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Impact of fetal growth restriction on pregnancy outcome in women undergoing expectant management for preterm pre-eclampsia

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KEYWORDS: Cesarean section; delivery; fetal growth restriction; induction; latency; neonatal morbidity; neonatal mortality; pre-eclampsia; preterm pre-eclampsia

CONTRIBUTION

What are the novel findings of this work?
The presence of coexisting fetal growth restriction among women with preterm pre-eclampsia managed expectantly was associated with poorer outcome, especially for the fetus. Fetal growth restriction was associated with shorter pregnancy latency, emergency Cesarean delivery, lower probability of successful induction and increased rates of neonatal morbidity and mortality.

What are the clinical implications of this work?
Fetal growth restriction in the setting of expectant management for preterm pre-eclampsia is associated with substantially poorer perinatal outcome.

ABSTRACT

Objectives *To assess whether coexisting fetal growth restriction (FGR) influences pregnancy latency among women with preterm pre-eclampsia undergoing expectant management. Secondary outcomes assessed were indication for delivery, mode of delivery and rate of serious adverse maternal and perinatal outcomes.*

Methods *We conducted a secondary analysis of the Pre-eclampsia Intervention (PIE) and the Pre-eclampsia Intervention 2 (PI2) trial data. These randomized controlled trials evaluated whether esomeprazole and metformin could prolong gestation of women diagnosed with pre-eclampsia between 26 and 32 weeks of gestation undergoing expectant management. Delivery indications were deteriorating maternal or fetal status, or reaching 34 weeks' gestation. FGR (defined by Delphi consensus) at the time of pre-eclampsia diagnosis was examined as a predictor of outcome. Only placebo data from PI2 were included, as the trial showed that metformin use was associated with prolonged gestation. All outcome data were collected prospectively from diagnosis of pre-eclampsia to 6 weeks after the expected due date.*

Results *Of the 202 women included, 92 (45.5%) had FGR at the time of pre-eclampsia diagnosis. Median pregnancy latency was 6.8 days in the FGR group and 15.3 days in the control group (difference 8.5 days; adjusted 0.49-fold change (95% CI, 0.33–0.74); P < 0.001). FGR pregnancies were less likely to reach 34 weeks' gestation (12.0% vs 30.9%; adjusted relative risk (aRR), 0.44 (95% CI, 0.23–0.83)) and more likely to be delivered for suspected fetal compromise (64.1% vs 36.4%; aRR, 1.84 (95% CI, 1.36–2.47)). More women with FGR underwent a prelabor emergency Cesarean section (66.3% vs 43.6%; aRR, 1.56 (95% CI, 1.20–2.03)) and were less likely to have a successful induction of labor (4.3% vs 14.5%; aRR, 0.32 (95% CI, 0.10–1.00)), compared to those without FGR. The rate*

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of maternal complications did not differ significantly between the two groups. FGR was associated with a higher rate of infant death (14.1% vs 4.5%; aRR, 3.26 (95% CI, 1.08–9.81)) and need for intubation and mechanical ventilation (15.2% vs 5.5%; aRR, 2.97 (95% CI, 1.11–7.90)).

Conclusion *FGR is commonly present in women with early preterm pre-eclampsia and outcome is poorer. FGR is associated with shorter pregnancy latency, more emergency Cesarean deliveries, fewer successful inductions and increased rates of neonatal morbidity and mortality.* © *2023 The Authors. Ultrasound in Obstetrics & Gynecology published by John Wiley & Sons Ltd on behalf of International Society of Ultrasound in Obstetrics and Gynecology.*

INTRODUCTION

Pre-eclampsia occurring before 34 weeks' gestation is associated with serious complications for both mother and fetus[1,2]. This poses a serious clinical dilemma. Expectant management exposes the mother to risks of worsening disease, yet the only alternative is delivery, with the attendant risks to the newborn of mortality and morbidity associated with preterm birth.

Around 60% of women with preterm pre-eclampsia may be considered suitable for expectant management[3]. Previous studies have suggested there can be an average pregnancy prolongation of between 7 and 14 days[2,4–6], but the presence of coexisting fetal growth restriction (FGR) may affect the duration of latency. The impact of coexisting FGR on pregnancy outcome has thus far been poorly characterized. Two retrospective studies have both shown a shorter prolongation of pregnancy with FGR, but definitions for FGR differed, with one assessing both an estimated fetal weight (EFW) less than the 5th centile and 10th centile[7] and the other defining FGR as an EFW less than the 10th centile or an abdominal circumference less than the 5th centile with abnormal umbilical artery Doppler findings[8]. Additionally, the study by Chammas *et al.*[7] included only 14 women with FGR, and McKinney *et al.*[8] included 60. A limitation of these studies is that a standard definition for FGR was not used, and only retrospective data were assessed. The Society for Maternal–Fetal Medicine has highlighted that this evidence gap would be best addressed with the collection of high-quality prospective data[1].

