ISSN: 2577 - 8005

Case Report

Medical & Clinical Research

Labor Induction in Case of Fetal Growth Restriction (FGR)

S. Felis*, F. Cremonini, A. Tomasi

Department of Obstetrics & Gynecology, IRCCS San Martino Hospital, Genova, Italy.

*Corresponding Author
Felis S, Department of Obstetrics & Gynecology, IRCCS San Martino Hospital, Genova, Italy.

Submitted:05 Sep 2023;**Accepted**: 11 Sep 2023;**Published**: 02 Oct 2023

Citation: *Felis S, Cremonini F, Tomasi A (2023). Labor Induction in Case of Fetal Growth Restriction (FGR). Med Clin Res, 8(10), 01-07.*

Abstract

Clinicians consider a range of variables when formulating decisions regarding the diagnosis, monitoring plan, and ultimately the decision to recommend the delivery of a growth-restricted fetus. The differential diagnosis of a pathological fetal growth pattern is initially considered via the history, a physical and laboratory examination of the pregnant person, as well as a comprehensive fetal ultrasound examination. These factors allow a broad distinction between pre-existing disease in the pregnant person, constitutionally small normal growth, placenta-mediated Fetal Growth Restriction (FGR), and intrinsic fetal disease. Most commonly, pathological growth restriction is mediated by underlying placental diseases, of which maternal vascular malperfusion is the most common, and often results in co-existent hypertension. A program of combined monitoring of the pregnant person and fetus, comprising hypertension assessment, and serial fetal ultrasound, including Doppler studies is then instituted, and may be combined with biochemical markers, such as Placental Growth Factor, for greater clinical precision. Recommendations on timing to deliver the growth-restricted fetus worldwide are converging, with similar guidance from clinical practice guidelines informed by high-quality Randomized Controlled Trials (RCTs) and large cohort studies. In most instances, it is reasonable to recommend delivery of all growth-restricted fetuses by approximately 38 weeks. Timing of delivery should take into consideration both short-term neonatal outcomes and long-term outcomes at school age. Mode of delivery is based on many factors, and induction of labor is a safe approach, especially after 34 weeks. Mechanical methods of induction may be preferred to pharmacologic methods, although both have a role and the choice of method is based on individualized assessment. Elective Cesarean birth thereby bypassing fetal stress during labor, is recommended in preterm growth-restricted fetuses with signs of adaptive fetal compromise, especially when ductus venosus flow is abnormal, or a contraction stress test is positive.

Keywords: Doppler, Fetal Growth Restriction, Induction, Preterm Birth.

Introduction

In the literature, various definitions of Fetal Growth Restriction (FGR) can be found, but the most commonly used definition for initiating screening of FGR refers to fetuses that have an estimated fetal weight (EFW) <10th percentile on ultrasound [1-10]. These fetuses are designated as "small for gestational age" (SGA). Depending on gestational age, maternal characteristics, and the methodology used to obtain the EFW percentile, the percentage of SGA fetuses that are simply small and healthy, having reached their biological growth potential, will vary compared to those with pathological FGR mediated by placental insufficiency.

When a doctor has to manage fetuses with an EFW reported <10th percentile, the following considerations should be made:

- What method was used, and how accurate is this conclusion?
- Are there previous assessments to compare fetal growth over time?
- What, if any, Doppler studies other than the umbilical artery (UA) have been performed?
- What are the maternal conditions?
- What is the likelihood of underlying fetal pathology?

The earlier a diagnosis of suspected FGR is made, the more likely it is that severe placental pathology is present, or that a rare fetal diagnosis of FGR may be encountered.

The factors involved in formulating a care plan for an FGR fetus include:

1. Making a secure diagnosis of placental dysfunction in the context of an FGR fetus.
2. Carefully assessing the current health status of the fetus.
3. Evaluating parameters that predict a safe trial of labor induction.
4. If induction is a safe option, what is the optimal pathway for induction?

Diagnosis of a Pathological Growth Pattern

There are numerous international guidelines [1-10] and literature reviews on Fetal Growth Restriction (FGR), including the most recent FIGO 2021 International Guideline [1]. This guideline provides an excellent summary of the principles in the diagnosis and management of FGR.

