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Early-pregnancy events and subsequent antenatal, delivery and neonatal outcomes: prospective cohort study

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KEYWORDS: adverse pregnancy outcome; early-pregnancy events; miscarriage; preterm birth; threatened miscarriage

CONTRIBUTION

What are the novel findings of this work?
Vaginal bleeding and/or pelvic pain in the first trimester are associated with an increased risk of antenatal complications.

What are the clinical implications of this work?
Women presenting with vaginal bleeding and/or pelvic pain in early pregnancy should be counseled about the associated risks. Further work is required to identify the subgroups of women at greatest risk.

ABSTRACT

Objective *To assess prospectively the association between pelvic pain, vaginal bleeding, and nausea and vomiting occurring in the first trimester of pregnancy and the incidence of later adverse pregnancy outcomes.*

Methods *This was a prospective observational cohort study of consecutive women with confirmed intrauterine singleton pregnancy between 5 and 14 weeks' gestation recruited at Queen Charlotte's & Chelsea Hospital, London, UK, from March 2014 to March 2016. Serial ultrasound scans were performed in the first trimester. Participants completed validated symptom scores for vaginal bleeding, pelvic pain, and nausea and vomiting. The key symptom of interest was any pelvic pain and/or vaginal bleeding during the first trimester. Pregnancies were followed up until the final outcome was known. Antenatal, delivery and neonatal outcomes were obtained from hospital records. Logistic regression analysis was used to assess the association between first-trimester symptoms and pregnancy complications by calculating adjusted odds ratios (aOR) with correction for maternal age.*

Results *Of 1003 women recruited, 847 pregnancies were included in the final analysis following exclusion of cases due to first-trimester miscarriage (*n = *99), termination of pregnancy (*n = *20), loss to follow-up (*n = *32) or withdrawal from the study (*n = *5). Adverse antenatal complications were observed in 166/645 (26%) women with pelvic pain and/or vaginal bleeding in the first trimester (aOR = 1.79; 95% CI, 1.17–2.76) and in 30/181 (17%) women with no symptoms. Neonatal complications were observed in 66/634 (10%) women with and 11/176 (6%) without pelvic pain and/or vaginal bleeding (aOR = 1.73; 95% CI, 0.89–3.36). Delivery complications were observed in 402/615 (65%) women with and 110/174 (63%) without pelvic pain and/or vaginal bleeding during the first trimester (aOR = 1.16; 95% CI, 0.81–1.65). For 18 of 20 individual antenatal complications evaluated, incidence was higher among women with pelvic pain and/or vaginal bleeding, despite the overall incidences being low. Nausea and vomiting in pregnancy showed little association with adverse pregnancy outcomes.*

Conclusions *Our study suggests that there is an increased incidence of antenatal complications in women experiencing pelvic pain and/or vaginal bleeding in the first trimester. This should be considered when advising women attending early-pregnancy units.* Copyright © *2019 ISUOG. Published by John Wiley & Sons Ltd.*

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INTRODUCTION

Vaginal bleeding, pelvic pain, and nausea and vomiting are common early-pregnancy symptoms leading women to seek medical attention. Vaginal bleeding occurs in 20% of clinically recognized pregnancies[1,2]. Generally, it is considered reassuring if the vaginal bleeding resolves and the pregnancy continues beyond the first trimester. In clinical practice, women with pelvic pain and/or vaginal bleeding in early pregnancy are not considered to be a high-risk group that merits closer surveillance.

There is some evidence to suggest that this approach may be misplaced. Some studies have concluded that vaginal bleeding and pelvic pain in early pregnancy may be associated with subsequent complications, including fetal growth restriction (FGR) and preterm birth (PTB)[3,4]. Hyperemesis gravidarum has also been linked to some of these complications[3]. Discrepancies between observed and expected gestational age have been associated with pregnancies being small-for-gestational age and at increased risk of PTB[3]. The majority of these studies are retrospective and subject to recall bias[5–7], and there is a paucity of prospective publications to help guide management.

When looking into some of these publications in more detail, the inclusion criteria and the definition of 'first trimester' differ, with some studies using a cut-off of 12 or 14 weeks[6–9] and others 20 weeks[8,9], whilst in some studies, first trimester is not defined in terms of gestational weeks[10–12]. In addition, collection of outcome data may be subject to inaccuracies with one study relying solely on telephone interviews to obtain final outcomes[13]. A further concern is the lack of clarity regarding the definition of 'threatened miscarriage' and the characterization of symptoms[6]. Few studies quantified symptoms of pelvic pain and vaginal bleeding[10,13–15], or used validated symptom-scoring questionnaires[10,13–16].

