OBSTETRICS

The implications of the Fetal Medicine Foundation 35- to 36-week preeclampsia prediction competing-risk model on timing of birth

Peter von Dadelszen, MBChB, DPhil; Argyro Syngelaki, RM, PhD; Alan Wright, PhD; Ranjit Akolekar, MD; Laura A. Magee, MD, MSc; David Wright, PhD; Kypros H. Nicolaides, MD

BACKGROUND: Preeclampsia is associated with increased risks of life-threatening, -altering, and -ending complications. Assessment of risk for preeclampsia at 35 to 36 weeks' gestation by the Fetal Medicine Foundation 36-week competing-risk model identifies approximately 75% of women who will develop term preeclampsia, at a 10% screen-positive rate.

OBJECTIVE: This study aimed to assess whether the Fetal Medicine Foundation 36-week model can provide personalized guidance to women about the probable timing of their delivery, whether or not they develop pregnancy hypertension.

STUDY DESIGN: In this prospective nonintervention screening study at 2 maternity hospitals in England, women who did not have preeclampsia (American College of Obstetricians and Gynecologists definition) and were attending a routine hospital visit at 35 0/7 to 36 6/7 weeks' gestation underwent assessment of risk for preeclampsia, including maternal demographic characteristics, medical history, mean arterial pressure, and serum placental growth factor and soluble fms-like tyrosine kinase-1. Fetal Medicine Foundation 36-week model risk categories for subsequent preeclampsia were defined as: A, $\geq$0.500; B, 0.20 to 0.499; C, 0.05 to 0.199; D, 0.020 to 0.049; and E, $<$0.020. Obstetrical records were examined for all women to identify their gestational age at delivery, and whether they experienced a spontaneous onset of labor (irrespective of mode of delivery) or had a medically indicated birth (either induction of labor or unlabored cesarean delivery). The cumulative incidence of delivery and risk ratios, for all deliveries and for spontaneous deliveries, was assessed.

RESULTS: Among 29,035 women with singleton pregnancies, 1.0%, 2.9%, 3.3%, 5.0%, 9.9%, and 77.9% were in A, B, C, D, and E risk strata, respectively. In the A (vs E) stratum, 71.95% (vs 33.52%) of births were medically indicated. Compared with women in stratum E, women in higher risk strata were more likely to deliver, and to deliver following spontaneous labor, before their due date. For example, of the women in stratum A (vs E), 14.2% (vs 1.1%; risk ratio, 12.5 [95% confidence interval, 9.45—15.35]), 48.5% (vs 5.1%; risk ratio, 8.47 [7.48—9.35]), 69.6% (vs 15.5%; risk ratio, 3.86 [3.59—4.08]), and 90.1% (vs 44.8%; risk ratio, 6.72 [4.53—9.95]) gave birth before 37 0/7, 38 0/7, 39 0/7, and 40 0/7 weeks, respectively. For women in stratum A (vs E), when censored for medically indicated births, spontaneous labor occurred more commonly before 37 0/7 (risk ratio, 4.31 [1.99—6.57]), 38 0/7 (risk ratio, 3.71 [2.48—4.88]), 39 0/7 (risk ratio, 2.87 [2.22—3.46]), and 40 0/7 (risk ratio, 1.42 [1.14—1.77]) weeks.

CONCLUSION: Women in higher-risk strata gave birth earlier, and more frequently following medically indicated delivery, compared with those in lower-risk strata. Importantly, the proportion of women who gave birth following spontaneous onset of labor before their due date was also greater in higher-risk than in lower-risk women. The Fetal Medicine Foundation 36-week competing-risk model incorporates biomarkers of placental aging, including angiogenic imbalance; these results imply that a fetoplacental response to placental aging may be an important trigger for the onset of labor at term.

Key words: angiogenic imbalance, competing-risk model, gestational age at delivery, placental aging, spontaneous labor

Introduction

Preeclampsia (PE), as defined by the American College of Obstetricians and Gynecologists,[1] remains a major cause of maternal and perinatal morbidity and mortality.[2] Using the Fetal Medicine Foundation (FMF) 35- to 36-week competing-risk (FMF36) model and a 10% test-positive rate, it is possible to identify 75% of women who will develop PE at term.[3–5] Risks can be derived from maternal history and any combination of biomarkers. At this gestational age, useful markers are mean arterial pressure (MAP), serum placental growth factor (PlGF), and soluble fms-like tyrosine kinase (sFlt-1).[3–5]

Circulating maternal levels of both PlGF and sFlt-1 are markers of angiogenic balance, and reduced PlGF and elevated sFlt-1 identify pregnancies complicated by placental dysfunction beyond solely PE, including fetal growth restriction.[6] In addition, angiogenic imbalance has been observed in women destined to develop spontaneous preterm labor,[7] and in association with reduced fetal growth velocity, early-term spontaneous labor.[8] It has been unclear how near-term angiogenic imbalance relates to the timing and nature of term birth.

