

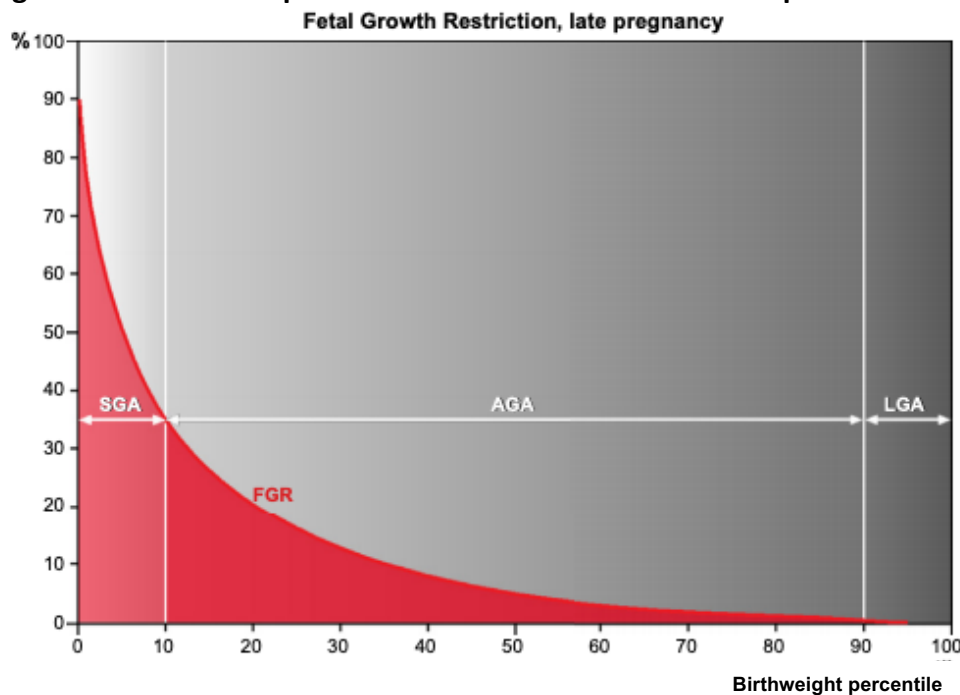
Recognition and management of small for gestational age pregnancies

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1. Definitions of small for gestational age and fetal growth restriction

The terms small for gestational age (SGA) and fetal growth restriction (FGR) are often used interchangeably in the obstetric literature. Whilst there is considerable overlap, these terms are not synonymous. SGA is defined as an infant with birthweight less than the 10th centile or a fetus with an estimated fetal weight (EFW) on a customised growth chart less than the 10th centile for gestation.^{1, 2} Customised birthweight centiles adjust fetal size and birthweight for maternal characteristics that influence fetal growth (height, weight, parity and ethnicity)³ and better identify fetuses at high risk of morbidity and mortality than population standards.⁴ FGR (a fetus that has failed to reach its growth potential) is more difficult to define in practice as not all growth restricted infants are SGA (figure 1).⁵

Figure 1: Schematic representation of the theoretical overlap between FGR and SGA ⁵



AGA, appropriate for gestational age; FGR, fetal growth restriction; LGA, larger for gestational age; SGA, small for gestational age. Ganzevoort et al. *Fetal growth and risk assessment*. *Am J Obstet Gynecol* 2019.

In NZ SGA pregnancies identified before birth that have evidence of placental insufficiency (abnormal umbilical artery, uterine artery, middle cerebral artery, or cerebro-placental ratio Doppler indices) or extreme smallness (estimated fetal weight <3rd centile) are considered to have FGR.^{1, 6} In addition, a fetus that is not SGA but has estimated fetal weight or abdominal circumference reducing centiles by >30% on serial scans is also considered to have FGR.

2. Pathophysiology

SGA/FGR is not a single disease entity but the result of a variety of fetal, maternal and placental conditions causing failure to achieve full growth potential. In general terms, most cases of FGR can be considered to result from reduced tissue deposition caused by reduced nutritional supply. This may be due to insufficient remodelling of the maternal spiral arteries leading to reduced and abnormal utero-

placental blood flow and subsequent oxidative stress resulting in placental damage and poor placental transport of nutrients. For a detailed review see Burton, and Jauniaux.⁷

In about 5% of cases FGR/SGA is secondary to a fetal cause such as chromosomal abnormality, congenital infection (e.g. cytomegalovirus) or major structural abnormality. This is more likely to be the case when FGR occurs early (i.e. in the second or early third trimester).