The primary aim of this study was to evaluate prospectively the association between pelvic pain and/or vaginal bleeding occurring in early pregnancy and the incidence of antenatal, delivery and neonatal complications. Secondary aims were to assess the relationship between pregnancy complications and nausea and/or vomiting in the first trimester, as well as with any discrepancy in the gestational age estimated by ultrasound dating and that calculated using menstrual dates. Finally we conducted an exploratory assessment of whether quantification of pelvic pain and vaginal bleeding is more predictive of outcome than merely recording their presence.

METHODS

Study design and inclusion criteria

This was a prospective observational cohort study that took place at Queen Charlotte's & Chelsea Hospital, London, between March 2014 and March 2016. The study was approved by the NHS National Research Ethics Service (NRES) Riverside Committee London (REC 14/LO/0199), and all participants provided written informed consent.

Women in the first trimester of pregnancy (< 14 weeks' gestation by last menstrual period (LMP) or ultrasound scan dating based on crown–rump length (CRL) measurement when LMP was not known) with intrauterine pregnancy were invited to participate. An intrauterine pregnancy was defined on the basis of an ultrasound scan showing an intrauterine gestational sac with or without a visible embryo and heart beat. Women < 16 and > 50 years of age were excluded. Participants were recruited via open advertisements (using posters) in local GP surgeries, in local hospitals, and at the university in which the study was conducted (Imperial College London). The majority of women were recruited after attending the hospital Ultrasound Department or Early Pregnancy Assessment Unit.

All study visits took place at Queen Charlotte's & Chelsea Hospital. A detailed questionnaire regarding demographic details and past medical, gynecological and obstetric history was completed. The date of the LMP was recorded and participants were asked to rate their certainty of recall for this date using a visual analog scale, scored from 0 (uncertain) to 10 (very certain), similar to that used for assessment of pain. Participants were asked about their symptoms at each study visit, which were rated using validated symptom scores. Depending on the gestational age at the time of recruitment and clinical need, participants were seen a minimum of two times and up to five times in the first trimester. Serial ultrasound scans were performed until the end of the first trimester. Routine measurements, including mean gestational-sac diameter (MSD) and embryo CRL, were taken at each visit[17]. Participants were subsequently seen at the time of their routine dating scan (11–14 weeks' gestation) and anomaly scan (18–22 weeks' gestation), and underwent an additional ultrasound assessment of fetal growth between 31 and 36 weeks' gestation.

Participants were encouraged to contact the research team if they had any complications, such as vaginal bleeding, and when necessary were invited to attend for an additional ultrasound scan. Pregnancy outcomes were collected from hospital medical records. The incidence of most individual pregnancy-related complications in our population is low. For example, the incidence of PTB in a UK population is 8%[4]. Therefore, our planned sample size was a compromise between feasibility and the aim to include cases with a variety of individual complications. We planned to recruit a minimum of 1000 participants.

Assessment of symptoms

The following validated tools were used at each first-trimester study visit to assess early-pregnancy symptoms. Vaginal bleeding was assessed based on the bleeding score (numerical scale of 0 (no bleeding) to 4 (heavy bleeding)) obtained from a modified pictorial blood-assessment chart[18]. Participants were asked to record the amount of vaginal bleeding they were experiencing on the day they attended for the study visit, the worst vaginal bleeding

they had experienced prior to their visit and the duration of bleeding in days. Participants were asked to score their pelvic pain on the day of the study visit and the worst pain they had experienced until that point, using a visual analog scale from 0 (no pain) to 10 (maximum pain). They were also asked to document the duration of pelvic pain in days[19]. The Motherisk pregnancy-unique quantification of emesis and nausea (PUQE) score was used to assess nausea and vomiting in pregnancy and was repeated at each visit in the first trimester (score of 3 (no symptoms) to 15 (worst symptoms))[20].

For the analysis, the key symptom was the presence of any episode of pelvic pain and/or vaginal bleeding during the first trimester. Additionally, vaginal bleeding was evaluated as the presence of bleeding at any time during the first trimester, the worst bleeding score reported in the first trimester and the total number of bleeding days reported during the first trimester. Analogous quantifications were evaluated for pelvic pain, i.e. presence of pain at any time, highest score and total number of days with pain during the first trimester. Nausea and/or vomiting were evaluated based on the highest PUQE score reported during the first trimester. Finally, we also examined the discrepancy in the gestational age (GA) expected based on the LMP and that estimated by ultrasound scan performed at the first study visit (calculated as an average of GA provided by CRL and MSD measurements), where positive values reflect higher GA estimated by LMP than that estimated from ultrasound measurements and negative values higher GA based on ultrasound measurements[17]. Using both MSD and CRL to estimate the GA allowed us to include more patients than using CRL alone. Little difference has been observed between CRL alone and ultrasound scan mean in terms of calculated GA[17].

