should not commence until 26^{+0}–28^{+6} weeks to coincide with the routine 28-week appointment. SBLCBv3 recommends that the first measurement should be taken before 28^{+6} weeks.[6] The timing of the first routine SFH measurement is determined by the schedule of antenatal appointments for all pregnant women and nulliparous women. If not undertaken at 28 weeks for all pregnant women, then the next routine antenatal contact would be 34 weeks. *[Evidence level 4]*

Maternal BMI greater than 35 kg/m^2, abnormal fetal lie, large fibroids, hydramnios and fetal head engagement contribute to the limited predictive accuracy of SFH measurement. SFH is associated with significant intra- and inter-observer variation and serial measurement may improve predictive accuracy.[178,179] Women must be assessed at booking for conditions where SFH measurements are not appropriate (e.g. raised BMI 35 kg/m^2 or above at booking; presence of fibroids in uterus [based on clinical judgement]).

SFH should be measured from the fundus (variable point) to the symphysis pubis (fixed point) with the measurement hidden from the examiner.[174] Women with a single SFH which plots below the 10th centile should be referred for further investigation with ultrasound assessment (Appendix II). There are no high-quality data that enable recommendations on how reducing SFH velocity should be defined, but if measurements more than 2 weeks apart do show not any increase in SFH then women should be referred for a single ultrasound assessment of fetal growth. The urgency of this ultrasound assessment will depend on additional clinical findings, for example fetal movements and maternal blood pressure.[18] *[Evidence level 4]*

Standard, population, and customised charts to plot SFH are available (adjusted for maternal characteristics) and were assessed in a Cochrane review. No trials were identified that compared different types of SFH charts and thus evidence for their effectiveness on outcomes such as perinatal morbidity/mortality is lacking.[176] The introduction of a customised SFH chart has been associated with improved detection of SGA (29%–48%), yet this is in the context of a training programme which included the standardisation of the performance of SFH measurements and robust referral pathways when abnormalities were detected, and therefore it is difficult to determine if the customisation of the SFH chart or the programme improved detection rates.[180] The Intergrowth SFH charts[181,182] (published in 2015) were designed with robust methodology and can be downloaded and incorporated into electronic patient records. However, there is limited assessment of their performance within a heterogenous population. Providers should determine which charts they are going to use antenatally to record SFH and staff should be trained in the use of these. *[Evidence level 4]*

7.1.2 | Universal ultrasound

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Routine measurement of fetal AC or EFW in the third trimester does not reduce the incidence of an SGA newborn nor does it improve perinatal outcome.	**1–**	**A**	While studies have demonstrated an increase in detection of SGA with universal rather than selective ultrasound, this has not been demonstrated in clinical trials to translate into improved outcome.

A Cochrane meta-analysis of 13 trials assessing universal late pregnancy ultrasonography in low risk or unselected women demonstrated no beneficial effect, with the recommendation that it should not be offered routinely in the third trimester.[183] There are several criticisms of the included studies in the Cochrane review including variation in the definition of a "screen positive", no diagnostic assessment of the test element, wide variation in gestational age and no studies included an intervention that could then have an impact on outcomes.[184] NICE reviewed the evidence for the antenatal care guideline up to September 2020. They came to the same conclusion that at present the evidence did not demonstrate an effect on outcomes of routine third trimester USS in uncomplicated singleton pregnancies.[185] Other studies suggest increased detection of SGA with routine third trimester ultrasound assessment of growth.[186] In a pragmatic screening study in nulliparous women, SGA was detected in 57% with routine third trimester USS compared with 20% with USS by clinical indication, but it is only when fetal growth velocity was combined with fetal biometry that a subset of SGA fetuses at risk of increased neonatal morbidity was identified.[187] Studies published since the

NICE review have similarly demonstrated an unclear effect on perinatal mortality,[188,189] and a systematic review of diagnostic performance concluded that for a fixed 10% false positive rate sensitivity was higher for AC than EFW and better performance when the scan was carried out near term and to detect FGR rather than SGA.[190] The NICE committee did note that the evidence in their review was overall moderate to low quality and that within their recommendation not to offer routine third trimester USS there is an inherent assumption that risk assessment and selective scanning is being appropriately applied. They also noted a lack of evidence for the impact on maternal anxiety.[185] *[Evidence level 1–]*

A further important consideration is the potential to cause harm for those women who are screen false positive on ultrasound and then have an unwarranted intervention such as induction of labour (IOL) causing iatrogenic prematurity. A French study evaluating implementation of universal third trimester ultrasound demonstrated that there was an increased risk of iatrogenic preterm and early term birth for true and false positives and an increased risk of adverse outcome in the false negatives (although not statistically significant).[191] *[Evidence level 2–]*

A health technology assessment assessed other components of a universal late pregnancy ultrasound (umbilical artery Doppler, cerebroplacental ratio (CPR), severe/borderline oligohydramnios) for the prediction of adverse outcome and cost-effectiveness. It concluded that the primary literature on the diagnostic effectiveness of ultrasound in late pregnancy is weak and does not support universal ultrasonic screening for fetal growth disorders. Cost-effectiveness analysis was limited by uncertainty around costs related to the difference between an induced birth and expectant management.[184] Further research is thus recommended (section 13).

7.2 | Moderate risk

7.2.1 | Ultrasound biometry

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Maternity providers should ensure that they have guidance that promotes the use of standard planes of acquisition and calliper placement when performing USS for fetal growth assessment. Quality control of images and measurements should form part of the monitoring process.	**2+**	**C**	There is a significant association between the quality of the biometric ultrasound images and EFW accuracy.
Women in the moderate risk category are at risk of late onset FGR and so require serial assessment of fetal growth commencing at 32 weeks. For the majority of women, a scan interval of 4 weeks is appropriate.	**2++**	**B**	Early onset FGR is uncommon. Ultrasounds can thus commence at 32 weeks but should continue until birth because of the risk of late onset FGR. An interval of 4 weeks between scans has a low false positive rate.
If two EFW measurements are to be used to estimate velocity, they should ideally be a minimum of 3–4 weeks apart to minimise false positive rates for diagnosing FGR.	**2++**	**B**	Performing scans at intervals shorter than 14 days increases the false positive rate for diagnosing FGR.
Assessment of the fetal AC may help in determining the fetus that is FGR.	**2+**	**C**	AC and AC growth velocity can help determine those at increased risk of neonatal morbidity.
When assessing fetal size the Hadlock formula should be used with HC, AC and FL.	**2+**	**C**	The Hadlock formula performed the best in evaluation of optimal formula for predicting EFW.
Changing EFW formula during growth monitoring can lead to an artefactual change in growth trajectory and should be avoided where possible or the potential impact of such a change on growth velocity recognised if the formula is changed.	**2–**	**C**	There is a difference between EFW calculated using HC, AC and FL results and EFW calculated using AC and FL results alone, depending on fetal proportions.
Maternity providers should ensure that they clearly identify the reference charts to plot individual biometry and EFW measurements to calculate centiles. For individual biometry measurements the method used for measurement should be the same as those used in the development of the individual biometry and fetal growth chart.	**4**	**GPP**	

Recommendation	Evidence quality	Strength	Rationale for the recommendation
When determining which charts are to be used to plot EFW the following should be considered:			
• **Fetal growth charts must be based on sonographic EFW not newborn birthweight standards.**	**2–**	**C**	Newborn birthweight standards will include babies born prematurely.
• **Fetal growth charts should be developed using methodology that is of the lowest bias with population level data, ideally obtained prospectively and related to prescriptive fetal growth.**	**4**	**GPP**	
• **Universal reference charts may need to be adjusted to local or regional populations, either for population characteristics, or the centile that is used to determine further surveillance and investigation for growth concerns.**	**2–**	**C**	Studies comparing different charts with adverse outcomes have demonstrated that different centile thresholds had to be used to determine the same risk of adverse outcome.
Maternity providers may wish to evaluate the impact of different reference charts in their local population to ensure that the reference chart is appropriate or how it should be adjusted using local data sets.	**4**	**GPP**	
Maternity providers should ensure that they monitor the number of fetuses considered < 3rd centile to ensure that their growth pathway and growth chart is appropriate.	**4**	**GPP**	

Ultrasound is a core component of fetal growth surveillance and management. In this context it may be carried out by several different practitioners including doctors, midwifery sonographers, maternal fetal medicine specialists and ultrasonographers. A diagnosis of a growth disorder, or decision about management based on fetal wellbeing, should be informed by high quality measurements and reports. This requires appropriate training, time for the examination, quality assurance and audit. The British Medical Ultrasound Society (BMUS) have produced detailed guidance on performance of fetal growth scans[192] and in collaboration with the Society of Radiographers (SoR) have produced *Guidelines for Professional Ultrasound Practice*.[193]

When and how often should USS surveillance be undertaken?

Serial scanning is recommended for women at increased risk of fetal growth disorders. Women at moderate risk of FGR do not require uterine artery Doppler assessment as they do not have risk factors for early onset FGR but are still at risk of later onset FGR so require serial ultrasound assessment of fetal growth from 32 weeks. Although a scan at 32 weeks can identify 90% of SGA below the 5th centile being born preterm, it only identifies 60% of SGA births near term (for a 10% false positive rate). An ultrasound scan at 36 weeks improves the detection of term SGA (SGA below the 5th centile at 37 weeks or more) from 58% to 70% but this is at the expense of missing preterm SGA.[194] Thus, the recommendation for surveillance for late FGR and SGA is to commence at 32 weeks. It is recognised that these women will have an antenatal appointment at 28 weeks at which SFH may be measured if appropriate. In this group of women, the planned surveillance is by USS and thus SFH should cease after USS surveillance begins.

The interval between scans should be no more frequent than every 14 days, with optimum assessment for growth velocity being 21–28 days.[195] Mongelli et al. used a mathematical model to estimate the impact of time interval between examinations on the false positive rates for FGR (defined as no apparent growth in fetal AC between two consecutive examinations).[196] When the initial scan was performed at 32 weeks of gestation, the false positive rates were 30.8%, 16.9%, 8.1% and 3.2% for intervals of 1, 2, 3 and 4 weeks respectively. False positive rates were higher when the first scan was carried out at 36 weeks of gestation (34.4%, 22.1%, 12.7% and 6.9% respectively). These findings suggest that if two measurements are to be used to estimate velocity, they should be a minimum of 3 weeks apart to minimise false positive rates for diagnosing FGR.[195,196] This recommendation does not preclude more frequent ultrasound measurements of AC/EFW to predict fetal size at birth but rather indicates which measurements should be used to interpret growth. For many pregnancies in the moderate risk category or in those unsuitable for SFH measurements, an interval of 4 weeks is appropriate and reducing scan interval (from 4 weeks to 2 weeks) has not been demonstrated to improve pregnancy outcome.[197] *[Evidence level 2++]*

How should fetal biometry be assessed?