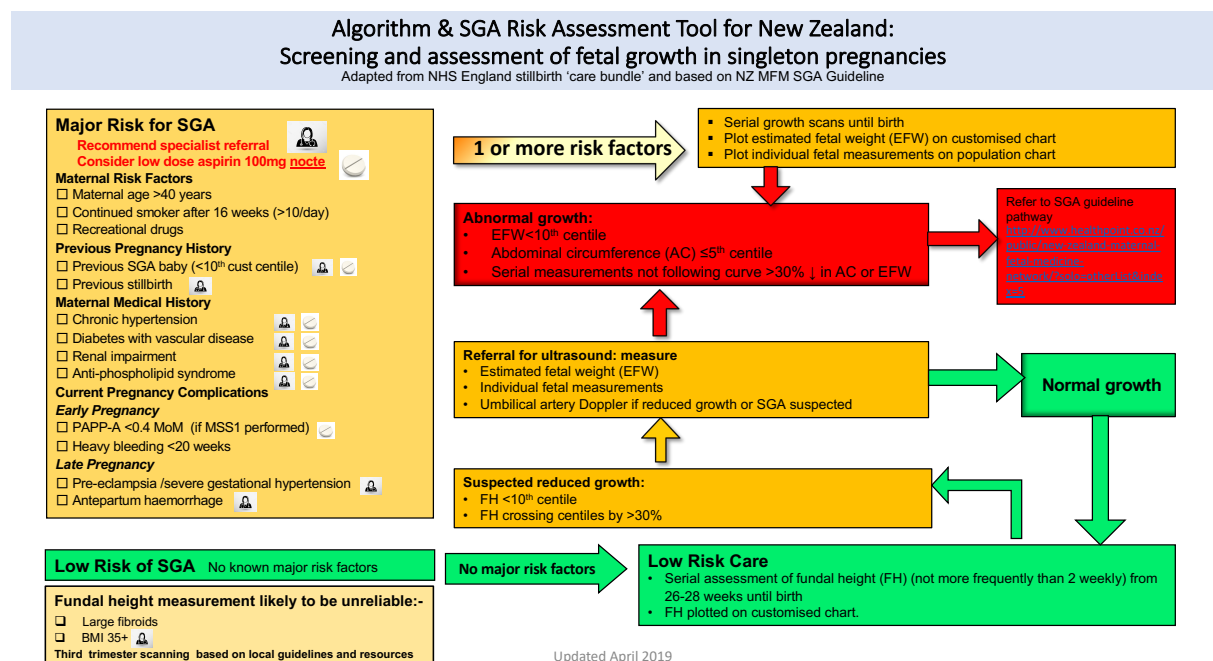
3. Why does SGA/FGR matter?

Babies who are born SGA are at increased risk of perinatal mortality - 30% of stillbirths ≥ 28 weeks' in NZ have a birthweight $< 10^{\text{th}}$ customised centile.⁸ They also have increased perinatal morbidity including neonatal encephalopathy.⁸ Childhood complications such as short stature, high blood pressure and cerebral palsy are more common⁹⁻¹¹ and as adults they are more likely to develop diabetes and experience cardiovascular morbidity and mortality.¹² If women at high risk can be identified early in pregnancy and prophylactic measures and appropriate surveillance instigated, some of these growth restricted babies and their subsequent complications in the perinatal period and in later life may be preventable. Currently there are no treatments for established FGR/SGA.

4. Identification of SGA pregnancies

In routine clinical practice less than 30% of SGA fetuses are identified as being SGA before birth. The Growth Assessment Programme (GAP) has recently been introduced into maternity care in New Zealand. This programme involves education about standardised measurement of fundal height (see video <https://vimeo.com/148707303>: password measureright) and use of Gestation Related Optimum Weight (GROW) charts to plot fundal height (or estimated fetal weight from ultrasound), education about major risk factors for SGA and which women should be offered low dose aspirin (LDA) to reduce SGA risk, recommendations for serial scanning in women with major risk factors, and optimum management with timely delivery according to the NZMFM SGA Guideline if SGA is suspected.¹ After GAP training 50-60% of SGA pregnancies are typically identified correctly before birth compared to about 30% before implementation of training.

Figure 2: SGA Risk Assessment Tool for NZ (J Cowan, L McCowan, L Sadler 2018)



5. Clinical risk factors for SGA

There are a number of major maternal clinical risk factors for non-anomalous SGA (figure 2) many of which can be identified at the first antenatal visit and others which develop during pregnancy. Clinical pathways for SGA management vary according to degree of risk as summarised in figure 2.