Outcome measures

Outcome measures were defined as antenatal, delivery and neonatal complications.

Antenatal complications included hypertensive disorders of pregnancy, gestational diabetes, antepartum hemorrhage, placental abruption, second-trimester miscarriage, PTB, preterm delivery and preterm prelabor rupture of membranes (PPROM), FGR and low birth weight (LBW), and stillbirth.

Pre-eclampsia was defined as blood pressure $\geq$ 140/90 mmHg on two occasions 4 h apart at $>$ 20 weeks' gestation in a woman with previously normal blood pressure, with proteinuria, quantified using the urine protein creatinine ratio (UPCR $>$ 0.3 mg/dL) or by 24-h urine collection ($>$ 3 g/24 h)[21]. In addition, a diagnosis of pre-eclampsia was also given if pregnancy-induced hypertension (PIH) occurred with FGR, in the case of eclampsia, or in the case of PIH with deranged blood tests (thrombocytopenia $< 100 \times 10^9$/L, serum creatinine concentrations $>$ 1.1 mg/dL or a doubling of this in the absence of renal disease, or elevated liver transaminases to twice the normal concentration)[21]. PIH was defined as blood pressure $\geq$ 140/90 mmHg without proteinuria, FGR and abnormal blood tests[21]. Gestational proteinuria was defined as UPCR $>$ 0.3 mg/dL or a 24-h urine collection protein level $>$ 3 g in the absence of hypertension[21].

Gestational diabetes was diagnosed if the fasting plasma glucose was $>$ 5.6 mmol/L or if the 2-h plasma glucose level was $>$ 7.8 mmol/L after an oral glucose tolerance test[22]. Antepartum hemorrhage was described when vaginal bleeding occurred after 24 weeks' gestation and before birth of the baby. This is most commonly unexplained, but may also be associated with placental abruption or placenta previa[23]. Placental abruption was defined as a clinical diagnosis of the placenta sheering away from the uterine lining, occurring antenatally or during delivery[23]. Second-trimester miscarriage was defined as miscarriage after 14 weeks and before 23 completed weeks of gestation as defined by CRL taken at the time of the 11–14-week dating ultrasound scan[24].

PTB was described as any delivery after 24 weeks and before 37 completed weeks of gestation (as dated by a routine dating scan) and included both iatrogenic preterm delivery and spontaneous preterm labor[25]. PPROM was defined as rupture of membranes before 37 weeks' gestation (as defined by a routine dating scan) occurring more than 24 h before delivery[25].

The term FGR was used to describe an ultrasound-based antenatal diagnosis of estimated fetal weight $<$ 10th centile for GA with abnormal umbilical artery Doppler results (pulsatility index $>$ 95th percentile with or without reversed or absent end-diastolic flow)[26,27]. LBW was defined in accordance with WHO criteria and WHO centiles as delivery weight $<$ 10th percentile for GA, where the final GA was estimated using the dating scan (performed at 11–14 weeks' gestation) as a reference[28].

Intrauterine death or stillbirth was described when there was intrauterine fetal demise and the fetus was born dead after 24 weeks' gestation[29].

Delivery details were collected, including date of delivery (from which GA can be calculated), mode of delivery and any complications. Mode of delivery encompassed spontaneous vaginal delivery (SVD), elective and emergency Cesarean section, and instrumental delivery (forceps and ventouse delivery). Information as to the indication for delivery was collected, including failure to progress, fetal distress or maternal exhaustion. Meconium staining of amniotic fluid and a diagnosis of sepsis in labor were also noted. This was defined in accordance with the NICE intrapartum guideline[30].

The amount of bleeding at delivery was recorded. For a vaginal delivery (including SVD, forceps and ventouse delivery), an estimated blood loss $>$ 500 mL was classified as postpartum hemorrhage (PPH). At Cesarean section (emergency and elective), an estimated blood loss $>$ 1000 mL was recorded as PPH. Any delivery with estimated blood loss $>$ 1500 mL was characterized as massive obstetric hemorrhage (MOH)[31]. The cause of bleeding as documented by the care provider during birth was noted as atony, trauma, retained placenta or morbidly adherent placenta. Manual removal of placenta was defined when traditional controlled cord traction was insufficient to

complete the third stage of labor and additional manual maneuvers were required to achieve delivery of placenta.

