Editor summary:
In 1,088 pregnant individuals, assessment of abnormal serum angiogenic factors proved non inferior to the standard clinical approach based on EFW and Doppler percentiles, for the identification of foetuses at a higher risk of neonatal acidosis or Cesarean delivery, thus offering a a beneficial option in settings where Doppler or experienced sonographers are not easily available.

Editor recognition statement:
Primary Handling editor: Sonia Muliyil, in collaboration with the Nature Medicine team.

Peer review information:
Nature Medicine thanks Lee Middleton, Lina Bergman, Joshua Vogel and the other, anonymous, reviewer(s) for their contribution to the peer review of this work.

1. Extended Data

Figure or Table # Please group Extended Data items by type, in sequential order. Total number of items (Figs. + Tables) must not exceed 10.	**Figure/Table title** One sentence only	**Filename** Whole original file name including extension. i.e.: Smith_ED_Fig1.jpg	**Figure/Table Legend** If you are citing a reference for the first time in these legends, please include all new references in the main text Methods References section, and carry on the numbering from the main References section of the paper. If your paper does not have a Methods section, include all new references at the end of the main Reference list.
Extended Data Fig. 1	Management protocol	Extended_Figure_1.ppt	AEDF: absent end-diastolic flow; CPR: cerebroplacental ratio; CTG: cardiotocography; EFW: estimated fetal weight; MCA: middle cerebral artery; PI: pulsatility index; PlGF: placental growth factor; REDF: reversed end-diastolic flow; sFlt-1: soluble fms-like tyrosine kinase-1; UA: umbilical artery.
Extended Data Fig. 2	Kaplan–Meier curves for time to delivery in the per protocol analysis, for all participants (A) and for participants electively delivered (B).	Extended_Figure_2.ppt	CI, confidence interval; HR, hazard ratio; w, weeks The analysis used a Cox proportional hazards model, and the p-values were two-sided. No adjustments were made for multiple comparisons.

2. Supplementary Information:

A. PDF Files

Item	Present?	Filename Whole original file name including extension. i.e.: Smith_SI.pdf. The extension must be .pdf	A brief, numerical description of file contents. i.e.: *Supplementary Figures 1-4, Supplementary Discussion, and Supplementary Tables 1-4.*
Supplementary Information	Yes	Supplementary_information_R3.pdf	Supplementary Tables 1-9
Reporting Summary	Yes	NMED-A134686D_rs.pdf	
Peer Review Information	No	*N/A*	

Angiogenic factors versus feto-maternal Doppler for fetal growth restriction at term: open label, randomized, controlled trial

Pablo Garcia-Manau, MD[1,2] (0000-0002-2415-1626); Erika Bonacina, PhD[1,2] (0000-0002-8042-8247); Raquel Martin-Alonso, MD[3,4]; Lourdes Martin, MD[5]; Ana Palacios, PhD[6,7,8]; Maria Luisa Sanchez-Camps, MD[9,10]; Cristina Lesmes, PhD[1,11]; Ivan Hurtado, PhD[1,12,13]; Esther Perez, MD[14,15]; Albert Tubau, PhD[16,17]; Patricia Ibañez, MD[18,19]; Marina Alcoz, MD[20]; Nuria Valiño, PhD[21,22]; Elena Moreno, MD[23]; Carlota Borrero, MD[24,25]; Esperanza Garcia, MD[26,27]; Eva Lopez-Quesada, PhD[28]; Sonia Diaz, MD[29]; Jose Roman Broullon, MD[30,31]; Mireia Teixidor, MD[32,33]; Carolina Chulilla, MD[34]; Roser Ferrer-Costa, PhD[35]; Maria M Gil, PhD[3,4]; Monica Lopez, MD[5]; Gemma M Ramos-Forner, MD[6,8]; José Eliseo Blanco, MD[9,10]; Anna Moreno, MD[11]; Marta Lázaro-Rodríguez, MD[12]; Oscar Vaquerizo, MD[14,15]; Beatriz Soriano, MD[16,17]; Marta Fabre, PhD[19,36]; Elena Gomez-Valencia, MD[20]; Ana Cuiña, MD[21,22]; Nicolas Alayon, MD[23,37]; Jose Antonio Sainz-Bueno, PhD[24,25]; Angels Vives, MD[26,27]; Esther Esteve, MD[28]; Vanesa Ocaña, MD[29]; Miguel Ángel López, MD[30]; Anna Maroto, PhD[32,33]; Elena Carreras, PhD[1,2]*; and Manel Mendoza, PhD[1,2]* (0000-0002-3030-3833).

*These authors contributed equally.

[1]Departament de Pediatria, Obstetrícia i Ginecologia i de Medicina Preventiva i Salut Pública, Universitat Autònoma de Barcelona, Bellaterra, Spain

[2]Department of Obstetrics, Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain
[3]Department of Obstetrics, Hospital Universitario de Torrejón, Madrid, Spain
[4]School of Medicine, Universidad Francisco de Vitoria, Madrid, Spain
[5]Department of Obstetrics, Hospital Universitari de Tarragona Joan XXIII, Tarragona, Spain
[6]Department of Obstetrics, Hospital General Universitari Dr. Balmis, Alicante, Spain
[7]Miguel Hernandez University, Alicante, Spain
[8]Alicante Institute for Health and Biomedical Research, Alicante, Spain
[9]Department of Obstetrics, Hospital Clínico Universitario Virgen de la Arrixaca, Murcia, Spain
[10]Universidad de Murcia, Murcia, Spain
[11]Department of Obstetrics, Parc Taulí Hospital Universitari, Sabadell, Spain
[12]Department of Obstetrics, Hospital Universitari Germans Trias i Pujol, Badalona, Spain
[13]Germans Trias i Pujol Research Institute (IGTP), Badalona, Spain
[14]Department of Obstetrics, Hospital Universitario de Cabueñes, Gijón, Spain
[15]Universidad de Oviedo, Oviedo, Spain
[16]Department of Obstetrics, Hospital Universitari Son Llàtzer, Palma de Mallorca, Spain
[17]Universitat de les Illes Balears, Palma de Mallorca, Spain
[18]Department of Obstetrics, Hospital Clínico Universitario Lozano Blesa, Zaragoza, Spain
[19]Aragon Institute for Health Research, Zaragoza, Spain
[20]Department of Obstetrics, Fundació Althaia, Manresa, Spain
[21]Department of Obstetrics, Hospital Universitario de A Coruña, A Coruña, Spain
[22]Universidade da Coruña, A Coruña, Spain
[23]Department of Obstetrics, Hospital General Universitario de Elche, Elche, Spain
[24]Department of Obstetrics, Hospital Universitario Virgen de Valme, Sevilla, Spain
[25]Universidad de Sevilla, Sevilla, Spain
[26]Department of Obstetrics, Consorci Sanitari de Terrassa, Terrassa, Spain
[27]Universitat Internacional de Catalunya, Terrassa, Spain
[28]Department of Obstetrics, Hospital Universitari Mútua Terrassa, Terrassa, Spain
[29]Department of Obstetrics, Hospital Universitario de Getafe, Getafe, Spain
[30]Department of Obstetrics, Hospital Universitario Puerta del Mar, Cádiz, Spain
[31]Universidad de Cádiz, Cádiz, Spain

[32]Department of Obstetrics, Hospital Universitari de Girona Doctor Josep Trueta, Girona, Spain
[33]Universitat de Girona, Girona, Spain
[34]Department of Obstetrics, Hospital Universitario Nuestra Señora de Candelaria, Santa Cruz de Tenerife, Spain
[35]Department of Clinical Biochemistry, Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain
[36]Department of Clinical Biochemistry, Hospital Clínico Universitario Lozano Blesa, Zaragoza, Spain
[37]Universidad Miguel Hernández, Elche, Spain

Correspondence to Dr Manel Mendoza, Department of Obstetrics, Vall d'Hebron Barcelona Hospital Campus, Universitat Autònoma de Barcelona, Passeig de la Vall d'Hebron, 119-129, 08035, Barcelona, Spain. manel.mendoza@uab.cat

