Feidhmeannacht na Seirbhíse Sláinte
Health Service Executive

INSTITUTE OF OBSTETRICIANS & GYNAECOLOGISTS
ROYAL COLLEGE OF PHYSICIANS OF IRELAND

CLINICAL PRACTICE GUIDELINE

FETAL GROWTH RESTRICTION - RECOGNITION, DIAGNOSIS & MANAGEMENT

Institute of Obstetricians and Gynaecologists,
Royal College of Physicians of Ireland
and
Directorate of Clinical Strategy and Programmes,
Health Service Executive

Version: 1.1
Guideline No: 28
Publication date: March 2014
Revision date: March 2017

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1. Revision History

Version No.	Date	Modified By	Description
1.1	23/10/15	CP	Modification comprised of formatting into O&G Programme template and guideline number change. No content has been changed.

2. Key Recommendations

1.1 A comprehensive medical and obstetric history should be taken from every patient booking for antenatal care, ideally prior to 14 weeks gestation, to assess risk factors for fetal growth restriction (FGR). In addition, assignment of estimated date of delivery (EDD) should occur at this visit based on menstrual history or, more appropriately, on dating ultrasound.

1.2 Consideration should be given to producing a customised fetal growth chart for every woman at the booking visit which may aid with the interpretation of fundal height measurements and sonographic fetal weight estimation throughout the pregnancy.

1.3 In the presence of significant risk factors for FGR, serial evaluation of fetal growth, amniotic fluid volume and umbilical artery Doppler is recommended from 26 weeks gestation in 2 to 4-weekly intervals until birth.

1.4 In the presence of significant risk factors for FGR, the use of low-dose Aspirin (LDA) in relation to FGR prevention is recommended and should be initiated prior to 16 weeks gestation. Treatment with low molecular weight (LMWH) can be considered in individual cases and should be discussed with an experienced clinician.

1.5 Women with previous adverse pregnancy outcome (i.e. prior perinatal death, FGR resulting in preterm delivery <34 weeks, mid-trimester or recurrent pregnancy loss, significant medical co-morbidities) should be managed in a high risk, consultant led clinic with regular sonographic surveillance (Recommendation 3).

1.6 Every woman should undergo a comprehensive evaluation of the fetal anatomy (by a sonographer or clinician who is experienced in ultrasound) between 20 and 22 weeks gestation to rule out structural abnormalities and to assess for soft markers as a sign of chromosomal abnormalities. Referral to a fetal medicine specialist should occur as per local protocol.

1.7 Clinical assessment of fetal size should occur at every visit. The fundal height (FH) measurement should be recorded in cm and plotted in the customised chart if available. Referral for sonographic evaluation should occur if FGR is suspected or if new risk factors are present.

1.8 Clinical assessment of fetal size may be difficult in women with multiple fibroids or increased body mass index, thus a low threshold for sonographic evaluation of fetal weight may be adopted.

1.9 Criteria for FGR diagnosis include an EFW <10th centile on ultrasound based on accurate dating. In particular, an EFW <3rd centile and/or abnormal umbilical artery (UA) Doppler, significantly increase the risk of adverse perinatal outcome.

1.10 The fetal biometry should be assessed no more frequently than every 2 weeks.

1.11 Once FGR is diagnosed, 2-weekly assessment of fetal growth is recommended. In addition, amniotic fluid volume and umbilical artery Doppler assessment should be carried out.

1.12 If the umbilical artery Doppler demonstrates increased resistance (Pulsatility Index >95th centile), the sonographic surveillance should be increased to weekly intervals or more frequently if deemed necessary by the managing clinician.

1.13 Additional Doppler indices such as middle cerebral artery (MCA) or ductus venosus (DV) assessment can be carried out however should not be used to indicate delivery.

1.14 If there is absent end-diastolic flow in the umbilical artery (AEDF) prior to 34 weeks gestation, daily CTG monitoring, twice weekly UA Doppler and amniotic fluid volume assessment is recommended. In many cases this may require admission to hospital in order to provide this degree of fetal surveillance. These women should be discussed with the team consultant on a daily basis.

1.15 If there is reversed end-diastolic flow in the umbilical artery (REDF) prior to 30 weeks gestation, admission to hospital with daily CTG monitoring, three-times weekly UA Doppler and amniotic fluid volume assessment is recommended; an opinion from a fetal medicine specialist may be sought to determine fetal viability and guide further management.

1.16 In cases of AEDF, delivery should be considered no later than 34 weeks gestation. Earlier delivery may be indicated in cases of poor interval growth, or a deterioration of sonographic variables (Doppler, amniotic fluid).

1.17 In cases of REDF, delivery should be considered no later than 30 weeks gestation. Earlier delivery may be indicated by a deterioration of sonographic variables.

1.18 Prenatal corticosteroids for fetal lung maturation should be considered between 24^{+0} and 34^{+0} weeks gestation, but may be given up until 38^{+0} weeks in cases of elective delivery by Caesarean section. Steroids should be administered in a timed manner. Multiple courses of steroids are not recommended.

1.19 Decisions regarding the optimal timing of delivery need to be made on an individual basis and may require the involvement of an experienced obstetrician or fetal medicine specialist, in particular in severe, very preterm FGR.

1.20 In cases of isolated FGR (EFW <10th centile and normal UA Doppler), delivery can be delayed until at least 37 weeks, and even until 38-39 weeks gestation.

1.21 Magnesium sulfate for fetal neuroprotection should be administered in gestations prior to 32 weeks in accordance with the National Guideline No. 23.

1.22 Mode of delivery needs to be discussed on an individual basis but Caesarean section is likely when AREDF UA Doppler waveforms are present, or in very preterm gestations.

1.23 If induction of labour is considered in women with abnormal UA Doppler, a continuous CTG should be performed once contractions have started, with a low threshold for Caesarean delivery.

1.24 Cord arterial and venous pH should be recorded for all FGR infants.

1.25 Histopathological examination of the placenta is strongly recommended in all cases where FGR is diagnosed prenatally or at birth to understand the underlying causes and guide management in a subsequent pregnancy.

1.26 Women who have delivered a growth restricted infant <34 weeks gestation should be offered an appointment for postnatal counselling, review of placental histology and investigation of underlying causes such as thrombophilia screening.

1.27 A plan for future pregnancies and preventative strategies (in particular smoking cessation, Aspirin treatment) should be recorded in the notes and discussed with the mother. This plan should be communicated to the GP. Given the recurrence risk of approximately 25%, early booking in a subsequent pregnancy should be encouraged.

3. Purpose and Scope

This guideline is primarily intended as a resource for obstetricians, trainees and midwives working in Ireland but might also be useful for women and their partners, general practitioners and commissioners of healthcare. The aim of this guideline is to standardise and improve antenatal care of pregnancies affected by intrauterine growth restriction based on best evidence based clinical practice approach.

This guideline does not address:

- Management of FGR fetuses with chromosomal and/or structural abnormalities
- Management of FGR in multiple gestations
- Management of FGR in gestations which are considered pre-viable (i.e. gestational age <24 weeks and estimated fetal weight <500grams)

This guideline is designed to guide clinical judgment, but not replace it. Given the complexity and heterogeneity of the clinical problem, in individual cases a healthcare professional may, after careful consideration, decide not to follow this guideline if it is deemed to be in the best interest of the patient.