Neonatal complications recorded comprised admission to the neonatal unit, 1-min Apgar score of less than 7 and 5-min Apgar score of less than 7.

Statistical analysis

The statistical analysis of this largely exploratory study focused on precision by reporting 95% CI, without focus on statistical significance. Hence, no correction for multiple comparisons was performed[32]. The main results involve the association of any pelvic pain and/or vaginal bleeding with any adverse antenatal, neonatal and delivery complications. Results for individual complications, or for other first-trimester symptoms, are secondary.

Logistic regression analysis was used to assess the association between first-trimester symptoms and pregnancy complications, reporting the adjusted odds ratio (aOR) with 95% CI, correcting for the confounding effect of maternal age. For the comparison of different approaches to quantify vaginal bleeding and pelvic pain, we also calculated the area under the curve (AUC) with 95% CI of the logistic regression model used to compute the aOR.

The analysis of antenatal complications was performed on all pregnancies that were still viable at the end of the first trimester. Delivery and neonatal complications analyses were performed on only pregnancies resulting in live birth (excluding stillbirths and second-trimester miscarriages). Regarding the GA discrepancy variable, we first excluded pregnancies when the certainty of LMP recall was rated $< 7/10$ ($n = 153$). Additionally, pregnancies with an absolute GA discrepancy greater than 14 days ($n = 46$) were also excluded to avoid outliers who were known to have irregular menstrual cycles. Analysis of PPH and MOH was performed on a subset of patients, excluding patients with traumatic PPH ($n = 53$) and traumatic MOH ($n = 10$).

Analyses were performed only on cases with complete data available. All the features analyzed contained $< 1\%$ of missing values, except for the variable GA discrepancy, which contained $< 2\%$ of missing values ($n = 8$), mostly due to the absence of ultrasound measurement to date the pregnancy at the first scan. The majority of outcomes also had no missing values except for the following: LBW, which had $< 3\%$ ($n = 21$) missing values (mostly due to the birth weight being unavailable); PPH and MOH, which had $< 5\%$ ($n = 37$) missing data (due to absence of blood-loss quantification data); meconium, which had $< 1\%$ ($n = 6$) missing data; and Apgar score, which had $< 2\%$ ($n = 16$) missing data.

All analyses were performed using Python 3.6.0 (Python Software Foundation, Beaverton, OR, USA).

RESULTS

Of 1242 consecutive women who were screened during the study period, 1003 were recruited. Reasons for declining to participate in the study included inability to attend follow-up, choosing to book antenatal care in another hospital and patient personal choice. Patients who experienced first-trimester miscarriage ($n = 99$), underwent termination of pregnancy ($n = 20$), withdrew from the study ($n = 5$) or were lost to follow-up ($n = 32$) were excluded from the analysis, leaving 847 women for inclusion in the final analysis (Figure 1). Descriptive statistics for patient characteristics and first-trimester symptoms are presented in Tables 1 and 2, respectively.