6. Prevention of SGA

Cigarette Smoking.

At a population level smoking is the single most avoidable cause of adverse pregnancy outcomes, including SGA births. Smoking in pregnancy is also an important contributor to disparities in adverse pregnancy outcomes in New Zealand, as rates of smoking among Māori (37%) and also Pacific women (12%) are higher than among European women (7%).¹³ All women should have a smoking history taken at pregnancy booking, including exposure to passive smoking. Ceasing smoking early in pregnancy (by 16 weeks of gestation) is an effective strategy to reduce the incidence of SGA¹⁴ and stopping smoking at a later time in pregnancy will improve birthweight.¹⁵ Additional benefits of stopping smoking early in pregnancy include reduced preterm birth and stillbirth as well as improved child health.^{14, 16} Referral to smokefree services should be arranged for all pregnant women who smoke and incentive based programs are the most effective to support cessation.^{17, 18}

Low dose aspirin (LDA)

Women with major medical risk factors for SGA /FGR (figure 2) or with a previous SGA /FGR baby should be offered prophylactic treatment with low dose aspirin 100mg nocte started before 16 weeks of gestation (ideal gestation to initiate treatment=12 weeks').¹⁹ A recent systematic review reported that LDA treatment initiated at ≤ 16 weeks' was associated with a 44% reduction in FGR, RR 0.56 95%CI (0.44-0.70). There was a dose response relationship with LDA dosage with 100mg having greater efficacy than 60mg.¹⁹ The effect of LDA on reducing FGR and also preeclampsia²⁰ is likely multifactorial including: inhibition of the potent vaso-constrictor thromboxane-A2, enhancement of the vasodilator nitric oxide, and reduced oxidative stress.²¹

Low molecular weight heparin

Disappointingly trials of low molecular weight heparin have not been effective in the prevention of FGR or preeclampsia.^{21, 22}

7. Clinical assessment– measurement of fundal height and use of GROW charts

An individualised GROW chart should be generated for pregnant women at booking for pregnancy care. Height and weight must be measured and not self-reported. BMI is calculated automatically by the GROW software after entering height and weight. If there are previous birth(s) and birthweight and gestation are known a birthweight centile is generated for previous babies. This allows clinicians to identify mothers with previous SGA infants.

Software for GROW charts is available for demonstration purposes as a free download:

<https://demo.growservice.org/NZ/Account/Login> (login and password demo_nz). Note this link should not be used to download charts for clinical use.

When GROW is used for pregnant women in the District Health Board (DHB) system a unique ID is generated in the GROW program and the GROW chart is linked to the birthweight centile when the baby is born. You may have an opportunity to attend GAP training and e-learning is available from the Perinatal Institute by emailing ehassan@perinatal.org.uk. On completion of GAP education the login and password for the GROW-App for clinical practice is provided by the Perinatal Institute.

At fortnightly intervals from 26-28 weeks' the fundal height is measured using the standardised method and plotted on the GROW chart (x) which incorporates the individual maternal factors included in customised centiles.

Women who do not have major risk factors for SGA and in whom it is possible to obtain a reliable measurement of fundal height, do not require routine growth scans. If fundal height is less than the 10th centile or is crossing centiles by >30% then a growth scan is recommended with referral to a specialist if there is concern re SGA or FGR after scanning.

If an ultrasound is performed, estimated fetal weight is also plotted (●) on the GROW chart. Use of a GROW chart has been shown to increase antenatal detection of SGA pregnancies and has the potential to improve clinical decision-making both by reducing the number of ultrasound scans performed for small women with appropriately sized babies and prompting further investigation with Doppler studies for those with suspected SGA/FGR. Examples of GROW charts are shown in figures 3a and 3b.

Figure 3a: Ms Tall GROW chart:

Previous SGA infant, current pregnancy SGA by fundal height (x) and scan (●) and birthweight 2800g at 38 weeks 4days (SGA).