ABSTRACT

Small fetuses, with estimated fetal weight (EFW) below the tenth percentile, are classified as fetal growth restriction (FGR) or small for gestational age (SGA) based on prenatal ultrasound. FGR fetuses have a greater risk of stillbirth and perinatal complications and may benefit from serial ultrasounds to guide early delivery. Abnormal serum angiogenic factors, such as soluble fms-like tyrosine kinase-1 (sFlt-1) to placental growth factor (PlGF) ratio, have shown potential to more accurately distinguish FGR from SGA, with fewer false positives. This randomized controlled trial compared a management protocol based on the sFlt-1/PlGF to EFW and Doppler ultrasound in avoiding adverse perinatal outcomes in small fetuses after 36 weeks of gestation. A total of 1,088 pregnant individuals with singleton pregnancies were randomized to either the Doppler-based (control) or sFlt-1/PlGF-based (intervention) protocol. The primary outcome, neonatal acidosis or Cesarean delivery due to abnormal cardiotocography, was assessed in 1,013 participants. The incidence was 10.5% in the intervention group and 10.0% in the control group (absolute difference, 0.53 [-3.21 to 4.26]), with the upper limit of the confidence interval below 8.5%, confirming non-inferiority. Thus, the sFlt-1/PlGF was non-inferior to EFW and Doppler ultrasound in avoiding neonatal acidosis or Cesarean delivery due to non-reassuring fetal status in small fetuses after 36 weeks. ClinicalTrials.gov registration: NCT04502823.

INTRODUCTION

Fetal smallness occurs in approximately 10% of pregnancies[1] and is a major cause of perinatal, neonatal and maternal morbidity and mortality.[2] Most cases are diagnosed after 32 weeks of gestation and there is no clear consensus regarding the appropriate management and delivery timing for these late-onset cases.[3,4]

Based on the severity of the smallness, two conditions can be identified by prenatal ultrasound: fetal growth restriction (FGR) and small for gestational age (SGA). FGR is defined as the fetus failing to reach its genetically determined growth potential and has a greater risk of fetal demise and other perinatal complications.[5] By contrast, SGA is defined as the fetus being constitutionally small, usually with normal pregnancy outcomes.[1] In order to prevent adverse perinatal outcomes, most guidelines recommend delivery for FGR cases at 37 to 38 weeks of gestation and for SGA cases, at 39 to 40 weeks of gestation.[2] SGA and FGR can be discriminated based on ultrasound parameters, such as estimated fetal weight (EFW) percentiles, fetal growth velocity and Doppler studies.[3,6] However, this classification requires experienced sonographers and 60% of fetuses will be classified as FGR and, subsequently, will be electively delivered at 37-38 weeks of gestation.[3,7] Recently, abnormal maternal serum concentrations of angiogenic factors (AF), such as an increased soluble fms-like tyrosine kinase-1 (sFlt-1) to placental growth factor (PlGF) ratio, have shown to be associated with a poorer prognosis for small fetuses and a higher risk of developing preeclampsia.[8–11] A large observational study compared Doppler assessment with an approach based on the sFlt-1/PlGF ratio to identify FGR cases among all small fetuses.[12] In that study, 521 fetuses had an ultrasonographic estimated EFW below the 10th percentile. Among these, 412 exhibited abnormal Doppler parameters, while only 102 had abnormal sFlt-1/PlGF ratio values (≥38). Despite this, both approaches demonstrated similar negative predictive values for excluding adverse

perinatal outcomes (99.3% and 99.0%, respectively). Therefore, the Doppler-based protocol would have identified 79.1% (412/521) of the small fetuses as FGR, whereas according to the AF approach, only 19.6% (102/521) of the small fetuses would have been classified as FGR. That study concluded that the classification of small fetuses based on AF seemed to be more accurate and may result in a lower false-positive rate than the Doppler-based protocol. Reducing the number of pregnancies classified as FGR by up to 75.2% (from 79.1% to 19.6%) is not only statistically significant, but also noteworthy, as these pregnancies would undergo unnecessary early induction of labor, resulting in a greater proportion of early term newborns (born between 37 weeks and 0 days to 38 weeks and 6 days of gestation). These infants have an increased risk of immediate postnatal morbidity, such as admission to the neonatal intensive care unit (NICU) for respiratory support, and poorer long-term outcomes, mainly due to cardiovascular, metabolic and respiratory conditions.[13–15] Thus, a reduction in the number of cases classified as FGR may decrease hospital length of stay by reducing the number of inductions, and may also improve short and long-term postnatal outcomes by delaying elective deliveries until reaching full term (≥39 weeks of gestation).

The GRAFD Trial was designed to test the hypothesis that classification of small fetuses as SGA or FGR based on AF is non-inferior to the standard clinical approach (based on EFW and Doppler percentiles) for the identification of fetuses at a higher risk of neonatal acidosis or Cesarean delivery due to non-reassuring fetal status.

RESULTS

Patient disposition

Recruitment commenced on September 28, 2020, and the last participant was enrolled on November 30, 2022. Out of 1,107 participants, 553 were allocated to the intervention

group and 554 to the control group. Seven participants were excluded from the intervention group (two were excluded due to withdrawal of consent and five were lost to follow-up) and 12 were excluded from the control group (three were excluded due to withdrawal of consent and 9 were lost to follow-up). The reasons for withdrawing consent in all participants were being dissatisfied with the assigned group. Finally, 1,088 (98.3%) pregnant individuals were included in the intention to treat analysis, 546 (50.2%) from the intervention group and 542 (49.8%) from the control group. Of those, 1,013 (91.5%) participants had available data to assess the primary outcome (neonatal acidosis or Cesarean delivery due to non-reassuring fetal status), 513 (50.6%) were from the intervention group and 500 (49.4%) were from the control group (Figure 1). Baseline characteristics did not differ between groups (Table 1). In February 2022, 522 pregnant individuals met the inclusion criteria for the interim analysis. The incidence of the primary outcome in the intervention group was 9.2% and 10.7% in the control group (absolute difference, -1.46 [-6.69 to 3.77]). With these results, the Independent Data Monitoring Committee concluded that non-inferiority was confirmed and suggested stopping the trial. However, they noted that the observed event rate was lower than expected. For this reason, the trial promoter decided to continue recruiting participants to achieve the originally planned sample size.

Primary outcome

Among the 1,088 participants included in the intention to treat analysis, the incidence of the primary outcome was 10.5% (54 of 513 participants) in the intervention group and 10.0% (50 of 500 participants) in the control group (absolute difference, 0.53 [-3.25 to 4.29]). (Figure 2 and Table 2).

Secondary outcomes

For the secondary outcomes, the incidence of composite adverse perinatal outcomes was 8.1% in the intervention group and 11.8% in the control group, this difference being statistically significant (absolute difference, -3.75% [95% CI, -7.35% to -0.19%]). The reduction of adverse perinatal outcomes was mainly due to a lower incidence of preeclampsia (absolute difference, -1.66% [95% CI, -3.25% to -0.35%]). Regarding the composite adverse neonatal outcomes, no differences were found between groups (absolute difference, -1.95% [95% CI, -6.19% to 2.29%]). However, in the control group, 5 (0.9%) neonates required ventilatory support, whereas no neonates required such support in the intervention group (absolute difference, -0.92% [95% CI, -2.14% to -0.05%]), this difference being statistically significant. When analyzing placental-related complications, postpartum hemorrhage was significantly less frequent in the intervention group (0.6% [3/546]) than in the control group (2.0% [11/542]) (absolute difference, -1.48% [95% CI, -3.09% to -0.10%]). Moreover, at least one adverse maternal outcome occurred in 11 (2.0%) participants in the intervention group versus 23 (4.2%) participants in the control group (absolute difference, -2.23% [95% CI, -4.46% to -0.14%]). Regarding other secondary outcomes, median gestational age at delivery was significantly greater in the intervention group (39.0 weeks [IQR, 37.9-40.0]) than in the control group (38.4 weeks [IQR, 37.6-39.7]), ($p<0.001$). The rates of delivery below 38, 39, and 40 weeks of gestation were significantly lower in the intervention group by 11.04% (-16.53 to -5.45), 10.97% (-16.79 to -5.03), and 5.76% (-10.74 to -0.74), respectively (Figure 3 and Table 3). Median birthweight was 2,540 g (IQR, 2,330-2,770) in the control group and 2,615 g (2,390-2,870) in the intervention group ($p=0.002$), and the rate of cases with a birthweight <2,500 g was significantly reduced by -6.54% (95% CI, -12.30% to -0.73%). There were no statistically significant differences between the rates of spontaneous or cesarean

deliveries between groups. More details about other perinatal, neonatal and maternal outcomes are provided in Table 2 and Table 3.