Three systematic reviews have assessed the accuracy of ultrasound biometric measures, both as individual measures, as ratios, and combined (as the EFW).[198-200] The most recent study demonstrated that AC is comparable to EFW in predicting SGA.[200] The largest prospective study within the systematic review demonstrated that prediction of SGA provided by the fetal AC is better than HC or FL, but inferior to the three measurements combined as EFW.[201] Within the prospective Pregnancy Outcome Prediction (POP) study, the addition of AC growth velocity was the only biometric measure that identified babies at increased risk of neonatal morbidity.[187] *[Evidence level 2+]*

The largest study to assess formulas for calculation of EFW[202] suggested that the most accurate model was that of Hadlock et al. incorporating HC, FL and AC.[203] The addition of biparietal diameter (BPD) to the Hadlock equation was not shown to increase accuracy and studies have shown that there is considerable variation in BPD ranges across different populations. Comparative studies have indicated that the Hadlock equation may more accurately estimate fetal size than the original Intergrowth 21 equation,[204] including both analysis of routinely collected unblinded ultrasound scans and a prospective cohort study of blinded ultrasound scans at 28 and 36 weeks of gestational age.[205] Given this and the much greater experience of its use, the Hadlock equation is recommended for the estimation of fetal weight. *[Evidence level 2+]*

How to ensure high quality measurements?

Those performing USS for biometry should be aware of the need for appropriate training in fetal biometry assessment, time for the examination, quality assurance and audit.[192] All measurements should be taken following the same methodology as that used in the studies which produced the reference curves being used. *[Evidence level 4]*

As an example, when plotting individual measurements (HC, AC, FL) if these are to be plotted on Chitty charts then the appropriate section for HC would be the transventricular.[206] When using EFW and the Hadlock formula then the ellipse methods would be used for HC (transthalamic section) and AC and plotted on a reference chart developed using EFW derived from Hadlock equation. *[Evidence level 4]*

Of note, BMUS recommends the two diameter methods for AC and the International Society for Ultrasound in Obstetrics and Gynaecology (ISUOG) recommends the ellipse method.[207] It should be appreciated that there is likely to be a difference between EFW calculated using HC, AC and FL results and EFW calculated using AC and FL results only, depending on fetal proportions.[208] Thus, changing formula during growth monitoring can lead to an artefactual change in growth trajectory and when a change in formula has to be used (e.g. late gestation and unable to get HC) this needs to be taken into account when comparing with previous assessments of EFW. *[Evidence level 4]*

Maternity providers should ensure that they have guidance that promotes the use of standard planes of acquisition and calliper placement as this has been shown to improve reproducibility of measurements.[209] *[Evidence level 2+]*

Quality control of images and measurements should form part of the assessment. *[Evidence level 4]*

It is important that the imprecision of EFW is recognised when interpreting results. Imprecision can be caused by the accuracy of the equation used to calculate EFW, most fall within +/–10% with the error greater at extremes of fetal weight and gestation.[210,211] There is also a significant association between the quality of the biometric ultrasound images and EFW accuracy.[212] There are published scores that have been used to assess quality.[209,213]

Which fetal growth charts should be used?

Integral to the assessment of fetal size, determined by EFW, is being able to interpret the measurement relative to a given expected growth standard using a fetal growth chart with reference curves. There are several types of charts available with reference ranges being either descriptive (how a population has grown at a particular time) or prescriptive (how a population should grow). Another important distinction is between universal and customised charts. Prescriptive charts assume that under optimal conditions all fetuses will have the same growth potential and the only difference observed in growth across populations will be due to environmental factors, examples are World Health Organization (WHO) fetal charts (with country specific charts)[214] and Intergrowth 21st (universal charts).[182] Customised charts have been proposed as an alternative to universal charts and are based on the premise that fetal growth varies across countries and ethnicities and that adjustment should occur at a population level for these factors, e.g. National Institute of Child Health and Human Development (NICHD) charts with separate charts for white, Black, Hispanic and Asian women.[215] Another approach, often also called customisation is to adjust for other variables (e.g. maternal height, weight, parity and fetal sex as well as ethnicity) at an individual level, e.g. GROW.[215-217] The GROW software can incorporate ethnicity, height, weight, parity +/–fetal sex to calculate the predicted optimal weight at 40 weeks for each individual fetus.[218-219] The customised growth curve is then determined retrospectively, based on a proportionality growth function derived from the ultrasound based Hadlock standard.[220] However, there are concerns that these are factors at an individual level that are associated with pathological fetal growth and thus customisation at an individual level risks normalising pathology. It should be noted that the GROW software allows selection of variables that are used in the adjustment, and when all variables are removed the charts default to a population standard. This is retrospectively derived from a database of 2.7 million pregnancies characterised as low risk in a UK population.[218]

Individual trajectories for the fetus can be developed and this is discussed further in section 7.3.2.

A number of studies have investigated the association of individual customised charts with adverse outcome and different charts and rates of SGA and FGR in populations. Several studies have found that customised charts perform better at predicting stillbirth and adverse neonatal outcomes, including a study that analysed 10 years of stillbirth data in England between 2008 and 2017 and demonstrates an overall reduction in stillbirths, with the steepest decline in units with complete implementation of the GAP programme.[221] Other studies have demonstrated no benefit.[222-224] Further analysis of the POP cohort (a prospective cohort of nulliparous women in UK 2018–2013) demonstrated that previous findings of the beneficial effects of customisation are likely to relate to more preterm infants being classified as SGA by customised standards, and the women giving birth to these infants more likely to have a higher BMI.[180] This raises concerns that customisation may "account" for apparent

physiologic determinants of growth that actually are causal and associated with risk of adverse outcome.[180]

The DESiGN trial was a cluster RCT to assess the effectiveness of the GAP programme with the primary outcome being antenatal detection of SGA.[225] The trial was not designed to evaluate the customised charts of GROW compared with population growth charts. It concluded that there was no effect observed of GAP on antenatal detection of SGA compared with standard care (25.9% versus 27.7%, adjusted difference 2.2%, 95% CI −6.4% to 10.7%) but noted the variable implementation of GAP.[225] Concerns have been raised about certain aspects of the methodology and execution of the trial including: an inadequate control group (trial coincided with the role out of SBLCBv2 with a fetal growth element), implementation of the GAP programme not meeting predefined criteria in all participating units, and the trial period being too short so that implementation was incomplete in some units. Other concerns have been raised related to the cluster summary approach used.[226] An analysis of all trial participants demonstrated a reduction in both stillbirth and neonatal mortality; however these were secondary outcomes and it is difficult to attribute this to any single intervention due to the concerns discussed above. A significant and incremental increase of detection of SGA was seen in the GAP DESiGN centres after trial data collection had ceased[227] but this cannot be compared with the outcomes in the standard care centres.

As recommended by the WHO, there is a need to understand local population characteristics, as even under optimal nutritional and environmental conditions there appears to be variation in fetal growth. EFW centiles on the INTERGROWTH-21st chart are lower than those on the Hadlock et al., WHO and FMF charts.[203,204,228,229] The consequences of this were highlighted by Francis et al. who showed that in a normal population the INTERGROWTH-21st chart identified only 4.4% of babies as SGA (below 10th centile) and 20.6% of babies as large for gestational age (above 90th centile).[230] Thus, universal charts should not be employed without consideration of local population variation and consideration of adjusting thresholds to avoid under or over detection of SGA.[228] This will require maternity providers to understand and monitor their local data for metrics such as the number of fetuses considered <3rd centile and statistically validate these.[231] The international populations for which the WHO and Intergrowth 21 charts were produced may not represent local populations in which they may be applied for conventional centile cut-offs (< 10th or < 3rd) and thus heterogeneous populations require alterations of thresholds for delivery recommendations based on local perinatal mortality and morbidity. This is illustrated in a Swedish study comparing birthweight centile thresholds for adverse perinatal outcomes across population, customised and Intergrowth charts, where the association was markedly increased, i.e. doubling at the 10th centile for population and customised and the 25th centile for Intergrowth 21 and thus highlights the considerations needed in determining the growth charts used within maternity systems.[231] *[Evidence level 2–]*

Importantly, the development of charts should be with high quality methodology and evidence suggests that this is true for only a limited number of descriptive, population or universal charts.[232] The WHO describes criteria to be considered when developing growth charts as described in ISUOG guidance.[207] These criteria were used in the development of international standards for fetal biometry, describing optimal growth in fetuses at low risk of FGR in Intergrowth 21[182] and WHO fetal charts.[228] These charts also have a birthweight standard which is important when assessing detection of abnormal growth antenatally and determining postnatal management particularly when born preterm.

What should maternity providers ensure?

Maternity providers should ensure that they have clear guidance and processes for the following:

- Individual measurements for fetal biometry (HC, AC, FL) with standard planes of acquisition and calliper placement.
- When assessing fetal size and calculating EFW the Hadlock formula should be used with HC, AC and FL.
- Quality control of images and measurements should be undertaken.
- Clearly identify the reference charts to be used for individual biometry measurement and the components for EFW calculation. These should be based on those used in the development of the chosen reference charts for fetal growth.
- Maternity providers may wish to evaluate the impact of different reference charts in their local population to ensure that it is appropriate and whether there needs to be adaptation to the local population.
- Maternity providers should ensure that they monitor the number of fetuses considered <3rd centile to ensure that their growth pathway and growth chart is appropriate. *[Evidence level 4]*

7.2.2 | Other ultrasound measurements

There is some contradictory evidence for whether the precision of EFW can be improved by 3D ultrasound volumetry.[233-235] Fractional limb volume combined with 2D biometry has been shown to improve the precision of EFW and serve as an index of nutritional status.[236-237] Evidence suggests that EFW using magnetic resonance imaging (MRI) may be more accurate than ultrasound in the prediction of both SGA and LGA newborns but needs more research to overcome poor interobserver agreement.[238,239] *[Evidence level 2–]*

7.3 | High risk

7.3.1 | Uterine artery Doppler waveform

Recommendation	Evidence quality	Strength	Rationale for the recommendation
In high-risk populations uterine artery Doppler should be carried out at the time of the routine anomaly scan to determine when ultrasound surveillance of fetal growth should commence. Subsequently repeating uterine artery Doppler is of limited value in this situation.	**2++**	**B**	In high-risk populations uterine artery Doppler at 20^{+0}–24^{+6} weeks of pregnancy has a moderate predictive value for early onset SGA. In women with an abnormal uterine artery Doppler at 20^{+0}–24^{+6} weeks of pregnancy, subsequent normalisation of flow velocity indices is still associated with an increased risk of an SGA newborn.
Woman who are at a high risk with a normal uterine artery Doppler midtrimester and normal fetal biometry serial scanning for fetal biometry can commence at 32 weeks. Women with an abnormal uterine artery Doppler can commence at 24^{+0}–28^{+6} weeks and should be determined individually.	**2++**	**B**	For women with a normal uterine artery Doppler PI (mean ≤ 95th centile) the risk of these disorders is low and thus serial scanning for fetal biometry can be commenced in the third trimester (from 32 weeks).

