



29th World Congress on Ultrasound in Obstetrics and Gynecology

12-16 October 2019
Berlin, Germany

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The impact of early pregnancy events on long-term pregnancy outcomes: a prospective cohort study

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Short title: Impact of early pregnancy events

Keywords: early pregnancy events, adverse pregnancy outcomes, threatened miscarriage, miscarriage, preterm birth

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/uog.20262

Abstract

Objectives: To prospectively assess the impact of pelvic pain, vaginal bleeding and nausea and vomiting in the first trimester of pregnancy on long-term pregnancy outcomes.

Methods: Prospective observational cohort study at Queen Charlotte's & Chelsea Hospital, London, UK, from March 2014-2016. Consecutive women with confirmed intrauterine pregnancies between 5-14 weeks gestation were recruited. 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. Pregnancies were followed up until the final outcome was known. Antenatal, delivery, and neonatal outcomes were obtained from hospital records. We calculated adjusted odds ratios (aOR) using logistic regression with correction for maternal age.

Results: We recruited 1003 women. After excluding first trimester miscarriages (N=99), terminations (N=20), lost to follow up (N=32) and withdrawals (N=5), 847 pregnancies were analysed. Adverse antenatal complications were observed in 166/645 (26%) women with pain and/or bleeding, and in 30/181 (17%) women without (aOR=1.79, 95% CI=1.17-2.76). Neonatal complications were observed in 66/635 (10%) women

with and 11/176 (6%) women without pain and/or bleeding (aOR=1.73, 95% CI=0.89-3.36). Delivery complications were observed in 402/615 (65%) women with and 110/174 (63%) women without pain and/or bleeding (aOR=1.16, 95% CI=0.81-1.65). For 18 of 20 individual antenatal complications, incidence was higher among women with pain and/or 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 with pelvic pain and/or vaginal bleeding in the first trimester. This should be considered when advising women attending early pregnancy units.

Introduction

Vaginal bleeding, pelvic pain, nausea and vomiting are common early pregnancy symptoms leading women to seek medical attention. Vaginal bleeding occurs in 20% of clinically recognised 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 merit closer surveillance.

There is some evidence to suggest this approach may be misplaced. Some studies have concluded vaginal bleeding and pelvic pain in early pregnancy may be associated with complications including fetal growth restriction (FGR) and preterm birth (PTB).³ ⁴Hyperemesis gravidarum has also been linked to some of these complications.³ Discrepancies between observed and expected gestational age has been associated with pregnancies being small for gestational age and an increased risk

of PTB.³ The majority of these studies are retrospective and subject to recall bias⁵⁻⁷, and there are a paucity of prospective publications to help guide management.

When taking a closer look at some of these publications, inclusion criteria and the definition of “first trimester” differ with some using a cut-off of 12 or 14 weeks⁶⁻⁹, others 20 weeks,^{8,9} whilst in some cases gestational age in week is not defined at all.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 characterisation of symptoms.⁶ Few studies have quantified symptoms of pelvic pain and vaginal bleeding,^{10, 13-15} or used validated symptom scoring questionnaires.^{10,}

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In this study the primary aim was to prospectively evaluate the impact of any pelvic pain and/or vaginal bleeding in early pregnancy on antenatal, delivery, and neonatal complications. The secondary aims were an assessment of the relationship between pregnancy complications with vomiting as well as any discrepancy found between ultrasound dating of a pregnancy and dating using menstrual dates. Finally we conducted an exploratory assessment of whether quantification of pelvic pain and vaginal bleeding are more predictive than merely recording their presence.

Methods

Study Design and Ethical Approval

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

Inclusion Criteria

Women in the first trimester of pregnancy (< 14 weeks gestation by last menstrual period (LMP) or ultrasound scan dating based on crown rump length measurements (CRL) where LMP was not known), with intrauterine pregnancies were invited to participate. An intrauterine pregnancy was defined on the basis of an ultrasound scan showing an intrauterine gestation sac with or without a visible embryo and heartbeat. Women aged less than 16 and over 50 were excluded. Participants were recruited via open advertisements (using posters) in local GP surgeries, in local hospitals, and at the university where the study is being conducted (Imperial College). The majority of women were recruited after attending the hospital Ultrasound Department or Early Pregnancy Assessment Unit.