4. Glossary

Given the inconsistencies of terminology and definitions used to describe suboptimal growth in utero, the following terms will be used for the purpose of this guideline:

- **Fetal growth restriction (FGR)**
  - Will be used as a general term to describe fetuses with EFW <10th centile
- **Small-for-gestational age (SGA) or isolated FGR**
  - Will be used to describe a physiologically small fetus (ie EFW<10th centile, normal amniotic fluid volume and normal umbilical artery Doppler)
- **Intrauterine growth restriction (IUGR)**
  - Will be used to describe a pathologically small fetus (ie EFW<10th centile, oligohydramnios, abnormal UA Doppler AND/ OR poor interval growth velocity AND/ OR EFW <3rd centile)

5. Background

Definition, Diagnosis and Perinatal Outcome of FGR

Fetal growth restriction (FGR) is a common and complex clinical problem which confers a considerable risk of morbidity. In addition to infectious causes and congenital malformations, FGR has been identified as a major contributor to perinatal mortality [Manning *et al*, 2013].

Intrauterine growth failure affects up to 10% of pregnancies and is often referred to as small-for gestational age (SGA), intrauterine growth restriction (IUGR) or fetal growth restriction (FGR) in an inconsistent and confusing manner. Traditionally, an estimated fetal weight (EFW) or abdominal circumference (AC) below the 10th centile raises concerns over suboptimal intrauterine growth, however the distinction between normal and pathologic growth often cannot reliably be made at this arbitrary cut-off. In addition, approximately 70% of fetuses below the 10th centile will have a normal perinatal outcome [Lees *et al*, 2013]. The risk of adverse outcome is proportional to the degree of growth restriction with those below the 3rd centile and/ or abnormal umbilical artery Doppler measurements at greatest risk of morbidity or mortality [Unterscheider *et al*, 2013]. In addition, analysis of fetal growth trajectories has been identified as an important factor in the differentiation between physiological SGA and pathological IUGR [Barker *et al*, 2013].

Suboptimal fetal growth is linked to adverse short and long term outcomes. Neonatal complications include haematological and metabolic problems and impaired thermoregulation. In addition, intraventricular haemorrhage, necrotising enterocolitis, seizures, sepsis, respiratory distress syndrome, retinopathy of prematurity and neonatal death contribute to the perinatal morbidity.

Together with the profound perinatal impact of FGR, consequences may continue into adult life in the form of metabolic disease as a result of prenatal reprogramming and postnatal compensatory catch-up growth. It is now well established, that an adverse intrauterine environment increases disease risk in adulthood leading to metabolic

syndrome, hypertension, insulin resistance and type 2 diabetes mellitus, coronary heart disease and stroke [Barker *et al*, 1990; 1993].

Antenatal Detection and Recognition of Risk Factors

The antenatal detection of FGR is of particular concern, given that currently only one third of such pregnancies are prenatally recognised [Chauhan *et al*, 2013; McCowan *et al*, 2010]. Abdominal palpation and fundal height (FH) measurement have poor sensitivities and specificities; they are, however, the only physical examination methods available. Serial sonographic assessment of EFW is not feasible in all pregnancies, therefore FH measurement can be used as a proxy for estimating the gestational age of the pregnancy [Rondo *et al*, 2003] or the weight of the fetus [Mongelli *et al*, 2004]. More commonly, it is used for fetal growth screening. A prospective, non-randomised controlled study of 1272 patients [Gardosi *et al*, 1999] found an increased detection of FGR with customised FH charts (48% vs 29%, odds ratio 2.2, 95% confidence interval 1.1-4.5) which was coupled with reduced false-positive assessments. In another study, FH measurement in cm and plotting on a customised fundal height chart shows an improved, but still low, detection of FGR antenatally when compared with conventional methods (36% vs 16%) [Wright *et al*, 2006]. This alarmingly low detection rate of FGR translates into a significantly increased risk of adverse perinatal outcomes for these pregnancies. In particular, pregnancies with unrecognised FGR carry an over 8-fold increased risk of stillbirth when compared to pregnancies without IUGR (19.8 versus 2.4/ 1000 births) [Gardosi *et al*, 2013]. It may therefore be reasonable to consider using customised FH and fetal weight standards, which may aid with the interpretation of clinical assessment findings.

Antenatal recognition of risk factors which may lead to suboptimal fetal growth in utero is crucial. FGR is the manifestation of underlying placental, fetal, parental and environmental causes and therefore represents a heterogenous condition. **Appendix I** summarises the underlying aetiologies of FGR which should be considered when stratifying the antenatal management of each pregnancy.

Sonographic Surveillance and Management

Sonographic surveillance, in particular Doppler ultrasound, of pregnancies with IUGR plays a critical role in improving perinatal outcomes by increasing prenatal surveillance and timely delivery. There is very little evidence from randomised controlled trials to inform best practice for antenatal surveillance regimens in FGR pregnancies [Grivell *et al*, 2012], in particular, no single individual test is available to predict outcome in IUGR, and therefore a combination of examinations is recommended in the careful assessment of growth restricted fetuses.

<u>Biometry, population and customised fetal weight estimation</u>
Evaluation by ultrasound is indicated when small fetal size is suspected clinically. The Hadlock formula is the most widely accepted method of estimating fetal weight using a composite sonographic measurement of fetal head, abdomen and femur [Hadlock *et al*, 1985].
An EFW below the 10th centile is concerning for suboptimal fetal growth, recognising the limitations of this arbitrary cut-off to inform perinatal outcome and the multitude of formulae to calculate EFW. Fetal weight estimation is also influenced by the ultrasound

equipment, operator experience, training and competence. In addition, any interpretation of fetal weight in relation to gestational age relies on accurate dating of pregnancies.

Customisation of fetal growth takes into account maternal constitutional variation (ethnicity, height, weight, parity) and has been proposed for a more appropriate identification of fetal growth failure [Gardosi *et al*, 1992]. Therefore, in fetuses with EFW below the 10th centile, a customised reference may be obtained to aid with the interpretation of this value. A customised growth standard was developed using pregnancy data of over 11,000 women in Ireland [Unterscheider *et al,* 2013]. The usefulness of fetal weight customisation in the Irish setting is validated in the analysis of 1,116 PORTO fetuses with population based EFW< 10th centile. If customised norms would have been used in the original study, 28% would not have been labelled as FGR, which also translated into improved targeting of infants at risk of adverse perinatal outcome (RR=1.25). This finding is in agreement with other published literature on this subject [Figueras *et al*, 2007; Groom *et al*, 2007; McCowan *et al*, 2005]. An example of a customised chart is in **Appendix II**.

Additional features on ultrasound such as detailed information on fetal anatomy, placental morphology, amniotic fluid volume and umbilical artery Doppler may help in the differentiation between physiological and pathological FGR. If there is evidence of any additional concerning sonographic features, such as polyhydramnios/ anhydramnios, structural abnormalities or soft markers, referral to a fetal medicine specialist is indicated as per local protocol.