FGR, particularly when severe (birthweight below the 3rd centile) or necessitating birth before 36 weeks of gestation, is characterised by lack of adequate trophoblast invasion of the myometrial uterine spiral arteries and reduced uteroplacental blood flow resulting in persistent notching or abnormal flow velocity ratios.[240] However, reduced endovascular trophoblast invasion of decidual spiral arteries has been associated with the same waveform abnormalities as early as 10–14 weeks of pregnancy.[241] *[Evidence level 2+]*

Uterine artery Doppler has been incorporated into first trimester screening algorithms and combined with maternal risk factors/characteristics and biomarkers to predict adverse pregnancy outcomes related to SGA births.[242] However, studies where aspirin is administered to test positive women while demonstrating a reduction in preterm pre-eclampsia did not demonstrate any effect on birthweight. This observation highlights the fact that much of the benefit of uterine artery Doppler risk assessment for FGR is through identifying women at risk for early-onset pre-eclampsia.[242] *[Evidence level 2+]*

In women with a low risk/who were unselected, uterine artery Doppler has insufficient predictive ability as a test,[243] in either the first or second trimester, to be clinically useful as shown in RCTs and large cohort studies.[244,245] *[Evidence level 1+]*

Using uterine artery Doppler alongside maternal factors and fetal biometry at a midtrimester scan (19^{+0}–24^{+6} weeks) has been shown to be able to detect 89% of very preterm SGA below the 5th centile (10% false positive rate before 32 weeks) with 77% detected with uterine artery Doppler alone.[246-247] Thus, although the predictive value of abnormal uterine Doppler is limited, it can be used in the second trimester (18^{+0}–24^{+6} weeks alongside the routine fetal anomaly scan) to further determine the risk of placental dysfunction and therefore risk of hypertensive disorders or early onset FGR for women at high risk, including those with abnormal serum analytes.[248] While there are no effective interventions to reduce this risk, the uterine artery Doppler can help determine further growth surveillance pathways.[249] For women with a normal uterine artery Doppler PI (mean 95th centile or below) the risk of these disorders is low and thus serial scanning for fetal biometry can be commenced in the third trimester (from 32 weeks). Women with a poor obstetric history or the presence of a significant background risk may benefit from a bespoke scan schedule and the evidence presented here forms the basis of the minimal recommended standard.[250] *[Evidence level 2++]*

Abnormal uterine artery Doppler may normalise later in the second trimester, while normalisation is associated with improved outcomes compared with women with persistently abnormal waveforms, there is still an increased risk in those women in whom there is normalisation.[251-253] Thus at present the evidence suggests that repeating uterine artery Doppler later in the second trimester appears to be of limited value. *[Evidence level 2–]*

The mean uterine artery PI is recommended as the index of measurement.[254] The assessment of uterine artery notching is not recommended as it is a qualitative assessment, it is not uncommon in the first trimester of pregnancy (43% of cases) and notching in the second trimester has similar sensitivity to increased PI but with a higher screen positive rate.[243,255,256] It should be noted that there are reference ranges available for uterine artery Doppler PI throughout pregnancy and thus while offering alongside the fetal anomaly scan is appropriate (for resource use and convenience), the measurement may be performed at other times during pregnancy.[7] *[Evidence level 2+]*

Third trimester uterine artery Doppler is not an effective risk assessment tool in unselected pregnancies,[257] but has been used to help identify where cases of FGR are because of placental dysfunction when diagnosed later in pregnancy, and is moderately useful in predicting adverse outcome in pregnancies with suspected SGA in the third trimester but not as a standalone test.[258] *[Evidence level 2++]*

For women at high risk with a normal uterine artery Doppler, serial scans are recommended to commence at 32 weeks and for women with an abnormal uterine artery

Doppler these can commence at 24^{+0}–28^{+6} weeks and should be determined individually. Scans should be undertaken every 2–4 weeks with the scan interval confirmed following the first assessment for fetal growth. For women in the high risk group, in whom uterine artery Doppler assessment has not been undertaken, serial scans should be commenced from 28 weeks.

7.3.2 | Ultrasound biometry

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Fetal size alone is not sufficient to identify FGR, unless AC or EFW is below the 3rd centile.	**2–**	**C**	Many fetuses with growth below the 10th centile are healthy and constitutionally small.
Fetal growth disorders are suspected when there is suboptimal, reduced growth velocity and static growth. FGR can be diagnosed when there is a drop of more than 50 centiles in EFW or AC. This should prompt a full review.	**4**	**GPP**	When assessing fetal growth, a pattern of slowing growth velocity (i.e. a downward trend in the centiles) indicates an increased risk of morbidity and stillbirth and should necessitate review. This review should include assessment of all fetal biometry measurements since the anomaly scan to identify potentially erroneous single measurements and also the presence or absence of other risk factors for FGR. Particular attention should be paid to a downward trend in AC growth velocity. A further assessment of maternal and fetal wellbeing and re-evaluation of fetal monitoring plans should be undertaken.
Doppler velocimetry of uteroplacental circulation may be used to help distinguish between SGA and FGR in the third trimester.	**4**	**GPP**	For fetal growth disorders diagnosed in the third trimester, uterine artery Dopplers can be used to assess for placental dysfunction and are moderately useful in predicting adverse outcome in pregnancies with suspected SGA in the third trimester but not as a standalone test.
When a fetal growth disorder is diagnosed an assessment of fetal wellbeing should be made to include a discussion regarding fetal movements and a computerised CTG (cCTG) where there are concerns. A maternal assessment should be made to include a blood pressure and proteinuria assessment.	**4**	**GPP**	Management of a fetal growth disorder needs to be individualised, but it is important to make an initial assessment of fetal wellbeing and maternal wellbeing, owing to association with hypertensive disorders of pregnancy

It is intuitive to consider that assessment of growth would improve the diagnosis of FGR and of those at greater risk of adverse outcome and there is some evidence that this is true in high risk women, particularly in the SGA group.[187,259,260] However, the optimal approach to interpret the information from serial measurements of the same fetus remains unclear and is hampered by the non-linear growth across pregnancy. Several approaches are available including fetal growth velocity (change in fetal size between two time points), conditional centiles (calculation of EFW centile expected at time point is determined by previous weight estimation of same fetus earlier in pregnancy), projection based methods (models to predict EFW at a later point in gestation are based on two or more observations of EFW combining size and velocity information) and defining abnormal growth velocity by limiting the false positive rate.[261-264] A study using customised centiles developed and tested a model for defining normal limits of growth velocity specific to the fetal weight measurement. This demonstrated that cut-offs for normal growth rate varied with length of measurement interval at a fixed positive rate of 10%. Slow growth was associated with stillbirth and neonatal death and particularly between the last highest when slow growth and SGA were present.[264] These data have been incorporated into a fetal growth calculator when using customised charts.[265] All of these approaches require information on the mean and standard deviations of fetal growth at different gestations and have methodological limitations including the spacing of the USS and inherent error in measurements. Further research is required to quantify the predictive accuracy of different methods, to determine the optimal timing of the first ultrasound, the optimal interval between scans and the cost-effectiveness of a screening programme with appropriate neonatal outcomes. *[Evidence level 2–]*

Thus, the following are advised are based on the fact that fetal size alone is not sufficient to identify FGR, unless AC or EFW is below the 3rd centile:

- When assessing fetal growth, a pattern of slowing growth velocity (i.e. a downward trend in the centile) indicates an increased risk of morbidity and stillbirth and should

necessitate review. This review should include assessment of all fetal biometry measurements since the anomaly scan to identify potentially erroneous single measurements and also the presence or absence of other risk factors for FGR. Particular attention should be paid to a downward trend in AC growth velocity.
- When a fetal growth disorder is suspected or diagnosed an assessment of fetal wellbeing should be made to include a discussion regarding fetal movements and a cCTG where there are concerns. A maternal assessment should be made to include a blood pressure and proteinuria assessment.
- For fetal growth disorders diagnosed in the third trimester, uterine artery Dopplers can be used to assess for placental dysfunction and are moderately useful in predicting adverse outcome in pregnancies with suspected SGA in the third trimester but not as a standalone test.[258]

Further guidance regarding management of SGA and FGR is given in section 10.

7.4 | Other methods

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Clinical tests that measure placental growth factor (PlGF), soluble fms-like tyrosine kinase-1 (s-flt1) or the ratio between the two are now clinically available and recommended for the diagnosis of pre-eclampsia. Although SGA/FGR are strongly associated with pre-eclampsia and placental dysfunction, the use of PlGF/s-flt1 testing for the prediction and diagnosis in non-hypertensive women is not routinely recommended.	2++	B	In the absence of features of maternal hypertensive disease there are limited data to support performing angiogenic marker testing unless there is diagnostic uncertainty regarding the presence or absence of placental dysfunction as a cause of FGR (e.g. in circumstances where fetal growth is suggestive of genetically small fetuses in conjunction with uterine artery Doppler features of placental dysfunction).

7.4.1 | Placental morphology and biometry

FGR that results from placental dysfunction is known to be associated with placentas that have smaller diameters and increased depth,[266] lower volumes[267] and irregular shapes.[268] As a result of these findings there have been multiple studies examining whether antenatal assessment of placental morphometry using either ultrasound or MRI can predict early and late FGR.[91,266,267,269,270] *[Evidence level 2+]*

In low risk populations the addition of placental biometry has not been shown to be effective at predicting SGA or FGR as there are relatively weak associations between placental size and birthweight.[271] In high risk women with abnormal uterine artery doppler PI between 20 and 24 weeks, abnormal placental morphometry is associated with an increased risk of birth before 32 weeks (OR 4.7, CI 1.4–15.1).[272] However, concerns have been raised around the reliability and reproducibility of 2D ultrasound techniques,[273] and it remains unclear what role the measurement of 2D placental biometry should have in current clinical models used to predict FGR. *[Evidence level 2–]*

MRI can overcome some of the potential accuracy difficulties in assessing placental volume/shape with ultrasound[274] and can provide placental functional data that further delineate FGR from non-FGR babies and SGA pregnancies,[275] but at present the high cost and time required for each examination limits its clinical applicability outside of research studies. *[Evidence level 2–]*

7.4.2 | Biomarkers

There are several biomarkers that have been proposed as adjuncts to serial ultrasound measurements to identify women at high risk of SGA and stillbirth. Addition of these biomarkers within the serial ultrasound screening pathway and the use of the biomarkers to delineate who needs serial scans has been evaluated in both high and low risk women. There is significant interest in placental function biomarkers to identify women at risk of SGA, pre-eclampsia and stillbirth. Potential biomarkers include human placental lactogen (hPL), oestriol, Placental growth factor (PIGF), urinary oestriol and soluble fms-like tyrosine kinase-1 (s-flt1). A Cochrane review demonstrated that USS had the best diagnostic test accuracy for SGA than biomarkers alone to identify pregnancies that will end in the birth of an SGA neonate. However, biomarkers show promise in the ability to improve diagnostic test accuracy of ultrasound for SGA and stillbirth.[276] *[Evidence 2++]*

