2. Invited commentary: Fetal growth restriction and the risk of perinatal mortality

Fetal growth restriction (FGR) is an important and common complication of pregnancy that is associated with increased perinatal morbidity and mortality.[33,34] It is estimated that FGR affects up to 10% of pregnancies. In addition to congenital malformations and infectious causes, FGR has been identified as a major contributor to perinatal mortality.[35,36]

Perinatal deaths commonly occur in women with coexistent maternal co-morbidities or who have a history of adverse pregnancy outcomes, such as recurrent pregnancy loss, stillbirth or neonatal death.[37] In addition, ethnic minorities are an overrepresented group among women who experience perinatal deaths.[38,39] The perinatal outcome of FGR fetuses is largely dependent on the severity of growth restriction with those below the 3rd centile and/ or with abnormal umbilical artery (UA) Doppler measurements at greatest risk of adverse outcome.[40,41] Other important prenatal determinants of perinatal outcome are gestational age at delivery and birthweight.[42]

Definition, Diagnosis and Management of FGR

There is no international consensus as to which clinical and sonographic parameters are the most appropriate to define intrauterine growth failure. The traditional cut-off used to define FGR, a term often interchangeably used with small-for-gestational age (SGA) or intrauterine growth restriction (IUGR), is an abdominal circumference (AC) or estimated fetal weight (EFW) below the 10th centile plotted against population[43] or customised[44] growth standards. The 10th centile has been suggested as a cut-off, given that at this level the risk of perinatal morbidity and mortality increases. At this arbitrary cut-off however the distinction between normal and pathologic growth often cannot reliably be made in the antenatal setting, and approximately 50-70% will be constitutionally healthy small infants not at risk of adverse perinatal outcome.[45,46] In contrast, some infants born above the 10th centile, who might have been destined, for example, to be on the 80th centile, will be growth restricted.

Unsurprisingly, the inconsistencies in FGR definition and diagnosis lead to further uncertainties regarding the optimal antenatal surveillance and management of affected pregnancies. Unfortunately, there is very little evidence from randomised controlled trials to inform best practice for antenatal surveillance regimens in FGR. In order to improve and standardise the care of pregnancies affected by FGR, a clinical practice guideline applicable for the Irish maternity setting was recently published.[47]

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34 Baschat AA, Cosmi E, Bilardo CM, et al. Predictors of neonatal outcome in early-onset placental dysfunction. Obstet Gynecol 2007;109(2 Pt 1):253-261.
35 Manning E, Corcoran P, Meaney S, Greene RA, on behalf of the Perinatal Mortality Group. Perinatal Mortality in Ireland, Annual Report 2011. Cork: National Perinatal Epidemiology Centre. 2013.
36 Gardosi J, Madurasinghe V, Williams M, Malik A, Francis A. Maternal and fetal risk factors for stillbirth: population based study. BMJ 2013;346:f108.
37 Frias AE, Jr., Luikenaar RA, Sullivan AE, et al. Poor obstetric outcome in subsequent pregnancies in women with prior fetal death. Obstet Gynecol 2004;104(3):521-526.
38 Unterscheider J, O'Donoghue K, Daly S, et al. Fetal growth restriction and the risk of perinatal mortality-case studies from the multicentre PORTO study. BMC Pregnancy Childbirth 2014;14:63.
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40 Lees C, Marlow N, Arabin B, et al. Perinatal morbidity and mortality in early-onset fetal growth restriction: cohort outcomes of the trial of randomized umbilical and fetal flow in Europe (TRUFFLE). Ultrasound Obstet Gynecol 2013;42(4):400-408.
41 Unterscheider J, Daly S, Geary MP, et al. Optimizing the definition of intrauterine growth restriction: the multicenter prospective PORTO Study. Am J Obstet Gynecol 2013;208(4):290 e291-296.
42 Baschat AA, Cosmi E, Bilardo CM, et al. Predictors of neonatal outcome in early-onset placental dysfunction. Obstet Gynecol 2007;109(2 Pt 1):253-261.
43 Hadlock FP, Harrist RB, Sharman RS, Deter RL, Park SK. Estimation of fetal weight with the use of head, body, and femur measurements--a prospective study. Am J Obstet Gynecol 1985;151(3):333-337.
44 Gardosi J, Chang A, Kalyan B, Sahota D, Symonds EM. Customised antenatal growth charts. Lancet 1992;339(8788):283-287.
45 Lees C, Marlow N, Arabin B, et al. Perinatal morbidity and mortality in early-onset fetal growth restriction: cohort outcomes of the trial of randomized umbilical and fetal flow in Europe (TRUFFLE). Ultrasound Obstet Gynecol 2013;42(4):400-408.
46 Unterscheider J, Daly S, Geary MP, et al. Optimizing the definition of intrauterine growth restriction: the multicenter prospective PORTO Study. Am J Obstet Gynecol 2013;208(4):290 e291-296.
47 Clinical Practice Guideline No 29 (2014). Fetal Growth Restriction – Recognition, Diagnosis and Management: Institute of Obstetricians and Gynaecologists, Royal College of Physicians of Ireland and Directorate of Strategy and Clinical Programmes, Health Service Executive.