Per protocol analysis

Among the 992 participants included in the per protocol analysis, the incidence of the primary outcome was 10.2% (48 of 470 participants) in the intervention group and 10.8% (50 of 462 participants) in the control group (absolute difference, -0.61 [-4.59 to 3.36]). Regarding baseline characteristics and secondary outcomes, similar findings to those of the intention to treat analysis were found. More details of the per protocol analysis can be found in Figure 2, Supplementary Table 1, Supplementary Table 2, and Extended Data Figure 1.

Subgroup analyses

According to Doppler classification at enrollment, there were 433 pregnancies classified as FGR (211 [48.7%] in the intervention group and 222 [51.3%] in the control group). Of those, the prevalence of the primary outcome did not differ significantly between the intervention group (13.9%) and the control group (13.9%) (absolute difference, -0.01% [95% CI, -6.73% to 6.70]). The reasons for indicating elective delivery in FGR cases from both groups are detailed in Supplementary Tables 3 and 4.

For the sub-analysis conducted for the 655 SGA cases (335 in the intervention group [51.1%] and 320 in the control group [48.9%]), there was no statistically significant difference in the prevalence of the primary outcome between the intervention group (8.3%) and the control group (7.2%) (absolute difference, 1.14% [95% CI, -3.12% to 5.41%]).

More details about the FGR and SGA subgroup characteristics and pregnancy outcomes can be seen in Supplementary Tables 5, 6, 7 and 8.

The subgroup analysis included a treatment-by-subgroup interaction for the primary outcome and each of the three composite outcomes.[16] The interaction p-values for the primary adverse outcome, perinatal outcomes, neonatal outcomes, and placental-related outcomes were 0.711, 0.596, 0.955, and 0.743, respectively, all greater than 0.10. This indicates that the noninferiority of the sFlt-1/PlGF protocol is consistent across the FGR and SGA subgroups, as there were no significant treatment-by-subgroup interactions for any of the outcomes analyzed (Supplementary Table 9).

DISCUSSION

This trial showed that a classification of fetuses with an ultrasonographic EFW ≤10th percentile after 36 weeks of gestation based on AF is non-inferior to feto-maternal Doppler and EFW to avoid neonatal acidosis or Cesarean delivery due to non-reassuring fetal status. In addition, elective delivery according to AF instead of EFW and Doppler may improve neonatal, maternal, and perinatal outcomes as well as reduce the rate of unnecessary inductions of labor and therefore, the rate of deliveries below 38, 39, and 40 weeks of gestation. Additionally, the non-inferiority of the management based on AF was confirmed after analyzing the primary outcome by per protocol analysis and in FGR and SGA cases separately.

There were several strengths of this study. Firstly, this is the first randomized clinical trial to assess the role of Doppler and AF for identifying FGR and avoiding adverse outcomes in small fetuses. Secondly, the sample size was considerably larger than in any previous study conducted in pregnancies with small fetuses, which provides enough statistical power for performing analyses for a range of clinically relevant maternal and neonatal outcomes. Thirdly, our trial has a robust randomized controlled design with prior publication of the study protocol. The trial was rigorously conducted according to that protocol, without any changes, in 20 maternities across Spain. Additionally, follow-up

was conducted under real-life routine practice conditions, thereby reinforcing the external validity of the results. Finally, this trial provided results that may be readily applicable to pregnancies with FGR and SGA at term, especially in settings where Doppler or experienced sonographers are not easily available.

There were several limitations in this study. Firstly, it was not possible to conceal group allocation to participants and investigators. Secondly, the rate of the primary adverse outcome in the control group was 10.0%, which is lower than the expected 26.0%. Despite this is a common issue for clinical trials, this result was unexpected since the reference data used for sample size estimation were derived from pregnancies within the same region and following identical management protocols.[7] Given that the reference study was published in 2015, the observed lower rate of complications may reflect the current event rate, likely due to improvements in intrapartum care or new methods used for induction of labor in recent years. This lower rate may challenge the non-inferiority margin of 8.5%; however, despite the lower observed event rates, the large sample size of this trial and the almost identical rates of the primary outcome in both groups support the non-inferiority of the sFlt-1/PlGF approach. Additionally, beyond demonstrating the non-inferiority of the primary outcome, the use of sFlt-1/PlGF did not worsen any pregnancy outcome and, on the contrary, resulted in multiple improved perinatal outcomes for both mother and fetus. Some of these benefits could extend beyond the perinatal period, including reductions in the long-term cardiovascular and neurological consequences of preeclampsia and early-term births. Lastly, although the EFW and Doppler ultrasound protocol is the current standard of care, its validity is uncertain since it has not been previously confirmed in a clinical trial. This is the largest clinical trial conducted in term FGR/SGA, and we believe that all the aforementioned points support the validity of the trial results, confirming the non-inferiority of the sFlt-1/PlGF protocol.

Third, ~80% of participants were of White origin, which may reduce the external validity of our findings. Nevertheless, a previous study showed that sFlt-1/PlGF values between 35 and 37 weeks of gestation ranged from 6.54 to 8.51 among different ethnicities.[17] Therefore, a cutoff of 38 may probably be suitable for different ethnicities. Finally, these results may only apply to sites that follow a Doppler-based protocol akin to the one used in the control group of this trial. However, it is worth noting that most international guidelines recommend management protocols similar to the one used in this trial.

Only one previous randomized clinical trial has compared the pregnancy outcomes of two management protocols (induction of labor versus expectant management) in 650 pregnancies with poor fetal growth at term. The DIGITAT study concluded that there were no differences in pregnancy outcomes between groups and that both approaches were reasonable options for small fetuses at term.[18] However, the DIGITAT study, published in 2010, did not evaluate feto-maternal Doppler or AF as methods to differentiate between FGR and SGA. Consequently, some cases delivered at 37 weeks of gestation were probably SGA, which have a comparable risk of complications to normally grown fetuses. This may partly explain why that study failed to demonstrate a benefit of labor induction compared to expectant management. In the subsequent years, several observational studies demonstrated that the addition of feto-maternal Doppler to EFW may improve identification of a specific subset of small fetuses who are at a higher risk of experiencing adverse perinatal outcomes (i.e., FGR), for whom induction of labor after 37 weeks of gestation may be beneficial.[1,7,19–21] Based on these findings, numerous scientific societies endorsed in their guidelines the management approach consisting of feto-maternal Doppler with EFW, which became the prevailing accepted standard of care for small fetuses at term.[2] Regarding the use of AF in late-onset FGR and SGA, several observational studies have shown that these are good predictors of adverse perinatal

outcomes.[10,12,22] However, neither the performance of Doppler studies nor AF had been previously evaluated in a clinical trial.

Our study demonstrates that using AF may result in fewer cases being misclassified as FGR, thereby reducing the rate of labor inductions and unnecessary early-term deliveries. This approach led to increased gestational age and birthweight and avoided pregnancy complications such as preeclampsia, postpartum hemorrhage and the need for neonatal invasive ventilatory support. It might seem contradictory that a higher gestational age at delivery is associated with a reduction in the rate of preeclampsia in the intervention group. However, previous studies have shown that pregnancies with elevated sFlt-1/PlGF levels are at higher risk of developing preeclampsia. Consequently, induction of labor only for cases with sFlt-1/PlGF ≥38 allows for the extension of gestation while also reducing preeclampsia rates. Medical care is progressively shifting towards personalized approaches. The approach based on AF facilitates the provision of personalized and less invasive care for patients, reducing interventions and safely extending gestational age at birth. Moreover, Doppler criteria for indicating elective delivery vary among guidelines and Doppler parameters have inter- and intra-observer variability, requiring experienced sonographers.[23–25] In order to reduce these limitations, the approach based on AF may be used as an alternative to Doppler, potentially standardizing protocols across diverse scientific societies.