Once FGR is diagnosed, a follow up growth examination with amniotic fluid and umbilical artery Doppler evaluation in 14 days should be arranged given the association between poor interval growth and adverse perinatal outcome. Subsequently, serial follow up of growth is recommended. This approach is helpful as it allows the study of growth trajectories which may further aid in the differentiation between physiological and pathological FGR [Barker *et al*, 2013]. Biometry assessment any more frequently than at 2-weekly intervals is not recommended because of the limitations and error ranges associated with ultrasound and the fetal growth rate. In addition, a single biometry assessment in the third trimester does not improve perinatal outcome and is therefore not recommended, unless clinically indicated [Bricker *et al*, 2008].

<u>Doppler surveillance</u>
In addition to biometry assessment, various studies have described patterns of Doppler deterioration in IUGR fetuses aiming at understanding the underlying pathophysiology, optimising surveillance strategies and guiding the optimal timing of delivery.

Umbilical artery (UA) Doppler is widely accepted as the primary assessment tool in IUGR [Alfirevic *et al*, 2010] however there is on-going debate and controversy on the benefit of assessing vessels other than the UA in the setting of IUGR. Several studies have contributed to the understanding of longitudinal Doppler changes occurring in IUGR. However, these studies have been either retrospective or comprised small patient numbers. Furthermore, it is important to note that in fact most of these papers describing a temporal sequence refer to Doppler abnormalities *within a population* of IUGR fetuses rather than a predictable progressive sequence occurring *within the individual fetus*. It is plausible therefore that such prior population data may not

actually be applicable to the longitudinal surveillance of the individual fetus in clinical practice [Unterscheider *et al*, 2013]. In the PORTO study, the mean time-to-delivery interval for UA PI >95th centile, AEDF and REDF was 26, 12 and 4 days respectively.

Uterine artery (UtA) Doppler assessment, in particular the persistence of UtA notching or a pulsatility index (PI) >95th centile, has been proposed as a promising predictor of pre-eclampsia (PET) and FGR. This approach has been found to be of little value in the low risk pregnant population, and performs better for the prediction of PET, but with only moderate sensitivity [Cnossen *et al*, 2008]. Therefore screening for uterine artery abnormalities is not recommended, in particular in the absence of useful therapies.

As the SMFM clinical guideline on Doppler assessment in IUGR states, there is a large variability in manifestation of Doppler changes in the umbilical, middle cerebral artery (MCA) and ductus venosus (DV). The cerebroplacental ratio (CPR) is evaluated using MCA Doppler, and is calculated by dividing the MCA pulsatility index (PI) by the UA PI, with a normal value being >1. A CPR <1 signifies cerebral redistribution with increased blood flow to the fetal brain, and has been reported as an adaptive response to a suboptimal intrauterine environment. Prospective data from the PORTO study showed that brainsparing was significantly associated with adverse perinatal outcomes and that integration of CPR evaluation may be beneficial (specificity 87%, sensitivity 61%). The role of venous Doppler assessment in IUGR, in particular DV Doppler, has been suggested as a more precise predictor of fetal deterioration. While some authors have suggested use of DV Doppler to guide delivery decisions, it may however have limited utility as DV abnormalities are exhibited by only a minority of IUGR fetuses, usually in close proximity to an abnormal CTG requiring delivery [Ferrazzi *et al*, 2002; Bilardo *et al*, 2004]. To date, evidence from randomised trials supporting a role for additional Doppler surveillance of middle cerebral artery and ductus venosus in IUGR management is still lacking. The ***Trial of Randomized Umbilical and Fetal Flow in Europe*** (TRUFFLE) is a three-arm randomised intervention trial assessing the role of ductus venosus in guiding the timing of delivery. This trial is expected to report its main findings in the next months which might change views on Doppler management in IUGR [Lees *et al*, 2005; 2013]. However in the absence of evidence from randomised or intervention trials at this current time, Doppler studies other than the UA should be reserved solely for research protocols.

<u>Cardiotocography (CTG)</u>

Given that no individual test can precisely predict perinatal outcome, fetal well-being is often assessed with multiple modalities. CTG is widely accepted as the primary method of antenatal fetal monitoring to assess the current status of the fetus. CTG, although highly sensitive, has a 50% false positive rate for the prediction of adverse outcome [Evertson *et al*, 1979]. In addition, a meta-analysis [Pattison *et al*, 2000] of its application in high-risk pregnancies failed to demonstrate any beneficial effect in reducing perinatal mortality. CTG is useful in the detection of acute hypoxia but is a poor test for chronic hypoxia. Nevertheless, a normal CTG is significantly more likely to be followed by a normal delivery and a normal perinatal outcome than an abnormal test. The use of a computerised CTG [Dawes *et al*, 1992] is thought to be more reliable, objective and accurate than visual inspection [Bracero *et al*, 1999]. Reduced short term variability on a computerised CTG analysis may be more closely correlated with acidosis and hypoxia at the time of delivery.

Biophysical Profile (BPP)
Combining biophysical tests with Doppler ultrasound may help improve the prediction of adverse outcomes and initiate delivery before fetal demise occurs. The biophysical profile score (BPP) is a non-invasive test to assess fetal well-being [Manning *et al*, 1980]; an abnormal score is a predictor of significant fetal acidaemia [Manning *et al*, 1995]. The BPP integrates 5 parameters to yield a maximum of 10 points (0= abnormal, 2= normal):

- Amniotic fluid measurement
- Fetal breathing movements
- Fetal body movements
- Fetal tone
- (CTG) - In general, if all of the sonographic variables are normal, the CTG may be excluded, giving a maximum score of 8/8.

The usual time to complete a BPP is less than 5 minutes [Manning *et al*, 1981]. The variables however are subject to fetal sleep cycles; thus, continuous observation for at least 30 minutes must occur before a variable can be defined as absent (abnormal). Adding a BPP to Doppler ultrasound may improve the identification of fetuses at increased risk of poor neonatal outcome, but evidence from prospective, randomised studies is lacking. If assessed, delivery is indicated at scores ≤4/10 and close monitoring or delivery should be considered at scores ≤6/10. It is also important to recognize the limitations of BPP to inform fetal well-being in preterm FGR fetuses.

Timing and Mode of Delivery

Management of FGR in relation to the optimal timing of delivery, in particular when severe and very preterm, requires a careful clinical balance between the risk of antepartum stillbirth due to delaying delivery and iatrogenic prematurity potentially causing significant morbidity or neonatal death by early intervention. Timing of delivery should be individualised, depending on the suspected underlying cause of FGR; in some cases, the optimal mode of delivery is determined following a multi-disciplinary case discussion involving fetal medicine specialists.

The main goals of prolonging intrauterine life are:

- avoiding mortality (24-26 weeks)
- gaining survival (26-28 weeks)
- avoiding morbidity (28-30 weeks)
- gaining maturity (>30 weeks)

Important prenatal determinants of perinatal outcome are gestational age at delivery and birthweight, with best prospects of intact survival at weights over 800grams and gestational ages over 29 weeks [Baschat *et al*, 2007]. The timing of delivery is therefore guided by the degree of growth restriction and gestational age at diagnosis. Additional information on interval growth, amniotic fluid volume, umbilical artery Doppler, biophysical profiling and CTG monitoring is also important in optimising the timing of delivery.