PlGF is a member of the vascular endothelial growth factor family produced in pregnancy by the placenta; in the circulation it binds to s-flt1.[277] The observation that women with pre-eclampsia have high circulating levels of s-flt1 has been extensively investigated and it is recognised that low levels of PlGF and/or high levels of s-flt1 are strongly associated with placental dysfunction and pre-eclampsia.[100,278,279] Clinical tests that measure PlGF, s-flt1 or the ratio between the two are now clinically available and recommended for the diagnosis of pre-eclampsia.[279] Although SGA/FGR are strongly associated with pre-eclampsia and placental dysfunction, the use of PlGF/s-flt1 testing for the prediction and diagnosis of FGR in non-hypertensive women remains uncertain. *[Evidence level 2++]*

Meta-analysis of first trimester measurement in women destined to give birth to SGA babies shows low sensitivity (27%, CI 20–36) and specificity (90%, CI 83–94).[101]

Measurement of PlGF/s-flt1 in the second trimester is similarly hampered by low sensitivity when distant from disease.[280] However, if measured near disease in the third trimester, PlGF/s-flt1 levels may be more clinically useful particularly when used in combination with EFW or uterine artery Doppler or other indicators of FGR.[281,282] A study of 9360 women who had PlGF combined with EFW measurement at 30–34 weeks demonstrated 85% sensitivity for SGA and 92% sensitivity for FGR (at a fixed 10% false positive rate) for infants born within 5 weeks of the test.[283] More recently, a large study in a low risk population of 3737 women demonstrated that the combination of EFW below the 10th centile with PlGF/s-flt1 resulted in dramatically improved specificity in SGA infant with complicating features suggestive of FGR compared with EFW below the 10th centile alone (97.8%, CI 97.3–98.3 versus 86.9%, CI 85.8–88.0), but at the expense of sensitivity.[284] It may therefore be that PlGF/s-flt1 testing enables the antenatal identification of early and late onset FGR within SGA and even within non-SGA cohorts. The addition of placental function test in 19 209 singleton pregnancies between 35 and 36^{+6} weeks demonstrated only marginal improvement in the prediction of SGA above the standard use of USS EFW, Dopplers and maternal factors.[285] A study investigating the role of placental biomarkers in the second trimester demonstrated that the combination of maternal risk factors, EFW, uterine artery PI and PlGF provided effective second trimester prediction of SGA. Serum PlGF was found to be useful for predicting a SGA neonate with birthweight <3rd centile born <30 weeks after an inclusive assessment by maternal risk factors and biophysical markers.[286] However, this requires confirmation with prospective RCTs and cost-effectiveness evaluations. *[Evidence level 2++]*

8 | WHICH PREGNANCIES COMPLICATED BY FETAL GROWTH DISORDERS SHOULD BE FURTHER INVESTIGATED?

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Offer referral to fetal medicine if EFW is below the 3rd centile or below the 10th centile with abnormal uterine artery Doppler at the midtrimester anomaly scan.	**4**	**GPP**	To assess the risk of aneuploidy a detailed anatomical survey and assessment for uteroplacental insufficiency is carried out.
Invasive diagnostic testing should be offered in severely SGA fetuses with structural anomalies and considered in non-anomalous fetuses detected before 23 weeks of gestation, especially if uterine artery Doppler is normal. Analysis should include a microarray to detect microdeletions and microinsertions. Prenatal exome sequencing should only be considered in cases with multisystem abnormalities or isolated short long bones.	**2++**	**B**	Invasive testing for aneuploidy would generally be reserved for those with other structural anomalies following a detailed anatomical survey.
Serological screening for congenital cytomegalovirus (CMV) and toxoplasmosis infection should be offered in severe SGA.	**2–**	**B**	Fetal infections are responsible for up to 5% of SGA fetuses.
Testing for malaria and Zika should be considered in high risk populations.	**4**	**GPP**	Fetal infections are responsible for up to 5% of SGA fetuses, of which the most common causes are CMV and toxoplasmosis. For those that have had recent travel to relevant areas Zika and malaria should be considered.

Historically, identification of severe SGA (either EFW below the 3rd or 5th centile) was used as a marker for aneuploidy and studies which predated widespread population based screening for aneuploidy reported aneuploidy rates of up to 20%.[287-289] These data are less applicable in modern practice, because of the widespread use of population-based screening for aneuploidy. However, invasive testing should be considered in the context of severe SGA because of the possibility of other chromosomal abnormalities which can be detected using DNA microarrays. A systematic review and meta-analysis demonstrated that

in fetuses undergoing invasive testing for FGR with no other structural anomalies there was a 4% incremental yield of chromosomal microarray analysis (CMA) over karyotyping and a 10% incremental yield in FGR with associated fetal malformations.[290] *[Evidence level 2++]*

Prenatal exome sequencing has limited incremental yield over standard karyotyping and microarray in fetuses with isolated FGR. *[Evidence 2++]*

A large population-based study from Israel reported a 3% detection rate of pathological abnormalities using microarray in the context of FGR, and only a single case out of 13 was an aneuploidy, underlining the transformative effect of population screening for aneuploidy on this association.[291] Therefore, when invasive testing is undertaken in the context of SGA fetal biometry, analysis of specimens should include CMA for the detection of microdeletions and microinsertions. In early onset FGR CMA demonstrated an incremental yield over karyotyping of 4.8% in isolated FGR, 10% in FGR with non-structural anomalies and 10.5% in FGR with structural anomalies.[292] *[Evidence level 2+]*

A retrospective cohort study reported the associations with a below the 5th centile FL at the time of a 17–22-week anomaly scan (with or without other features).[293] The positive likelihood ratio for trisomy 21 was 8.8, for 13/18 it was 6.5 and for other unbalanced structural chromosomal abnormalities it was 17.4, with an absolute risk of 1 in 339. There was an approximate four-fold subsequent risk of both PTB and birth of an SGA infant. This has been confirmed in a systematic review, which demonstrated that an isolated short FL is significantly associated with SGA (OR 4.04, 95% CI 3.63–4.50) and PTB (OR 3.09, 95% CI 1.57–6.08).[294] *[Evidence level 2++]*

A case series of 158 fetuses with an AC of the 5th centile or below during a detailed scan at 18–24 weeks (isolated feature) demonstrated two cases of trisomy 21 and a single case of an unbalanced structural chromosomal abnormality (detected by SNP array).[295] *[Evidence level 2–]*

Hence, invasive diagnostic testing (amniocentesis, fetal blood sampling or placental biopsy/chorionic villus sampling) should be offered in severely SGA fetuses with structural anomalies and considered in non-anomalous fetuses detected before 23 weeks of gestation, especially if uterine artery Doppler is normal.

Follow-up scans should also be arranged given the association with subsequent birth of an SGA infant and the timing of commencement and frequency individualised following the additional investigations.

Fetal infections are responsible for up to 5% of SGA fetuses.[296] The most common pathogens are reported to be cytomegalovirus (CMV), toxoplasmosis, malaria and syphilis, although a multicentre study found no association between congenital toxoplasmosis and incidence of a SGA infant.[296,297] A full maternal TORCH screen is unnecessary and testing should be based on history and presentation.[298] Malaria is a significant cause of PTB and LBW worldwide and it should be considered in those from, or who have travelled in, endemic areas.[299] In congenital Zika virus infection, FGR is seen in 10% of affected pregnancies, and a femur-sparing pattern of FGR is commonly seen.[300] *[Evidence level 2–]*

9 | WHAT INTERVENTIONS SHOULD BE CONSIDERED WHEN A FETAL GROWTH DISORDER HAS BEEN DIAGNOSED?

Recommendation	Evidence quality	Strength	Rationale for the recommendation
LMWH should not be prescribed to women in whom fetal growth disorders have been diagnosed.	**1++**	**A**	Prospective trial evidence has failed to demonstrate a reduction in FGR in any at- risk group including those with heritable clotting disposition.
Women should not be prescribed phosphodiesterase 5 (PDE5) inhibitors to treat FGR outside of RCTs.	**1+**	**A**	There is no evidence in human studies, with a low risk of bias, of benefit from PDE5 inhibitors prescription.

There are no proven interventions in SGA and FGR other than birth of the baby. Experimental treatments under investigation in early phase clinical trials/studies include maternal VEGF (vascular endothelial growth factor) gene therapy, melatonin and for pre-eclampsia with the potential to impact on fetal growth; statins, nitric oxide donors, proton pump inhibitors and N-acetycysteine. Preclinical investigations are underway in nanoparticles, microRNAs, hydrogen sulphide and creatinine.[301]

PDE5 inhibitors have been tested in women with early onset placental disease, including FGR pregnancies to determine if they can improve outcomes. Most studies have focused on sildenafil (Viagra) which was shown to improve Doppler parameters in animal models and suggested in case series to be effective in increasing human fetal growth velocity.[302,303] A small RCT of sildenafil (50 mg three times daily [TDS]) in women with early onset pre-eclampsia reported a prolongation of pregnancy by 4 days, although only 60% of participants had recorded SGA and there was no effect of treatment on birthweight.[304] However, prospective RCTs focusing on FGR have failed to show any benefit. Results from the international STRIDER collaboration did not show any prolongation in pregnancy or improvement in outcome from sildenafil (25 mg TDS) treatment.[305,306] The Dutch arm of STRIDER study was stopped early because of safety concerns, although meta-analysis of outcomes from the three studies has failed to show a conclusively detrimental effect.[307] Tadalafil, a longer acting PDE5 inhibitor has also been tested in case reports with reported improved neonatal outcome and no adverse effects, but no RCT evidence is currently available.[308,309] Therefore although some studies have suggested benefit using PDE5 inhibitors to improve outcomes in

FGR pregnancies, the negative results from STRIDER do not support the use of these drugs outside of clinical trials for the treatment or prevention of FGR. *[Evidence level 1+]*

RCT evidence does not support the use of LMWH as an effective treatment to prevent SGA or FGR, even in the presence of heritable thrombophilia, and should only be used in women at risk of thromboembolic disease.[158,159,161,162] There is insufficient evidence that administration of LMWH to pregnancies with FGR prolongs or improves pregnancy outcome.[310] *[Evidence level 1++]*

10 | WHAT IS THE OPTIMAL METHOD AND FREQUENCY OF FETAL SURVEILLANCE WHEN A FETAL GROWTH DISORDER HAS BEEN DIAGNOSED AND WHEN SHOULD BIRTH OCCUR?