Therefore, this study was designed to assess whether the FMF36 model can provide personalized guidance to women about the probable timing and nature of onset of their delivery; associations with spontaneous labor would provide insights into triggers for the onset of labor at term.

Materials and Methods

Study design and participants

This was a prospective observational cohort study of women who attended a

Cite this article as: von Dadelszen P, Syngelaki A, Wright A, et al. The implications of the Fetal Medicine Foundation 35- to 36-week preeclampsia prediction competing-risk model on timing of birth. Am J Obstet Gynecol 2023;228:457.e1-7.

0002-9378/$36.00

https://doi.org/10.1016/j.ajog.2022.09.047

AJOG at a Glance

Why was this study conducted?

This study was conducted to determine the timing and nature of birth following assessment of risk for preeclampsia by the Fetal Medicine Foundation 36-week model, with a particular focus on spontaneous onset of labor.

Key findings

A larger proportion of women at highest risk of preeclampsia (risk ≥0.500) gave birth before 37 0/7, 38 0/7, 39 0/7, and 40 0/7 weeks' gestation compared with women at low risk (risk <0.020). A larger proportion of women who experienced spontaneous onset of labor in the 2 highest risk strata (risk ≥0.500 and 0.200 −0.499) gave birth before 37 0/7, 38 0/7, 39 0/7, and 40 0/7 weeks' gestation compared with women at low risk (risk <0.020), respectively.

What does this add to what is known?

More women in high-risk strata delivered before their due date compared with those in lower-risk strata, both following spontaneous labor and medically indicated delivery, which is important information for personalized care and counseling. Given that the Fetal Medicine Foundation 36-week model incorporates biomarkers of placental aging (ie, angiogenic imbalance), these results imply that a fetoplacental response to placental aging may be an important trigger for the onset of labor at term.

routine hospital visit at 35 0/7 to 36 6/7 weeks' gestation at King's College Hospital, London and Medway Maritime Hospital, Gillingham, United Kingdom between October 18, 2016 and September 29, 2021. The women gave written informed consent to participate in the study, which was approved by the National Health Service Research Ethics Committee.

This visit at 35 0/7 to 36 6/7 weeks' gestation included the following: recording of maternal demographics and medical history; MAP; ultrasound examination for fetal anatomy and estimated fetal weight; and measurement of maternal serum PlGF and sFlt-1 by an automated biochemical analyzer (BRAHMS KRYPTOR compact PLUS; Thermo Fisher Scientific, Hennigsdorf, Germany).

Gestational age was determined by the measurement of fetal crown−rump length at 11 to 13 weeks' gestation or the fetal head circumference at 19 to 24 weeks' gestation.[9,10]

The inclusion criteria for this analysis were singleton pregnancies that delivered a nonmalformed live-born or stillborn infant. We excluded pregnancies with aneuploidies and major fetal abnormalities.

Risk strata

Risks of PE were calculated using the FMF36 model, combining the previous distribution of gestational age at delivery with likelihoods from multiples of the median (MoM) values of MAP, PlGF, and sFlt-1.[5]

Data were stratified according to risks: ≥0.500 (≥1 in 2); 0.20 to 0.499 (≥1 in 5 and <1 in 2); 0.05 to 0.199 (≥1 in 20 and <1 in 5); 0.020 to 0.049 (≥1 in 50 and <1 in 20); and <0.020 (<1 in 50).

Outcome measures

The outcomes of interest were term delivery before certain gestational ages, and whether labor occurred spontaneously or was medically indicated (induction of labor or unlabored cesarean delivery).