The differential diagnosis of FGR has traditionally been divided into maternal, fetal and placental risk factors. Maternal risk factors involve, but are not limited to, those affecting systemic vascularization. These include chronic hypertension, pre-existing diabetes, kidney diseases, autoimmune diseases, and thromboembolic disease. Fetal pathological complications, including genetic disorders, congenital anomalies, infections, and exposure to drugs/toxins, are all contributing risk factors to the development of FGR. The single most common cause of FGR is maternal placental vascular malperfusion, which is variably present in over 10% of nulliparous women [11,12].

Differential Diagnosis and Prognosis in FGR

After a diagnosis of Fetal Growth Restriction (FGR) secondary to placental pathologies, the next step is to assess the important factors involved in making the decision to continue monitoring the pregnancy or recommending delivery. The first factor is gestational age, with a useful broad distinction between early-onset (<32 weeks) and late-onset (>32 weeks) FGR [13]. Other factors that should be initially considered include maternal hypertensive status (especially to rule out Hemolysis, Elevated Liver enzymes, Low Platelet count (HELLP) syndrome and severe symptomatic preeclampsia) and other concurrent medical conditions such as diabetes, as well as maternal perception of fetal movements [14].

Biochemical factors, such as Placental Growth Factor (PlGF), are increasingly used as components of maternal assessment between 20-36 weeks. PlGF is a pro-angiogenic placental-derived protein that protects against preeclampsia and indicates normal placental function [15]. Pregnant women with low circulating PlGF levels (<100 pg/ml) require a comprehensive maternal and fetal evaluation, whereas those with normal PlGF levels during pregnancy are more likely to have an SGA fetus and, if hypertensive, to have gestational hypertension [16]. Although it is not yet part of routine clinical care, this is a rapidly evolving field where results can be useful in assessing higher-risk groups.

The fetal factors to be assessed via ultrasound include: gestational age, fetal anatomy analysis, EFW (Estimated Fetal Weight), amniotic fluid volume, biophysical profile, and Doppler studies. Doppler examinations of the umbilical artery (UA), middle cerebral artery (MCA) [to derive the cerebro-placental ratio (CPR)], are crucial observations in cases of suspected late-onset FGR, while uterine artery Doppler and fetal ductus venosus (DV) should be included in investigations for suspected early-onset FGR. Recommendations regarding amniocentesis to verify microarray anomaly testing and TORCH screening for congenital infection should be incorporated and discussed based on all available clinical factors and non-invasive test results. After birth, it is advisable to perform a histological examination of the placenta.

This evaluative process more commonly leads to a prenatal diagnosis of maternal placental vascular malperfusion in the context of FGR. Physicians should be aware that placental malperfusion encompasses a spectrum of disease expressions, both maternal and fetal, which can range from completely asymptomatic [17] to requiring iatrogenic preterm delivery for severe hypertensive complications, peri-viable FGR, and even inevitable stillbirth [15]. All pregnant women with this diagnosis before 32 weeks should be informed about preeclampsia. Administration of steroids for fetal lung maturation is indicated; the timing of administration depends on the individual clinical situation. Under ideal circumstances, fetal exposure to steroids should occur at least 48 hours before delivery and within 10 days of birth.

Contraindications to Labor Induction in Fetal Growth Restriction (FGR)

Contraindications to labor induction in fetal growth restriction depend on the specific clinical circumstances and maternal and fetal conditions. Here are some considerations:

- **Maternal Placental Vascular Disease:** In cases where maternal placental vascular disease presents acutely with severe hypertension, especially in nulliparous women who haven't undergone any form of preeclampsia screening and aspirin prophylaxis, a confirmed HELLP syndrome with severe thrombocytopenia (<50,000 10^9/L), especially in nulliparous women, would strongly indicate planned cesarean section.
- *Severe Maternal Hypertensive Disease:* Women with severe hypertensive disease and a previous uterine surgery might be better suited for a repeat cesarean section. The same applies to women with fetal malpresentation, placenta previa, or significant previous placental abruption.
- Gestational age also plays a role. If these circumstances arise before 34 weeks of gestation, the administration of steroids for fetal lung maturity, combined with magnesium sulfate for maternal seizure prophylaxis and fetal neuroprotection, may be considered, with an intentional delay in delivery.
- *Abnormal Doppler Results:* In cases where maternal manifestations are mild, but the fetus shows severe FGR and fetal umbilical artery Doppler results predict poor tolerance to labor, careful monitoring is essential. If a nulliparous woman has absent or reversed end-diastolic velocity (EDV) in the fetal umbilical arteries before 34 weeks, a planned cesarean section should be considered, as the risk of cesarean section after a trial of labor can reach 90%. This is particularly important for both abnormal DV waveforms before 32 weeks or abnormal cerebro-placental ratio (CPR) (<1.0).