10.1 | SGA fetuses

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Ultrasound biometry should be carried out every 2 weeks in fetuses identified to be SGA.	**2–**	**C**	More frequent measurements increase the false positive rate for diagnosing FGR.
Umbilical artery Doppler is the primary surveillance tool and should be undertaken at the point of diagnosis of SGA and during follow-up as a minimum every 2 weeks.	**2+**	**B**	Use of umbilical artery Doppler in high risk pregnancy has been shown to reduce perinatal morbidity and mortality, reduce antenatal admissions and inductions of labour.
In fetuses with an EFW between the 3rd and 10th centile, other features must be present for birth to be recommended prior to 39 weeks: either maternal (maternal medical conditions or concerns regarding fetal movements) or fetal compromise (a diagnosis of FGR based on Doppler assessment or a concern on CTG).	**2–**	**C**	Timing of birth should be optimised to ensure balance of risks. The risks to be considered include those for person giving birth and baby (fetal and neonatal).
For fetuses with an EFW or AC less than the 10th centile where FGR has been excluded, birth or the initiation of IOL should be considered at 39^{+0} weeks after discussion with the woman and her partner/family/support network. Birth should occur by 39^{+6} weeks.	**1+**	**B**	Timing of birth should be optimised to ensure balance of risks. The risks to be considered include those for person giving birth and baby (fetal and neonatal).
For women who are recommended for IOL or planned birth after 39^{+0} weeks for SGA but who wish to continue the pregnancy, counselling must include a discussion regarding evidence that there is no additional risk for the baby or for the woman from planned birth/induction at this gestation when compared with expectant care. An individual plan for the continuation of the pregnancy must be made.	**4**	**GPP**	There is no evidence to determine how fetuses with SGA/FGR should be monitored if pregnancy continues in this context.
After 37^{+0} weeks, an abnormal middle cerebral artery (MCA), cerebroplacental ratio (CPR) or umbilico-cerebral ratio (UCR) can be used to guide timing of birth. A normal MCA, CPR or UCR does not provide reassurance that the fetus is not compromised and in all cases birth is recommended prior to 39^{+6} weeks.	**2+**	**C**	In the term SGA fetus with normal umbilical artery Doppler, an abnormal MCA Doppler (PI<5th centile) has moderate predictive value for acidosis at birth and should be used to time delivery.
IOL is not contraindicated in the SGA fetus.	**2–**	**C**	Compared with non-SGA babies, SGA fetuses are at greater risk of fetal heart rate abnormalities in labour and thus unplanned (emergency) caesarean birth.

SGA fetuses (see section 2) are those whose AC or EFW is below the 10th centile but with normal growth velocity and do not exhibit Doppler changes, where there are normal fetal movements and normal amniotic fluid. For these pregnancies where there are no additional maternal risk factors (for example maternal hypertension) ultrasound surveillance every 2 weeks is appropriate.[311] Some cases of SGA progress to FGR depending on gestation at diagnosis, this risk being greater with SGA detected early on. *[Evidence level 2–]*

Umbilical artery Doppler is the primary surveillance tool. Its use in high risk pregnancy has been shown to reduce perinatal morbidity and mortality, reduce antenatal admissions and inductions of labour.[312] *[Evidence level 2+]*

Amniotic fluid can be assessed by the single deepest vertical pocket (SDVP) or amniotic fluid index (AFI) methods; although both correlate poorly with actual amniotic fluid volume.[313] A Cochrane systematic review compared the two methods and concluded that there was no evidence that one method was superior in the prevention of adverse perinatal outcomes. However, compared with a SDVP less than 2 cm, when an AFI of 5 cm or less was used more cases of oligohydramnios were diagnosed and more women had IOL without an improvement in perinatal outcome.[314] In a prospective study of pregnancies with FGR and oligohydramnios monitored for 8 weeks after the initial diagnosis of oligohydramnios, mean EFW centile did not change significantly (remaining on 3rd centile in SGA fetuses) suggesting that oligohydramnios in this context is not associated with an increased risk of progression.[315] Systematic reviews of observational and RCT data have demonstrated that while there is an association with oligohydramnios and SGA and adverse pregnancy outcome, it is not significant as a predictive test and in RCTs was only shown to be associated with an abnormal 5 minute Apgar but not acidosis or perinatal death in SGA.[316-317] Thus while ultrasound assessment of amniotic fluid volume can be used as a form of monitoring to inform overall assessment of fetal wellbeing, it should not be used to determine management in isolation. *[Evidence level 2++]*

For SGA fetuses the recommendations for birth are based on the findings of the Disproportionate Growth Intervention Trial at Term Study (DIGITAT) and consideration of data related to morbidity related to "early term" (37–38 week) birth.[318] In DIGITAT 650 women with suspected growth disorder (defined as fetal AC below the 10th centile, EFW below the 10th centile, flattening of the growth curve in the third trimester [as judged by a clinician], or the presence of all three factors) above 36 weeks were randomised to induction or expectant management with twice weekly surveillance. There was no difference between the groups in severe neonatal morbidity or in caesarean birth but there was an increase in neonatal unit admission with induction before 38 weeks. The trial was not powered to assess perinatal mortality. Longer term childhood adverse outcomes were related to severe FGR (birthweight less than 2.3 centile).[319] A health economics analysis demonstrated lower costs with induction at 38 weeks compared with earlier.[320] It is noted that in the expectant management group more babies were likely to be born with a birthweight less than 3rd centile, reflecting the difficulty in distinguishing between FGR and SGA at term, and these were the babies at greatest risk of adverse neonatal outcome. *[Evidence level 1+]*

A Cochrane review of the management of 'compromised babies' at term showed no difference in perinatal or long-term outcome with a policy of early birth versus expectant management.[321] Only three trials were included: two included small babies, both part of the DIGITAT study.[318,322] The third included babies with reduced amniotic fluid.[323] *[Evidence level 1+]*

Stock et al. compared the risk of neonatal unit admission with IOL at each given week (compared with the previous week) and demonstrated that at 37 weeks the risk was aOR 2.01 (95% CI 1.80–2.25) and at 38 weeks aOR 1.53 (95% CI 1.41–1.67).[15] While, there was a decreased odds of perinatal mortality with planned induction (37 weeks aOR 0.05 [0.03–0.68] and 38 weeks 0.23 [0.09–0.58]) 10 inductions would lead to one additional baby being admitted for neonatal care and it would require more than 700 inductions to prevent each perinatal death.[15] There is also an association with early term birth and risk of subsequent special educational needs (SEN). After adjusting for maternal and obstetric characteristics, and expressed relative to birth at 40 weeks, the risk of SEN was increased by 36% at 37 weeks, by 19% at 38 weeks and by 9% at 39 weeks.[14] The ARRIVE trial randomised low risk nulliparous women to IOL at 39 weeks or expectant management and while it did not result in a significantly lower frequency of a composite perinatal outcome, there was a lower frequency of caesarean birth in the induction group.[324] *[Evidence level 2+]*

Thus, IOL between 37^{+0} and 38^{+6} weeks must only be considered as an intervention for fetuses at significantly increased risk of perinatal mortality (maternal or fetal compromise). For all fetuses with an EFW or AC less than the 10th centile where FGR has been excluded, birth or the initiation of IOL should be considered at 39^{+0} weeks after discussion with the woman and her partner/family/support network. Birth should occur by 39^{+6} weeks.[325] There are studies that have reported a protocol for management of "low risk cases" of SGA with expectant management up to 41 weeks and demonstrated a reduced adverse neonatal outcome in this group.[326,327] Larger numbers and RCT data are needed to assess any impact on perinatal mortality and thus for women who do not wish induction of labour, counselling must include a discussion regarding evidence that there is no additional risk for the baby or for the woman from planned birth/induction at this gestation when compared with expectant care. An individual plan for the continuation of the pregnancy must be made. *[Evidence level 4]*

10.2 | FGR fetuses

FGR fetuses defined as those whose AC or EFW below the 10^{th} centile with Doppler changes (as described in the

definitions of FGR) or AC/EFW less than the 3rd centile, or growth crossing 50 centiles are a higher risk category and, in contrast to SGA, FGR is more frequently associated with maternal hypertension (occurring in 70% of early onset [before 32 weeks] FGR cases).[328] While early and late FGR are in reality a continuum, there are important differences with respect to the sequencing of Doppler, CTG and amniotic fluid changes and therefore it is important to differentiate between them with respect to surveillance for fetal wellbeing.[329,330] Most experts differentiate early from late FGR at 32–34 weeks of gestation. Prior to 32 weeks the care for FGR is informed by RCT evidence.[328] After this time the evidence is inconclusive. The high variability in Doppler reference ranges and indices used has a major clinical impact on prenatal diagnosis, monitoring, decision making around timing of birth, reproducibility and comparison of findings between research studies, efficacy of clinical policies and protocols, and many other aspects.[331] A study by Ruiz-Martinez exploring the variation in the proposed cut offs demonstrated significant variability. The MCA-PI showed the greatest variability, with differences of up to 51% in the 5th centile value at term. Additionally, variability in the 95th centile of UA-PI and the 5th centile of CPR at each gestational week ranged from 21% to 41% and 15% to 33%, respectively, when these charts were used in simulation analysis; these differences in Doppler cut-off values were associated with large variation in the clinical management of SGA fetuses.[332] *[Evidence 2++]*

Maternity providers should ensure that there is consistency of the Doppler charts used across systems used within different departments (e.g., radiology, fetal medicine). *[Evidence level 4]*

10.2.1 | Early FGR

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Pregnancies with early FGR should be monitored and managed with input from tertiary level units with the highest level neonatal care. Care should be multidisciplinary by neonatology and obstetricians with fetal medicine expertise, particularly when extremely preterm (before 28 weeks).	**4**	**GPP**	When considering birth of a preterm fetus with FGR, particularly when very preterm before 28 weeks and severe, counselling of the parents by an experienced obstetrician and neonatologist should occur. Decisions for birth should consider predictors of survival and morbidity (i.e. weight, gestation).
Biometry in FGR should be repeated every 2 weeks.	**1–**	**B**	More frequent measurements increase the false-positive rate for diagnosing FGR.
In early FGR, the frequency of assessment of fetal wellbeing will be based on the severity of FGR and UA Doppler assessment with a minimum of weekly, when there are no other concerns, and 2–3 times weekly when there are UA abnormalities. Assessment of fetal wellbeing can include multiple modalities but must include cCTG and/or ductus venosus.	**1–**	**B**	The frequency of monitoring in early FGR has not been subjected to any prospective randomised studies. Nevertheless, analysis of TRUFFLE and other early FGR cohorts suggests that sudden deterioration can occur.
Maternity providers should ensure that there is consistency across departments in the reference charts used for fetal Doppler assessment.	**4**	**GPP**	High variability in Doppler reference ranges and indices used has a major clinical impact on prenatal diagnosis, monitoring, decision making around timing of birth and reproducibility.
cCTG analysis using the Dawes-Redman CTG system is recommended with the short-term variation (STV) being the key parameter.	**2–**	**C**	A large prospective observational study of early FGR compared monitoring parameters and found that the ductus venosus and cCTG changes were most discriminatory in relation to the timing of birth. Of all parameters measured, the most marked changes immediately prior to birth were of raised ductus venosus pulsatility index for veins (PIV) and low cCTG STV.
MCA CPR/UCR can inform monitoring strategy and frequency. MCA CPR/UCR should not be used to determine birth decisions prior to 37^{+0} weeks.	**4**	**GPP**	A weak relationship between cerebral redistribution and adverse perinatal and 2 year outcome was found with MCA PI and, for the latter, UCR but not CPR.