Statistical analysis

Data were summarized descriptively for different strata of PE risk, and summarized by percentages and 95% confidence intervals (CIs) for categorical variables and means and 95% CIs for continuous variables across these strata. The cumulative incidence of delivery was plotted against gestational age at delivery for each of the 5 strata, firstly for all deliveries and secondly for spontaneous deliveries, censoring for medically indicated deliveries. Proportions of women who had given birth by 37 0/7, 38 0/7, 39 0/7, and 40 0/7 weeks' gestation were determined, and the risk ratios relative to the lowest-risk group (ie, <0.020), were calculated for each of the remaining risk groups for all deliveries and for spontaneous deliveries, censoring for medically indicated deliveries.

Results

Study participants

Table 1 summarizes the maternal and pregnancy characteristics of the 29,035 women in the study population, details of their screening marker results, and gestational age at delivery. There were 303 (1.0%), 839 (2.9%), 962 (3.3%), 1449 (5.0%), 2860 (9.9%), 3087 (10.6%), and 19,535 (67.3%) women in the ≥0.500, 0.20 to 0.499, 0.05 to 0.199, 0.020 to 0.049, and <0.020 risk strata, respectively.

On average, women were in their early 30s and overweight, with average body mass indices higher with higher strata of risk. A disproportionate number of White women were in the lower-risk strata; conversely, Black and Asian women were overrepresented in the higher risk strata. Women in higher risk strata were more likely to have either chronic hypertension, type 1 or 2 diabetes mellitus, or a family history of PE. Few women were cigarette smokers.

Most conceptions were natural, but in vitro fertilization and nulliparity were associated with higher risk. Higher risk was associated with both a history of PE and longer interpregnancy intervals among parous women. The assessment occurred at a median of 36 weeks; MoM were higher for sFlt-1 and lower for PlGF, with increasing risk.

Proportions of births before 40 0/7 weeks' gestation

In the higher risk strata, birth occurred earlier and was more frequently medically indicated (Table 2; Figure 1), such

TABLE 1
Characteristics of the cohort at 35 to 36 weeks' gestation and gestational age at delivery, by risk stratum (number [%] or median [interquartile range])

Characteristic	Risk stratum for preeclampsia				
	A (≥1 in 2) (n=303)	B (<1 in 2 and ≥1 in 5) (n=839)	C (<1 in 5 and ≥1 in 20) (n=2411)	D (<1 in 20 and ≥1 in 50) (n=2860)	E (<1 in 50) (n=22,622)
Maternal age (y)	32.7 (32.0–33.5)	32.5 (32.1–32.9)	32.1 (31.9–32.3)	32.1 (31.9–32.3)	32.1 (32.0–32.2)