Future studies should compare the performance of the sFlt-1/PlGF protocol with other protocols for managing FGR and SGA at term. Additionally, further research should investigate whether PlGF alone can achieve results similar to those observed with sFlt-1/PlGF in this trial, or if combining AF with Doppler ultrasound could improve accuracy in identifying cases that would benefit from earlier elective delivery. Finally, in this trial, the use of AF led to an increase in gestational age at birth by delaying elective delivery;

therefore, future research could investigate the long-term neurodevelopmental impact on children born to participants of this trial.

To conclude, the present study confirmed that the sFlt-1/PlGF ratio is non-inferior to EFW and feto-maternal Doppler ultrasound for avoiding neonatal acidosis or Cesarean delivery due to non-reassuring fetal status in small fetuses after 36 weeks of gestation.

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Author contributions

Concept and design: Carreras and Mendoza

Acquistion, analysis, or interpretation of data: Mendoza, Garcia-Manau, Bonacina, Martin-Alonso, Martin, Palacios, Sanchez-Camps, Lesmes, Hurtado, Perez, Tubau, Ibañez, Alcoz, Valiño, Moreno, Borrero, Garcia, Lopez-Quesada, Diaz, Broullon, Teixidor, Chulilla, Ferrer-Costa, Gil, Lopez, Ramos-Forner, Blanco, Moreno, Lázaro-Rodríguez, Vaquerizo, Soriano, Fabre, Gomez-Valencia, Cuiña, Alayon, Sainz-Bueno, Vives, Esteve, Ocaña, López, Maroto, and Carreras.

Drafting of the manuscript: Mendoza, and Garcia-Manau.

Critical revision of the manuscript for important intellectual content: Mendoza, Garcia-Manau, Bonacina, Martin-Alonso, Martin, Palacios, Sanchez-Camps, Lesmes, Hurtado, Perez, Tubau, Ibañez, Alcoz, Valiño, Moreno, Borrero, Garcia, Lopez-Quesada, Diaz, Broullon, Teixidor, Chulilla, Ferrer-Costa, Gil, Lopez, Ramos Forner, Blanco, Moreno,

Lázaro-Rodríguez, Vaquerizo, Soriano, Fabre, Gomez-Valencia, Cuiña, Alayon, Sainz-Bueno, Vives, Esteve, Ocaña, López, Maroto, and Carreras

Statistical analysis: Mendoza, and Carreras.

Administrative, technical, or material support: Mendoza, Garcia-Manau, Bonacina, Martin-Alonso, Martin, Palacios, Sanchez-Camps, Lesmes, Hurtado, Perez, Tubau, Ibañez, Alcoz, Valiño, Moreno, Borrero, Garcia, Lopez-Quesada, Diaz, Broullon, Teixidor, Chulilla, Ferrer-Costa, Gil, Lopez, Ramos Forner, Blanco, Moreno, Lázaro-Rodríguez, Vaquerizo, Soriano, Fabre, Gomez-Valencia, Cuiña, Alayon, Sainz-Bueno, Vives, Esteve, Ocaña, López, Maroto, and Carreras.

Supervision: Carreras and Mendoza.

Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/disclosure-of-interest and declare: All authors declare having received reagents from Roche Diagnostics for the submitted work. MM, and AP declared receiving lecture and fees from Roche Diagnostics. MM declared receiving consulting fees from Roche Diagnostics. MG declared having received reagents, and travel support for attending conferences from Thermo Fisher and Perkin Elmer. MG declared receiving lecture fees from Thermo Fisher. MM, EB, EG, ELQ, JRB, PGM, and AV declared receiving travel support for attending conferences from Roche Diagnostics. All other authors have no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

382 **Table 1. Baseline characteristics of participants at trial entry (intention to treat)**

Characteristic	Intervention group (n=546)	Control group (n=542)
Gestational age at randomization, weeks	36.7 (36.3-37.1)	36.7 (36.3-37.1)
Age, years	32.9 (28.1-36.2)	32.8 (28.4-36.2)
Body-mass index, kg/m^2	22.9 (20.4-26.1)	22.9 (20.5-25.8)
Race or ethnic group*		
Black	20 (3.7%)	16 (3.0%)
East Asian	4 (0.7%)	6 (1.1%)
Latin American	59 (10.8%)	43 (7.9%)
Mixed race	14 (2.6%)	13 (2.4%)
South Asian	18 (3.3%)	19 (3.5%)
White	431 (78.9%)	445 (82.1%)
Method of conception		
Natural	514 (94.1%)	508 (93.7%)
Assisted by use of ovulation drugs	3 (0.6%)	5 (0.9%)
In vitro fertilization	29 (5.3%)	29 (5.4%)
Current cigarette smoking	102 (18.7%)	108 (19.9%)
Medical history		
Type 1 or 2 diabetes mellitus	2 (0.4%)	0
Chronic hypertension	8 (1.5%)	1 (0.2%)
Systemic lupus erythematosus	2 (0.4%)	7 (1.3%)
Antiphospholipid syndrome	3 (0.5%)	6 (1.1%)
Obstetrical history		
Multiparous	216 (39.6%)	216 (39.9%)
Nulliparous	330 (60.4%)	326 (60.1%)
sFlt-1/PlGF at randomization	15.1 (5.6-37.4)	16.2 (6.6-37.2)
sFlt-1/PlGF ≥38 at randomization	132 (24.2%)	128 (23.6%)

Estimated fetal weight at randomization, grams	2387 (2293-2468)	2374 (2262-2464)
Fetal growth restriction at randomization (non-exclusively)[†]	211 (38.6%)	222 (41.0%)
Estimated fetal weight <3rd percentile at randomization	112 (20.5%)	118 (21.8%)
Cerebroplacental ratio <5th percentile at randomization	78 (14.3%)	74 (13.7%)
Middle cerebral artery <5th percentile at randomization	38 (7.0%)	40 (7.4%)
Mean uterine artery pulsatility index >95th percentile at randomization	74 (13.6%)	85 (15.7%)
Umbilical artery pulsatility index >95th percentile at randomization	29 (5.3%)	25 (4.6%)

Data is reported as the number of events (%) or the median (IQR).

*****Race or ethnic group was reported by the participant. [†]Fetal growth restriction was determined based on the usual Doppler classification. Percentiles for estimated fetal weight and Doppler studies were assessed using the reference charts of each participating site.

PlGF, placental growth factor; sFlt-1, soluble fms-like tyrosine kinase-1.

390 **Table 2. Pregnancy outcomes in trial participants (intention to treat)**

	Intervention group (n=546)	**Control group (n=542)**	**Incidence difference 95%CI**	**Relative risk (95%CI)**
Adverse primary outcome				
Neonatal acidosis*****	11/513 (2.1%)	12/500 (2.4%)	-0.26 (-2.24 to 1.69)	0.89 (0.40-2.01)
Cesarean for abnormal CTG	44/513 (8.6)	40/500 (8.0%)	0.58 (-2.87 to 4.01)	1.07 (0.71-1.62)
Any	54/513 (10.5%)	50/500 (10.0%)	0.53 (-3.25 to 4.29)	1.05 (0.73-1.52)
Adverse perinatal outcome				
Stillbirth	0	1 (0.2%)	-0.18 (-1.04 to 0.53)	--
5-min Apgar score <7	4 (0.7%)	2 (0.4%)	0.36 (-0.70 to 1.53)	1.99 (0.37-10.81)
Umbilical artery pH <7.05	6/508 (1.2%)	14/500 (2.8%)	-1.62 (-3.57 to 0.15)	0.42 (0.16-1.09)
Admission to the NICU >48 h	39 (7.2%)	45 (8.3%)	-1.15 (-4.38 to 2.06)	0.86 (0.57-1.30)
Birthweight <2000 g	15 (2.7%)	15 (2.8%)	-0.02 (-2.07 to 2.03)	0.99 (0.49-2.01)
Maternal admission to the ICU >48 h	1 (0.2%)	1 (0.2%)	-0.00 (-0.87 to 0.86)	0.99 (0.03-15.86)
Preeclampsia	2 (0.4%)	11 (2.0%)	-1.66 (-3.25 to -0.35)	0.18 (0.04-0.81)
Any	44 (8.1%)	64 (11.8%)	-3.75 (-7.35 to -0.19)	0.68 (0.47-0.98)
Adverse neonatal outcome				
Respiratory distress syndrome	5 (0.9%)	9 (1.7%)	-0.74 (-2.30 to 0.70)	0.55 (0.19-1.64)
Transient tachypnea	12 (2.2%)	13 (2.4%)	-0.20 (-2.10 to 1.69)	0.92 (0.42-1.99)
Invasive ventilatory support	0	5 (0.9%)	-0.92 (-2.14 to -0.05)	--
Intraventricular hemorrhage III-IV	0	1 (0.2%)	-0.18 (-1.04 to 0.53)	--
Sepsis	2 (0.4%)	1 (0.2%)	0.18 (-0.71 to 1.16)	1.99 (0.18-21.87)
Hypoglycemia	19 (3.5%)	24 (4.4%)	-0.94 (-3.36 to 1.43)	0.79 (0.44-1.42)
Necrotizing enterocolitis	0	0	0	--
Jaundice treated with phototherapy	44 (8.1%)	50 (9.2%)	-1.17 (-4.55 to 2.20)	0.87 (0.59-1.29)