The decision-making process for cesarean section versus a trial of labor has not been adequately researched, particularly for preterm fetuses with growth restriction. Many studies have primarily focused on the safe prolongation of pregnancy in these cases. Therefore, individualized clinical assessment and consultation with

a healthcare provider are crucial in determining the appropriate course of action.

Timing of Labor Induction in FGR

To date, only three randomized clinical trials (RCTs) have addressed the timing of delivery in pregnancies with suspected fetal growth restriction (FGR).

The first was the GRIT study [21], conducted in the UK during a period before the use of the cerebro-placental ratio (CPR) and when Doppler assessment of the uterine artery was not commonly performed or reported, and maternal placental growth factor (PlGF) or the sFlt-1/PlGF ratio test was not in use. Participants in this study were recruited from pregnant women with fetal compromise between 24 and 36 weeks, a recorded UA Doppler waveform, and clinical uncertainty about whether immediate delivery was indicated. The results included data from 587 pregnancies. In the group where delivery was "immediate," the median time to delivery was 0.9 days, with a cesarean section rate of 91%. In the group where delivery was "delayed," the median time to delivery was 4.9 days, with a cesarean section rate of 79%. There was no difference in overall deaths before discharge, and 40% of participants did not show postnatal evidence of FGR. Placental histological examination was not performed. A follow-up study conducted in the subsequent two years defined "disability" as a Griffith's developmental quotient of 70 or less or the presence of severe motor or perceptual disability. Overall, no significant difference was found between the two groups, although the data showed a tendency to favor delayed delivery in fetuses recruited before 30 weeks.

The subsequent TRUFFLE study [23] was a prospective multicenter non-blind study in which preterm pregnancies with FGR were randomized to delivery based on a result from Doppler velocimetry (DV) or computerized cardiotocography with short-term variability monitoring. The timing of delivery was determined based on the presence of an abnormality in one of three different prenatal monitoring groups. These groups were: 1) reduced short-term fetal heart rate variability, 2) early DV changes (DV PI > 95th percentile), and 3) late DV changes (defined as the "a" wave at or below baseline). The inclusion criteria for this study were more strict, defining FGR as an abdominal circumference (AC) <10th percentile and UA pulsatility index (PI) > 95th percentile. The primary outcome was child development at two years of age. After two years of follow-up, children delivered in the "late DV changes" group had the best neurological development outcomes compared to the other groups. The mode of delivery was mostly cesarean section (97%) in all three groups. Limitations of the study included the lack of placental histological examination and the performance of angiogenic growth factor testing.

The DIGITAT RCT [24] randomized women to early induction or expectant management when FGR was suspected near or at term (36-41 weeks). In this study, inclusion criteria for defining FGR included one or more of the following: AC or EFW <10th percentile, reduced fetal growth velocity, or abnormal UA PI. Exclusion criteria included maternal issues (hypertension) or fetal comorbidities. The primary outcome of the study was a composite adverse perinatal outcome that did not differ between the groups, and there were no perinatal deaths. The immediate induction group delivered 10 days earlier, resulting in infants with a lower mean birth weight. The delayed delivery group had lower birth weights in terms of percentiles and meconium-stained amniotic fluid. The groups had similar rates of cesarean section, but for different indications. The authors concluded that fetuses with suspected term FGR can be safely monitored; however, the choice of induction to potentially prevent neonatal morbidity and stillbirth is reasonable. The two-year follow-up of the DIGITAT study [25] did not indicate overall differences in adverse neonatal outcomes and suggested that the optimal time for delivery for this group of fetuses with suspected FGR is at 38 weeks, with the argument that the antepartum stillbirth rate increases with gestational age in FGR fetuses. In an economic analysis, beyond 38 weeks, there is no appreciable medical or cost benefit in delaying delivery due to resource utilization [26]. Additionally, no difference was found in maternal long-term quality of life after labor induction [27]. In a secondary analysis of maternal and fetal factors that may contribute to recommending early labor induction, the only significant factor in favor of induction was a higher maternal body mass index (BMI) [28].