Ms Tall

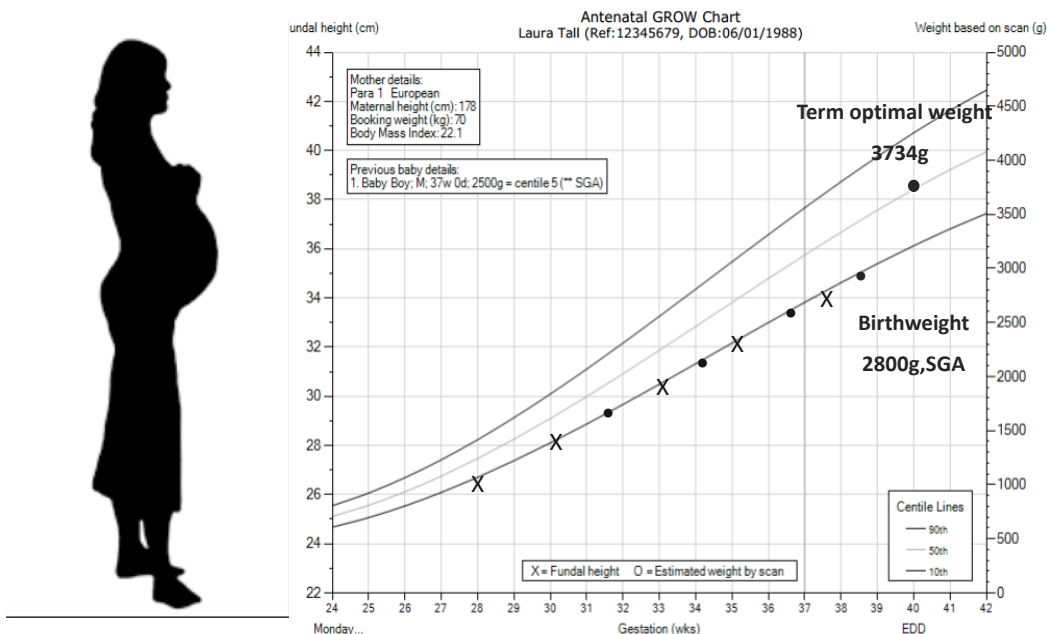


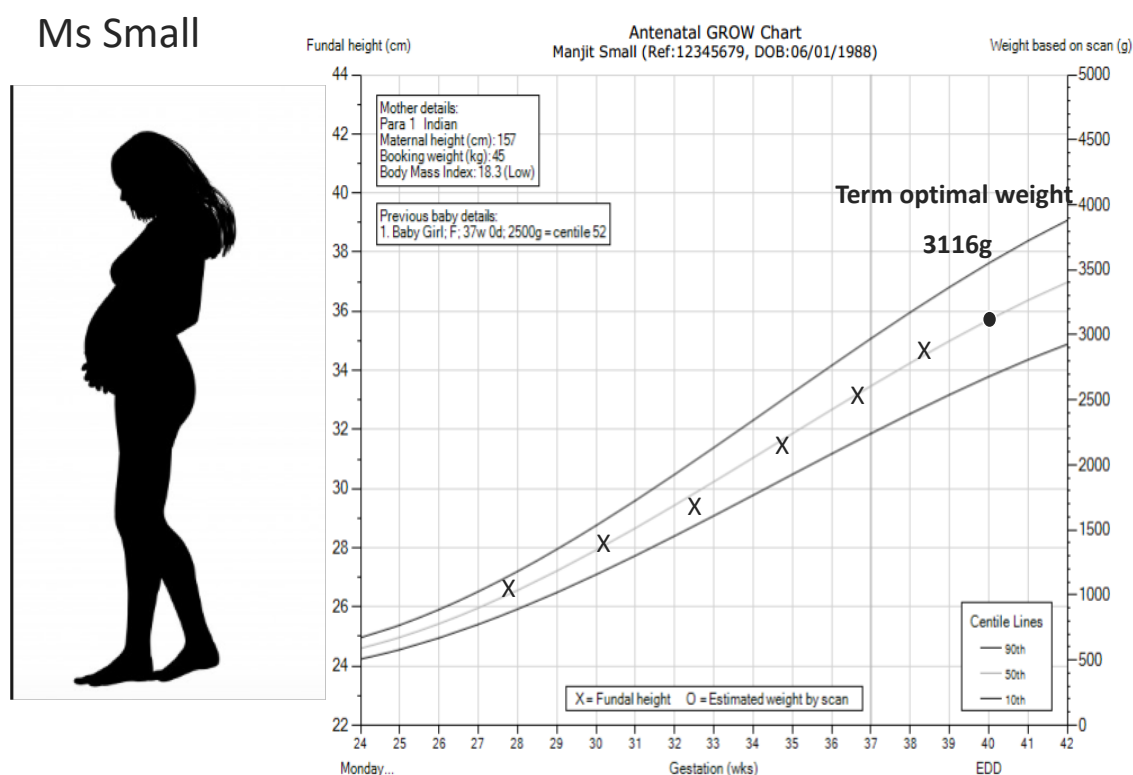
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GROW chart generated by LM McCowan

After the GROW chart was generated it was recognised that Ms Tall had a previous SGA baby and she therefore received serial growth scans in addition to fundal height measurements. Her current baby was found to be SGA by fundal height and ultrasound and she was induced just after 38 weeks'. This baby's birthweight was 2800gm whereas the average weight at term (term optimal weight) for Ms Tall would have been 3734g.