Seizures	0	0	0	--
Pneumonia	0	1 (0.2%)	-0.18 (-1.04 to 0.53)	--
Meningitis	0	0	0	--
Neonatal death	1 (0.2%)	0	0.18 (-0.54 to 1.03)	--
Any	76 (13.9%)	86 (15.9%)	-1.95 (-6.19 to 2.29)	0.88 (0.66-1.17)
Placental-related complications				
Placental abruption	2 (0.4%)	1 (0.2%)	0.18 (-0.71 to 1.16)	1.99 (0.18-21.87)
Gestational hypertension	7 (1.3%)	2 (0.4%)	0.92 (-0.26 to 2.28)	3.48 (0.73-16.68)
Preeclampsia with severity features	0	3 (0.6%)	-0.55 (-1.61 to 0.23)	--
Eclampsia	0	0	0	--
Stroke	0	0	0	--
Maternal death	0	0	0	--
Postpartum hemorrhage	3 (0.6%)	11 (2.0%)	-1.48 (-3.09 to -0.10)	0.27 (0.08-0.97)
Any	11 (2.0%)	23 (4.2%)	-2.23 (-4.46 to -0.14)	0.47 (0.23-0.96)

*****Neonatal acidosis was defined as a UA pH <7.15 and a base excess greater than –12 mEq/L.

Data are n (%) or n/N (%) where data are missing. CTG, cardiotocography; ICU, intensive care unit; NICU, neonatal intensive care unit.

Table 3. Other secondary adverse outcomes in trial participants (intention to treat)

Other secondary outcomes	Intervention group (n=546)	Control group (n=542)	Incidence difference 95%CI	Relative risk (95%CI)
Delivery <38 weeks	150 (27.5%)	209 (38.6%)	-11.04 (-16.53 to -5.45)	0.71 (0.60-0.85)
Delivery <39 weeks	260 (47.7%)	318 (58.7%)	-10.97 (-16.79 to -5.03)	0.81 (0.73-0.91)
Delivery <40 weeks	403 (73.9%)	432 (79.7%)	-5.76 (-10.74 to -0.74)	0.93 (0.87-0.99)
Elective delivery <38 weeks	103 (18.9%)	159 (29.3%)	-10.44 (-15.45 to -5.36)	0.64 (0.52-0.80)
Elective delivery <39 weeks	158 (29.0%)	221 (40.8%)	-11.78 (-17.34 to -6.12)	0.71 (0.60-0.84)
Elective delivery <40 weeks	208 (38.2%)	256 (47.2%)	-9.07 (-14.86 to -3.19)	0.81 (0.70-0.93)
Spontaneous onset of labor	137 (25.1%)	128 (23.7%)	1.48 (-3.63 to 6.57)	1.06 (0.86-1.31)
Birthweight <2500 g	199 (36.4%)	233 (43.0%)	-6.54 (-12.30 to -0.73)	0.85 (0.73-0.98)
Umbilical artery pH <7.10	21 (4.1%)	28 (5.6%)	-1.47 (-4.23 to 1.24)	0.74 (0.42-1.28)
Cesarean delivery due to failed induction of labor	30 (5.5%)	29 (5.4%)	0.14 (-2.61 to 2.90)	1.03 (0.63-1.69)
Cesarean delivery	118 (21.7%)	106 (19.6%)	2.06 (-2.76 to 6.86)	1.11 (0.87-1.40)
Emergency operative vaginal delivery	42 (7.7%)	47 (8.7%)	-0.98 (-4.29 to 2.31)	0.89 (0.60-1.32)

Figure legends

Figure 1. Screening, Randomization, and Follow-up in the GRAFD Trial

Figure 2. Primary adverse outcome in the population included in the intention to treat analysis and in the subanalysis by Doppler classification at enrolment.

FGR, fetal growth restriction, ITT, intention to treat; PP, per protocol; SGA, small for gestational age.

The forest plot shows the risk difference for each outcome (indicated by a point) between the intervention and control groups. Horizontal lines represent the 95% confidence intervals for these risk differences.

Figure 3. Kaplan–Meier curves for time to delivery in the intention-to-treat analysis, for all participants (A) and for participants electively delivered (B).

CI, confidence interval; HR, hazard ratio; w, weeks

The analysis used a Cox proportional hazards model, and the p-values were two-sided. No adjustments were made for multiple comparisons.

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METHODS

Trial Design

The GRAFD (growth restriction at term: angiogènic factors versus Doppler) trial was a multicentre, open-label, randomized, non-inferiority, controlled trial conducted at 20 Spanish maternities. The trial was approved by the Vall d'Hebron Ethics Committee (PR[AMI]527/2019) on February 18, 2020 and subsequent approval by individual ethical committees was granted. The study was registered at ClinicalTrials.gov (https://www.clinicaltrials.gov/study/NCT04502823; NCT04502823) and the protocol was published on October 11, 2022.[26] No substantial changes were made to the study design or methods after starting the trial. We used the CONSORT (Consolidated Standards of Reporting Trials) checklist when writing this report.[27]

Participants

Inclusion criteria at enrolment were: aged at least 16 years, singleton pregnancy, ultrasonographic EFW ≤10th percentile, sFlt-1/PlGF ratio measured between 36 weeks and 0 days and 37 weeks and 6 days of gestation. Exclusion criteria were: fetal death, major malformations or genetic disorders, absent or reversed end-diastolic flow in umbilical artery (UA) Doppler, non-reassuring cardiotocography (CTG), preeclampsia, reduced fetal movements, and oligohydramnios.[16] All participants provided individual written consent before randomization and did not receive any compensation for their involvement in the study. All participants in the study were identified as female; however, their gender identity was not recorded.

Randomization and trial procedures

Participants were randomly assigned, in a 1:1 ratio, either to the control group, where the standard Doppler-based protocol was followed, or to the intervention group, where the

sFlt-1/PlGF ratio was used. Randomization and data collection were managed using the REDCap (Research Electronic Data Capture) platform, hosted at Vall d'Hebron Institut de Recerca[28] The randomization sequence was centralized and entered into REDCap by an independent statistician. An independent researcher generated the block randomization sequence using the web-based Sealed Envelope (Sealed Envelope Ltd) system,[29] which was concealed from the investigators. Due to the nature of the intervention, the GRAFD trial was an open-label study.