FGR and Perinatal Mortality

Advances in obstetrical and critical neonatal care are reflected in a substantial decrease in the overall perinatal mortality rate (PNMR) in high income countries.[48] While this effect is mainly seen in a reduction of early neonatal deaths, stillbirth rates have remained largely unchanged over the past years.[49,50] Stillbirth affects 1 in 200 pregnancies; as outlined in this report there were 71,755 births and 445 perinatal deaths in 2012. Similar to the previous NPEC perinatal mortality report,[51] stillbirths and early neonatal deaths accounted for 68% (n=304) and 32% (n=141) of perinatal deaths respectively, corresponding to a PMR of 6.2/ 1,000 births. Of the 445 perinatal deaths, a third (n=148) were attributed to congenital structural or genetic abnormalities (corrected PMR 4.1/ 1,000). Half of infants affected by perinatal deaths in 2012 were identified as having birthweights below the 10th customised centile.

As outlined in Figure 2.1, whether or not FGR is identified prenatally influences the risk of stillbirth. While the risk of stillbirth (SB) in pregnancies with prenatally identified FGR is 1% (9.7/ 1,000 births), pregnancies with unrecognised FGR carry an over 8-fold increased risk of SB when compared to pregnancies without FGR (19.8 versus 2.4/ 1,000 births).[52] Some studies state that FGR may be overestimated as attributing factor in perinatal mortality cases due to intrauterine retention following intrauterine demise and the effect of maceration.[53]