Recently, Selvaratnam et al. [29] conducted a retrospective population-based cohort study to assess whether there was an association between iatrogenic delivery for FGR and childhood development and educational test scores. These scores were nationally assessed in Australia for children in grades 3, 5, and 7. Severe SGA was defined as <3rd percentile, and these children were divided into three groups: 1) severe SGA with medically indicated delivery due to suspected FGR, 2) severe SGA with suspected FGR but not delivered for this indication, and 3) severe SGA without suspected FGR. For children born >32 weeks, these groups were then examined for their outcomes in the National Assessment Program for Literacy and Numeracy, based on their birth weight, and separately based on whether they were delivered for suspected FGR or not.

It was found that those in groups 1 and 2 had significantly lower gestational age at birth (37.9 and 38.3 weeks) compared to group 3 (39.4 weeks). Those in group 1, who had birth weight <3rd percentile, consistently showed a significantly increased likelihood of poor developmental outcomes. This group had a lower average gestational age at birth. Interestingly, over the years, there was "cognitive catch-up," and the differences in scores were not as significant when the children were in grade 7. Children born with birth weight >10th percentile in any of these groups showed no differences in development. The authors concluded that the difference is likely due to iatrogenic prematurity and birth weight <3rd percentile and agreed that doctors should delay delivery until at least 38 weeks when it's safe to do so. Silver et al. [30] commented that this study is "hypothesis-generating," and

"studies evaluating medium and long-term outcomes of obstetric interventions are required."

There is reasonable consistency among international guidelines regarding timing of delivery both at term and preterm in FGR fetuses. In preterm FGR with abnormal UA Doppler, recommendations for timing of delivery are based on the severity of Doppler changes. Those affected by AEDV should deliver between 32 and 34 weeks, and those with REDV between 30 and 34 weeks. Cesarean section is recommended in most cases [5]. Within these same guidelines, recommendations for timing of delivery in late-onset FGR are between 37 and 38 weeks and are based on the GRIT and DIGITAT studies. The recent FIGO 2021 guidelines [1] are more specific and narrow the cesarean delivery window in preterm FGR with AEDV to 32-34 weeks and REDV to 30-32 weeks. There's also a specific recommendation for FGR pregnancies where DV is abnormal, with a recommendation for cesarean delivery between 26 and 30 weeks.

It's clear that gestational age is one of the most significant factors in making a decision to recommend delivery in an FGR-affected pregnancy. As term approaches, the advantage of keeping the fetus in uterus diminishes, and the optimal timing is still not defined, with long-term data continuing to emerge. The decision ultimately rests with the attending physician and is also based on local factors, including access to fetal monitoring, expert consultants, and neonatal management expertise.

Suggested Mode of Delivery without Independent Indication for Cesarean Delivery

In early-onset FGR, typically accompanied by abnormal UA Doppler, the primary goal is safe prolongation of the pregnancy through intensive fetal monitoring. The consequence of this strategy is that it can compromise the fetus's ability to withstand uterine contractions. Consequently, the cesarean section rates in such fetuses are at least 80% [1].

In subsequent pregnancies, the uterus may be more responsive to the induction process, especially in multiparous women with previous vaginal deliveries. Additionally, many late-onset FGR fetuses show normal UA Doppler and, therefore, have much better fetal-placental blood flow and gas exchange. Consequently, evidence from the DIGITAT study and other studies [31] suggests that induction can be safely attempted in carefully selected near-term FGR fetuses.

Several factors should be considered when deciding to attempt labor induction in the context of near-term FGR. The first is amniotic fluid because oligohydramnios confers a higher risk of cesarean section [32]. Decreased amniotic fluid volume is a sign of placental insufficiency and may be accompanied by an abnormal CPR Doppler ratio of <1.0.