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Birth should be based on fetal wellbeing assessment or maternal indication (e.g. severe pre-eclampsia), as follows:			A comparative analysis of the GRIT and TRUFFLE studies suggested that long-term (2 year) outcomes were best in those women who were cared for based on cCTG and ductus venosus Doppler changes and thus timing of birth should be based on these parameters prior to 32 weeks. Consensus management of late preterm FGR following TRUFFLE suggests birth if the umbilical artery EDF is reversed at 32 weeks and absent at 34 weeks. Birth can be considered from 30 weeks and 32 weeks respectively and, if continuing to the later gestation, monitoring should be carried out with DV and cCTG.
• **Owing to a lack of RCT evidence care of fetuses before 26 weeks needs to be personalised.**	**4**	**GPP**	

• **From 26^{+0} weeks, birth if any of the following is present:**
  • **Spontaneous repeated persistent unprovoked fetal heart rate decelerations;**
  • **26^{+0} to 28^{+6} weeks: birth if ductus venosus a-wave is at or below baseline or STV is below 2.6 ms;**
  • **29^{+0} to 31^{+6} weeks: birth if ductus venosus a-wave is at or below baseline or STV is below 3.0 ms;**
  • **32^{+0} to 33^{+6} weeks (consider after 30^{+0} weeks): birth if UA-EDF is reversed or STV is below 3.5 ms;**
  • **From 34^{+0} weeks (consider after 32^{+0} weeks): birth if UA-EDF is absent or STV is below 4.5 ms.**
	1+	**B**	

Abnormal umbilical vein Doppler with pulsations may be seen in early FGR and should prompt assessment of the ductus venosus waveform.	**4**	**GPP**	
In early FGR a woman's subjective assessment of reduced fetal movements or reduced or absent movements on ultrasound should prompt an assessment with cCTG.	**4**	**GPP**	

Pregnancies with early FGR should be monitored and managed with input from tertiary level units with the highest level neonatal care. Care should be multidisciplinary by neonatology and obstetricians with fetal medicine expertise, particularly when very preterm (before 28 weeks). Management of early FGR requires regional network specialist fetal medicine input to determine the most appropriate monitoring for fetal wellbeing and timing of birth where fetal compromise is demonstrated needs sub-speciality input.[6] *[Evidence level 4]*

A large prospective observational study of early FGR compared monitoring parameters and found that the ductus venosus and cCTG changes were most discriminatory in relation to the timing of birth.[333] Of all parameters measured, the most marked changes immediately prior to birth were of raised ductus venosus pulsatility index for veins (PIV) and low cCTG short-term variability (STV); these were of a greater magnitude than changes in the umbilical and MCA Dopplers, and amniotic fluid. In a later study relating these findings to adverse outcome, only ductus venosus contributed in a multivariable model.[334] *[Evidence level 2+]*

Assessment of fetal heart rate variability is an important parameter in assessment of fetal wellbeing. However, visual inspection of conventional CTG is subjective and associated with low intra- and interobserver reproducibility. The fetal heart rate STV is a biophysical parameter obtained by cCTG. It reflects autonomic nervous system function and in the context of fetuses with FGR can reflect changes in autonomic activity induced by hypoxia; this has been validated with invasive testing demonstrating fetal hypoxaemia and acidaemia.[335] *[Evidence level 3]*

The optimum management of early FGR has largely been defined by the TRUFFLE (trial of umbilical and fetal flow in Europe) study.[328,336] In this study of growth restriction diagnosed between 26 and 32 weeks, abnormal umbilical artery Doppler defined entry to the study (to confirm diagnosis of FGR), but did not play a part in management until after 32 weeks. Women were randomised to one of three groups with triggers for birth: a) reduced short-term variation (STV) using gestation specific thresholds; b) early changes in the DV waveform (DV-PI >95th centile or CTG-STV below a "safety net" and c) late changes in the DV waveform (DV 'a' wave at or below baseline or CTG-STV safety net). There were statistically significantly more neurologically intact 2-year-old babies in the group randomised to late DV changes (or owing to the CTG-STV safety net) compared with those randomised to CTG: the proportion without neurodevelopmental impairment at 2 years was 85% in the CTG-STV group, 91% in the early-DV group and 95% in the late-DV group. This improvement in neurodevelopmental outcome was accompanied by a non-significant increase in perinatal and infant mortality. The overall perinatal death rate was 8% and cerebral palsy rate 1%.[328] The earlier GRIT randomised controlled study did not give a clear answer on whether compromised babies are best born immediately or managed expectantly.[337]

A comparative analysis of the two studies suggested that long-term (2 year) outcomes were best in those women who were cared for based on cCTG and ductus venosus Doppler.[338] A weak relationship between cerebral redistribution and adverse perinatal and 2 year outcome was found with MCA PI and, for the latter, UCR but not CPR.[339] *[Evidence level 1+]*

The frequency of monitoring in early FGR has not been subjected to any prospective randomised studies. Nevertheless, analysis of TRUFFLE and other early FGR cohorts suggests that sudden deterioration can occur.[340] *[Evidence level 1–]*

Umbilical artery Doppler changes are defined as: PI above the 95th centile (borderline), absent end diastolic flow (EDF) (pre-critical), reversed EDF (critical).

Ductus venosus Doppler changes are defined as: raised PIV above the 95th centile (borderline), absent 'a' wave to baseline (pre-critical), or reversed 'a' wave (critical).

Depending on the severity of FGR, repeat USS (umbilical and ductus venosus Doppler) and CTG monitoring is normally undertaken every week where the umbilical Doppler changes are borderline, to alternate daily in the case of early onset FGR with pre-critical umbilical Doppler changes. Where the umbilical Doppler changes are critical, daily cCTG and/or Ductus venosus Doppler are indicated as sudden deterioration of the fetal condition may occur.

Birth should be planned when the Ductus venosus 'a' wave is at (absent) or below baseline (reversed) or there are CTG abnormalities; STV less than 2.6 ms at 26^{+0}–28^{+6} weeks or less than 3.0 ms at 29^{+0}–31^{+6} weeks.

When considering birth of a preterm fetus with FGR, particularly when very preterm before 28 weeks and severe, counselling of the parents by an experienced obstetrician and neonatologist should occur. Decisions for birth should consider predictors of survival and morbidity (i.e. weight and gestation).[341,342] *[Evidence level 4]*

10.2.2 | Late FGR

Recommendation	Evidence quality	Strength	Rationale for the recommendation
In late and term FGR, assessing the ductus venosus waveform is unlikely to be informative as it is very unlikely to show severe abnormalities.	**4**	**GPP**	Ductus venosus has been assessed as a surveillance tool in early onset FGR only.

In pregnancies with late FGR, birth should be based on fetal wellbeing assessments or maternal indication (e.g. severe pre-eclampsia). For fetal assessment, birth should occur if any of the following are present:
• **Spontaneous repeated persistent unprovoked fetal heart rate decelerations.**
• **cCTG STV less than 3.5 ms at 32^{+0} to 33^{+6} weeks and less than 4.5 ms at 34^{+0} weeks or above.**
• **Or abnormal UA Doppler as follows:**
  • **Absent end diastolic flow, considered at 32 weeks and absolute by 34 weeks.**
  • **raised umbilical PI above the 95th centile, 36^{+0} to 36^{+6} weeks.**
	4	**GPP**	In this group, a normal umbilical artery Doppler cannot exclude placental dysfunction and therefore it is important that other methods of surveillance are used.

In pregnancies with FGR, birth should be initiated from 37^{+0} weeks to be completed by 37^{+6} weeks.	**1+**	**A**	Fetuses at term with birthweight below the 3rd centile have the highest risk of stillbirth, therefore these pregnancies should not exceed 37^{+6} weeks of gestation, independent of Doppler findings
Cerebral Doppler: abnormal MCA CPR/ UCR can inform monitoring strategy and frequency but should not be used to determine birth decisions prior to 37 weeks. After 37^{+0} weeks, an abnormal MCA, CPR or UCR can be used to guide timing of birth. A normal MCA, CPR or UCR does not provide reassurance that the fetus is not compromised and in all cases birth is recommended prior to 37^{+6} weeks.	**2++**	**D**	It is likely that an association exists between cerebral redistribution and adverse perinatal outcome, it is not established that birth based on MCA Doppler changes would improve outcome and there is the potential that it might be harmful. Furthermore, it is not clear that cerebral Doppler changes are independently associated with adverse neurodevelopmental outcome.
In late FGR a woman's subjective assessment of reduced fetal movements or absent movements on ultrasound should prompt an assessment with cCTG.	**4**	**GPP**	A reduction or alteration in fetal movements is associated with risk factors such as FGR, SGA and stillbirth.

In this group, a normal umbilical artery Doppler cannot exclude placental dysfunction and therefore it is important that other methods of surveillance are used.[260,342,343] An abnormal umbilical artery Doppler should also prompt further assessment. There has been renewed recent interest in cerebral Doppler changes in FGR.[344-347] While it is likely that an association exists between cerebral redistribution and adverse perinatal outcome, it is not established that birth based on MCA Doppler changes would improve outcome and there is the potential that actually it might be harmful. Furthermore, it is not clear that cerebral Doppler changes are independently associated with adverse neurodevelopmental outcome.[348] Uterine artery Doppler has also been assessed in this group and an abnormal uterine artery Doppler is associated with an increased risk of intrapartum fetal distress, emergency caesarean birth and admission to neonatal intensive care unit.[349-351] *[Evidence level 2++]*

The TRUFFLE2 study is ongoing and aims to address the question of the optimal monitoring and thresholds for birth in late onset FGR. It will investigate the hypothesis that commencement of birth on evidence of cerebral blood flow redistribution reduces a composite of perinatal poor outcome, death, and short-term hypoxia-related morbidity, with no worsening of neurodevelopmental outcome at 2 years.[352]

There is no Cochrane Review on the optimal time of birth in late preterm babies and there has only been one trial of late preterm timed birth. The Growth Restriction Intervention Trial included 210 babies at risk of late preterm growth restriction or compromise between 33^{+0} and 36^{+6} weeks, of whom 107 were randomised to early birth and 103 to delayed.[353] Mortality and a range of neurodevelopmental measures were similarly distributed between the groups. Limitations of this study are the use of only one Doppler measure (umbilical artery Doppler), visual inspection of the CTG, and management prior to birth was not standardised, but left to the clinician's discretion. Consensus management of late preterm FGR suggests birth if the umbilical artery EDF is reversed at 32 weeks, absent at 34 weeks and raised PI at 36 weeks. For all babies with FGR, birth should be planned for and initiated by 37 weeks with birth occurring by 37^{+6} weeks.[354] *[Evidence level 1+]*

Recent data from those women that declined randomisation in the DIGITAT study of term FGR, showed a significantly higher perinatal mortality. In these women, three of four pregnancies proceeded beyond 40 weeks.[325] *[Evidence level 1+]*

11 | HOW SHOULD FETUSES WITH FETAL GROWTH DISORDERS BE BORN AND PREPARED FOR BIRTH?