Maternal weight (kg)	85.7 (83.6–87.9)	84.5 (83.3–85.7)	82.7 (82.1–83.4)	82.4 (81.8–83.0)	79.6 (79.4–79.8)
Maternal height (m)	1.63 (1.63–1.64)	1.64 (1.64–1.64)	1.64 (1.64–1.65)	165 (1.64–1.65)	1.66 (1.66–1.66)
Body mass index (kg/m^2)	32.2 (31.4–32.9)	31.5 (31.0–31.9)	30.7 (30.5–30.9)	30.5 (30.3–30.7)	29.0 (29.0–29.1)
GA (wk)	35.9 (35.9–36.0)	35.9 (35.9–36.0)	36.0 (36.0–36.0)	36.0 (35.9–36.0)	36.0 (36.0–36.0)
Ethnic origin					
Black, n (%)	72 (23.76)	150 (17.88)	373 (15.47)	475 (16.61)	2006 (8.87)
East Asian, n (%)	9 (2.97)	13 (1.55)	48 (1.99)	51 (1.78)	475 (2.10)
Mixed, n (%)	6 (1.98)	15 (1.79)	71 (2.94)	84 (2.94)	636 (2.81)
South Asian, n (%)	26 (8.58)	62 (7.39)	148 (6.14)	156 (5.45)	993 (4.39)
White, n (%)	190 (62.71)	599 (71.39)	1771 (73.45)	2094 (73.22)	18,512 (81.83)
Medical history					
Chronic hypertension, n (%)	23 (7.59)	45 (5.36)	66 (2.74)	47 (1.64)	70 (0.31)
Type 1 diabetes mellitus, n (%)	6 (1.98)	19 (2.26)	19 (0.79)	15 (0.52)	21 (0.09)
Type 2 diabetes mellitus, n (%)	15 (4.95)	16 (1.91)	42 (1.74)	31 (1.08)	88 (0.39)
SLE/APS, n (%)	0 (0.00)	8 (0.95)	15 (0.62)	11 (0.38)	40 (0.18)
Smoker, n (%)	21 (6.93)	52 (6.20)	142 (5.89)	166 (5.80)	1169 (5.17)
Family history					
Mother had preeclampsia, n (%)	34 (11.22)	75 (8.94)	184 (7.63)	172 (6.01)	699 (3.09)
Method of conception					
In vitro fertilization, n (%)	35 (11.55)	67 (7.99)	176 (7.30)	202 (7.06)	751 (3.32)
Ovulation induction, n (%)	5 (1.65)	5 (0.60)	18 (0.75)	14 (0.49)	130 (0.57)
Spontaneous, n (%)	263 (86.80)	767 (91.42)	2217 (91.95)	2644 (92.45)	21,741 (96.11)
Parity					
Nulliparous, n (%)	177 (58.42)	531 (63.29)	1419 (58.86)	1659 (58.01)	9981 (44.12)
Parous, no history of preeclampsia, n (%)	92 (30.36)	254 (30.27)	883 (36.62)	1094 (38.25)	12,291 (54.33)
Parous, history of preeclampsia, n (%)	34 (11.22)	54 (6.44)	109 (4.52)	107 (3.74)	350 (1.55)
Parous, interpregnancy interval (y)	4.0 (3.4–4.7)	3.6 (3.3–3.9)	3.3 (3.2–3.5)	3.2 (3.1–3.4)	2.5 (2.5–2.5)
Biomarkers					
Mean arterial pressure (MoM)	1.17 (1.16–1.18)	1.10 (1.09–1.10)	1.06 (1.06–1.06)	1.04 (1.03–1.04)	0.99 (0.99–0.99)
Placental growth factor (MoM)	0.21 (0.20–0.22)	0.29 (0.28–0.30)	0.39 (0.38–0.40)	0.54 (0.53–0.55)	1.22 (1.21–1.23)
Soluble fms-like tyrosine kinase (MoM)	4.00 (3.82–4.18)	2.93 (2.85–3.01)	2.07 (2.04–2.10)	1.52 (1.50–1.54)	0.86 (0.85–0.86)
Mode and time of onset of delivery					
GA at delivery for all women in risk category (wk)	38.1 (38.0–38.3)	38.9 (38.8–39.0)	39.4 (39.3–39.4)	39.7 (39.6–39.7)	40.0 (40.0–40.0)
Medically indicated birth, n (%)	218 (71.95%)	410 (48.87%)	912 (37.83%)	993 (34.72%)	7582 (33.52%)