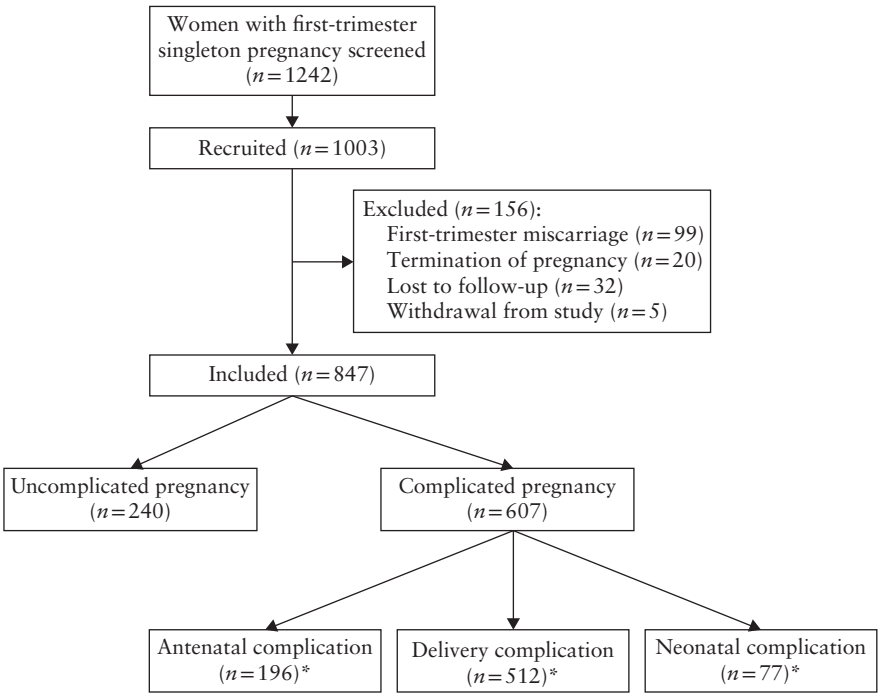

Figure 1 Flowchart showing inclusion of participants in study. *Some pregnancies experienced more than one type of complication.

Table 3 shows the association of each pelvic-pain and vaginal-bleeding feature with antenatal, neonatal and delivery complications. The absolute numbers of each adverse outcome assessed within the study are presented in Table 4. The incidence was 24% (196/826) for antenatal, 65% (512/789) for delivery, and 10% (77/810) for neonatal complications.

Table 1 Characteristics of 847 women with singleton pregnancy included in study cohort

Characteristic	*Value*
Maternal age (years)	32 (17–48)
Paternal age (years)	34 (17–55)
Maternal ethnicity	
Caucasian	555 (65.5)
Asian	114 (13.5)
Afro-Caribbean	105 (12.4)
Other	72 (8.5)
Unknown	1 (0.1)
Body mass index (kg/m^2)	23.7 (15.8–53.9)
Parity	
0	437 (51.6)
1	285 (33.6)
2	87 (10.3)
3	22 (2.6)
≥ 4	16 (1.9)
Previous Cesarean section	
None	715 (84.4)
1	106 (12.5)
2	20 (2.4)
≥ 3	6 (0.7)
Previous first-trimester miscarriage	
None	464 (54.8)
1	244 (28.8)
2	95 (11.2)
≥ 3	44 (5.2)
Previous second-trimester miscarriage	
None	817 (96.5)
1	29 (3.4)
≥ 2	1 (0.1)
History of surgery	
Cervix	27 (3.2)
Uterus	328 (38.7)
GA at birth (days)*	276 (170–302)
Birth weight (g)*	3340 (700–4830)

Data are given as median (range) or *n* (%). *Data are for 829 pregnancies that resulted in live birth. GA, gestational age.

Any episodes of pelvic pain and/or vaginal bleeding and complications

Overall, any episodes of pelvic pain and/or vaginal bleeding in the first trimester were associated with an increased risk of adverse antenatal outcomes (aOR = 1.79; 95% CI, 1.17–2.76; Table 3 and Figure 2a). Of those who experienced any pelvic pain and/or vaginal bleeding in the first trimester, 26% (166/645) experienced an antenatal complication compared with 17% (30/181) in the group with no symptoms (Table 4). Regarding the

Table 2 First-trimester symptoms in 847 women with singleton pregnancy included in study cohort

First-trimester symptom	*Value*
Any episode of vaginal bleeding and/or pelvic pain	662 (78.2)
Any episode of vaginal bleeding	477 (56.3)
Any episode of pelvic pain	510 (60.2)
Total days of vaginal bleeding	1 (0–50)
Highest bleeding score*	1 (0–4)
Total days of pelvic pain	1 (0–39)
Highest pelvic pain score†	2 (0–10)
Highest PUQE score‡	6 (3–15)
GA discrepancy between LMP and USS§ at first visit (days)	1.35 (−13 to 14)

Data are given as *n* (%) or median (range). *Assessed on numerical scale of 0 (no bleeding) to 4 (heavy bleeding) based on modified pictorial blood assessment chart[18]. †Assessed using visual analog scale from 0 (no pain) to 10 (maximum pain)[19]. ‡Assessed using Motherisk pregnancy-unique quantification of emesis and nausea (PUQE) scale of 3 (no symptoms) to 15 (worst symptoms)[20]. §Gestational age (GA) on ultrasound scan (USS) calculated as average of GA provided by crown–rump length and mean gestational-sac diameter measurements at first visit. LMP, last menstrual period.