Doppler abnormalities and the rate of cesarean delivery have been addressed in various studies. Simeone et al. [33] retrospectively examined a group of 187 patients with FGR after 34 weeks of gestation, with or without Doppler abnormalities. Of these, 100 patients were candidates for induction with normal Doppler findings. The overall cesarean birth rate was 32% due to non-reassuring fetal status during labor. Progressive abnormalities in UA, MCA, and CPR were all significantly correlated with a higher risk of cesarean section, while one subgroup was predicted to have an acceptably low cesarean section rate. In a similar observational study by Cruz-Martinez et al. [34], birth outcomes of 210 near-term SGA fetuses with normal UA Doppler were compared to a control group of age-matched non-SGA pregnancies. In this study, SGA was defined as EFW <10th percentile and normal UA PI. MCA and CPR were recorded for the SGA group, and induction was initiated. Cesarean section rates were higher when either MCA alone or CPR Doppler ratio was abnormal. The lowest cesarean section rate was in those with normal UA and MCA Doppler, although this group still had a higher cesarean section rate compared to the non-SGA control group (37.6% vs. 19.5%, P <.001). The group with abnormal CPR had a cesarean section rate twice as high as those with normal CPR (51.4% vs. 27.5%, P<.01). Patients can, therefore, be appropriately counseled using these results, taking into consideration both previous obstetric history and pelvic examination findings. Continuous fetal heart rate monitoring throughout the induction process is recommended [1,6-8,10].

Pharmacological Methods vs. Mechanical Induction Methods

A pelvic examination is performed to determine the need for cervical ripening when the Bishop score is <6 [35]. Cervical ripening can be achieved using prostaglandins, such as slow-release PGE2 or Misoprostol (PGE1), and/or mechanical methods using a Cook's balloon or Foley catheter. A balloon method can be combined with oxytocin, PGE2, or oral Misoprostol. The combination of a balloon catheter and oxytocin is the modern equivalent of the oxytocin challenge test (OCT or Stress test) [19]. The fetal heart rate response to the initial uterine contractions will inform us about the clinical course, whether to continue labor induction to epidural anesthesia placement, or to discontinue induction and proceed to a cesarean section.

Several researchers have reported outcomes with cervical ripening methods in women undergoing induction for suspected FGR [36-38]. A recent meta-analysis suggests that for cervical ripening, the use of a mechanical method is preferable to prostaglandins [39]. Twelve studies were included in this meta-analysis. The primary outcome in this meta-analysis was a composite measure of intrapartum adverse outcomes, including cesarean section or operative vaginal delivery for non-reassuring fetal status. The included studies were classified based on their definitions of FGR, SGA, and whether specific Doppler changes were present. From this meta-analysis, it was concluded that the composite measure of intrapartum adverse outcomes was significantly lower when a mechanical method was chosen. Significant limitations of this conclusion include small numbers and the lack of an RCT study design.

Since definitive recommendations for cervical ripening cannot be drawn, it's important to recognize that prostaglandin methods can be a reasonable choice under optimal circumstances. Sequential and combined use of cervical balloon methods is also likely safe when all precautions, including continuous fetal heart rate monitoring, are considered.

Misoprostol is an economical and stable PGE1 analogue that can be safely used for labor induction in a cost-effective manner [40]. Several studies have reported the use of misoprostol for induction in the context of FGR [37]. The reported success rates for vaginal delivery were encouraging, with no major complications. Rossi et al. [37], in a single-center cohort study, included 260 inductions where birth weight was <10th percentile. They reported similar cesarean section rates in the three study groups: misoprostol 25.6%, dinoprostone 26.3%, and oxytocin/Cook catheter 22.0%. In a retrospective chart review by Duro-Gomez et al. [36], a comparison of misoprostol, dinoprostone, and the Cook cervical catheter revealed a lower cesarean section rate when using 25 mg of intravaginal misoprostol every four hours, up to a maximum of four doses. Chavukla et al. [38] conducted an RCT of 100 patients undergoing induction for SGA. Patients were randomized into one of two groups: 25 mg of intravaginal misoprostol and Foley catheter (+/- oxytocin as needed). A higher cesarean section rate was observed in the Foley catheter group compared to the misoprostol group (29.6% with Foley vs. 15.2% with misoprostol; P=0.168). Other studies on the use of misoprostol in FGR pregnancies [41] have reported similar results and favorable safety with the use of misoprostol. Results for vaginal dinoprostone are conflicting, with some studies reporting similar cesarean section rates to mechanical methods [42], and others reporting a lower cesarean section rate with mechanical methods [43].