Von Dadelszen. Timing of birth following near-term preeclampsia risk assessment. Am J Obstet Gynecol 2023. *(continued)*

TABLE 1
Characteristics of the cohort at 35 to 36 weeks' gestation and gestational age at delivery, by risk stratum (number [%] or median [interquartile range]) *(continued)*

Characteristic	Risk stratum for preeclampsia				
	A (≥1 in 2) (n=303)	B (<1 in 2 and ≥1 in 5) (n=839)	C (<1 in 5 and ≥1 in 20) (n=2411)	D (<1 in 20 and ≥1 in 50) (n=2860)	E (<1 in 50) (n=22,622)
GA at delivery (wk)	38.0 (37.9–38.2)	38.8 (38.7–39.0)	39.4 (39.3–39.5)	39.6 (39.5–39.6)	39.9 (39.9–40.0)
Spontaneous onset of labor, n (%)	85 (28.05%)	429 (51.13%)	1499 (62.17%)	1867 (65.28%)	15,040 (66.48%)
GA at delivery (wk)	38.4 (38.1–38.6)	38.9 (38.8–39.0)	39.4 (39.3–39.5)	39.7 (39.6–39.8)	40.1 (40.0–40.1)

APS, antiphospholipid syndrome; *GA*, gestational age; *MoM*, multiple of the median; *SLE*, systemic lupus erythematosus.
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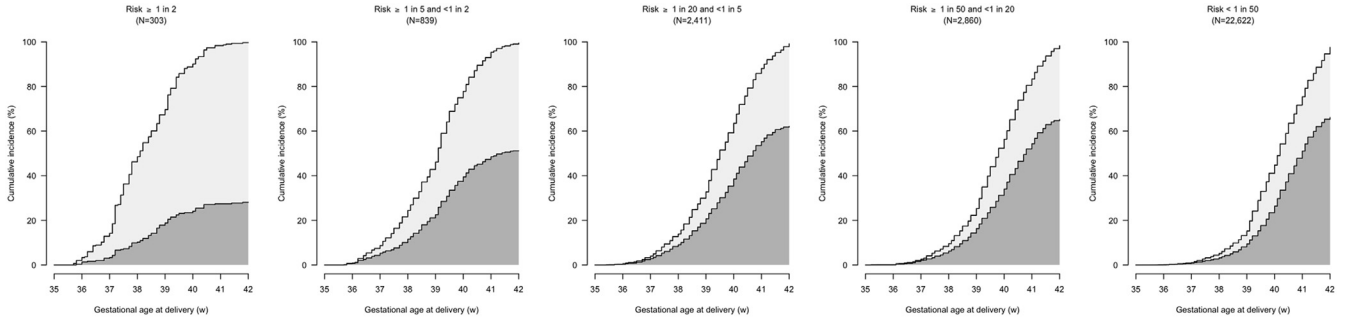
TABLE 2
Proportion of 29,035 unselected women with singleton pregnancies giving birth according to Fetal Medicine Foundation 36-week model risk stratum and manner of onset of the birth process (irrespective of mode of delivery) (number % [95% confidence interval])

Risk stratum	Delivery (wk)	N	Spontaneous onset of labor	Medically indicated birth
A (≥1 in 2)	<37 0/7	43	10 (23.3 [11.8–38.6])	33 (76.7 [61.4–88.2])
	<38 0/7	147	31 (21.1 [14.8–28.6])	116 (78.9 [71.4–85.2])
	<39 0/7	211	57 (27.0 [21.2–33.5])	154 (73.0 [66.5–78.9])
	<40 0/7	273	73 (26.7 [21.6–32.4])	200 (73.3 [67.6–78.4])
	All	303	85 (28.1 [23.1–33.5])	218 (72.0 [66.5–76.9])
B (<1 in 2 and ≥1 in 5)	<37 0/7	73	44 (60.3 [48.1–71.6])	29 (39.7 [28.5–51.9])
	<38 0/7	205	97 (47.3 [40.3–54.4])	108 (52.7 [45.6–59.7])
	<39 0/7	387	189 (48.8 [43.8–53.9])	198 (51.2 [46.1–56.3])
	<40 0/7	653	331 (50.7 [46.8–54.6])	322 (49.3 [45.4–53.2])
	All	839	429 (51.1 [47.7–54.6])	410 (48.9 [45.4–52.3])
C (<1 in 5 and ≥1 in 20)	<37 0/7	95	67 (70.5 [60.3–79.4])	28 (29.5 [20. 6–39.7])
	<38 0/7	334	218 (65.3 [59.9–70.4])	116 (34.7 [29.6–40.1])
	<39 0/7	790	499 (63.2 [59.7–66.5])	291 (36.8 [33.5–40.3])
	<40 0/7	1531	928 (60.6 [58.1–63.1])	603 (39.4 [36.9–41.9])
	All	2411	1499 (62.2 [60.2–64.1])	912 (37.8 [35.9–39.8])
D (<1 in 20 and ≥1 in 50)	<37 0/7	74	58 (78.4 [67.3–87.1])	16 (21.6 [12.9–32.7])
	<38 0/7	273	177 (64.8 [58.9–70.5])	96 (35.2 [29.5–41.2])
	<39 0/7	723	466 (64.5 [60.8–68.0])	257 (35.6 [32.1–39.2])
	<40 0/7	1612	973 (60.4 [57.9–62.8])	639 (39.4 [37.2–42.1])
	All	2860	1867 (65.3 [63.5–67.0])	993 (34.7 [33.0–36.5])
E (<1 in 50)	<37 0/7	238	188 (79.0 [73.3–84.0])	50 (21.0 [16.0–26.7])
	<38 0/7	1158	711 (61.4 [58.5–64.2])	447 (38.6 [35.8–41.5])
	<39 0/7	3438	2133 (62.0 [60.4–63.7])	1305 (38.0 [36.3–39.6])
	<40 0/7	10,128	5958 (58.8 [57.9–59.8])	4170 (41.2 [40.2–42.1])
	All	22,622	15,040 (66.48 [65.9–67.1])	7582 (33.5 [32.9–34.1])

Von Dadelszen. Timing of birth following near-term preeclampsia risk assessment. Am J Obstet Gynecol 2023.