We have recently reported the results of two randomized controlled trials evaluating the effect of therapeutics in prolonging gestation among women being managed expectantly for preterm pre-eclampsia: the Pre-eclampsia Intervention with Esomeprazole (PIE) trial and the Pre-eclampsia Intervention 2 (PI2) trial with metformin[4,6]. These studies provide valuable prospective data with which to assess the impact of antenatally diagnosed FGR on both pregnancy duration and perinatal outcome. Thus, we used these data to assess whether the presence of coexisting FGR, using the consensus definition of Gordijn *et al.*[9], among women diagnosed with preterm pre-eclampsia between 26 + 0 and 31 + 6 weeks' gestation influences pregnancy latency, indication for delivery, mode of delivery and rate of serious adverse maternal and perinatal outcomes.

METHODS

Study cohort

The PIE and PI2 trials were double-blind randomized placebo-controlled trials that recruited women with preterm pre-eclampsia at a gestational age between 26 + 0 and 31 + 6 weeks and undergoing expectant management at Tygerberg Hospital, Cape Town, South Africa between January 2016 and April 2017 for PIE and from February 2018 to March 2020 for PI2. The trial protocols have been published[10,11], but, in brief, women who qualified for expectant management were randomized 1:1 to 40 mg oral esomeprazole or matched placebo daily for PIE or 1 g metformin or a matched placebo three times a day for PI2, for the remainder of their pregnancy. Pre-eclampsia was defined according to the International Society for the Study of Hypertension in Pregnancy criteria, but the presence of proteinuria (more than 0.3 g total urinary protein excreted over a 24-h period) was also required. Expectant management involved hospital admission with close maternal and fetal surveillance and ended at 34 weeks' gestation. Delivery prior to 34 weeks' gestation on fetal or maternal grounds was a clinical decision made by a dedicated management team. Exclusion criteria included established maternal or fetal compromise mandating immediate delivery. After delivery, neonates were transferred out, based on clinical criteria, to a primary or secondary hospital or discharged home. Data were collected prospectively and entered into a REDCap database[12].

Exposure and outcome

To assess the impact of FGR on pregnancy latency, we divided the study cohort according to the presence or absence of FGR on ultrasound assessment at the time of recruitment into the trials. FGR was defined according to a Delphi definition for early FGR before 32 weeks' gestation[9]. Pregnancies were considered to have FGR if one or more of the following criteria were present: EFW or abdominal circumference less than the 3rd centile; absent or reversed end-diastolic flow in the umbilical artery; or an EFW or abdominal circumference less than the 10th centile with uterine artery and/or umbilical artery pulsatility index above the 95th centile. The EFW was calculated using the Hadlock formula derived from the head circumference, biparietal diameter, abdominal circumference and the femur length measurements[13]. Fetal-weight centiles were calculated using GROW centiles[14] customized for maternal weight, height, ethnicity, parity and fetal sex. All ultrasound examinations were performed by maternal–fetal medicine specialists, trainees in

maternal–fetal medicine or obstetrics and gynecology, or qualified sonographers.

Data from the esomeprazole and placebo groups were combined for the PIE trial, given that the PIE trial yielded a negative finding. Only data from the placebo arm of the PI2 trial were included, as metformin use was associated with a prolongation of pregnancy of 17.7 (interquartile range (IQR), 5.4–29.4) days compared to 10.1 (IQR, 3.7–24.1) days, with a median difference of 7.6 days. Data were collected with the rigor of clinical trial methodology, including individual case record forms, which were filled in contemporaneously for every participant and double-checked for errors.

The primary outcome was prolongation of gestation, measured from the time of taking the first dose of trial medication until delivery. Secondary outcomes were gestational age at delivery, indication for delivery, mode of delivery and vaginal delivery after induction, if performed. Exploratory outcomes included maternal and perinatal outcomes. The baby was followed up until 6 weeks after the expected due date.