Isolated FGR
In cases of isolated FGR (biometry <10th centile, normal amniotic fluid volume and normal umbilical artery Doppler) it is reasonable to delay delivery until at least 37 weeks, and even until 38-39 weeks gestation. The ***Disproportionate Intrauterine***

Growth Intervention Trial At Term (DIGITAT) examined induction of labour versus expectant management in 650 women with suspected IUGR between 36^{+0} and 41^{+0} weeks gestation. Outcomes were comparable with respect to composite neonatal morbidity (5.3% vs 6.1%) and Caesarean delivery rates (14% vs 13.7%). Interestingly, infants in the expectant group more commonly had birthweights <3rd centile when compared to the induction group (30.6% vs 12.5%). This would suggest that a substantial number of fetuses in the expectant group had worse degree of IUGR or did not continue to grow therefore making a compelling argument for induction of labour once IUGR is suspected. The authors conclude that there seems to be 'equivalent fetal and maternal outcomes for induction and expectant monitoring in women with suspected IUGR at term, indicating that both approaches are acceptable' [Boers *et al*, 2007; 2012]. Given the increased risk of stillbirth (RR 2.3) in FGR pregnancies after the 37th week of gestation [Trudell *et al*, 2013], induction of labour or elective delivery should be considered between 37 and 38 weeks. This applies in particular to fetuses <3rd centile, who are at up to 7-fold increased risk of stillbirth than fetuses between the 5th and 10th centile [Pilliod *et al*, 2012].

Complicated FGR

An abnormal umbilical artery Doppler in the setting of FGR confers the highest risk of perinatal morbidity and mortality, and this increased risk exists irrespective of gestational age at delivery [Unterscheider *et al*, 2013]. Therefore, in cases of complicated FGR (biometry <10th centile, with abnormal umbilical arterial Dopplers, such as raised pulsatility index >95th centile, absent or reversed end-diastolic flow), antenatal corticosteroids to prevent respiratory morbidity should be administered in a timed manner between 24^{+0} and 34^{+0} weeks. There is growing evidence and long term safety data to support steroid administration even beyond 36 weeks for prevention of neonatal respiratory morbidity after elective Caesarean delivery [Stutchfield *et al*, 2005; 2013]. In this multicentre randomised trial, neonatal intensive care unit (NICU) admission rates for respiratory morbidity were lower for infants who received steroids 48 hours prior to delivery, and this effect was observed at 37 weeks (11.4% vs 5.2%), 38 weeks (6.2% vs 2.8%) and 39 weeks (1.5% vs 0.6%). The authors conclude that antenatal steroids should be considered for elective CS at 37-38 weeks of gestation.

The ***Growth Restriction Intervention Trial*** (GRIT) was an RCT comparing immediate versus delayed delivery of compromised fetuses between 24 and 36 weeks' gestation with respect to survival to hospital discharge and developmental quotient at two years of age. GRIT found, that when obstetricians were uncertain about the timing of delivery, they were prepared to wait for 4 days. The outcomes in the respective groups were comparable with a respect to death prior to discharge (10% vs 9%). No clear benefit of either immediate versus delayed delivery was identified with a trend towards more disability in the immediate delivery group (5% vs 1%).

In cases of increased resistance in the UA, it is reasonable to increase sonographic surveillance to weekly intervals or more frequently if deemed necessary by the managing clinician. Delivery should be considered at 37 weeks and induction of labour is possible with careful CTG monitoring once contractions have started and labour is established [Hornbuckle *et al*, 2000].

Delivery is indicated earlier in cases of AEDF or REDF in the umbilical artery. In this case, patients should be provided with daily CTG surveillance. In most cases this will require admission to hospital, although some units may have the ability to perform daily CTG surveillance as an outpatient. Following administration of corticosteroids,

delivery should occur no later than 34 weeks in cases of AEDF and no later than 30 weeks in cases of REDF. If there is uncertainty regarding the optimal surveillance and timing of delivery, consultation with fetal medicine specialists and neonatologists should take place to guide surveillance and timing of delivery. A management algorithm is found in **Appendix III**. It is likely, that fetuses with AREDF do not tolerate labour well and therefore an elective Caesarean delivery may be more appropriate.

Magnesium sulfate, which was originally used for seizure prevention and treatment in women with pre-eclampsia, is an effective fetal neuroprotective agent when administered prior to 32 weeks gestation and should be given according to guideline No 23.

Investigations – antenatal and postnatal

Given the association of IUGR and genetic syndromes, aneuploidy and intrauterine infection, a careful and detailed evaluation of the fetal anatomy is important in determining the underlying cause of FGR. In the presence of concomitant structural abnormalities, polyhydramnios or soft markers, referral to a fetal medicine specialist is recommended, as amniocentesis and/ or TORCH screening may be warranted.

Placental abnormalities such as maternal and fetal vascular injuries, placental developmental abnormalities or inflammatory lesions have been linked to adverse pregnancy outcomes including FGR, preterm delivery and stillbirth [Redline, 2008]. Evaluation of the placenta, cord and membranes can give an important insight into intrauterine environment and explain the origins of FGR. Knowledge of underlying placental causes of FGR may guide treatment and management in subsequent pregnancies given that some of these lesions tend to recur. To illustrate the importance of placental histopathology and its translation into clinical practice further we give some examples:

- Non-infectious chronic villitis of unknown etiology (VUE) is linked to maternal obesity and tends to recur in a more severe degree in subsequent pregnancies; there is uncertainty over prevention however treatment with LDA might be indicated in such cases.
- Fetal thrombotic vasculopathy has been described in association with parental thrombophilias and therefore thrombophilia testing in both parents may be indicated.
- Massive fibrin deposition and maternal floor infarction is rare and thought to be due to maternal malperfusion, hypercoagulability and trophoblast injury; it recurs in up to 50% of cases.
- Placental infarctions are associated with placental developmental abnormalities; treatment with LMWH has the potential to improve placentation and outcome [Kingdom *et al*, 2011; Dodd *et al*, 2013].

Risk of Recurrence and Preventative Strategies

Women, who delivered a growth restricted infant in their first pregnancy, are at significantly increased risk of recurrent FGR. This information is crucial for patient counselling and appropriate care in a subsequent pregnancy. The risk of recurrence

was quantified in a large prospective study of 259,481 pregnant women who delivered 2 subsequent singleton pregnancies within the study period [Voskamp *et al*, 2013]. In this study, the incidence of FGR was 5% (defined as birthweight below the 5th centile), the risk of recurrent FGR birth was 23%, and this rate was significantly increased when compared to women who delivered an appropriately grown infant in their first pregnancy (3.4%).

Unfortunately, no specific interventions or therapies have been proven to improve poor fetal growth. Preventative strategies involve a review of lifestyle factors such as smoking cessation and dietary advice. Depending on the underlying cause of FGR, treatment with low dose Aspirin (LDA) can be considered in placenta-mediated FGR, maternal hypertensive disease or obstetrical antiphospholipid syndrome. A protective effect of Aspirin is greatest when commenced prior to 16 weeks gestation [Bujold *et al*, 2010; Roberge *et al*, 2013]. Preliminary data have suggested that the use of low molecular weight heparin (LMWH) for women at particularly high risk of adverse pregnancy complications due to placental dysfunction may significantly reduce the risk of perinatal mortality, preterm birth and low birthweight; treatment with LMWH may be a promising intervention for prevention of these complications, although complete data on adverse infant outcomes are still lacking [Dodd *et al*, 2013; Kingdom *et al*, 2011].