Study Design

All study visits took place at Queen Charlotte's & Chelsea Hospital. A detailed questionnaire regarding demographic details, past medical, gynaecological and obstetric history was completed. The date of the last menstrual period was recorded and participants were asked to rate their certainty of recall for this date using a visual analogue score similar to that used for assessment of pain and scored from zero (uncertain) to ten (very certain). Participants were also asked about their symptoms using validated symptoms scores at each study visit. Depending on the gestational age at the time of recruitment and clinical need, participants were seen either 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 crown rump length (CRL) were taken at each visit.¹⁷ Participants were subsequently seen at the time of their routine dating scan (11 to 14 weeks gestation) and anomaly scan (18 to 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 with the team. Pregnancy outcomes were collected using hospital medical records. The incidence of most individual pregnancy-related complications in our population is low. For example, the incidence of preterm birth in 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 to assess symptoms in early pregnancy at each first trimester study visit. Vaginal bleeding was assessed using a modified pictorial blood assessment chart (PBAC) bleeding score (numerical scale 0-4).¹⁸ Participants were asked to record the amount of vaginal bleeding they were experiencing on the day they attended for a study visit, the worst vaginal bleeding they had experienced prior to their visit, and the duration of bleeding in days. Participants were asked to record their pelvic pain score using a Visual Analogue Score (VAS) on the day of their study visit attendance, and the worst pain they had experienced until that point (scale of 0 to 10). They were also asked to document the duration of their 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 (numerical score of 3 to 15).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. For pelvic pain, analogous quantifications were

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evaluated: presence of pain at any time, worst score and total number of days. Nausea and/or vomiting were evaluated through the worst PUQE score reported during the first trimester. Finally, we also examined the discrepancy in the gestational age (GA) expected based on the last menstrual period (LMP) and the GA estimated by ultrasound scan performed at the first study visit (as an average of GA provided by CRL and MSD measurements), where positive values reflect higher GA estimated by LMP than GA 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.¹⁷ Little difference has been observed between CRL alone and USS-mean in terms of calculated gestation.

Main outcome measures

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

1. Antenatal Complications

Hypertensive disorders of pregnancy

Pre-eclampsia (PET) was defined in accordance with as raised blood pressure greater than or equal to 140/90mmHg on two occasions four hours apart at >20 weeks gestation in a woman with previously normal blood pressure, with proteinuria, quantified using the urine protein creatinine ratio (UPCR>0.3mg/dL) or by 24 hour urine collection (>3g/24hours).²¹ In addition, a diagnosis of pre-eclampsia was also given if pregnancy induced hypertension (PIH) (no proteinuria) occurred with fetal

growth restriction, in the case of eclampsia, or in the case of PIH with deranged blood tests (thrombocytopenia $<100 \times 10^9 /l$, serum creatinine concentrations greater than 1.1mg/dL or a doubling of this in the absence of renal disease, or elevated liver transaminases to twice normal concentration).²¹ Pregnancy induced hypertension (PIH) was defined as raised blood pressure greater than or equal to 140/90mmHg without proteinuria, growth restriction and abnormal blood tests.²¹ Gestational proteinuria was defined as UPCR $>0.3\text{mg/dL}$ or a 24 hour urine collection protein level greater than 3g in the absence of hypertension.²¹

Gestational diabetes (GDM)

Gestational diabetes was diagnosed if the fasting plasma glucose was greater than 5.6mmol/l or if the 2-hour plasma glucose level was greater than 7.8mmol/l after an oral glucose tolerance test (OGTT).²²

Antepartum hemorrhage (APH)

Antepartum hemorrhage 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 praevia.²³

Placental abruption

Placenta abruption was a clinical diagnosis defined as when the placenta sheers away from uterine lining and may occur antenatally or during delivery.²³

Second Trimester Miscarriage

Miscarriage over 14 weeks and before 23 completed weeks of gestation as defined by CRL taken at the time of the 11 to 14 weeks dating ultrasound scan.²⁴