FIGURE 1
Profiles of GA at delivery by FMF36 model risk stratum



Dark gray: delivery following spontaneous onset of labor, irrespective of mode of delivery. *Light gray*: medically indicated birth (delivery following either induction of labor, irrespective of mode of delivery, or unlabored cesarean delivery).

FMF36, Fetal Medicine Foundation 36-week; *GA*, gestational age.

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that 90% of the women in the ≥0.500 stratum had given birth before their due date (of whom 73% had a medically indicated delivery) vs 45% of women in the <0.020 stratum (41% medically indicated). For example, of the women in the ≥0.500 (vs <0.020) stratum, 14.2% (vs 1.1%; relative risk [RR], 12.5; 95% CI, 9.45−15.35), 48.5% (vs 5.1%; RR, 8.47; 95% CI, 7.48−9.35), and 69.6% (vs 15.5%; RR, 3.86; 95% CI, 3.59−4.08) gave birth before 37 0/7, 38 0/7, and 39 0/7 weeks' gestation, respectively. The corollary is that 8.9% (vs 55.2%; RR, 0.15; 95% CI, 0.10−0.22) women gave birth on or after 40 0/7 weeks.

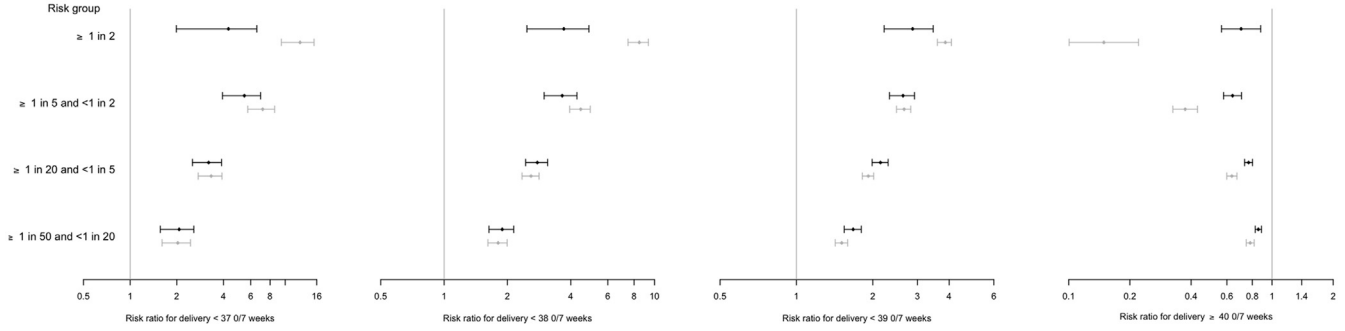
Having censored for medically indicated births, for women in all strata with risks ≥0.020, the rate of spontaneous onset of labor was higher than in women in the <0.020 stratum (Figure 2), particularly for the ≥0.500 stratum and for earlier near-term and at-term births. For example, among women in the ≥0.500 (vs <0.020) risk stratum, spontaneous labor occurred more commonly before 37 0/7 (RR, 4.31; 95% CI, 1.99−6.57), 38 0/7 (RR, 3.71; 95% CI, 2.48−4.88), and 39 0/7 (RR, 2.87; 95% CI, 2.22−3.46) weeks. The corollary is that women in the highest risk stratum were less likely to deliver on or after 40 0/7 weeks (RR, 0.70; 95% CI, 0.56−0.88).

Comments

Principal findings

In this study of almost 30,000 women attending 2 maternity units in the United Kingdom, we identified that the FMF36 model, designed to assess PE risk, identifies imminent delivery before the due date among women at greatest (vs lowest) risk for PE. Women at greatest risk of PE were less likely to give birth following spontaneous onset of labor. Among women who gave birth following spontaneous onset of labor, a larger proportion of those at higher (vs lower) risk for PE delivered before 37 0/7, 38 0/7, 39 0/7, and 40 0/7 weeks' gestation.

FIGURE 2
Risks for timing and mode of birth by risk stratum



Risk ratios (95% confidence intervals) for births before 37 0/7, 38 0/7, and 39 0/7, and at or after 40 0/7 weeks' gestation by Fetal Medicine Foundation 36-week model risk stratum, compared with the <1 in 50 risk stratum. Births following spontaneous onset of labor censored for medically indicated deliveries (induction of labor and unlabored cesarean delivery) (dark gray), and total births (light gray).