Figure 3b: Ms Small GROW chart

Appropriate growth. Note difference in term optimal weight for Ms Tall and Ms Small.



Courtesy of www.publicdomainpictures.net

GROW chart generated by LM McCowan

Ms Small's previous baby had a birthweight on the 52nd centile and in the current pregnancy fundal height measurements were normal and no growth scans were required. She gave birth after spontaneous labour at 39 weeks and 6 days to a baby weighing 3210 g.

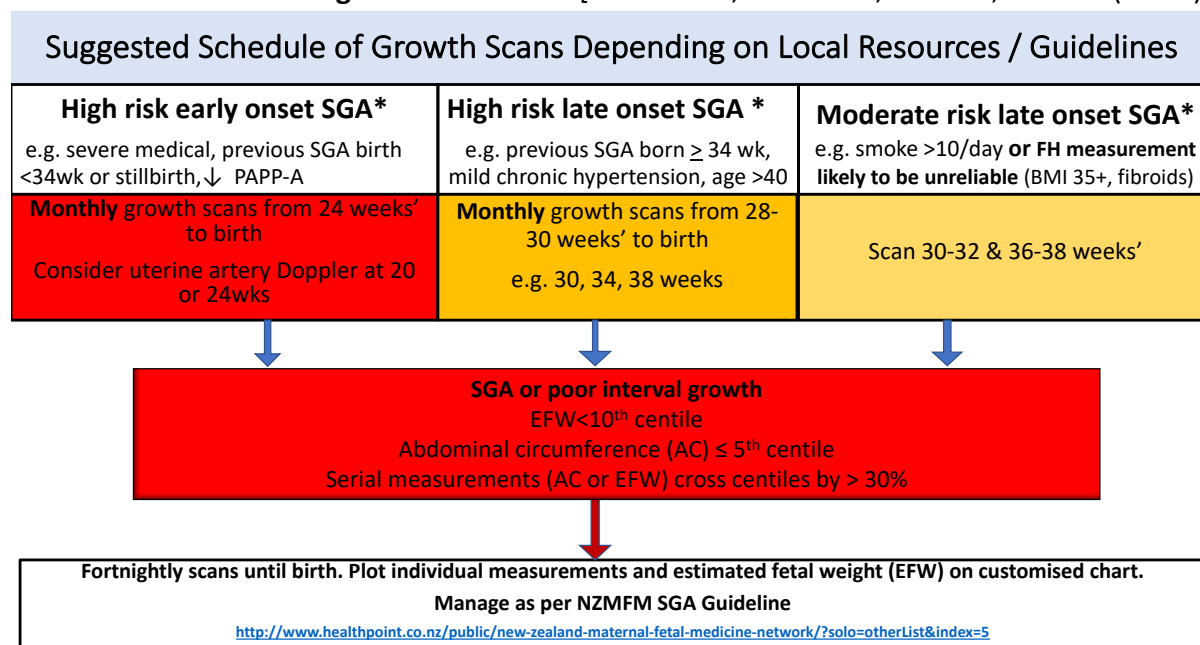
8. Ultrasound assessment of fetal growth

Early and accurate assessment of gestational age, ideally confirmed by a scan at 12 weeks' enhances later assessment of fetal growth. The anatomy scan, generally performed at 19-20 weeks', also includes assessment of fetal size and occasionally may detect evidence of early onset FGR.

For women with major risk factors for SGA, a schedule of regular growth scans should be planned with timing and frequency determined by the risk factors. In women with major risk factors scans should continue until birth as the majority (85 per cent) of SGA babies are born beyond 37 weeks.²³

Scans should include fetal biometry, head circumference (HC), biparietal diameter (BPD), abdominal circumference (AC) and femur length (FL) as well as an estimate of fetal weight (EFW). Biometry measurements should be plotted on a population growth chart and EFW on a customised growth chart. Serial measurements of AC and EFW are superior to a single measure for prediction of growth restriction. A suggested schedule of scanning is presented in figure 4. This approach has received support by the GAP Accident Compensation (ACC) working group, the New Zealand Clinical Directors in Obstetrics and NZ College of Midwives, although it is acknowledged that in some areas there is limited access to scanning and need for co-payment is a financial barrier for some women.