Table 3 Association between first-trimester symptoms and incidence of any antenatal, delivery or neonatal complications in women with singleton pregnancy

First-trimester symptom	*Odds ratio scale*	*Antenatal complication (n = 826)*	*Delivery complication (n = 789)*	*Neonatal complication (n = 810)*
Any episode of pelvic pain and/or vaginal bleeding	Yes *vs* no	1.79 (1.17–2.76)	1.16 (0.81–1.65)	1.73 (0.89–3.36)
Any episode of vaginal bleeding	Yes *vs* no	1.37 (0.99–1.91)	1.26 (0.94–1.69)	1.78 (1.08–2.95)
Any episode of pelvic pain	Yes *vs* no	1.69 (1.20–2.38)	1.04 (0.77–1.41)	1.17 (0.71–1.90)
Total days of vaginal bleeding	Per day	1.04 (1.02–1.06)	1.00 (0.98–1.03)	1.02 (0.98–1.05)
Highest bleeding score reported*	Per unit	1.18 (1.02–1.37)	1.04 (0.90–1.19)	1.27 (1.03–1.55)
Total days of pelvic pain	Per day	1.03 (1.00–1.06)	0.99 (0.96–1.02)	0.98 (0.93–1.03)
Highest pelvic pain score reported†	Per unit	1.07 (1.02–1.12)	1.03 (0.99–1.08)	1.00 (0.93–1.08)
Highest PUQE score reported‡	Per unit	0.96 (0.91–1.02)	0.96 (0.91–1.02)	1.02 (0.94–1.11)
GA discrepancy between USS§ and LMP at first visit	Per day	0.98 (0.94–1.02)	0.99 (0.95–1.03)	1.04 (0.97–1.10)

Analysis performed in cases with complete data. Data are odds ratio (95% CI) adjusted for maternal age. *Assessed on numerical scale of 0 (no bleeding) to 4 (heavy bleeding) based on modified pictorial blood assessment chart[18]. †Assessed using visual analog scale from 0 (no pain) to 10 (maximum pain)[19]. ‡Assessed using Motherisk pregnancy-unique quantification of emesis and nausea (PUQE) scale of 3 (no symptoms) to 15 (worst symptoms)[20]. §Gestational age (GA) on ultrasound scan (USS) calculated as average of GA provided by crown–rump length and mean gestational-sac diameter measurements at first visit. LMP, last menstrual period.

Table 4 Incidence of individual antenatal, neonatal and delivery complications in study cohort, in all women and according to whether they experienced pelvic pain and/or vaginal bleeding in first trimester

Complication	*All women*	*With any pelvic pain and/or vaginal bleeding*	*No pelvic pain and/or vaginal bleeding*
Any antenatal	196/826 (24)	166/645 (26)	30/181 (17)
Antepartum hemorrhage and placental abruption	57/847 (7)	47/662 (7)	10/185 (5)
Low birth weight	51/826 (6)	40/645 (6)	11/181 (6)
Preterm birth	47/847 (6)	41/662 (6)	6/185 (3)
Gestational diabetes	44/847 (5)	39/662 (6)	5/185 (3)
Pre-eclampsia	25/847 (3)	20/662 (3)	5/185 (3)
Preterm prelabor rupture of membranes	23/847 (3)	21/662 (3)	2/185 (1)
Fetal growth restriction	21/847 (2)	18/662 (3)	3/185 (2)
Pregnancy-induced hypertension	16/847 (2)	14/662 (2)	2/185 (1)
Second-trimester miscarriage	14/847 (2)	11/662 (2)	3/185 (2)
Gestational proteinuria	4/847 (0.5)	4/662 (0.6)	0/185 (0)
Stillbirth	4/847 (0.5)	4/662 (0.6)	0/185 (0)
Any delivery	512/789 (65)	402/615 (65)	110/174 (63)
Operative delivery	411/829 (50)	327/647 (51)	84/182 (46)
Postpartum hemorrhage*	159/727 (22)	125/567 (22)	34/160 (21)
Operative delivery for fetal distress	153/685 (22)	120/529 (23)	33/156 (21)
Meconium	92/823 (11)	70/642 (11)	22/181 (12)
Sepsis in labor	41/829 (5)	35/647 (5)	6/182 (3)
Massive obstetric hemorrhage*	33/727 (5)	27/567 (5)	6/160 (4)
Any neonatal	77/810 (10)	66/634 (10)	11/176 (6)
Abnormal 1-min Apgar score	59/813 (7)	49/635 (8)	10/178 (6)
Admission to neonatal unit	37/828 (4)	32/647 (5)	5/181 (3)
Abnormal 5-min Apgar score	7/811 (0.9)	7/634 (1)	0/177 (0)

Data are presented as *n*/*N* (%). Analysis performed only in cases with complete data. *Excluding cases with trauma.