The results of these individual studies and subsequent meta-analyses indicate that there is no specific induction method contraindicated in the context of FGR. All these studies are underpowered to identify major adverse events. Large RCTs will reasonably be completed, which will incorporate the latest prediction tests (uterine artery Doppler, placental growth factor, and MCA Doppler) and outcomes (neonatal ponderal index and placental pathology) that will provide greater diagnostic certainty of FGR versus SGA. Understandably, to date, no studies have compared outpatient induction versus hospital induction in pregnancies affected by FGR. Furthermore, there has been no formal evaluation of women's preferences in the context of labor induction for suspected FGR.

References

1. Melamed N, Baschat A, Yinon Y, Athanasiadis A, Mecacci F, et al.(2021) FIGO (international Federation of Gynecology and obstetrics) initiative on fetal growth: best practice advice for screening, diagnosis, and management of fetal growth restriction. Int J Gynaecol Obstet 152:3-57.
2. Society for Maternal-Fetal Medicine (SMFM) Society for maternal-fetal medicine consult series #52: diagnosis and management of fetal growth restriction: (replaces clinical guideline number 3, April 2012). Am J Obstet Gynecol 223(4):B2-17.
3. American College of Obstetricians and Gynecologists' Committee on Practice Bulletinsd Obstetrics and the Society for Maternal-Fetal Medicin (2019) ACOG practice bulletin No. 204: fetal growth restriction. Obstet Gynecol 133(2):e97-109.
4. Salomon LJ, Alfirevic Z, Da Silva Costa F, Deter RL, Figueras F, et al. (2-19) ISUOG Practice Guidelines: ultrasound assessment of fetal biometry and growth. Ultrasound Obstet Gynecol 53(6):715-23.
5. McCowan LM, Figueras F, Anderson NH (2018) Evidence-based national guidelines for the management of suspected fetal growth restriction: comparison, consensus, and controversy. Am J Obstet Gynecol 218(2S):S855-68.
6. Institute of Obstetricians and Gynecologists Royal College of Physicians of Ireland (2017) Fetal growth restriction, recognition, diagnosis management. Clinical practice guideline no. 28; 2017. Version 1.1. Available at: http://www.hse.ie/eng/services/ publications/Clinical-Strategyand-Programmes/Fetal-Growth-Restriction.pdf. [Accessed 10 September 2017]. March 2014. Updated March 2017.
7. Vayssi_ere C, Sentilhes L, Ego A, Bernard C, Cambourieu D, et al. (2015) Fetal growth restriction and intra-uterine growth restriction: guidelines for clinical practice from the French College of Gynaecologists and Obstetricians. Eur J Obstet Gynecol Reprod Biol 193:10-8.
8. New Zealand Maternal Fetal Medicine Network (2014) Guideline for the management of suspected small for gestational age singleton pregnancies and infants after 34 wk' gestation. New Zealand Maternal Fetal Medicine Network.
9. Lausman A, Kingdom J, Maternal Fetal Medicine Committee (2013) Intrauterine growth restriction: screening, diagnosis, and management. J Obstet Gynaecol Can 35(8):741-748.
10. Royal College of Obstetricians and Gynecologists (2013) The investigation and management of the small-for-gestational-age fetus. second ed. Green-top guideline no. 31. 2013; 2013
11. Burton GJ, Jauniaux E (2018) Pathophysiology of placental-derived fetal growth restriction. Am J Obstet Gynecol 218(2S):S745-761.
12. Zur RL, Kingdom JC, Parks WT, Hobson SR (2020) The placental basis of fetal growth restriction. Obstet Gynecol Clin N Am 47(1):81-98.
13. Aviram A, Sherman C, Kingdom J, Zaltz A, Barrett J,et al. (2019) Defining early vs late fetal growth restriction by placental pathology. Acta Obstet Gynecol Scand 98(3):365-373.
14. Tveit JV, Saastad E, Stray-Pedersen B, Børdahl PE, Flenady V,et al. (2009) Reduction of late stillbirth with the introduction of fetal movement information and guidelines-a clinical quality improvement. BMC Pregnancy Childbirth 9:32.
15. Smith GC, Crossley JA, Aitken DA, Jenkins N, Lyall F, et al. (2007) Circulating angiogenic factors in early pregnancy and the risk of preeclampsia, intrauterine growth restriction, spontaneous preterm birth, and stillbirth. Obstet Gynecol 109(6):1316-1324.