Preterm Birth, Preterm Delivery and Preterm pre-labor rupture of membranes

Preterm birth (PTB) described any delivery after 24 weeks and before 37 completed weeks gestation (as dated by a routine dating scan), which included both iatrogenic preterm delivery and spontaneous preterm labor.²⁵ Preterm pre-labor rupture of membranes (PPROM) was defined as rupture of membranes before 37 weeks gestation (as defined by a routine dating scan) occurring more than 24 hours before delivery.²⁵

Fetal Growth Restriction and low birth weight

Fetal growth restriction (FGR) was a term used to describe an ultrasound based antenatal diagnosis where the estimated fetal weight was less than the <10th centile for gestational age with abnormal umbilical artery Doppler results (pulsatility index > 95th percentile with or without reversed or absent end diastolic flow).^{26, 27} Low birth weight (LBW) was defined in accordance with WHO criteria and WHO centiles as delivery weight less than the 10th percentile for gestational age, where the final gestational age was estimated using the dating scan (performed at 11-14 weeks gestation) as a reference.²⁸

Stillbirth

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

2. Delivery Complications

Delivery details were collected including date of delivery (from which gestational age can be calculated), mode of delivery, and any complications. Mode of delivery included 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 liquor and a diagnosis of sepsis in labor were also noted. This was defined in accordance to NICE intra-partum guideline.³⁰

The amount of bleeding at delivery was recorded. For a vaginal delivery (including SVD, forceps and ventouse delivery), an estimated blood loss of greater than 500ml was classified as a “post-partum hemorrhage” (PPH). At Cesarean section (emergency and elective), an estimated blood loss of greater than 1000ml was recorded as PPH. Any delivery with estimated blood loss of greater than 1500ml was characterized as a massive obstetric hemorrhage (MOH).³¹ The cause of bleeding as documented by the care provider during birth was noted as either due to atony, trauma, retained placenta or morbidly adherent placenta. Manual removal of placenta (MROP) is where traditional controlled cord traction is insufficient to complete the third stage of labor and additional manual manoeuvres are required to achieve delivery of placenta.

3. Neonatal complications

The following neonatal complications were recorded: admission to neonatal unit and low one minute Apgar score of less than 7 and low five minute Apgar score of less than 7.

Statistical Analysis

The statistical analysis of this largely exploratory study focused on precision by reporting 95% confidence intervals (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 (a) any adverse antenatal, (b) any neonatal, and (c) any delivery complications. Results for individual complications, or for other first trimester symptoms are secondary.

Logistic regression (LR) was used to assess the association between first trimester symptoms and complications, reporting the adjusted odd 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 LR model used to compute the adjusted OR.

The analysis of antenatal complications was performed on all pregnancies that were still viable at the end of the first trimester. Delivery complications and neonatal complications analysis were performed on pregnancies resulting in live births only

(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. PPH and MOH analysis were performed on a subset of patients where patients with traumatic PPH ($n=53$) and MOH ($n=10$) were excluded.

All analyses were performed on complete cases only. All the features analysed contained less than 1 percent of missing values, except the GA discrepancy feature that contained less than 2% of missing values ($n=8$), mostly due to the absence of ultrasound measurement to date the pregnancy at first scan. The majority of outcomes also had no missing values except; LBW $< 3\%$ of missing values ($n=21$), mostly due to the baby birth weight being unavailable), PPH and MOH $< 5\%$ ($n=37$), due to the absence of blood loss quantification, meconium $<1\%$ ($n=6$) and Apgar score $< 2\%$ ($n=16$).

All analyses were performed with Python 3.6.0 (Python Software Foundation, Delaware, USA).

Results

One thousand two hundred and forty two consecutive women were screened and 1003 participants were recruited (fig 1). Reasons for declining to take part in the study included inability to attend follow up, choosing to book antenatal care in another hospital and patient personal choice. Those who experienced first trimester miscarriage (n=99) or underwent termination of pregnancy (n=20), withdrew from the study (n=5), or were lost to follow up (n=32) were excluded from this analysis (fig 1). Eight hundred and forty seven women were included in the final analysis (fig 1). Tables 1 and 2 present descriptive statistics for patient characteristics and first trimester symptoms. Table 3 shows each pelvic pain and vaginal bleeding feature and its association with antenatal, neonatal and delivery complications. The absolute numbers of each adverse outcome assessed within the study are demonstrated within table 4. The incidence was 24% (196/826) for antenatal, 65% (512/789) for delivery, and 10% (77/810) for neonatal complications.