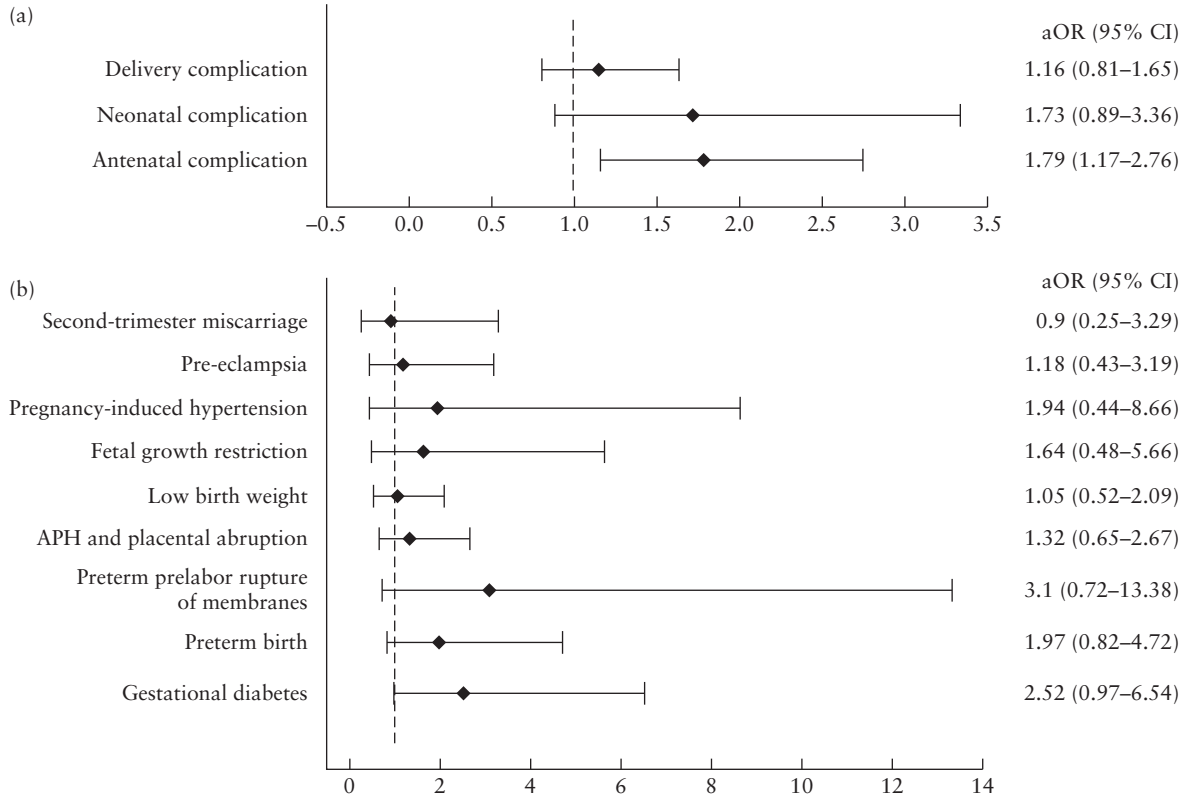

Figure 2 Forest plots showing association of first-trimester pelvic pain and/or vaginal bleeding with risk of any antenatal, delivery or neonatal complication (a) and individual antenatal complications (b). aOR, odds ratio adjusted for maternal age; APH, antepartum hemorrhage.

relationship between individual antenatal complications and any pelvic pain and/or vaginal bleeding during the first trimester, the highest ORs were observed for PPROM (aOR = 3.10; 95% CI, 0.72–13.4), gestational diabetes (aOR = 2.52; 95% CI, 0.97–6.54), PTB (aOR = 1.97; 95% CI, 0.82–4.72) and PIH (aOR = 1.94; 95% CI, 0.44–8.66) (Figure 2b and Table S1), but these show wide confidence intervals due to the small number of each individual complication.

The aOR of pelvic pain and/or vaginal bleeding was 1.73 (95% CI, 0.89–3.36) for neonatal complications and 1.16 (95% CI, 0.81–1.65) for delivery complications. Of women with any pelvic pain and/or vaginal bleeding in the first trimester, 10% (66/634) had a neonatal complication, compared with 6% in the no-symptom group (11/176), and 65% (402/615) had a delivery complication, compared with 63% (110/174) in the group with no symptoms.