Figure 4: Suggested schedule of ultrasound scans in women with SGA risk factors or unsuitable for fundal height measurement [LMcCowan, E Deverall, L Sadler, J Cowan(2018)].



* Early onset SGA=SGA baby born <34 weeks, late onset SGA = SGA baby born ≥34 weeks

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If the fetus is SGA, (AC or estimated fetal weight less than 10th centile), or if measurements of AC or EFW are crossing centiles by > 30%, then Doppler studies are recommended. When interpreting results of growth scans it is important to remember that the margin of error in measurements is between 5 and 15%.^{24, 25}

Routine scanning in the third trimester in low risk populations has not been shown to improve perinatal outcome and is not currently recommended but further very large trials are required.²⁶

9. Management of SGA/FGR

As there are no current treatments for SGA/FGR, optimal management aims to achieve delivery of the infant in the best possible condition, balancing the risks of prematurity against the risks of the in-utero environment. The goal of management/surveillance is therefore to identify the fetus at risk of intrauterine acidaemia and death. The optimum outcome is timely delivery before the onset of acidaemia while endeavouring to prevent unnecessary intervention and iatrogenic injury.

9.1 Identify other causes and co-existing disease

Five to ten percent of SGA is associated with fetal causes such as: chromosomal/genetic disorders, major structural abnormality or infection, with the risk being greater if SGA is diagnosed at the time of the anomaly scan or later in the second or early third trimester. Referral should be arranged to an MFM specialist service. Investigations will include review of fetal anatomy and consideration of amniocentesis for karyotype/microarray, infection serology +/- amniotic fluid PCR and other relevant investigations.

Abnormal placentation is important in the pathogenesis of both SGA/FGR and also in preeclampsia. However, the majority (more than 80 per cent) of cases of SGA occur in normotensive women. Early

onset SGA is more likely to be associated with preeclampsia, with almost 40 per cent of women delivering an SGA infant at less than 34 weeks having co-existing preeclampsia compared with only 4 per cent with SGA at term.²³ Women presenting with SGA should have regular blood pressure monitoring.

9.2 Fetal movement monitoring

Reduced intensity and frequency of fetal movements often precede fetal death and it is recommended that all women with known SGA/FGR fetuses promptly report any change in their normal fetal movement patterns to their care provider.²⁷

9.3 Doppler studies

Umbilical artery Doppler studies

During normal pregnancy, resistance in the umbilical circulation falls and blood flow velocities increase with advancing gestation (figure 5). Abnormal umbilical artery (UA) Doppler waveforms, especially the most extreme abnormalities with absent or reversed-end diastolic flow, are associated with major placental abnormalities, including hypo-vascularity in the small arterioles and capillaries and reduced placental villous surface area.^{28, 29} Fetal risk is related to the severity of the Doppler abnormality.³⁰

UA Doppler studies in high risk pregnancies reduce perinatal morbidity and mortality, by allowing timely delivery of the vulnerable fetus with abnormal Doppler waveforms.³¹ An umbilical artery Doppler should be performed routinely in all women where ultrasound identifies a SGA/FGR fetus.

Doppler studies in late onset SGA (≥ 34 weeks')

Abnormal UA Doppler waveforms are very uncommon in late onset SGA.³² Whilst normal UA Doppler findings exclude major feto-placental vascular pathology, approximately three quarters of these cases will have histological evidence of abnormal utero-placental perfusion and/or other pathological features on placental histology.³³ The morbidity and mortality in these SGA infants with normal UA Doppler is increased compared with appropriate-for-gestational-age infants, but to a lesser extent than in SGA infants with abnormal UA Doppler.³⁰ Subgroups of SGA infants with normal UA Doppler who are at higher risk of morbidity (acidosis at birth, LSCS for fetal distress) include those with:

- Elevated uterine artery Doppler indices (Pulsatility index (PI) $>95^{\text{th}}$ centile);^{34, 35} these fetuses have reduced placental blood flow from the maternal side
- Low middle cerebral artery indices (MCA) (PI $<5^{\text{th}}$ centile) or low ratio of MCA / UA indices (cerebro placental ratio (CPR) $<5^{\text{th}}$ centile);^{35, 36} these fetuses are responding to mild hypoxia by increasing the blood supply to the brain with cerebral Doppler indices showing reduced resistance
- Extreme SGA with estimated fetal weight $<3^{\text{rd}}$ centile³⁷