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Comparison with published literature

Angiogenic imbalance in both maternal circulation and amniotic fluid has been observed in women destined to develop spontaneous preterm labor.[7] Similarly, angiogenic imbalance is associated with reduced fetal growth velocity, rupture of membranes, intrauterine infection, and earlier gestational age at spontaneous onset of labor.[8,11] In addition, in pregnant women with hypertension without confirmed PE presenting to primary health centers in Maputo, Mozambique, low maternal plasma PlGF concentration was associated with earlier deliveries.[12] In our opinion, these observations imply a role of angiogenic imbalance in the parturition cascade.[13]

Clinical implications

We deem the nonspecific identification of presumptive placenta-mediated risk, rather than solely PE-related risk, to be important. For women and their maternity care providers in all settings, it is important to identify risk for individual women so that prenatal surveillance and anticipation of timing-of-delivery decisions and spontaneous labor can be tailored. Thereby, risk classification according to biomarker-based precision medicine can group individual women according to their imminent personal risks of both medically indicated and spontaneous delivery. In this study, we have determined that identifying angiogenic imbalance offers such risk classification capacity, irrespective of whether the woman has clinically confirmed PE.

Research implications

It is possible that women in higher risk strata would benefit from earlier-timed births, as opposed to women in the lowest risk stratum (<0.020). Women in the higher FMF36 risk strata develop more PE, with its attendant risks of maternal and perinatal complications,[3,14] and give birth earlier within the near-term and at-term gestational age range with PE. Therefore, we have designed, and are initiating, an individual patient randomized controlled trial wherein women will be randomized either to being offered timed birth at varying gestational ages according to their FMF36 risk stratum, or the current National Health Service standard of care guided by the National Institute for Health and Care Excellence.[15]

As previously proposed in relation to the cited study in Maputo, Mozambique,[12] these data suggest a role for the well-recognized fall in PlGF toward term in the prediction of the onset of term labor because reducing proangiogenic factors such as PlGF at term may aid placental separation and be protective against postpartum hemorrhage. This relationship between changing angiogenic balance and spontaneous onset of labor warrants further physiological investigation.

Strengths and limitations

Strengths of our study include a large sample size, unselected nature of women with singleton pregnancies presenting for a 36-week assessment, and the prospective, detailed documentation of baseline characteristics and timing and mode of birth outcomes. To guide counseling of women, we have assessed the importance of FMF36 results in terms of the likelihood of giving birth before weekly gestational age cutoffs before a woman's due date. In addition, we have identified a possible role for angiogenic imbalance in the pathway to the onset of spontaneous labor and proposed possible roles for that imbalance in labor physiology.

A limitation of our data is that all women enrolled had singleton pregnancies, thus our results do not necessarily apply to multiples. We studied a cohort of women who had reached near-term gestational age; although our results may not apply to preterm women, they are consistent with studies that have included such women before either preterm or early-term labor.[7,8,11,12]

Conclusions

A greater proportion of women in high-risk strata delivered early and following a medical intervention compared with those in lower-risk strata, which is important information for personalized care and counseling. Importantly, the proportion of women who gave birth before their due date following spontaneous onset of labor was greater in higher-risk than in lower-risk women. The FMF36 model incorporates biomarkers of placental aging, including angiogenic imbalance; these results imply that a fetoplacental response to placental aging may be an important trigger for the onset of labor at term. ■

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Author and article information

From the Department of Women and Children's Health, School of Life Course & Population Sciences, King's College London, London, United Kingdom (Drs von Dadelszen and Magee); Fetal Medicine Research Institute, King's College Hospital, London, United Kingdom (Drs Syngelaki and Nicolaides); Institute of Health Research, University of Exeter, Exeter, United Kingdom (Drs A Wright and D Wright); Fetal Medicine Unit, Medway Maritime Hospital, Gillingham, United Kingdom (Dr Akolekar); and Institute of Medical Sciences, Canterbury Christ Church University, Canterbury, United Kingdom (Dr Akolekar).

Received March 31, 2022; revised Sept. 12, 2022; accepted Sept. 30, 2022.

This study was supported by a grant from the Fetal Medicine Foundation (charity number 1037116). The machine and reagents for the assays were provided by Thermo Fisher Scientific, Hennigsdorf, Germany. The funding sources had no involvement in the study design; collection, analysis, and interpretation of data; writing of the report; and decision to submit the article for publication.

Corresponding author: Peter von Dadelszen, MBChB, DPhil. pvd@kcl.ac.uk