In pregnant individuals from the intervention group, the fetus was classified as FGR when the sFlt-1/PlGF ratio was ≥38 and as SGA when the sFlt-1/PlGF ratio was <38. In that group, EFW, umbilical artery (UA) pulsatility index (PI), middle cerebral artery (MCA) PI, cerebroplacental ratio (CPR) PI, and mean uterine artery (UtA) PI percentiles were concealed to investigators to avoid any influence on the management. In the control group, the sFlt-1/PlGF ratio was concealed to investigators, and the standard Doppler-based fetal monitoring was used.[3] In that group, fetuses with an EFW <3rd percentile or ≤10th percentile, accompanied by any abnormal feto-maternal Doppler parameter were classified as FGR, while the remaining cases were classified as SGA. In both groups, elective delivery at ≥37 weeks of gestation was recommended for fetuses classified as FGR, and at 40 weeks of gestation for fetuses classified as SGA. All participants in both groups underwent weekly follow-up from randomization to delivery, including fetal ultrasound, conventional CTG and sFlt-1/PlGF ratio. (Extended Data Figure 2) The assessment in both groups differed only in feto-maternal Doppler and sFlt-1/PlGF ratio values, which were concealed or revealed to clinicians, depending on the allocated group. Consequently, the groups essentially compared the effectiveness of feto-maternal Doppler and sFlt-1/PlGF ratio in identifying FGR among all small fetuses. AF levels were

measured using the automated Elecsys electrochemiluminescence immunoassay platform (Cobas Analyzers; Roche Diagnostics).

Outcomes

The primary outcome was the prevalence of neonatal acidosis or Cesarean delivery due to non-reassuring fetal status. Neonatal acidosis was defined as a UA pH <7.15 and a base excess greater than –12 mEq/L, consistent with the reference study used for sample size calculation.[7] This definition has been associated with neonatal morbidity at term.[30] The prespecified secondary outcomes were a set of perinatal, neonatal and placental-related adverse events. They are listed and described in the study protocol.[26]

Sample size

According to a previous study,[7] 26% of cases following the control group protocol would present the primary outcome (neonatal acidosis or Cesarean delivery due to non-reassuring fetal status). Therefore, when calculating the sample size, we assumed a 26% rate of pregnancies with the primary outcome and set the noninferiority margin at 8.5%. This margin was agreed upon by all the investigators involved in this trial, comprising 20 maternity units in Spain with highly experienced clinicians in the field. Assuming a statistical power of 80% and a two-sided significance level of 5%, the required sample size for a non-inferiority design was 1,000 participants (500 in each group). A dropout rate of 3% was anticipated (1,030 participants); however, if the dropout rate was greater, the number of participants would be increased so as to achieve 1,000 participants with complete data for the primary outcome. Non-inferiority was demonstrated if the upper limit of the 95% confidence interval (CI) for the difference between incidences of pregnancies with the primary outcome was less than 8.5%.

Statistical analysis

Analysis was done according a prespecified statistical analysis plan. Data were analyzed based on an intention-to-treat principle, including all randomized participants. Patients deemed ineligible after randomization (e.g., due to postnatal identification of congenital defects, or EFW >10th percentile, or selection errors) were excluded in the additional per-protocol analysis. Univariate descriptive analysis was performed on study variables, and differences between groups were assessed for primary and secondary outcomes by calculating incidence differences with a 95% CI, setting the error type I at 0.05. Furthermore, relative risks with a 95% CI were computed to offer an alternative measure of the impact and aid in the interpretation of the results. One interim analysis was performed by an independent statistician once 50% of the sample size had been recruited following O'Brien Fleming method, with a two-sided type I error of 0.0031.

Since FGR pregnancies have a higher risk of adverse outcomes, participants with SGA were expected to be more inclined to participate than FGR. For this reason, a prespecified subgroup analysis was performed separately for FGR and SGA pregnancies according to Doppler classification at enrollment.

Categorical variables were reported as frequency, normally distributed continuous variables were reported as the mean and standard deviation, and non-normally distributed continuous variables were reported as the median and interquartile range. The Fisher's exact test or Chi-square test were used for categorical variables, and the Student's t-test or Mann-Whitney U test were used for continuous variables. Statistical analysis was performed using the Stata Statistical Software (Stata Statistical Software: Release 15, StataCorp LLC.). The command artbin of the Stata Corp (2017) Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC was used for sample size estimation.

Patient and public involvement

Patients were not directly involved in setting the objectives of the trial; however, various patient associations, such as the International Alliance of Patients' Organizations and El Parto es Nuestro, have expressed concerns about the rising rate of labor inductions and emphasized the need for personalized selection methods in cases where induction offers benefits over expectant management. While there was no direct patient participation in the study design, the Vall d'Hebron Ethics Committee includes patient representatives who provided valuable perspectives and contributions to the study design and the participant information sheet.

Ethical approval

Ethical approval was obtained from the Vall d'Hebron Ethics Committee (PR[AMI]527/2019) and subsequent approval by individual ethical committees was granted.

Data availability

External researchers can make written requests for data sharing. Requests will be assessed on a case-by-case basis in consultation with the lead and coinvestigators. A brief analysis plan and data request will be required and reviewed by the investigators and the Vall d'Hebron Ethics Committee to approve data sharing. In all cases, a data transfer agreement (DTA) will have to be signed through our Data Protection and Legal Office before any data can be shared. After signing the DTA, data will be sent electronically as password-protected files. Overall, the entire process from request submission to data transfer may take around 2 to 3 months. All data sharing will abide by the rules and policies defined by the sponsor, relevant institutional review boards, and local, state and

federal laws and regulations. The data sharing mechanisms will ensure that the rights and privacy of individuals participating in this research will be protected at all times.

Code availability

The scripts for the statistical analysis are freely available at https://github.com/manelmendoza/GRAFD/tree/main.