The birth of a preterm, or early term newborn, based on concerns regarding fetal growth should be optimised. Caring for women and babies at the time of an extremely premature birth is challenging. Detailed guidance is provided by the British Association of Perinatal Medicine (BAPM).[355] This section refers to recommendations for perinatal optimisation when active care is planned for the birth of a baby with FGR. The care of babies at 22^{+0}–23^{+6} weeks of gestation is particularly challenging and parents must be supported by personalised counselling to help them decide how they wish their baby to be cared for as detailed in the BAPM framework.

11.1 | Antenatal corticosteroids

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Antenatal corticosteroids should be offered to women between 24^{+0} and 34^{+6} weeks, ideally 48 hours before an anticipated birth.	**1++**	**A**	High quality evidence, need to ensure optimal timing.

RCOG guidance states that antenatal corticosteroids should be offered to women between 24^{+0} and 34^{+6} weeks of gestation who are at high risk of imminent PTB (for example, having a planned PTB).[356] Clinicians and women should consider the balance of risks and benefits of corticosteroids in women at risk of imminent PTB beyond 35^{+0} weeks of gestation. The optimal timing of steroids is key to ensure their effectiveness, and a course of steroids given within the seven days prior to PTB reduces perinatal and neonatal death and respiratory distress syndrome.[357] *[Evidence level 1++]*

Further discussion on the use of corticosteroids and the evidence in SGA and FGR is detailed in the RCOG Green-top Guideline no. 74 *Antenatal corticosteroids to reduce neonatal morbidity and mortality.*[356]

11.2 | Intrauterine transfer

Recommendation	Evidence quality	Strength	Rationale for the recommendation
All women undergoing a PTB should be offered transfer to a unit with appropriate and available neonatal cot facilities when safe to do so.	**1–**	**B**	Babies less than 27 weeks or with EFW < below 800 g should be born in a unit with a neonatal intensive care unit.
Ensure the neonatal team are involved when a PTB is anticipated.	**4**	**GPP**	It is important that the woman and her family have appropriate counselling from the neonatal team and time to discuss options.

All women undergoing a PTB should be offered transfer to a unit with appropriate and available neonatal cot facilities when safe to do so and as agreed by the relevant neonatal Operational Delivery Network (ODN). Ensure the neonatal team are involved when a PTB is anticipated, so that they have time to discuss options with the woman and whoever may be supporting her prior to birth and to be present at the time of birth.[358,359] *[Evidence level 1–]*

11.3 | Magnesium sulphate for neuroprotection

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Magnesium sulphate for neuroprotection should be offered between 24^{+0} and 29^{+6} weeks and considered up to 33^{+6} weeks.	**1–**	**B**	Magnesium sulphate administration to the woman before the birth of a preterm newborn is neuroprotective, reducing the risk of cerebral palsy.

Magnesium sulphate administration to the woman before the birth of a preterm newborn is neuroprotective, reducing the risk of cerebral palsy. As standard practice within the UK it should be discussed for women between 23^{+0} and 23^{+6}, offered to all women between 24^{+0} and 29^{+6} weeks and considered for women between 30^{+0} and 33^{+6}.[357] In a growth restricted fetus there is evidence of neurological developmental abnormalities persisting at least into the later preterm period.[339] Therefore, in the absence of robust evidence, the gestational window for administration should be considered up to 33^{+6} weeks (i.e. balancing any risks to the woman of administration and any need to delay birth for administration). *[Evidence level 1–]*

11.4 | Mode of birth

Recommendation	Evidence quality	Strength	Rationale for the recommendation
In the FGR fetus with abnormal cCTG STV, ductus venosus alteration, umbilical artery absent or reversed end diastolic flow velocities (AREDV) caesarean birth is recommended and should occur after administration of steroids and magnesium sulphate.	**4**	**GPP**	The risk of unplanned (emergency) caesarean birth in this group will be very high.
In the SGA fetus or late FGR fetus with normal umbilical artery Doppler or with abnormal umbilical artery PI but end–diastolic velocities present, IOL can be offered but rates of unplanned (emergency) caesarean birth are increased, and continuous fetal heart rate monitoring is recommended from the onset of uterine contractions.	**4**	**GPP**	Compared with appropriately grown babies, SGA fetuses are at greater risk of fetal heart rate abnormalities in labour and thus unplanned (emergency) caesarean birth.
When IOL is being offered mechanical methods should be considered.	**2+**	**C**	Mechanical methods seem to be associated with a lower occurrence of adverse intrapartum outcomes
Early admission is recommended in women in spontaneous labour with a SGA/FGR fetus in order to instigate continuous fetal heart rate monitoring.	**4**	**GPP**	Fetuses with growth disorders are at greater risk of fetal heart rate decelerations in labour.

Compared with appropriate-for-gestational-age fetuses, term and near-term SGA fetuses are at increased risk of fetal heart rate (FHR) decelerations in labour, unplanned (emergency) caesarean birth for suspected fetal compromise and metabolic acidaemia at birth. This reflects a lower prelabour pO2 and pH, greater cord compression and a greater fall in pH and higher lactate levels when FHR decelerations are present.[339,360] Reported rates of unplanned (emergency) caesarean birth for suspected fetal compromise vary from 6–45%, with higher rates in those with serial AC or EFW measurements suggestive of FGR.[263,361,362] No RCTs of mode of birth in the SGA fetus were identified. *[Evidence level 2–]*

In all recent studies reporting outcome of viable SGA fetuses with UA AREDV birth has been by caesarean birth and therefore it is not possible to determine the likelihood of adverse outcome (including unplanned [emergency] caesarean birth for suspected fetal compromise) associated with induced / spontaneous labour.[336,363] Older series report rates of intrapartum fetal heart decelerations necessitating CS of 75–95%.[364,365] More recent prospective data on the outcome of labour in SGA fetuses with an abnormal UA Doppler but positive end-diastolic velocities are also extremely limited; suspected fetal compromise (necessitating emergency caesarean birth) has been reported in 17–32% of such cases, compared with 6–9% in SGA fetuses

with normal UA Doppler, although it is acknowledged that knowledge of Doppler may lower obstetricians' threshold for emergency caesarean birth.[361,362,366,367] The offer of IOL with continuous FHR monitoring is therefore reasonable in term and near term SGA/FGR fetuses without UA AREDV. The procedures for IOL should follow existing guidance and within this guidance it is noted that mechanical methods are less likely to cause hyperstimulation than pharmacological methods.[368] Studies looking specifically at IOL in the FGR group have demonstrated a lower risk of uterine tachysystole, caesarean or operative birth and adverse neonatal outcome compared with pharmacological methods.[369-372] A systematic review concluded that there was limited evidence on the optimal type of IOL in pregnancies with small fetuses but that mechanical methods seem to be associated with a lower occurrence of adverse intrapartum outcomes.[372] *[Evidence level 2+]*

12 | POSTNATAL INVESTIGATIONS AND PREPREGNANCY COUNSELLING

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Histopathological examination of the placenta may be useful where FGR is diagnosed prenatally or at birth to understand the underlying causes and guide management in a subsequent pregnancy.	**3**	**D**	To confirm placental disease and guide future pregnancy management.
Women who have given birth to a growth restricted infant should be offered an appointment for postnatal counselling, review of placental histology and consideration of investigations of underlying causes as appropriate e.g. acquired thrombophilias.	**4** **2-**	**GPP** **B**	Important to confirm pathology and optimise future pregnancy management and modify the women's health to improve future pregnancy outcomes. The British Society for Haematology recommends against testing for hereditary thrombophilias but for acquired thrombophilias can be considered as may aid risk stratification and treatment decisions.
A plan for future pregnancies and preventative strategies (smoking cessation, aspirin treatment) should be recorded in the notes and discussed with the woman.	**4**	**GPP**	It is important that a plan for future pregnancies is recorded to support continuity of care.

As discussed in section 4, the birth of a baby with FGR is a major risk factor for FGR in a subsequent pregnancy and the postnatal period offers an opportunity to address modifiable risk factors. The most important of these is reducing exposure to second-hand smoke. NICE guideline [NG209] recommends that maternity services establish links with contraceptive services, fertility clinics and antenatal and postnatal services so that everyone working in those organisations knows about local stop-smoking support. This will reduce the risk of newborn babies being exposed to second-hand smoke and reduce the number of women going into their next pregnancy as a smoker.[83]

Following the birth of a baby with FGR, investigations should be offered to try to determine the underlying cause and help provide an opportunity to discuss risk of recurrence and possible interventions to reduce risk at a prepregnancy appointment. These investigations should consider placental histopathology which may be useful[373] (as recommended by the Royal College of Pathologists defined as birthweight below the 10th centile with an abnormal fetal growth curve) and investigation for acquired thrombophilias.[374] *[Evidence level 2–]*

Modifiable risk factors should be addressed such as lifestyle factors (e.g. smoking, BMI) and medical conditions optimised. Plans for prevention (i.e. aspirin) and monitoring in future pregnancies should be discussed.

13 | RECOMMENDATIONS FOR FUTURE RESEARCH

- The interaction of multiple maternal risk factors is unknown and is an important area for further research. Research into development of prediction models that are designed specifically for FGR and FGR with adverse outcomes is needed.
- Further research is required to quantify the predictive accuracy of different methods, to determine the optimal timing of the first ultrasound, the optimal interval between scans and the benefits of universal growth scans. This should include cost-effectiveness of a screening programme with appropriate longer term neonatal outcomes.

- The use of biomarkers as a universal screening test to predict adverse pregnancy outcomes including cost effective analysis.
- RCTs are required to determine whether biomarkers enable further delineation of early and late onset FGR and whether their use can help further determine management when combined with other tests.
- Longitudinal studies of fetuses, whose birthweight falls within the normal range but who are suspected of abnormal fetal growth, should address whether additional measures of fetal growth e.g. ultrasound biometry and velocity, Doppler assessment and biomarkers can help determine those at risk of adverse outcome.
- Further research needs to assess the impact of different EFW reference charts in different populations to ensure that the reference charts used are appropriate or whether they need adjusting using local data sets.
- There is a need for research to determine better definitions of growth velocity at different gestations and to determine the relationship between growth velocity and adverse outcome.
- The role of MCA Doppler in timing of birth in late preterm and term FGR.
- Use of maternal and fetal Doppler in the management of FGR needs to be supported by research to homogenise the Doppler indices, thresholds and reference ranges used.
- Research into functional imaging of the placenta and its potential use in predicting adverse outcome.
- Research into discovering novel biomarkers of FGR.
- Further research into routine third trimester USS assessing a package of care (diagnostic accuracy of test and management pathways for screen positive and negative women) considering a range of outcomes are required.
- Further research into interventions, including pharmacological treatments, for FGR once diagnosed to reduce the risk of adverse outcome.