16. McLaughlin K, Snelgrove JW, Audette MC, Syed A, Hobson SR, et al. (2021) PlGF (placental growth factor) testing in clinical practice: evidence from a Canadian tertiary maternity referral center. Hypertension 77(6):2057-2065.
17. Wright E, Audette MC, Ye XY, Keating S, Hoffman B, et al. (2017) Maternal vascular malperfusion and adverse perinatal outcomes in low-risk nulliparous women. Obstet Gynecol 130(5):1112e20.
18. Guy GP, Leslie K, Diaz Gomez D, Forenc K, Buck E, et al. (2021) Implementation of routine first trimester combined screening for pre-eclampsia: a clinical effectiveness study. BJOG 128(2):149-156.
19. Ting JY, Kingdom JC, Shah PS (2018) Antenatal glucocorticoids, magnesium sulfate, and mode of birth in preterm fetal small for gestational age. Am J Obstet Gynecol 218(2S):S818e28.
20. Lees CC, Marlow N, van Wassenaer-Leemhuis A, Arabin B, Bilardo CM, et al. (2015) TRUFFLE study group. 2 year neurodevelopmental and intermediate perinatal outcomes in infants with very preterm fetal growth restriction (TRUFFLE): a randomised trial. Lancet 385(9983):2162e72.
21. GRIT Study Group (2003) A randomised trial of timed delivery for the compromised preterm fetus: short term outcomes and Bayesian interpretation. BJOG 110(1):27-32.
22. Thornton JG, Hornbuckle J, Vail A, Spiegelhalter DJ, Levene M, et al. (2004) Infant wellbeing at 2 years of age in the Growth Restriction Intervention Trial (GRIT): multicentred randomised controlled trial. Lancet 364(9433):513-520.
23. Lees C, Marlow N, Arabin B, Bilardo CM, Brezinka C, et al. (2013) TRUFFLE Group. 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 42(4):400-408.
24. Boers KE, Vijgen SM, Bijlenga D, van der Post JA, Bekedam DJ, et al. (2010) DIGITAT study group. Induction versus expectant monitoring for intrauterine growth restriction at term: randomised equivalence trial (DIGITAT). Br Med J 341:c7087.
25. Boers KE, van Wyk L, van der Post JA, Kwee A, et al. (2012) DIGITAT Study Group. Neonatal morbidity after induction vs expectant monitoring in intrauterine growth restriction at term: a subanalysis of the DIGITAT RCT. Am J Obstet Gynecol 206(4):344.e1-7.
26. Vijgen SM, Boers KE, Opmeer BC, Bijlenga D, Bekedam DJ, et al. (2013) Economic analysis comparing induction of labour and expectant management for intrauterine growth restriction at term (DIGITAT trial). Eur J Obstet Gynecol Reprod Biol 170(2):358-363.
27. Bijlenga D, Boers KE, Birnie E, Mol BW, Vijgen SC, et al. (2011) Maternal health-related quality of life after induction of labor or expectant monitoring in pregnancy complicated by intrauterine growth retardation beyond 36 weeks. Qual Life Res 20(9):1427-1436.
28. Tajik P, vanWyk L, Boers KE, le Cessie S, Zafarmand MH, et al. (2014) DIGITAT Study Group. Which intrauterine growth restricted fetuses at term benefit from early labour induction? A secondary analysis of the DIGITAT randomised trial. Eur J Obstet Gynecol Reprod Biol 172:20-25.
29. Selvaratnam RJ, Wallace EM, Wolfe R, Anderson PJ, Davey MA (2021) Association between iatrogenic delivery for suspected fetal growth restriction and childhood school outcomes. J Am Med Assoc 326(2):145e53.