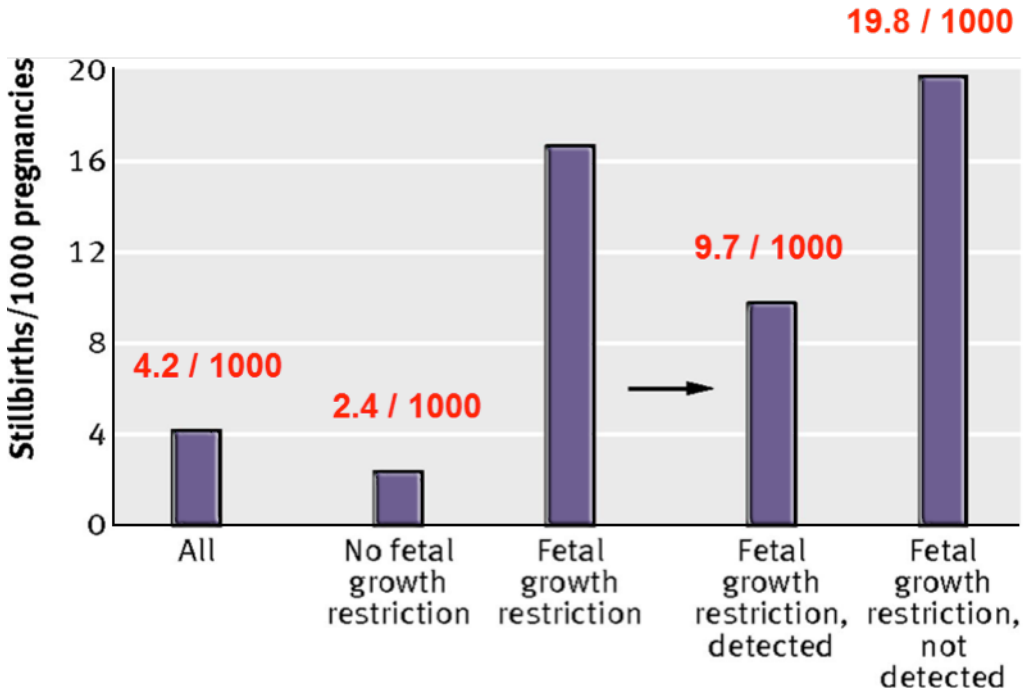
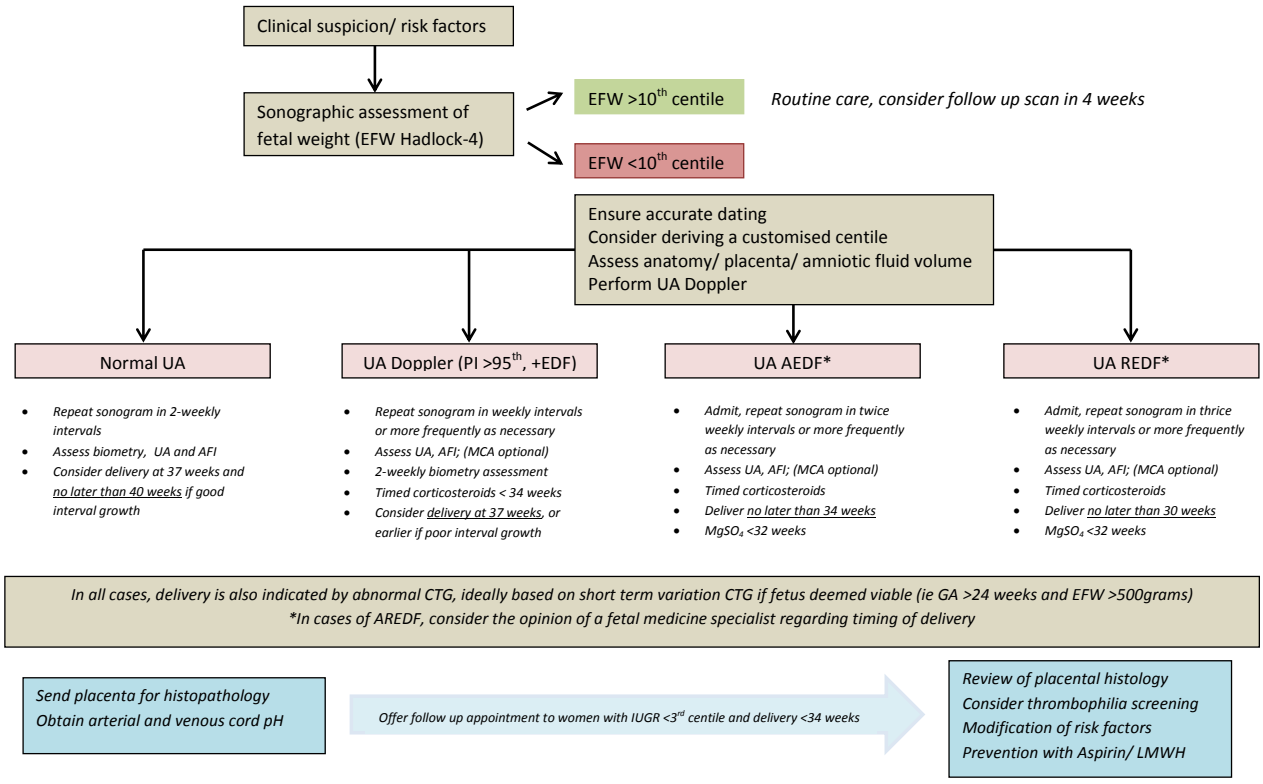


Figure 2.1: Stillbirth rates for pregnancies overall and for pregnancies with detected and undetected FGR (from Gardosi J)[54]