Indications for delivery included reaching a gestational age of 34 weeks, suspected fetal compromise (fetal distress on antenatal non-stress test monitoring, poor fetal growth and/or deteriorating Doppler findings on ultrasound as per local protocols), fetal death, placental abruption, specified deteriorating maternal condition, spontaneous preterm birth or if the mother declined further expectant management and requested delivery. Mode of delivery was defined as emergency or elective Cesarean section, spontaneous or induced vaginal delivery, failed induction needing emergency Cesarean section or failed induction needing a non-emergency Cesarean section.

Statistical analysis

Descriptive data are presented as mean ± SD or median (IQR) for numerical variables and as *n* (%) for categorical variables. Baseline comparisons between groups were performed using Fisher's exact test for binary variables and using the Fisher–Pitman non-parametric permutation test for the mean difference for continuous variables.

The primary outcome, prolongation of gestation, was analyzed using parametric time-to-event analysis. A log-linear regression model was used with a generalized gamma distribution for the response variable, which includes the log-normal distribution as a special case[15]. Pregnancies for which labor was induced at 34 weeks of gestation were considered censored observations. Fold-change between groups was calculated by exponentiating the regression coefficient corresponding to the group effect on log scale.

Secondary and exploratory binary outcomes were compared across groups using relative risks (RR) estimated by log-linear quasi-Poisson regression. Robust standard errors were used to account for violations against distributional assumptions. RR of outcomes with few events (fewer than two events in one of the groups) were handled using Firth correction. Numerical exploratory outcomes were analyzed using linear regression or median quantile regression, as appropriate.

Analyses were performed unadjusted and adjusted for maternal age, gestation at enrolment, smoking, body mass index and treatment with esomeprazole. All comparisons were performed at 5% significance level and presented with corresponding 95% CI. *P*-values were not calculated for the secondary and exploratory analyses. Statistical analyses were performed using SPSS 26.0. (IBM Corp., Armonk, NY, USA) and SAS version 9.4 (SAS Institute, Cary, NC, USA).

Ethical approval and clinical trial registration

Ethical approval was given by the Health Research Ethics Committee at Stellenbosch University, Cape Town, South Africa for the PIE and PI2 trials (PIE: M14/09/038; PI2: M16/09/037) and the current substudy (N22/07/085). All women gave written informed consent.

The PIE and the PI2 trials are registered with the Pan African Clinical Trials Registry (PIE: PACTR201 504 000 771 349; PI2: PACTR201608001752102).

RESULTS

Between January 2016 and March 2020, 300 women were enrolled in the PIE and PI2 trials (Figure 1)[4,6]. A total of 98 cases were excluded: five did not meet the requirements for a pre-eclampsia diagnosis, two declined further hospital treatment, one was under 18 years of age and 90 received metformin in the PI2 trial.

Of the remaining 202 participants, 92 (45.5%) had FGR at the time of recruitment, and the remaining 110 (54.5%) were considered appropriately grown (Figure 1). In the FGR group, there were 66 fetuses who had an EFW less than the 3rd centile and 26 whose EFW was less than the 10th centile with the umbilical artery and/or uterine artery pulsatility index above the 95th centile. Absent end-diastolic flow in the umbilical artery was present at enrolment in seven. In the control group, 96 had an EFW above the 10th centile and 14 had an estimated weight between the 3rd and 10th centile with normal Doppler studies and an abdominal circumference above the 3rd centile.

Women with coexisting FGR were significantly younger, had a higher hemoglobin level, a lower platelet count, and both the EFW and corresponding centiles were lower (Table 1). Baseline characteristics and outcome data for the PIE and PI2 trials can be found in Tables S1 and S2, respectively.

Primary outcome

Median pregnancy latency was 6.8 (IQR, 3.3–16.0) days in the FGR group and 15.3 (IQR, 4.4–24.1) days in the control group, a difference of 8.5 days rendering a 0.47-fold change (95% CI, 0.31–0.69; $P < 0.001$) (Table 2 and Figure 2). When adjusted for maternal age, gestation at enrolment, smoking, body mass index and

treatment with esomeprazole, there was a 0.49-fold change (95% CI, 0.33–0.74; $P < 0.001$). The median gestational age at delivery was 31 + 1 (IQR, 29 + 2 to 32 + 6) weeks in the FGR group and 31 + 6 (IQR, 30 + 0 to 34 + 0) weeks in the control group, with an adjusted median difference of −1.14 (95% CI, −2.18 to −0.11) weeks; $P = 0.03$).