Methods Only REFERENCES

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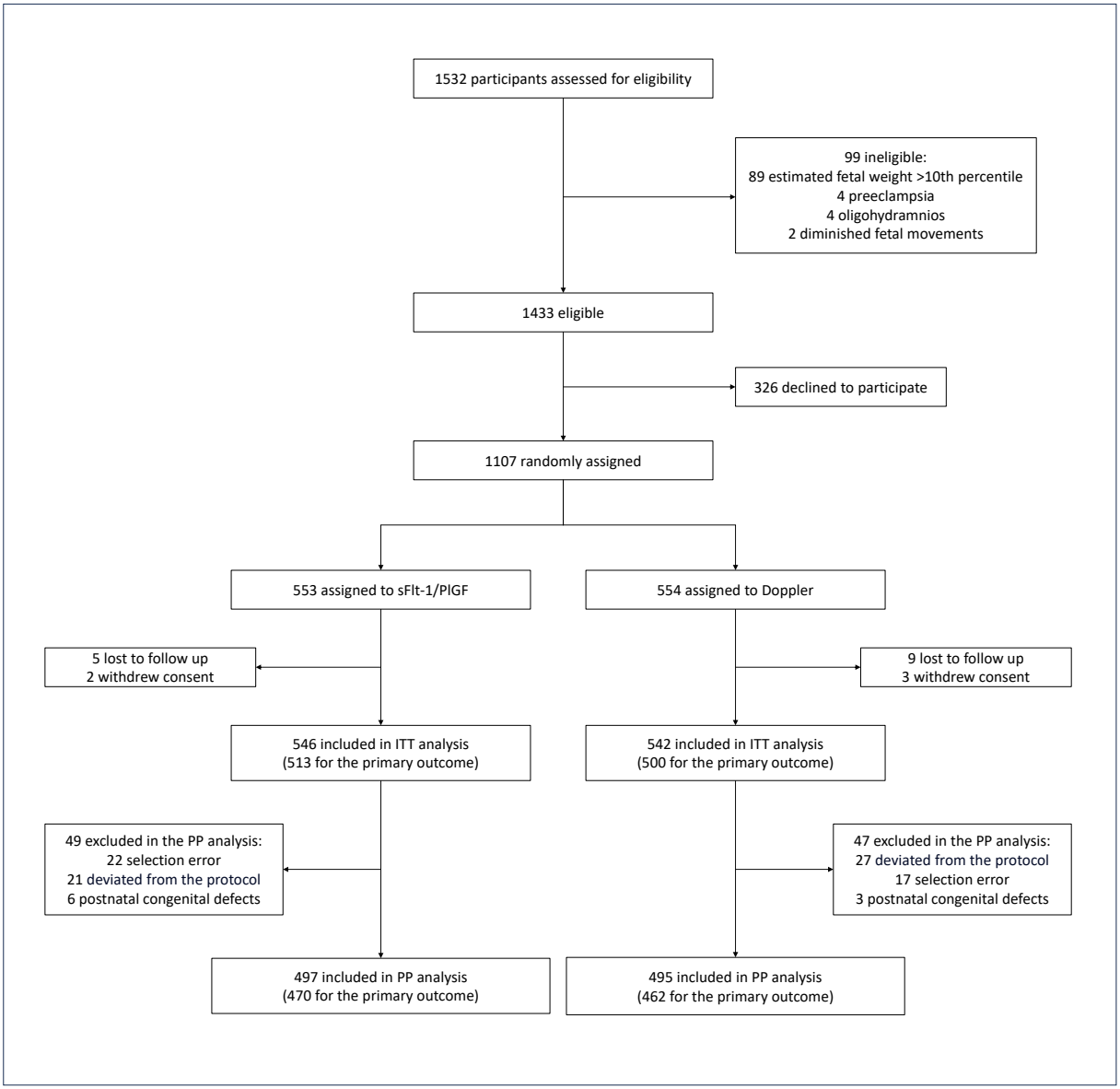
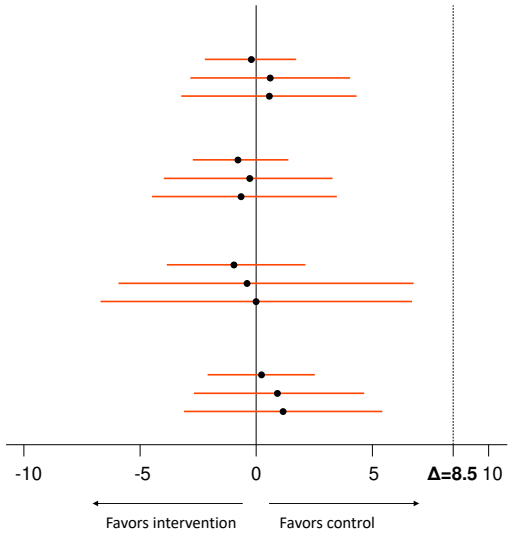
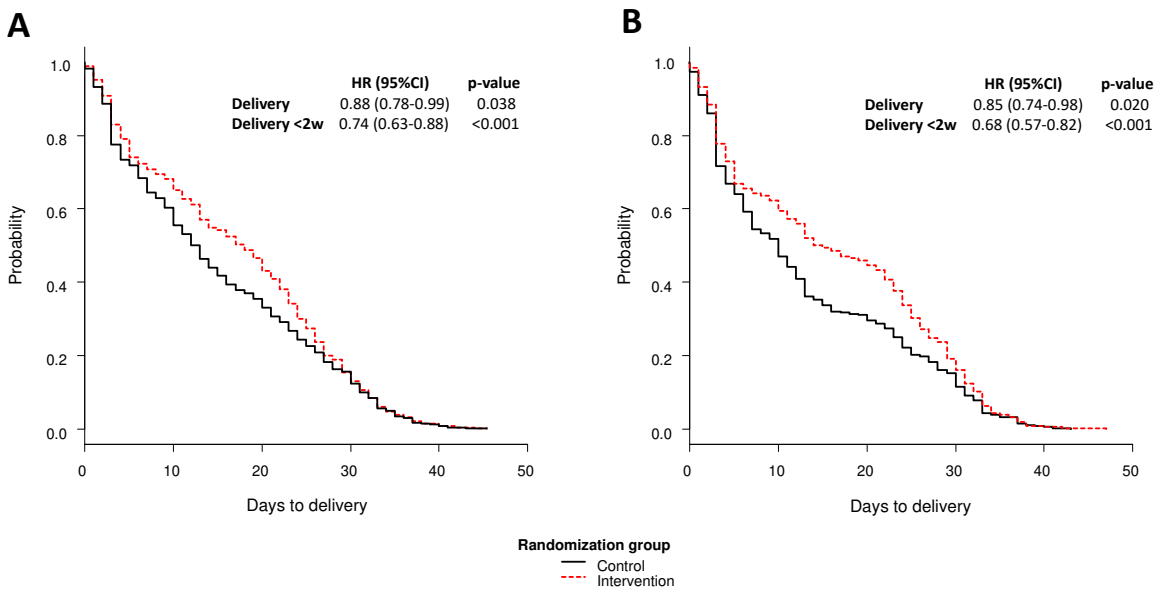
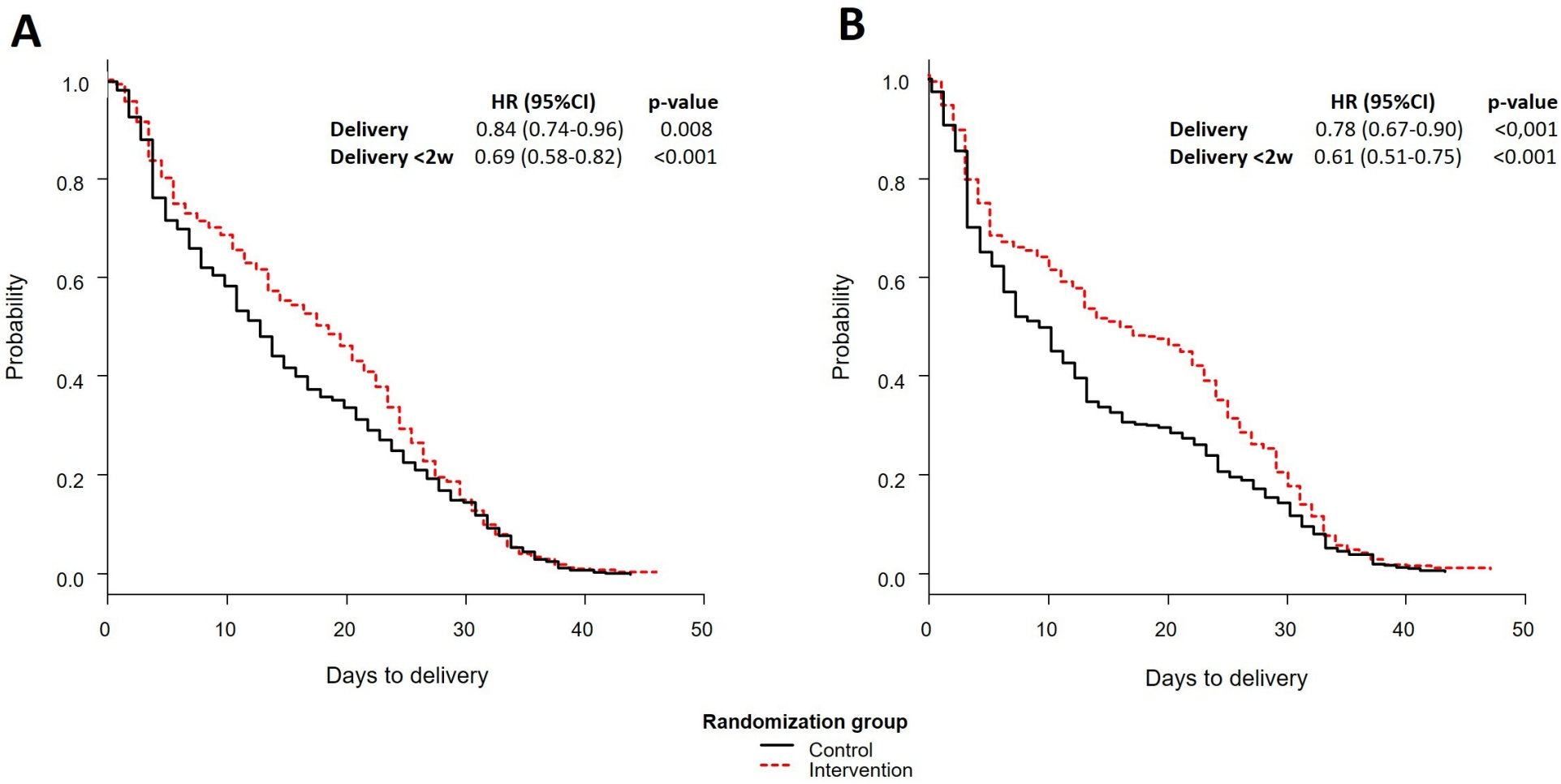
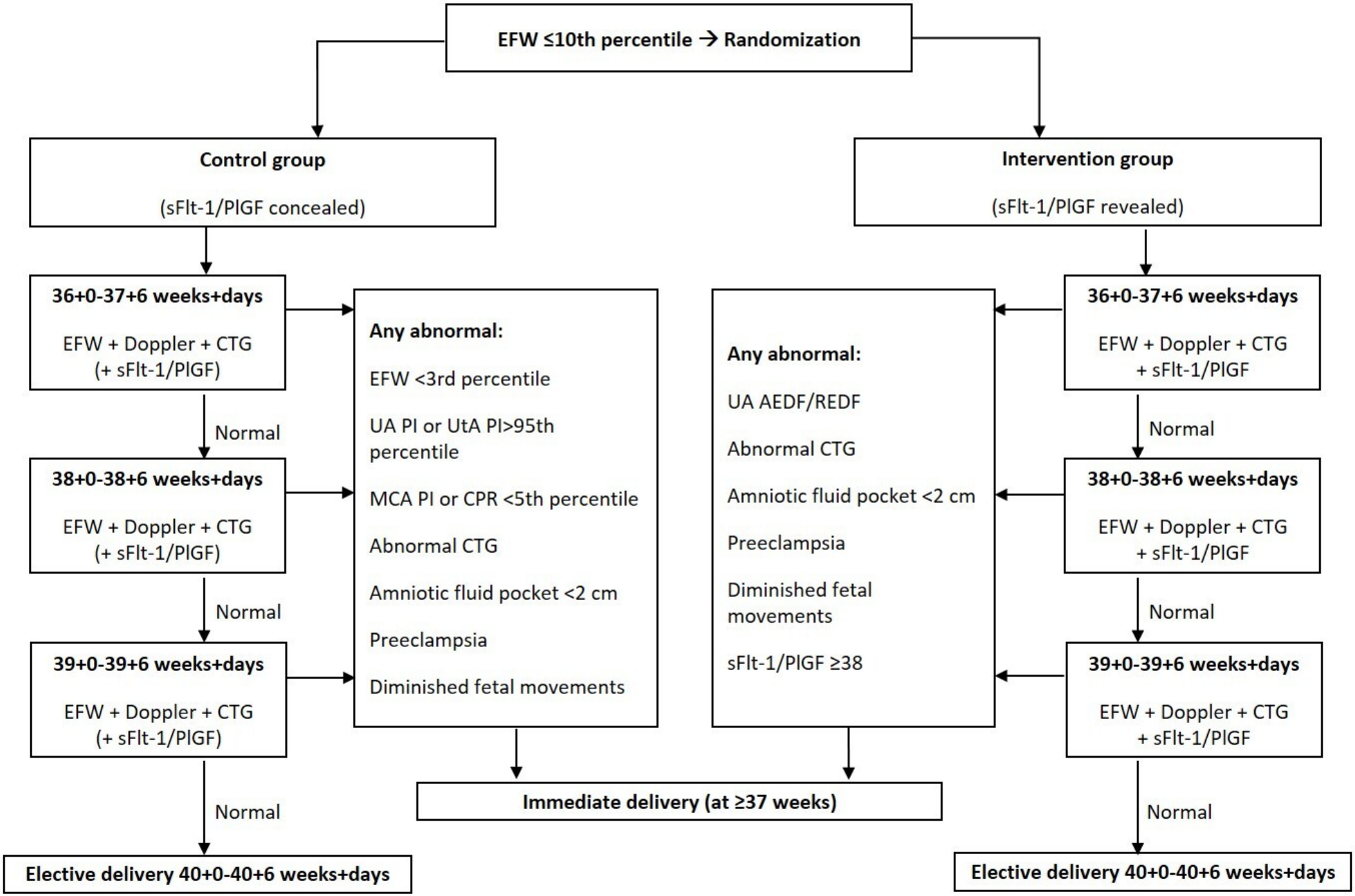