Presence *vs* quantification of pelvic pain and vaginal bleeding

We observed a stronger association between incidence of neonatal complications and vaginal bleeding (aOR = 1.78; 95% CI, 1.08–2.95) compared with pelvic pain (aOR = 1.17; 95% CI, 0.71–1.90) in the first trimester.

In terms of statistical significance, ORs for the presence of pelvic pain or vaginal bleeding were similar to those when considering the worst symptom score or total symptomatic days (Table 3). However, the AUC results suggested that quantification of pelvic pain or vaginal bleeding in terms of worst score or total symptomatic days did not provide a better prediction of the incidence of complications (Table S2).

aORs of different quantifications for individual symptoms are presented in Table S1.

Discrepancy in GA dating between LMP and ultrasound parameters

The level of discrepancy between the observed GA measured by ultrasound and that expected by LMP at first presentation had no clear association with antenatal, delivery or neonatal complications (aORs between 0.98 and 1.04; Table 3); however, there was an increased risk, albeit small, of second-trimester miscarriage (aOR per day, 1.18; 95% CI, 1.02–1.35) (Table S1).

Nausea and vomiting in pregnancy

We did not find evidence of an association between the highest PUQE score reported in the first trimester and adverse pregnancy outcomes (Tables 3 and S1).

DISCUSSION

Principal findings

Our findings suggest that any episode of pelvic pain and/or vaginal bleeding in the first trimester of pregnancy is associated with an increased overall risk of antenatal complications. The association was less clear-cut for neonatal complications, for which our findings suggest that vaginal bleeding has a stronger association than pelvic pain. We did not observe a meaningful association between pelvic pain and/or vaginal bleeding in the first trimester and delivery complications. Furthermore, our data suggested that a discrepancy in observed GA between ultrasound dating and LMP-based dates might increase the risk of second-trimester miscarriage. We did not find women with nausea and/or vomiting in the first trimester of pregnancy to be at greater risk of complications later on in gestation.

Comparison with other studies

Our finding of an increased overall risk of antenatal complications in women experiencing pelvic pain and/or vaginal bleeding in the first trimester is consistent with a previous systematic review on this subject[4]. Furthermore, other relatively small and largely retrospective studies have reported that the strongest association is with PTB[9,14,16,33]. In one of the few prospective studies on this topic, Hossain *et al.* demonstrated an increased risk of PTB associated with first-trimester bleeding (aOR = 1.4; 95% CI, 1.04–2.00), which increased further when both first- and second-trimester pregnancies with bleeding were included (aOR = 3.29; 95% CI, 1.31–8.24)[9].

A previous study quantified vaginal bleeding by comparing it to a woman's normal menstrual period[33]. However, this comparison is highly subjective and variable. Furthermore, in this study, bleeding episodes were reported via a telephone consultation at approximately 11–14 weeks' gestation, which is subject to recall bias[33]. Our findings suggested that it was the presence or absence of any pelvic pain and/or vaginal bleeding that was the most important factor, while quantification of symptoms was not of additional value.

Strengths and limitations

The strengths of our study are its prospective design, the consecutive recruitment, the well-characterized patient cohort and the use of validated symptom scores. This is the first study in which participants were followed up intensively in the first trimester and symptoms were assessed thoroughly in a prospective manner. This allowed us to demonstrate reliably the association between pelvic pain and/or vaginal bleeding in the first trimester and antenatal complications.

However, there are some limitations that need to be acknowledged. Although we recruited over 1000 women, there was a relatively small incidence of each individual adverse outcome, even though our reported incidences are similar to those in other studies[9,13]. As a result, although we adjusted for maternal age, we did not adjust for confounders such as ethnicity, parity and body mass index. Most participants were recruited through the Early Pregnancy Unit, which may constitute a higher-risk group. However, the incidence of PTB in the UK has been

reported to be 8% of all live births[34], whereas in our population, the incidence was 5.7%. During follow-up, an unavoidable bias prevalent in observational studies in this field is that some participants received intervention to prevent an adverse outcome as part of standard clinical practice. An example of this is the insertion of cervical cerclage ($n = 18$). This is likely to have resulted in fewer preterm deliveries in our cohort and so the overall impact of early-pregnancy symptoms may have been underestimated.

Conclusions and policy implications

Pregnancies affected by pelvic pain and/or vaginal bleeding in the first trimester are at increased risk of antenatal pregnancy complications, and women should be counseled accordingly. Future research should focus on identifying subgroups of women who are most at risk and establishing the precise risk of developing each individual type of antenatal pathology.

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SUPPORTING INFORMATION ON THE INTERNET

Tables S1 and **S2** may be found in the online version of this article.