6. Methodology

A search was conducted of current international guidelines in Canada, UK and USA. In addition, Medline was searched for literature published until November 10th, 2013. Articles were restricted to those published in English. The search words used were fetal growth restriction, IUGR, SGA, Doppler surveillance, perinatal morbidity and mortality. Relevant meta-analyses, systematic reviews, intervention and observational studies were reviewed. Particularly pertinent in the Irish setting are data originating from the National PORTO Study (*Prospective Observational Trial to Optimise Paediatric Health in IUGR*) conducted between January 2010 and June 2012 in the seven largest maternity units in Ireland, which offers contemporaneous data from 1,200 pregnancies with EFW <10th centile.

Guidelines reviewed included:

- RCOG Green-top Guideline No. 31 '**The Investigation and Management of the Small-for-Gestational-Age Fetus**' published by the *Royal College of Obstetricians and Gynaecologists* (February 2013)
- ACOG Practice Bulletin N. 134 '**Fetal Growth Restriction**' published by the *American Congress of Obstetricians and Gynecologists* and the *Society for Maternal-Fetal Medicine* (May 2013)
- SOGC Clinical Practice Guideline No. 295 '**Intrauterine Growth Restriction: Screening, Diagnosis , and Management**' published by the *Society of Obstetricians and Gynaecologists of Canada* (August 2013)

The principal guideline developer was Dr Julia Unterscheider (Perinatal Ireland & Royal College of Surgeons in Ireland, Rotunda Hospital, Dublin). The guideline was co-authored by Dr Keelin O'Donoghue (University College Cork, Cork University Maternity

Hospital) and Professor Fergal Malone (Royal College of Surgeons in Ireland, Rotunda Hospital, Dublin) and peer-reviewed by Dr Aisling Martin (Coombe Women and Infants University Hospital, Dublin), Dr Mairead Kennelly (UCD Centre for Human Reproduction, Coombe Women and Infants University Hospital, Dublin), Dr Paul Hughes (Kerry General Hospital), Dr Noirin Russell (Cork University Maternity Hospital) and Ms Mary Moran (O&G Ultrasound Programme, UCD School of Medicine and Medical Science). Finally, the guideline was reviewed and endorsed by the Programme's Clinical Advisory Group and National Working Party in December 2013.

7. Clinical Guideline

How can we best define growth restriction?

- Criteria for FGR diagnosis include an EFW <10th centile on ultrasound based on accurate dating, recognising the limitations of this cut-off to inform perinatal outcome (70% of fetuses in this cohort will have normal outcomes)
- In particular, an EFW<3rd centile and/or abnormal umbilical artery Doppler, significantly increase the risk of adverse perinatal outcome
- Additional concerns may relate to poor interval growth on biometry assessment (even if EFW >10th centile)
- The use of customised fetal weight standards taking into account maternal constitutional variation (ethnicity, parity, height, weight) improves the appropriate identification of FGR

How can we best detect growth restricted fetuses?

- Abdominal palpation and fundal height (FH) measurement have poor sensitivities and specificities; they are, however, the only physical examination methods available
- FH measurement in cm and plotting on a customised fundal height chart, if available, shows an improved, but still low, detection of FGR antenatally when compared with conventional methods. Use of such customised charts may be considered
- Evaluation by ultrasound is indicated when small fetal size is suspected clinically. This assessment should be performed on appropriate equipment by a sonographer or clinician who is experienced in ultrasound
- In the presence of significant risk factors for FGR, serial evaluation of fetal growth is recommended from 26 weeks gestation in 2 to 4-weekly intervals until birth

Which terminology is appropriate?

- **FGR** can be used as a general term to describe fetuses with EFW <10th centile
- **SGA** or **isolated FGR** can be used to describe a physiologically small fetus (ie EFW<10th centile, normal amniotic fluid volume and normal umbilical artery Doppler)
- **IUGR** can be used to describe a pathologically small fetus (ie EFW<10th centile, oligohydramnios, abnormal UA Doppler AND/ OR poor interval growth velocity AND/ OR EFW <3rd centile)

What is the optimal sonographic surveillance and management?

- Sonographic surveillance, in particular Doppler ultrasound, of pregnancies with

IUGR plays a critical role to improve perinatal outcomes

- No single individual test is available to predict outcome in IUGR, therefore a combination of examinations is recommended in the careful assessment of growth restricted fetuses
- The fetal biometry should be assessed no more frequently than every 2 weeks
- Once FGR is diagnosed, 2-weekly assessment of fetal growth is recommended. In addition, amniotic fluid volume and umbilical artery Doppler assessment should be carried out
- Umbilical artery (UA) Doppler is widely accepted as the primary assessment tool in IUGR
- To date, evidence for additional Doppler surveillance of middle cerebral artery and ductus venosus from randomised controlled and or intervention trials is still lacking
- In cases of associated increased resistance in the umbilical artery (Pulsatility Index > 95th centile), surveillance should be increased to weekly intervals or more frequently if deemed necessary by the managing clinician
- In cases of AEDF prior to 34 weeks gestation, daily CTG monitoring and administration of steroids is recommended. These patients should be discussed with the team consultant on a daily basis
- If there is absent end-diastolic flow in the umbilical artery (AEDF), surveillance should be increased to twice weekly intervals until delivery. Involvement of a fetal medicine specialist is advisable to guide surveillance and timing of delivery
- If there is reversed end-diastolic flow in the umbilical artery (REDF), surveillance should be increased to three-times weekly intervals until delivery. Involvement of a fetal medicine specialist is recommended to guide surveillance and timing of delivery

Do I need to involve fetal medicine specialists?

- Referral for a fetal medicine opinion is indicated when additional findings, such as amniotic fluid abnormalities (polyhydramnios or anyhdramnios), soft markers or structural abnormalities, are present. Amniocentesis and testing for Cytomegalovirus and Toxoplasmosis (TORCH screen) may be indicated in such cases
- A fetal medicine opinion should be sought in cases of very early and severe IUGR (i.e. gestational age <24 weeks and estimated fetal weight <500grams) to determine viability

Does every growth restricted infant need delivery in a tertiary centre?

- No. It is however advisable to consult with neonatology colleagues to discuss the individual case, in particular at very preterm gestations and very low estimated birthweights (i.e. severe IUGR with critically abnormal Doppler measurements or CTG traces). In selected cases, transfer to a tertiary level centre may be considered appropriate
- Corticosteroids for fetal lung maturation should be considered between 24^{+0} and 34^{+0} weeks gestation, but may be given up until 38^{+0} weeks, in particular if delivery is by elective Caesarean section; administered as a **single course** (as per local protocol) and in a **timed** manner (within 7 days to delivery)
- Magnesium sulphate for fetal neuroprotection should be administered when delivery is anticipated prior to 32 weeks gestation

What is the optimal timing of delivery?