1532 participants assessed for eligibility
99 ineligible:
89 estimated fetal weight >10th percentile
4 preeclampsia
4 oligohydramnios
2 diminished fetal movements
1433 eligible
326 declined to participate
1107 randomly assigned
553 assigned to sFlt-1/PlGF
554 assigned to Doppler
5 lost to follow up
2 withdrew consent
9 lost to follow up
3 withdrew consent
546 included in ITT analysis
(513 for the primary outcome)
542 included in ITT analysis
(500 for the primary outcome)
49 excluded in the PP analysis:
22 selection error
21 deviated from the protocol
6 postnatal congenital defects
47 excluded in the PP analysis:
27 deviated from the protocol
17 selection error
3 postnatal congenital defects
497 included in PP analysis
(470 for the primary outcome)
495 included in PP analysis
(462 for the primary outcome)

	Intervention (n/N (%))	Control (n/N (%))	Risk difference (95% CI)
All participants (ITT)			
Neonatal acidosis	11/513 (2.1)	12/500 (2.4)	-0.26 (-2.24 to 1.69)
Cesarean for abnormal cardiotocography	44/513 (8.6)	40/500 (8.0)	0.58(-2.87 to 4.01)
Adverse primary outcome	54/513 (10.5)	50/500 (10.0)	0.53 (-3.25 to 4.29)
All participants (PP)			
Neonatal acidosis	9/470 (1.9)	12/462 (2.6)	-0.68 (-2.78 to 1.33)
Cesarean for abnormal cardiotocography	39/470 (8.3)	40/462 (8.7)	-0.36 (-4.00 to 3.26)
Adverse primary outcome	48/470 (10.2)	50/462 (10.8)	-0.61 (-4.59 to 3.36)
Only FGR at enrolment			
Neonatal acidosis	4/201 (2.0)	6/208 (2.9)	-0.89 (-3.88 to 2.09)
Cesarean for abnormal cardiotocography	25/201 (12.4)	25/208 (12.0)	0.42 (-5.93 to 6.77)
Adverse primary outcome	28/201 (13.9)	29/208 (13.9)	-0.01 (-6.73 to 6.70)
Only SGA at enrolment			
Neonatal acidosis	7/312 (2.2)	6/292 (2.1)	0.19 (-2.12 to 2.50)
Cesarean for abnormal cardiotocography	19/312 (6.1)	15/292 (5.1)	0.95 (-2.71 to 4.62)
Adverse primary outcome	26/312 (8.3)	21/292 (7.2)	1.14 (-3.12 to 5.41)




A
B
HR (95%CI)
p-value
Delivery
0.88 (0.78-0.99)
0.038
Delivery <2w
0.74 (0.63-0.88)
<0.001
0.85 (0.74-0.98)
0.020
0.68 (0.57-0.82)
<0.001
Probability
Days to delivery
Randomization group
Control
Intervention


A
B
HR (95%CI)
p-value
Delivery
0.84 (0.74-0.96)
0.008
Delivery <2w
0.69 (0.58-0.82)
<0.001
0.78 (0.67-0.90)
<0,001
0.61 (0.51-0.75)
<0.001
Probability
Days to delivery
Randomization group
Control
Intervention


EFW ≤10th percentile → Randomization
Control group
(sFlt-1/PlGF concealed)
Intervention group
(sFlt-1/PlGF revealed)
36+0-37+6 weeks+days
EFW + Doppler + CTG
(+ sFlt-1/PlGF)
Normal
38+0-38+6 weeks+days
EFW + Doppler + CTG
(+ sFlt-1/PlGF)
Normal
39+0-39+6 weeks+days
EFW + Doppler + CTG
(+ sFlt-1/PlGF)
Normal
Elective delivery 40+0-40+6 weeks+days
Any abnormal:
EFW <3rd percentile
UA PI or UtA PI>95th percentile
MCA PI or CPR <5th percentile
Abnormal CTG
Amniotic fluid pocket <2 cm
Preeclampsia
Diminished fetal movements
Any abnormal:
UA AEDF/REDF
Abnormal CTG
Amniotic fluid pocket <2 cm
Preeclampsia
Diminished fetal movements
sFlt-1/PlGF ≥38
Immediate delivery (at ≥37 weeks)
36+0-37+6 weeks+days
EFW + Doppler + CTG
+ sFlt-1/PlGF
Normal
38+0-38+6 weeks+days
EFW + Doppler + CTG
+ sFlt-1/PlGF
Normal
39+0-39+6 weeks+days
EFW + Doppler + CTG
+ sFlt-1/PlGF
Normal
Elective delivery 40+0-40+6 weeks+days