Secondary outcomes

Indication for delivery

Pregnancies with FGR were less likely to reach 34 weeks of gestation (12.0% *vs* 30.9%; adjusted RR (aRR), 0.44 (95% CI, 0.23–0.83)) and more likely to be delivered due to suspected fetal compromise (64.1% *vs* 36.4%; aRR, 1.84 (95% CI, 1.36–2.47)) (Table 2). In the FGR group, 53 (57.6%) deliveries were for suspected fetal distress on cardiotocograph monitoring before labor, four (4.3%) for poor growth on serial ultrasounds and two (2.2%) for deteriorating Doppler studies. In the control group, 39 (35.5%) were delivered for suspected fetal distress on cardiotocograph monitoring before labor and one (0.9%) for deteriorating Doppler studies.

There were no differences for other delivery indications, including deteriorating maternal condition, placental abruption, spontaneous preterm birth, stillbirth or the maternal decision to decline further expectant management (Table 2).

Mode of delivery

Table 2 shows there was no difference in elective Cesarean section between the groups, but women with coexisting FGR were more likely to undergo a prelabor emergency Cesarean section (66.3% *vs* 43.6%; aRR, 1.56 (95% CI, 1.20–2.03)) and less likely to have a successful induction of labor (4.3% *vs* 14.5%; aRR,