48 Flenady V, Middleton P, Smith GC, et al. Stillbirths: the way forward in high-income countries. Lancet 2011;377(9778):1703-1717.
49 Lawn JE, Blencowe H, Pattinson R, et al. Stillbirths: Where? When? Why? How to make the data count? Lancet 2011;377(9775):1448-1463
50 Cousens S, Blencowe H, Stanton C, et al. National, regional, and worldwide estimates of stillbirth rates in 2009 with trends since 1995: a systematic analysis. Lancet 2011;377(9774):1319-1330.
51 Manning E, Corcoran P, Meaney S, Greene RA, on behalf of the Perinatal Mortality Group. Perinatal Mortality in Ireland, Annual Report 2011. Cork: National Perinatal Epidemiology Centre. 2013.
52 Gardosi J, Madurasinghe V, Williams M, Malik A, Francis A. Maternal and fetal risk factors for stillbirth: population based study. BMJ 2013;346:f108.
53 Maroun LL, Graem N. Autopsy standards of body parameters and fresh organ weights in nonmacerated and macerated human fetuses. Pediatr Dev Pathol 2005;8(2):204-217.
54 Gardosi J, Madurasinghe V, Williams M, Malik A, Francis A. Maternal and fetal risk factors for stillbirth: population based study. BMJ 2013;346:f108.

Improving the Antenatal Detection of FGR

One of the core problems in FGR is the poor detection rate in pregnancies that are at subsequent risk of adverse outcome, in particular stillbirth. Current antenatal detection rates of FGR are reported to be as low as 25 to 36%.[55,56] Therefore, a preventative strategy to reduce stillbirths is to improve the antenatal detection of fetal growth failure. Whenever FGR is diagnosed prenatally, increased surveillance and timely delivery aims to improve perinatal outcome in FGR, balancing the risk of antepartum stillbirth by remaining in utero and iatrogenic prematurity potentially causing significant morbidity or neonatal death by too early intervention. Figure 2.2 illustrates an algorithm for the management of fetal growth restriction as recommended in the national clinical practice guideline.[57]



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*, **LMWH**, *low molecular weight heparin.*

Figure 2.2: Algorithm for management of fetal growth restriction

55 McCowan LM, Roberts CT, Dekker GA, et al. Risk factors for small-for-gestational-age infants by customised birthweight centiles: data from an international prospective cohort study. BJOG 2010;117(13):1599-1607.
56 Chauhan SP, Beydoun H, Chang E, et al. Prenatal Detection of Fetal Growth Restriction in Newborns Classified as Small for Gestational Age: Correlates and Risk of Neonatal Morbidity. Am J Perinat 2014;31(3):187-94.
57 Clinical Practice Guideline No 29 (2014). Fetal Growth Restriction – Recognition, Diagnosis and Management: Institute of Obstetricians and Gynaecologists, Royal College of Physicians of Ireland and Directorate of Strategy and Clinical Programmes, Health Service Executive.

Abdominal palpation and fundal height measurement are imprecise in screening for fetal growth aberrations; they are, however, the only physical examination methods available. In current practice a scan for fetal biometry is only performed when clinical concerns over fetal size are raised, and in the presence of significant maternal risk factors or prior pregnancy complications.

In an effort to improve the antenatal detection of FGR in a maternity care system which does not provide serial ultrasound scanning for all pregnancies, Gardosi et al[58] have formulated customised fundal height charts which take into account physiological maternal variables. Another recent study focused on improving the prenatal detection by the provision of routine ultrasound scans at 28 and 36 weeks' gestation; a research group at Cambridge University recently presented level 1 evidence of diagnostic effectiveness that this approach performs well as a screening test to detect FGR in a population of unselected nulliparous women.[59]

A care model whereby every pregnant patient receives an ultrasound scan at least 4 weekly intervals would improve identification of growth failure based on population and customised growth standards. Given that FGR can also occur in infants born with birthweights above the 10th centile cut-off, this approach would also allow us to comment on growth trajectories which have been identified as an important factor in the prediction of morbidity and mortality outcomes.[60] The relevance to clinical practice in reducing perinatal morbidity and mortality could be the subject of future research studies comparing various models of antenatal care. This will impact on resource issues, increase obstetric intervention but no doubt will have an impact on the antenatal detection and reduction in perinatal deaths.

58 Gardosi J, Francis A. Controlled trial of fundal height measurement plotted on customised antenatal growth charts. BJOG 1999;106(4):309-317.
59 Sovia U, Smith G, Dacey A. Level 1 evidence for the diagnostic effectiveness of routine sonography as a screening test for small for gestational age (SGA) infants. Am J Obstet Gynecol 2014;210(1):S408.
60 Barker ED, McAuliffe FM, Alderdice F, et al. The role of growth trajectories in classifying fetal growth restriction. Obstet Gynecol 2013;122(2 Pt 1):248-254.