14 | AUDITABLE TOPICS

- Audit to report percentage of babies born <3rd centile and > 37^{+6} weeks and case note audit of those babies <3rd centile not detected antenatally to identify areas of improvement.
- Audit of babies born >39^{+6} weeks and < 10th centile to provide an indication of detection rates (%) and management of SGA babies.
- Use the PMRT to calculate the percentage of perinatal mortality cases annually where the risk assessment and management of FGR was a relevant issue.
- Appropriate risk assessment during pregnancy, assessed as percentage of pregnancies where a risk status for FGR is identified and recorded at booking, and prescribing of aspirin to those at risk of placental dysfunction.
- Audit and quality assurance of biometry images used in growth surveillance as recommended by BMUS.[192]

15 | USEFUL LINKS AND SUPPORT GROUPS

- Tommy's Charity [https://www.tommys.org]
- Sands Stillbirth and Neonatal Death Charity [https://www.sands.org.uk/]

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CONFLICT OF INTEREST STATEMENT

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None.

DATA AVAILABILITY STATEMENT

None.

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APPENDIX I

Explanation of guidelines and evidence levels

Clinical guidelines are 'systematically developed statements which assist clinicians and patients in making decisions about appropriate treatment for specific conditions'. Each guideline is systematically developed using a standardised methodology. Exact details of this process can be found in the RCOG handbook *Developing a Green-top Guideline: Guidance for developers*. These recommendations are not intended to dictate an exclusive course of management or treatment. They must be evaluated with reference to individual patient needs, resources and limitations unique to the institution and variations in local populations. It is hoped that this process of local ownership will help to in- corporate these guidelines into routine practice. Attention is drawn to areas of clinical uncertainty where further research may be indicated.

The evidence used in this guideline was graded using the scheme below and the recommendations formulated in a similar fashion with a standardised grading scheme.

Classification of evidence levels

1++	High-quality meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias
1–	Meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a high risk of bias
2++	High-quality systematic reviews of case–control or cohort studies or high-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
2+	Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2–	Case–control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal
3	Non-analytical studies, e.g. case reports, case series
4	Expert opinion

Grades of Recommendation

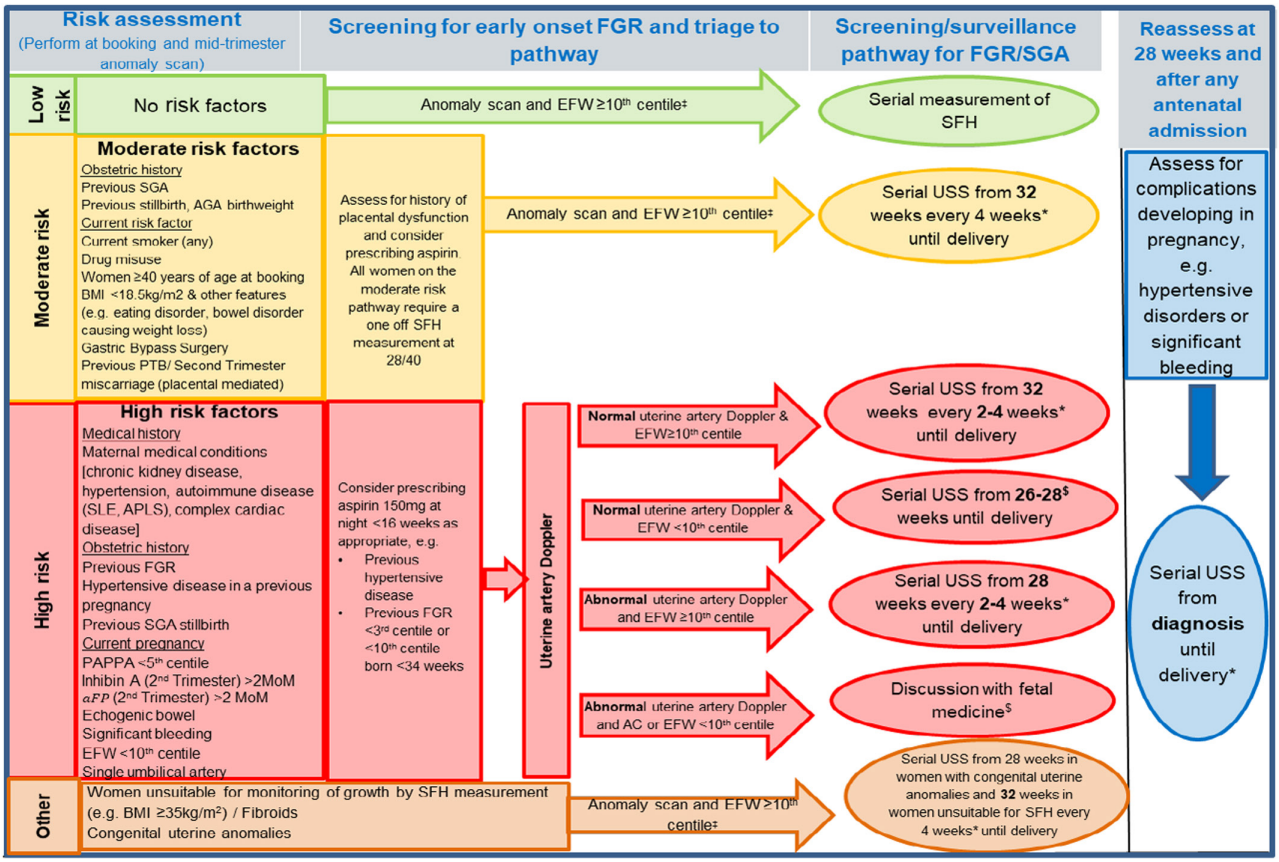
A	At least one meta-analysis, systematic reviews or RCT rated as 1++, and directly applicable to the target population; or a systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++ directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+ directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+

Good Practice Points

GPP	Recommended best practice based on the clinical experience of the guideline development group

APPENDIX II

Surveillance pathway following risk assessment for Fetal growth Fetal medicine refers to a clinician with fetal medicine expertise



Footnote Appendix II.

The risk factors listed in Appendix I constitute those routinely assessed at booking and at mid trimester scan. Other risk factors exist and risk assessment must always be individualised taking into account previous medical and obstetric history and current pregnancy history. For women with maternal medical conditions and individuals with disease progression, or institution of medical therapies, an individual's risk may increase and necessitate monitoring with serial scanning. For women with a previous stillbirth, management must be tailored to the previous history i.e. evidence of placental dysfunction or maternal medical conditions.

Serial measurement of SFH should be performed as per NICE guideline [CG62].

‡AC and/or EFW <10th centile at the anomaly scan is a high-risk factor.

$ An individualised plan of care should be made.

* Refer to risk assessment and screening section for advice on scan interval.

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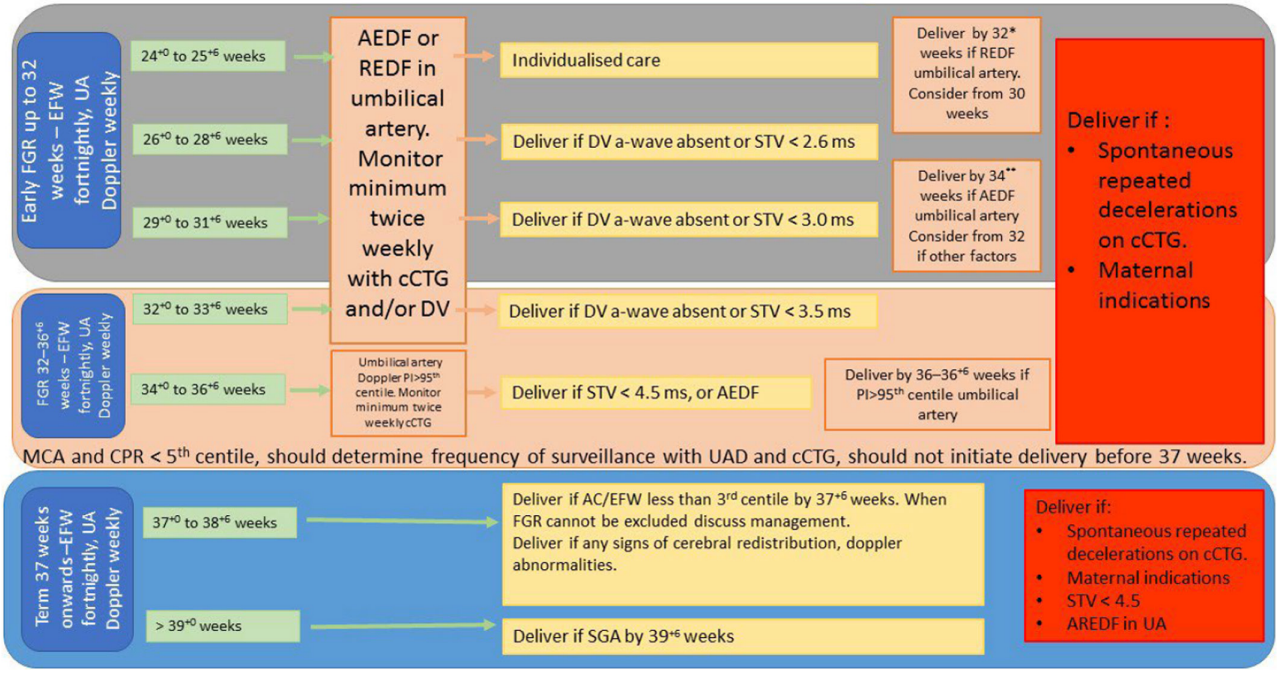
APPENDIX III

Management of fetal growth restriction (FGR)



*Consider after 30^{+0} weeks; **Consider after 32^{+0} weeks; EFW, estimated fetal weight; UA, umbilical artery; DV, ductus venosus; cCTG, computerised cardiotocograph; STV, short-term variation; ms, milliseconds; AC, abdominal circumference; PI, pulsatility index; AREDF, absent reversed end-diastolic flow.

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All RCOG guidance developers are asked to declare any conflicts of interest. A statement summarising any conflicts of interest for this guideline is available from: https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg31/

The final version is the responsibility of the Guidelines Committee of the RCOG.

The guideline will be considered for update 3 years after publication, with an intermediate assessment of the need to update 2 years after publication.