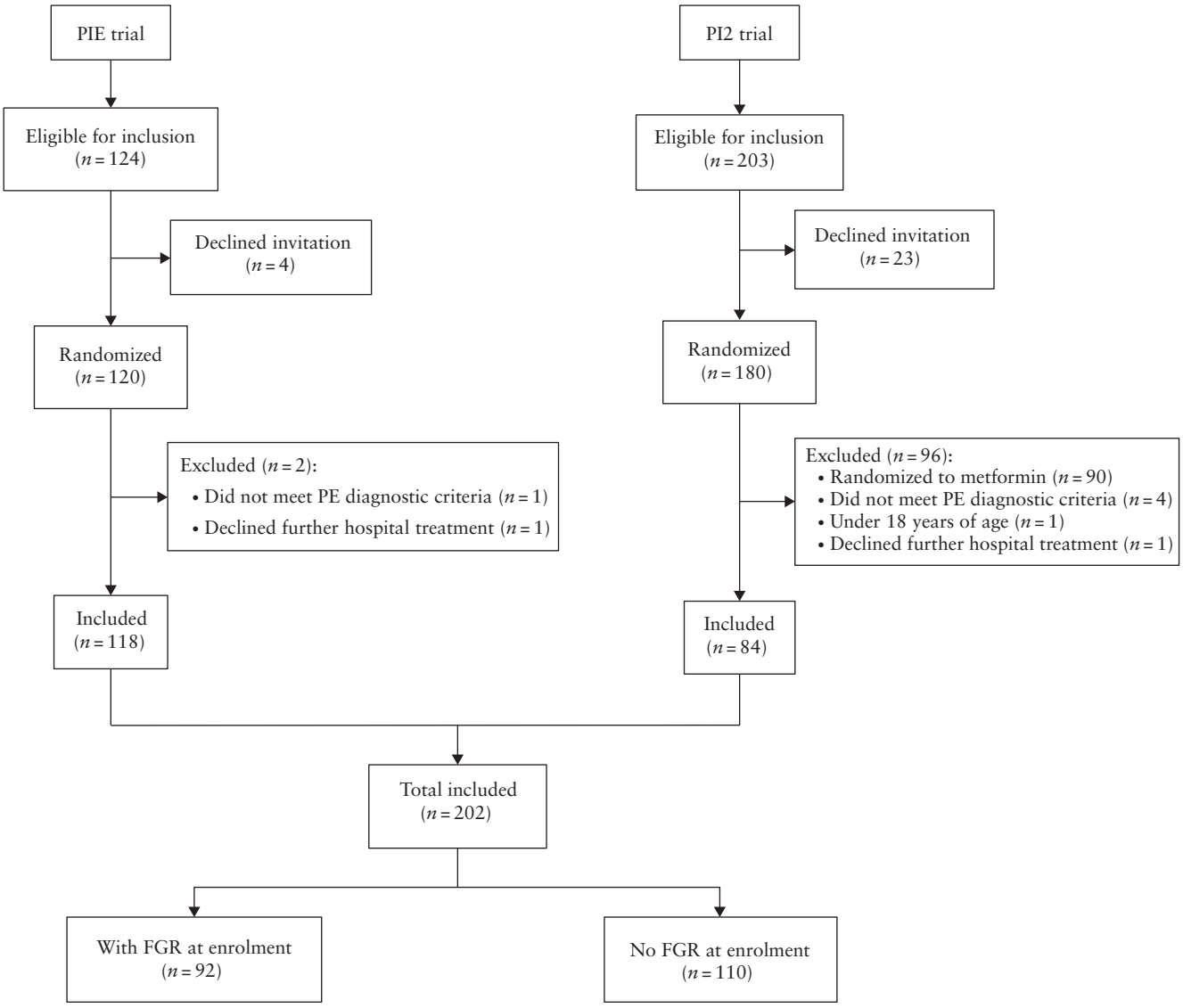

Figure 1 Flowchart showing participant inclusion in study of impact of fetal growth restriction (FGR) on pregnancy outcome in women undergoing expectant management for preterm pre-eclampsia (PE). PI2, Pre-eclampsia Intervention 2; PIE, Pre-eclampsia Intervention with Esomeprazole.

0.32 (95% CI, 0.10–1.00)). Fewer women with coexisting FGR were eligible for induction (22.8% *vs* 42.7%). Of those eligible for induction, those with coexisting FGR were less likely to have vaginal delivery after induction (19% *vs* 34%; aRR, 0.54 (95% CI, 0.15–1.90)) and more likely to require an urgent Cesarean section for suspected fetal compromise (76.2% *vs* 48.9%; aRR, 1.55 (95% CI, 0.92–2.62)), but these findings did not reach statistical significance.

There were four spontaneous preterm vaginal deliveries in the control group and none in the FGR group (Table 2).

Maternal and neonatal outcomes

Severe maternal complications occurred infrequently, and the rate did not differ significantly between the two groups (Table 3). There were no maternal deaths, cases of stroke, cortical blindness, retinal detachment, liver capsule

Table 1 Baseline characteristics of 202 pregnancies with preterm pre-eclampsia, according to presence of coexisting fetal growth restriction (FGR) at enrolment

Characteristic	*FGR (n = 92)*	*No FGR (n = 110)*	P
Maternal age (years)	26.7 ± 6.4	29.5 ± 6.8	0.004
Nulliparous	38 (41.3)	36 (32.7)	0.27
Body mass index (kg/m^2)	29.1 ± 7.4	30.7 ± 6.9	0.12
Smoking in pregnancy	11 (12.0)	11 (10.0)	0.82
HIV positive	13 (14.1)	27 (24.5)	0.09
Chronic hypertension	26 (28.3)	30 (27.3)	1.00
Highest systolic BP (mmHg)	167.3 ± 16.9	168.5 ± 16.2	0.60
Highest diastolic BP (mmHg)	104.4 ± 13.2	101.8 ± 13.5	0.17
Hemoglobin (g/dL)	12.3 ± 1.4	11.4 ± 1.3	< 0.001
Platelet count (×10^9/L)	208.8 ± 60.4	229.2 ± 70.8	0.030
Urea (mmol/L)	4.1 ± 1.5	3.7 ± 1.6	0.18
Creatinine (mg/dL)	55.2 ± 11.5	54.5 ± 15.7	0.73
Randomized to esomeprazole	31 (33.7)	27 (24.5)	0.20
GA at enrolment (weeks)	29.0 ± 1.5	29.0 ± 1.7	0.97
EFW at enrolment (g)	1011 ± 204	1254 ± 305	< 0.001
EFW centile at enrolment	2.3 ± 2.7	33.3 ± 24.6	< 0.001
AEDF in umbilical artery	7 (7.6)	0 (0.0)	0.007

Data are given as mean ± SD or *n* (%). Data missing from: FGR group, urea (*n* = 2); no-FGR group, body mass index (BMI) (*n* = 1), urea (*n* = 4), creatinine (*n* = 1). AEDF, absent end-diastolic flow; BP, blood pressure before enrolment; EFW, estimated fetal weight; GA, gestational age; HIV, human immunodeficiency virus.

Table 2 Primary outcome, indication for delivery and mode of delivery in 202 women with preterm pre-eclampsia, according to presence of coexisting fetal growth restriction (FGR)