- Every delivery should be individualised, depending on the suspected underlying cause of FGR; in some cases, the optimal timing of delivery is determined following a multi-disciplinary case discussion involving fetal medicine specialists
- In cases of isolated FGR, where the underlying cause is thought to be physiological, and there was adequate interval growth between assessments coupled with normal amniotic fluid volume and umbilical artery Doppler, delivery can be delayed until 37 weeks. In some cases it may be reasonable to delay delivery until 38-39 weeks gestation. Delaying delivery beyond 40 weeks gestation is not recommended
- In cases of associated **increased resistance in the umbilical artery** (Pulsatility Index > 95th centile), surveillance should be increased and delivery should be undertaken **no later than 37 weeks** gestation
- In cases of **AEDF in the umbilical artery**, delivery should be undertaken **no later than 34 weeks** gestation
- In cases of **REDF in the umbilical artery**, delivery should be undertaken **no later than 30 weeks** gestation
- Delivery should be undertaken for abnormal CTG tracing once viability is agreed; the use of computerised CTG improves interpretation, in particular at preterm gestations
- Delivery should not be informed, at present, based on ductus venosus flow abnormalities or middle cerebral artery Doppler findings

What is the optimal mode of delivery?

- Timing of delivery should be individualised in every case, depending on the suspected underlying cause of FGR; in some cases, the optimal mode of delivery is determined following a multi-disciplinary case discussion involving fetal medicine specialists
- Delivery by Caesarean section should be considered in cases of AREDF in the umbilical artery or at very preterm gestations (<34 weeks) depending on underlying aetiology, parity, reproductive history and cervical favourability
- Induction of labour should be offered for all other women
- Continuous CTG monitoring is recommended once contractions are regular and labour is established

What can be done to prevent FGR in a subsequent pregnancy?

- The recurrence risk of FGR in a subsequent pregnancy is around 25%
- It is recommended to review the underlying causes (placental histology, maternal co-morbidities) and modifiable risk factors (advice on smoking cessation)
- Consideration should be given to Aspirin 75mg daily prior to 16 weeks or low molecular weight heparin (in selected cases only and after discussion with experienced obstetrician)

8. References and Recommended Reading

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9. Implementation Strategy

- Distribution of guideline to all members of the Institute and to all maternity units.
- Distribution to the Director of the Acute Hospitals for dissemination through line management in all acute hospitals.
- Implementation through HSE Obstetrics and Gynaecology programme local implementation boards.
- Distribution to other interested parties and professional bodies.

10. Key Performance Indicators/ Auditable standards

- Percentage of stillbirths as a result of FGR in non-anomalous infants
- Percentage of FGR pregnancies, which were prenatally recognized
- Women with risk factors who appropriately received Aspirin for recurrence prevention
- Appropriately timed administration of corticosteroids (within 7 days)

11. Areas for Future Research

- Therapeutic interventions, especially for FGR prior to 24 weeks and EFW <500grams
- Evaluation of care models for improved detection of FGR, impact on resources and economic aspects ('private care model with provision of continuity of care and increased sonographic surveillance vs current public model vs midwifery led care')
- International working party: agreement on definition of FGR and development of GRADE recommendations

12. Qualifying Statement

This guideline has been prepared to promote and facilitate standardisation and consistency of practice, using a multidisciplinary approach. Clinical material offered in this guideline does not replace or remove clinical judgment or the professional care and duty necessary for each pregnant woman. Clinical care carried out in accordance with this guideline should be provided within the context of locally available resources and expertise.

This guideline does not address all elements of standard practice and assumes that individual clinicians are responsible to:

- Discuss care with women in an environment that is appropriate and which enables respectful confidential discussion.
- Advise women of their choices and ensure informed consent is obtained.
- Meet all legislative requirements and maintain standards of professional conduct.
- Apply standard precautions and additional precautions as necessary, when delivering care.
- Document all care in accordance with local and mandatory requirements.

13. Appendices

- Causes and Risk Factors of FGR
- Customised Growth Curve (FH and EFW) – Example
- Management Algorithm
- Comparison of Clinical Guidelines (Ireland, USA, UK, Canada)

APPENDIX I. Causes and Risk Factors of FGR

MATERNAL

- Parity
- Ethnicity (minorities, non-white)
- Malnutrition, low gestational weight gain
- Low pre-pregnancy fruit intake
- Vigorous daily exercise
- Previous IUGR pregnancy
- Extremes of maternal age (<16 years, >40 years)
- Assisted reproductive techniques
- Uterine malformations
- Low socio-economic status
- Low PAPP-A (<0.4 MoM)
- Hypertension/ pre-eclampsia
- Medical disorders (Systemic lupus erythematosus, pre-existing diabetes, renal disease, restrictive lung disease, cyanotic heart disease, antiphospholipid syndrome, anaemia/ haemoglobinopathy, Crohn's disease, ulcerative colitis)
- Rhesus positive blood type

PATERNAL

- Low birthweight

FETAL

- Female gender
- Chromosomal abnormalities (aneuploidies, microdeletions)
- Genetic syndromes
- Congenital malformations
- Intrauterine infections (CMV, Toxoplasmosis, Rubella, Varicella, Tuberculosis, HIV, Syphilis, congenital Malaria)
- Multiple pregnancy

PLACENTAL

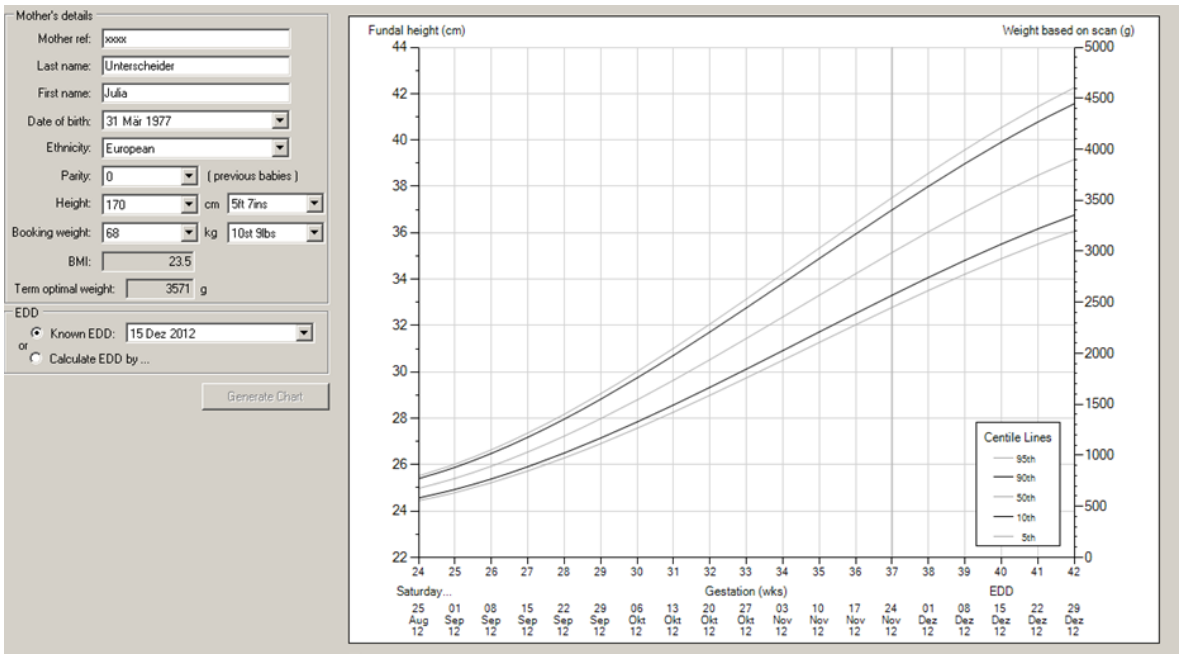
- Placental developmental abnormalities (abnormal placental shape/ position; chorangiomatosis; distal villous hypoplasia/ accelerated villous maturation/ increased syncytial knotting)
- Maternal vascular pathology (infarction; retroplacental haemorrhage; increased perivillous fibrinoid deposition)
- Fetal vascular pathology (cord hypercoiling; true cord knots; abnormal cord insertion; single umbilical artery; fetal thrombotic vasculopathy)
- Inflammatory Lesions (acute chorioamnionitis/ vasculitis; chronic villitis of unknown aetiology)
- Other (confined placental mosaicism, placental hypoplasia)