These sub-groups of SGA pregnancies are considered to have FGR.³⁸

In SGA pregnancies where all Doppler parameters are normal and the fetus has an estimated weight between the 3^{rd} and 10^{th} centile with normal interval growth the fetus is at low risk of adverse perinatal outcome and can be considered constitutionally small.³⁸

Figure 5: Schematic representation of patterns of umbilical artery Doppler waveforms³⁹

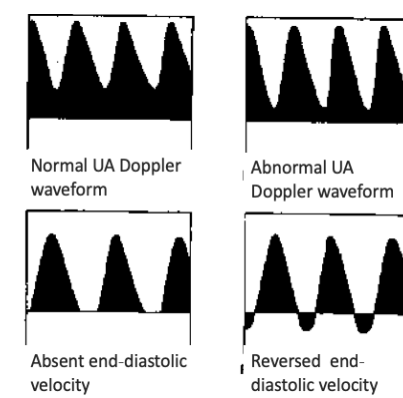
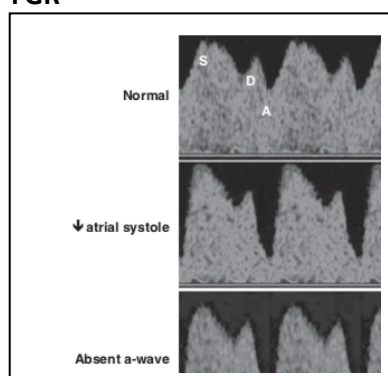


Figure 6: Progressive changes in ductus venosus Doppler waveforms as hypoxia increases in early onset FGR⁴⁰



Doppler studies in early onset SGA/FGR pregnancies

There is variation in opinion internationally as to whether early onset SGA/FGR should be defined as diagnosed <32 or <34 weeks⁶. In NZ we currently use <34 weeks to define early SGA/FGR as our current NZMFMN SGA Guideline refers to management of late onset SGA >34 weeks. UA Doppler studies are frequently abnormal in early SGA/FGR, including the most extreme abnormalities with absent or reversed end-diastolic flow. When UA Doppler is very abnormal in early SGA/FGR (i.e. absent or reversed end-diastolic flow) ductus venosus Doppler studies are indicated.

In severe early onset FGR, the ductus venosus responds to fetal hypoxaemia by dilating, diverting oxygenated blood from the liver to the heart and increasing supply of oxygenated blood to essential organs such as the brain, heart and adrenal glands via the foramen ovale.⁴⁰ This diversion of oxygenated blood and reduced flow to less important organs like muscles, bowel and kidney, enables the fetus to survive for a considerable period of time, especially if the fetus is under 30 completed weeks of gestation. As hypoxia worsens and the oxygen supply to the myocardium reaches its limit, the myocardium stiffens and the central venous pressure increases. As a result reduced flow occurs in the ductus venosus resulting in progressive changes of reduced, absent and then reversed A-wave (figure 6).

10. Timing of delivery

10.1 Late onset SGA (≥ 34 weeks')

In SGA pregnancies with evidence of FGR (EFW<3rd centile, abnormal UA, uterine, MCA or CPR Doppler indices) it is recommended that delivery is undertaken at approximately 38 weeks' (figure 7), as stillbirth risk increases after this gestation.⁴¹ Some FGR pregnancies will need delivery before 38 weeks' when maternal or fetal wellbeing deteriorates. When all Doppler indices are normal and EFW is between the 3rd and 10th centile delivery is recommended by 40 weeks'.^{38, 42}