			Fold-change/RR (95% CI)*	
Parameter	*FGR (n = 92)*	*No FGR (n = 110)*	*Unadjusted*	*Adjusted†*
Primary outcome				
Prolongation of gestation	6.8 (3.3–16.0)	15.3 (4.4–24.1)	0.47 (0.31–0.69)¶	0.49 (0.33–0.74)¶
Indication for delivery				
Reached 34 weeks' gestation	11 (12.0)	34 (30.9)	0.39 (0.21–0.73)	0.44 (0.23–0.83)
Suspected fetal compromise	59 (64.1)	40 (36.4)	1.76 (1.31–2.37)	1.84 (1.36–2.47)
Deteriorating maternal condition	21 (22.8)	29 (26.4)	0.87 (0.53–1.42)	0.78 (0.47–1.32)
Placental abruption‡	1 (1.1)	1 (0.9)	1.20 (0.10–14.72)	—
Spontaneous preterm birth‡	0 (0.0)	3 (2.7)	0.17 (0.00–1.76)	—
Stillbirth‡	0 (0.0)	1 (0.9)	0.40 (0.00–7.47)	—
Declined further expectant management‡	0 (0.0)	2 (1.8)	0.24 (0.00–2.94)	—
Mode of delivery				
Emergency CS without induction of labor	61 (66.3)	48 (43.6)	1.52 (1.17–1.97)	1.56 (1.20–2.03)
Elective CS	10 (10.9)	11 (10.0)	1.09 (0.48–2.48)	1.28 (0.58–2.81)
Induction with vaginal delivery	4 (4.3)	16 (14.5)	0.30 (0.10–0.88)	0.32 (0.10–1.00)
Failed induction with emergency CS§	16 (17.4)	23 (20.9)	0.83 (0.46–1.49)	0.80 (0.43–1.46)
Failed induction with non-emergency CS	1 (1.1)	8 (7.3)	0.15 (0.02–1.21)	0.13 (0.02–1.05)
Spontaneous preterm vaginal delivery‡	0 (0.0)	4 (3.6)	0.13 (0.00–1.24)	—
Eligible for induction of labor				
Induction with vaginal delivery	4/21 (19.0)	16/47 (34.0)	0.56 (0.20–1.57)	0.54 (0.15–1.90)
Induction with emergency CS§	16/21 (76.2)	23/47 (48.9)	1.56 (1.05–2.32)	1.55 (0.92–2.62)
Failed induction with non-emergency CS	1/21 (4.8)	8/47 (17.0)	0.28 (0.03–2.40)	0.22 (0.01–3.37)

Data are given as median (interquartile range), *n* (%) or *n*/*N* (%), unless stated otherwise. *Primary outcome only. †Adjusted for maternal age, gestational age at enrolment, smoking, body mass index and treatment with esomeprazole. ‡Relative risk (RR) estimated using Firth correction; adjusted analyses not performed. §For suspected fetal compromise. ¶$P < 0.001$. CS, Cesarean section.

hematoma or rupture, bronchopulmonary dysplasia or neonatal seizures. Infants with FGR had a significantly lower birth weight (mean, 1140 g *vs* 1579 g; adjusted mean difference, −427 (95% CI, −520 to −335) g), they were more likely to require intubation and mechanical ventilation (15.2% *vs* 5.5%; aRR, 2.97 (95% CI, 1.11–7.90)) and infant death was more likely (14.1% *vs* 4.5%; aRR, 3.26 (95% CI, 1.08–9.81)) (Table 3).

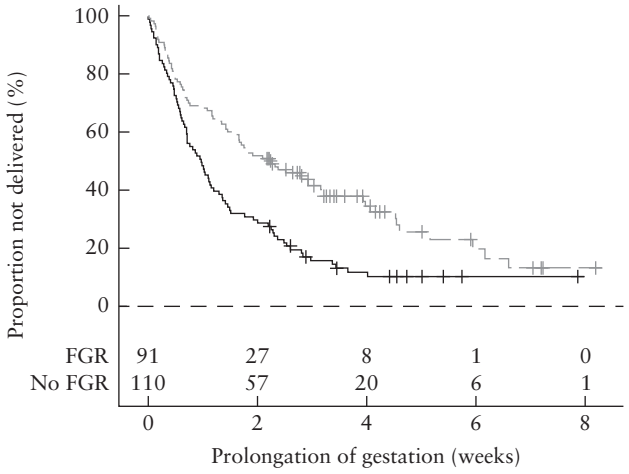

Figure 2 Kaplan–Meier curve showing prolongation of pregnancy in those with (——) and those without (– –) coexisting fetal growth restriction (FGR). +, pregnancies that reached 34 weeks' gestation.

DISCUSSION

Principal findings

Using prospectively collected trial data, we found that pregnancy latency was significantly reduced, and perinatal outcomes significantly worse, when preterm pre-eclampsia was accompanied by FGR at the time of diagnosis. These pregnancies were less likely to reach 34 weeks' gestation, more likely to develop fetal compromise, including fetal distress on routine antenatal non-stress test monitoring, and were more likely to require an emergency CS without induction of labor. There was also a significantly increased risk of infant death, and neonates were more likely to need invasive ventilation.