ENVIRONMENTAL

- Substance misuse
- Smoking
- High altitude/ hypoxia
- Irradiation
- Exposure to teratogens (Warfarin, anti-epileptic drugs, methotrexate)

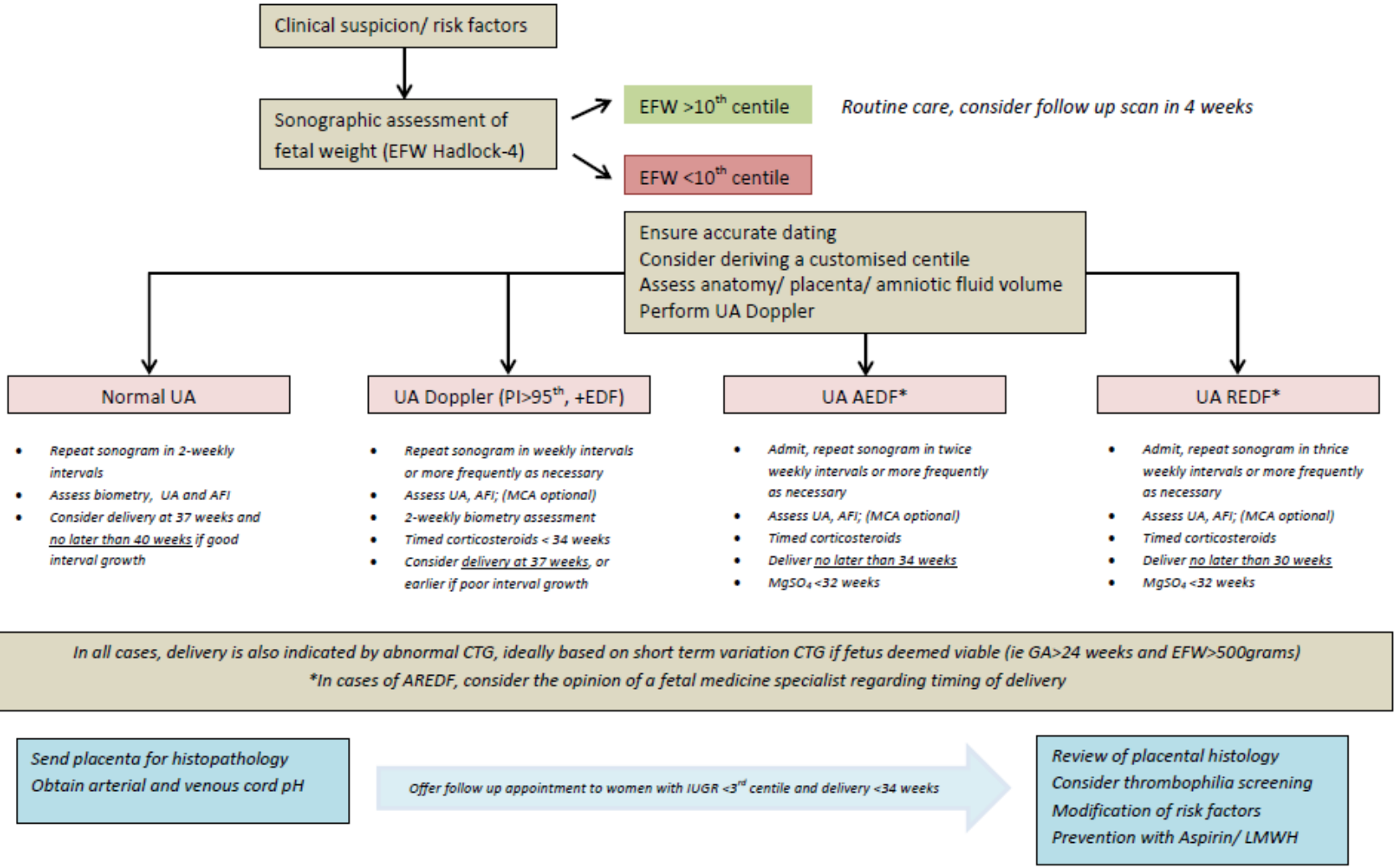
APPENDIX II. Customised Growth curve (FH and EFW) – Example

www.gestation.net**		Trial version ONLY	
		GROW chart WebApp	GROW chart WinApp
	United Kingdom	Access	Download
	Australia	Access	Download
	New Zealand	Access	Download
	United States	Access	Download
	Ireland	Access	Download
	Sweden	Access	Download
	Netherlands	Access	Download
	Universal *	Access	Download



** Please note that a licence fee applies when accessing this website. Similar growth curves and information on co-efficients in relation to customisation of fetal weight will shortly be available on www.perinatalireland.ie

APPENDIX III. Algorithm – Management of FGR



ABBREVIATIONS: **EFW**, *estimated fetal weight (Hadlock-4)*; **UA**, *umbilical artery*; **EDF**, *end-diastolic flow*; **AEDF**, *absent end-diastolic flow*; **REDF**, *reversed end-diastolic flow*; **AFI**, *amniotic fluid index*; **AREDF**, *absent or reversed end-diastolic flow in UA*; **CTG**, *cardiotocograph*; **MCA**; *middle cerebral artery*; **GA**, *gestational age*.