30. Silver RM, Blue NR (2021) Delivery before 39 Weeks' gestation for suspected fetal growth restriction: more harm than good? J Am Med Assoc 326(2):135-136.
31. Rhoades JS, Rampersad RM, Tuuli MG, Macones GA, Cahill AG, et al. (2017) Delivery outcomes after term induction of labor in small-for-gestational age fetuses. Am J Perinatol 34(6):544-549.
32. Horowitz KM, Feldman D (3025) Fetal growth restriction: risk factors for unplanned primary cesarean delivery. J Matern Fetal Neonatal Med 28(18):2131-2134.
33. Simeone S, Marchi L, Canarutto R, Pina Rambaldi M, Serena C, et al. (2017) Doppler velocimetry and adverse outcome in labor induction for late IUGR. J Matern Fetal Neonatal Med 30(3):323-328.
34. Cruz-Martínez R, Figueras F, Hernandez-Andrade E, Oros D, Gratacos E (2011) Fetal brain Doppler to predict cesarean delivery for nonreassuring fetal status in term small-for-gestational-age fetuses. Obstet Gynecol 117(3):618-626.
35. Haas DM, Daggy J, Flannery KM, Dorr ML, Bonsack C, et al. (2019) A comparison of vaginal versus buccal misoprostol for cervical ripening in women for labor induction at term (the IMPROVE trial): a triple-masked randomized controlled trial. Am J Obstet Gynecol 221(3):259.e1-259.e16.
36. Duro-G_omez J, Garrido-Oyarzún MF, Rodríguez-Marín AB, de la Torre Gonz_alez AJ, Arjona-Berral JE, Castelo-Branco C (2017) Efficacy and safety of misoprostol, dinoprostone and Cook's balloon for labour induction in women with foetal growth restriction at term. Arch Gynecol Obstet 296(4):777-781.
37. Rossi RM, Warshak CR, Masters HR, Regan JK, Kritzer SA, et al. (2018) Comparison of prostaglandin and mechanical cervical ripening in the setting of small for gestational age neonates. J Matern Fetal Neonatal Med 32(22):3841-3846.
38. Chavakula PR, Benjamin SJ, Abraham A, Londhe V, Jeyaseelan V, et al. (2015) Misoprostol versus Foley catheter insertion for induction of labor in pregnancies affected by fetal growth restriction. Int J Gynaecol Obstet 129(2):152-155.
39. Familiari A, Khalil A, Rizzo G, Odibo A, Vergani P, et al. (2020) Adverse intrapartum outcome in pregnancies complicated by small for gestational age and late fetal growth restriction undergoing induction of labor with Dinoprostone, Misoprostol or mechanical methods: a systematic review and meta-analysis. Eur J Obstet Gynecol Reprod Biol 252: 455-467.
40. Duro-G_omez J, Garrido-Oyarzún MF, Rodríguez-Marín AB, de la Torre Gonz_alez AJ, Arjona-Berral JE, et al. (2017) What can we do to reduce the associated costs in induction of labour of intrauterine growth restriction foetuses at term? A

cost-analysis study. Arch Gynecol Obstet 296(3):483e8.
41. Foeller ME, Cruz MO, Kominiarek MA, JU Hibbard (2015) Does induction with misoprostol impact the small for gestational age neonate? Am J Perinatol 32(14):1311-1317.
42. Ben-Haroush A, Yogev Y, Glickman H, Kaplan B, Hod M, et al. (2004) Mode of delivery in pregnancies with suspected fetal growth restriction following induction of labor with vaginal prostaglandin E2. Acta Obstet Gynecol Scand 83(1):52-57.
43. Villalain C, Herraiz I, Quezada MS, G_omez Arriaga P, Sim_on E, G_omez-Montes E, et al. (2018) Labor induction in late-onset fetal growth restriction: Foley balloon versus vaginal dinoprostone. Fetal Diagn Ther 46(1):67-74.