Reassuringly, there was no difference in maternal outcome even though the gain in gestation was more than double among those without a growth-restricted fetus.

Results in the context of what is known

The finding that pregnancy latency is reduced among women with preterm pre-eclampsia and FGR is consistent with two previous retrospective studies. Chammas *et al.*[7], reported on 47 cases of pre-eclampsia diagnosed before 34 weeks' gestation and McKinney *et al.*[8], on 199

Table 3 Maternal and perinatal outcome in 202 women with preterm pre-eclampsia, according to presence of coexisting fetal growth restriction (FGR)

Outcome	*FGR (n = 92)*	*No FGR (n = 110)*	*RR/mean diff/median diff (95% CI)*	
			Unadjusted	*Adjusted**
Maternal				
Eclampsia†‡	2 (2.2)	1 (0.9)	1.99 (0.27–21.78)	—
Pulmonary edema§	1 (1.1)	3 (2.7)	0.40 (0.04–3.91)	0.44 (0.03–6.66)
Acute kidney injury‡¶	0 (0.0)	2 (1.8)	0.24 (0.00–2.94)	—
Placental abruption	3 (3.3)	4 (3.6)	0.90 (0.20–4.00)	0.77 (0.12–4.88)
Major PPH**	1 (1.1)	2 (1.8)	0.60 (0.05–6.75)	0.55 (0.05–5.83)
HELLP syndrome††	6 (6.5)	9 (8.2)	0.80 (0.29–2.19)	0.61 (0.22–1.70)
Admission to ICU‡	0 (0.0)	1 (0.9)	0.40 (0.00–7.47)	—
Highest systolic BP (mmHg)	159.8 ± 12.7	158.5 ± 12.7	1.3 (−2.3 to 4.8)	1.5 (−2.1 to 5.2)
Highest diastolic BP (mmHg)	99.7 ± 9.6	98.8 ± 10.4	0.9 (−1.9 to 3.7)	0.1 (−2.6 to 2.8)
Perinatal				
Birth weight (g)	1140 ± 293	1579 ± 505	−439 (−552 to −326)	−427 (−520 to −335)
5-min Apgar score	9 (8–10)	9 (8–10)	0 (0–0)	0 (0–0)
Infant death	13 (14.1)	5 (4.5)	3.11 (1.13–8.53)	3.26 (1.08–9.81)
Intubation and mechanical ventilation	14 (15.2)	6 (5.5)	2.76 (1.09–7.01)	2.97 (1.11–7.90)
Grade 3 or 4 intraventricular hemorrhage	3 (3.3)	3 (2.8)	1.18 (0.24–5.88)	0.99 (0.17–5.93)
Necrotizing enterocolitis	8 (8.7)	7 (6.4)	1.35 (0.50–3.65)	1.32 (0.46–3.76)
Retinopathy of prematurity	2 (2.2)	2 (1.8)	1.20 (0.17–8.59)	1.64 (0.26–10.51)
Stillbirth‡	0 (0.0)	1 (0.9)	0.40 (0.00–7.47)	—
Bronchopulmonary dysplasia‡	1 (1.1)	0 (0.0)‡‡	3.55 (0.19–518.7)	—

Data are given as *n* (%), mean ± SD or median (interquartile range), unless stated otherwise. Comparisons between groups presented as relative risk (RR) for binary variables, and as mean or median difference (diff) for numerical variables. *Adjusted for maternal age, gestation at enrolment, smoking, body mass index and treatment with esomeprazole. †Defined as generalized tonic-clonic seizures occurring in a woman with pre-eclampsia with no other apparent cause. ‡RR estimated using Firth correction, adjusted analyses not performed. §Defined as oxygen saturation ≤ 90% with clinical symptoms and signs requiring treatment. ¶Defined as creatinine level > 125 μmol/L. **Defined as blood loss of ≥ 500 mL at vaginal delivery and ≥ 1000 mL at Cesarean section during first 24 h postpartum. ††Defined as platelet count $< 100 \times 10^9$/L, aspartate aminotransferase > 70 U/L and hemolysis (lactate dehydrogenase > 600 U/L or hemolysis on peripheral blood smear). ‡‡Missing data (*n* = 1). BP, blood pressure during expectant management; ICU, intensive care unit; PPH, postpartum hemorrhage.

cases before 37 weeks. They reported shorter pregnancy latencies among women with pre-eclampsia and FGR (3.1 and 3 days, respectively) compared to those without FGR (6.6 and 5 days, respectively). This study showed a median latency of 6.8 days in pregnancies with FGR and 15.3 days when there was no FGR at enrolment. These variances likely relate to differences in recruitment, as well as timing and triggers of delivery. Both quoted studies recruited right up until elective delivery was prescribed, meaning women recruited close to this gestational age had a reduced potential for latency. In contrast, PIE and PI2 assessed the potential for treatments to safely prolong gestation in preterm pre-eclampsia and, recruitment ceased at 32 weeks of gestation, allowing at least 14 days prior to the predetermined endpoint at 34 weeks. Accordingly, this study provides valuable prospective data on projected latency in, and the effect of modification of, FGR.