Figure 7: Recommended management and timing of delivery in late onset SGA

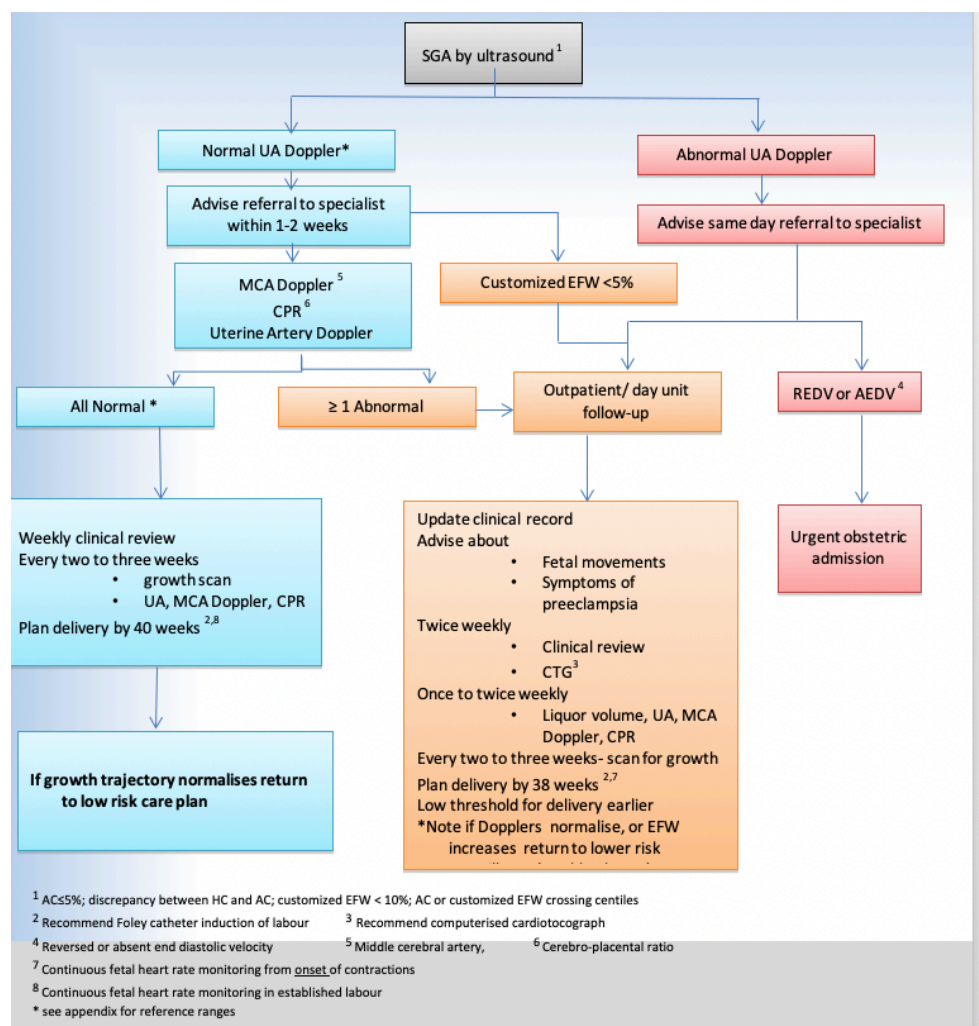


Figure 7 was adapted from figure 3 in NZMFM SGA guideline by L McCowan.¹

10.2 Timing of delivery in early onset SGA/FGR <34 weeks'

When early SGA/FGR is accompanied by absent or reversed end-diastolic flow in the umbilical artery antenatal admission in a tertiary centre and at least daily surveillance is generally recommended. Early delivery is almost always necessary with early FGR and timely administration of corticosteroids to improve fetal (lung) maturation should be considered. Early onset FGR is often associated with pre-eclampsia and delivery may be required for maternal indications. International consensus suggests that pregnancies with FGR and absent end-diastolic flow should be delivered by 32-34 weeks' and with reversed end-diastolic velocity by 30-32 weeks' ⁴³ Surveillance should include twice weekly assessment of umbilical and ductus venosus Doppler indices and computerised CTG. Recent evidence from the TRUFFLE trial suggests that delivery is indicated based on 1) computerised CTG if repeated unprovoked decelerations occur or there is reduced short-term variability (STV); 'STV <3.5 msec at <29 weeks' or STV <4 msec at ≥29 weeks' or 2) when there is a persistently absent or reverse A-wave in the ductus venosus. ⁴³ With less severe Doppler abnormalities delivery will be individualised according to gestation, maternal and fetal wellbeing.

11. Mode of delivery

Labour is the time of greatest risk for a fetus with FGR. In late onset FGR and SGA induction of labour

will usually be appropriate. When labour is induced a balloon catheter induction is recommended as this reduces hyperstimulation and Caesarean delivery.⁴⁴ When there are Doppler abnormalities or EFW is <3rd centile (FGR) continuous fetal monitoring is recommended at the onset of regular contractions, which may occur before the onset of established labour. In SGA pregnancies it is recommended that continuous fetal monitoring is initiated at least at the onset of active labour.

Fetuses with absent or reversed-end diastolic velocity are very unlikely to tolerate contractions without development of acidaemia, and caesarean section is recommended if the fetus is considered viable. Delivery should occur in a unit with appropriate neonatal facilities.

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