Table 1. Comparison of Clinical Practice Guidelines on FGR (UK, USA, Canada and Ireland)

	RCOG Green-top Guideline (No. 31)	ACOG/ SMFM Practice Bulletin (No. 134)	SOGC Clinical Practice Guideline (No. 295)	HSE/ RCPI Clinical Practice Guideline (No. 29)
Country	United Kingdom	United States	Canada	Ireland
Issued	February 2013	May 2013	August 2013	March 2014
Name	The Investigation and Management of the Small-for-Gestational-Age Fetus	Fetal Growth Restriction	Intrauterine Growth Restriction: Screening, Diagnosis, and Management	Fetal Growth Restriction – Recognition, Diagnosis & Management
Pages	34	12	8	26
References	197	142	55	48
Quality evaluation & Grading of recommendation	Yes, system not specified	US Preventive Services Task Force	Canadian Task Force on Preventive Health Care	No (given little RCT evidence for management of FGR pregnancies)
Definition	SGA: EFW/ AC <10th centile Severe SGA: EFW/ AC <3rd centile FGR: pathological restriction	FGR: EFW <10th centile SGA: BW <10th centile	SGA: EFW <10th centile IUGR: EFW <10th centile (pathological)	FGR: EFW <10th centile SGA: physiological IUGR: pathological (ie abnormal UA, poor interval growth velocity, EFW <3rd centile)
Viability	≥24 weeks and EFW ≥500grams	not mentioned	≥24 weeks and EFW ≥500grams	≥24 weeks and EFW ≥500grams
Detection	Palpation limited accuracy Serial customised SFH after 24 weeks	FH 65-85% sensitivity, 96% specificity Ultrasonography may be better screening modality (maternal obesity, multiple pregnancy, fibroids)	SFH poor sensitivity and specificity SFH limited value, however only physical examination available	FH limited value, however only physical examination available Clinical assessment of fetal size at each visit Ultrasound better screening modality (obesity, fibroids)
Screening	Assess risk factors First/ second trimester screening Women with RF: serial biometry and UA Women with 3+ RF: UtA Doppler 20-24 PAPP-A<0.415 MoM Fetal echogenic bowel	Assess risk factors Review medical/ obstetric history FH at each visit between 24-38 weeks Discrepancy >3cm concerning	Accurate dating, assess risk factors First/ second trimester screening Women with RF: UtA Doppler 19-23 weeks Discrepancy >3cm concerning	Accurate dating, assess risk factors Review medical/ obstetric history Women with RF: serial biometry and UA every 2-4 weeks Clinical assessment of fetal size at each visit, if concerns, refer for biometry

Customisation	Yes, may improve prediction of perinatal outcome	Not been shown to improve outcomes	Not mentioned	Consider, may improve prediction of perinatal outcome
Management	Examination of fetal anatomy Offer MFM referral Serial biometry every 3 weeks	Examination of fetal anatomy Serial biometry every 3-4 weeks	Examination of fetal anatomy Serial biometry every 2 weeks Detailed ultrasound of placenta, if abnormal → MFM consultation	Examination of fetal anatomy, if abnormal → MFM consultation Serial biometry, AFI and UA every 2 weeks
Amniocentesis	Consider if additional soft markers or structural abnormalities	Consider if additional soft markers or structural abnormalities	Consider if additional soft markers or structural abnormalities	Consider if additional soft markers or structural abnormalities
TORCH	Consider +/- malaria and syphilis	Not mentioned	Consider	Consider
UtA Doppler	Yes (20-24 weeks), moderate predictive value	Not mentioned	Yes (19-23 weeks)	Not recommended
UA Doppler	Yes	Yes	Yes	Yes
MCA	Limited accuracy, should not be used to time delivery	Not mentioned	Yes (if UA abnormal)	Optional (if UA abnormal), should not be used to time delivery
DV	Yes (if UA abnormal), use to time delivery	Not been shown to improve outcomes	Yes (if UA abnormal)	No
UV	Yes	Not mentioned	Consider	Not mentioned
CTG	Yes STV (not in isolation)	Yes	Yes (not in isolation)	Yes, ideally STV
Amniotic fluid	Assess single DVP (not in isolation)	Yes	Yes	Yes
BPP	Not in preterm SGA fetuses	Yes	Yes (consider weekly)	No, limitations preterm FGR
Delivery		Depends on underlying aetiology, patient-choice at preterm gestations, individualised, multidisciplinary		Individualised, multidisciplinary
Timing	Consider after 37 weeks AREDF UA: 30-32 weeks, earlier based on abnormal DV or UV Abnormal MCA: 37 weeks Abnormal UA > 32 weeks: 37 weeks	Isolated FGR: 38+0 – 39+6 weeks FGR+ additional RF (oligo, abnormal PI, maternal comorbidities): 34+0 – 37+6 weeks	Consider after 37 weeks Abnormal CTG (based on fetal viability) Isolated: 38-40 weeks	SGA: consider ≥ 37-40 weeks UA PI >95th centile: 37 weeks AEDF: no later than 34 weeks REDF: no later than 30 weeks Abnormal CTG (based on fetal viability)
Mode	CS if AREDF If positive EDF: offer IOL with continuous monitoring once contracting	FGR alone not an indication for CS	Not mentioned	CS likely if AREDF or preterm Abnormal UA: consider IOL with continuous monitoring once contracting

Steroids	Between 24+0 and 35+6 weeks	Prior to 34 weeks	Prior to 34 weeks	Between 24+0 and 34+0 weeks, up until 38+0 if elective CS
MgSO4	(Prior to 30 weeks)	Prior to 32 weeks	Not mentioned	Prior to 32 weeks
Placental histology	Not mentioned	Not mentioned	Yes	Yes
Prevention	Smoking cessation, Aspirin (prior to 16 weeks), no evidence for dietary modifications, progesterone, calcium	Insufficient evidence for Aspirin, bedrest, nutritional/ dietary supplementation	Smoking cessation, Aspirin (12-36 weeks)	Smoking cessation, Aspirin (prior to 16 weeks)
Recurrence	At least 2-fold	20%	Not mentioned	25%
Postnatal Management	Not mentioned	Not mentioned	Not mentioned	Postnatal counselling if IUGR and preterm delivery <34 weeks Review of placental histology and investigation of underlying causes (ie thrombophilia testing)

Abbreviations:

HSE; *Health Service Executive*; **RCPI**, *Royal College of Physicians of Ireland*; **RCOG**, *Royal College of Obstetricians & Gynaecologists (London)*; **ACOG**, *American College of Obstetricians & Gynecologists*; **SOGC**, *Society of Obstetricians & Gynaecologists of Canada*; **RCT**, *randomised controlled trial*; **FGR**, *fetal growth restriction*; **EFW**, *estimated fetal weight*; **SGA**, *small for gestational age*; **IUGR**, *intrauterine growth restriction*; **UA**, *umbilical artery*; **AC**, *abdominal circumference*; **BW**, *birthweight*; **FH**, *fundal height*; **SFH**, *symphysio-fundal height*; **RF**, *risk factor*; **UtA**, *uterine artery*; **PAPP-A**, *pregnancy-associated plasma protein A*; **MFM**, *maternal fetal medicine*; **AFI**, *amniotic fluid index*; **MCA**, *middle cerebral artery*; **DV**, *ductus venosus*; **UV**, *umbilical vein*; **CTG**, *cardiotocograph*; **STV**, *short term variation CTG*; **DVP**, *deepest vertical pocket*; **BPP**, *biophysical profile score*; **PI**, *pulsatility index*; **AEDF**, *absent end-diastolic flow*; **REDF**, *reversed end-diastolic flow*; **AREDF**, *absent or reversed end-diastolic flow*; **CS**, *Caesarean section*; **IOL**, *induction of labour*; **EDF**, *end-diastolic flow*.