This study is helpful by elucidating likely triggers for delivery and outcome of planned vaginal delivery. Our finding that the presence of FGR made a fetal indication for delivery more likely is in accordance with that of others[8,16,17]. This is unsurprising, given that infants with FGR are more likely to have underlying placental insufficiency and chronic hypoxia: circumstances in which fetal decompensation is more likely.

Identifying which pregnancies are most likely to achieve vaginal delivery is important, given the added maternal and fetal risks associated with emergency CS. We report that successful induction of labor with coexisting FGR is low (< 20%). Previous studies examining the impact of FGR on induction outcome in women with preterm pre-eclampsia have generated conflicting conclusions[18–21]. The largest study included 18 296 women at term and preterm gestations. Coexisting FGR was associated with less successful induction, but details on the number with preterm pre-eclampsia and coexisting FGR were not provided[22].

This study is the first to report prospective data on perinatal outcome in this setting. The high rate of adverse outcome reflects both the disease severity, and the challenges of providing advanced neonatal care in South Africa. FGR is a key determinant of neonatal mortality and morbidity, underscoring the fragile nature of severely growth-restricted fetuses in the setting of pre-eclampsia. McKinney *et al.*[8] also reported a higher rate of perinatal mortality among infants with FGR (13.3% *vs* 4.4%), although morbidity data were lacking and the duration of follow-up was not reported. It is notable that perinatal mortality in this study was dominated by infant death rather than stillbirth. This suggests that close surveillance can largely prevent stillbirth among women with preterm pre-eclampsia, but the postnatal risks, particularly among those with coexisting FGR, remain.

The major strength of this study is that it is based on prospective data collected according to clinical trial methodologies. Hence detailed phenotyping was collected contemporaneously and recorded in individual case report forms. This trial design allowed us to cleanly assess the natural latency of preterm pre-eclampsia among otherwise well-matched pregnancies with and without FGR at diagnosis. We also provide high-quality prospective data on delivery, and maternal and perinatal outcome, including neonatal outcome up until 6 weeks after the due date. By defining FGR using a Delphi consensus definition, rather than an EFW cut-off or EFW centile at recruitment, our data approximates real-time clinical decision-making, compared to retrospective reports that define cohorts based on birth weight[9]. Our data may be more clinically relevant in terms of bedside counseling and decision-making.

Clinical implications

Early preterm pre-eclampsia is often associated with coexisting FGR (45.5%), and this combination is associated with a shorter latency, an increased likelihood of emergency CS delivery, a lower probability of a successful induction, and increased rates of neonatal morbidity and death.

Research implications

Future studies involving expectant management of pre-eclampsia should incorporate prospective data collection of delivery, pregnancy and perinatal outcomes, which could usefully inform meta-analyses. These findings are particularly relevant as the search for new therapeutics that might arrest or ameliorate the progress of preterm pre-eclampsia and prolong gestation continues in the field[23]. Finally, our data should help inform design of future therapeutic trials for preterm pre-eclampsia as it is potentially worthwhile stratifying randomization according to whether there is coexisting FGR. Our data suggest it is likely that the fetal trigger for earlier delivery may persist even if an effective intervention were discovered to slow maternal disease progression.

Conclusion

Antenatally diagnosed FGR is an important determinant of pregnancy outcome among women managed expectantly for preterm pre-eclampsia, identifying a high-risk group for adverse delivery and perinatal outcomes. Coexisting FGR is associated with shorter pregnancy latency, emergency CS delivery, a lower probability of successful induction and increased rates of neonatal morbidity and mortality.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Table S1 Maternal and fetal characteristics at enrolment in Pre-eclampsia Intervention with Esomeprazole (PIE) and Pre-eclampsia Intervention 2 (PI2) with metformin trials

Table S2 Primary and secondary analyses for Pre-eclampsia Intervention with Esomeprazole (PIE) and Pre-eclampsia Intervention 2 (PI2) with metformin trials