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

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

relationship between individual antenatal complications and any pelvic pain and/or vaginal bleeding during the first trimester, the highest odds ratios 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) (Fig 3).

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

Presence vs quantification of pelvic pain and vaginal bleeding

We observed a stronger association between neonatal complications and bleeding (aOR 1.78; 95% CI 1.08 to 2.95) compared to pain (aOR 1.17; 95% CI 0.71 to 1.90).

In terms of statistical significance, results for the presence of pelvic pain or vaginal bleeding were similar to when we used the worst symptom score or total symptomatic days (table 3). However, the AUC results suggest 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 presence of complications (suppl table 2).

aORs of different quantifications for individual symptoms are presented in supplementary table 1.

Discrepancy in gestational age dating between last menstrual period and ultrasound parameters

The level of discrepancy between the observed gestational age measured by ultrasound and that expected by last menstrual period at first presentation had no clear general association with antenatal, delivery, or neonatal complications (aORs between 0.98 and 1.04; table 3). However, there was a suggestion of an increased risk of second trimester miscarriage (aOR per day 1.18; 95% CI 1.02-1.35) (suppl table 1).

Nausea and vomiting in pregnancy

We did not find evidence of a link between the worst PUQE score reported in the first trimester and adverse pregnancy outcomes (table 3, suppl table 1).

Discussion

Principal findings

Our results 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. For individual antenatal complications the strongest association was found with PPROM, PTB, PIH and gestational diabetes. The association was less clear-cut for neonatal complications, where our data suggested that this might be more with vaginal bleeding rather than pelvic pain. We did not observe a meaningful association with delivery complications. Further, our data suggested that a discrepancy in observed gestational age between ultrasound dating and LMP based dates might increase the risk of second trimester miscarriage. We did not find women with vomiting in pregnancy to be at greater risk of complications later in pregnancy.

Comparison with other studies

Our finding of an increased overall risk of antenatal complications is consistent with a previous systematic review on this subject.⁴ Furthermore other relatively small and largely retrospective studies have also reported the strongest association is with preterm birth.^{9, 14, 16, 33} In one of the few prospective studies on the issue, Hossain *et al* demonstrated an increased risk of preterm birth associated with first trimester

bleeding (adjusted OR 1.4; 95% CI 1.04 to 2.00), which increased further when both first and second trimester pregnancies were included (adjusted OR 3.29; 95% CI 1.31 to 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.³³ Furthermore in this study, bleeding episodes were reported via a telephone consultation at approximately 11 to 14 weeks gestation, which is subject to recall bias.³³ Our data did not suggest that quantification of symptoms was of additional value and it was the presence or absence of any pelvic pain and/or vaginal bleeding that was most important.

Strengths and limitations of the study

The strengths of our study are the prospective study design, consecutive recruitment, the well-characterized patient cohort and the use of validated symptom scores. To our knowledge, this is the first study where participants were followed up intensively in the first trimester and symptoms thoroughly assessed in a prospective manner. In this way, we have been able to reliably demonstrate the association between pelvic pain and/or vaginal bleeding in the first trimester and antenatal complications. However, there are limitations. Although we recruited over 1000 women, there was a relatively small number of each individual adverse outcome

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(while our reported incidences are similar to other studies).^{9, 13} As a result, although we adjusted for maternal age, we have not adjusted for confounders such as ethnicity, parity, and body mass index (BMI). Most of our participants were recruited through the Early Pregnancy Unit, which may constitute a higher risk group. However, the incidence of preterm birth in the UK has been reported as 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 complications in pregnancy, and women should be counselled accordingly. Future research should focus on identifying sub-groups of women most at risk and establishing the precise risk of developing each individual type of antenatal pathology.

Acknowledgements: We would like to thank all the participants that took part in the study.

Disclosures of interest: None to declare.

Contribution to Authorship: All authors have made a substantial contribution to this work. TB and DT were involved in conception and design of the work. MA, SS, HF, SB, CS, JF and MP were involved in recruitment of patients and data collection. Data cleaning was completed by MM, MP, GN and TV. BVC and BDM provided statistical expertise. BVC and TV performed the statistical analysis and interpreted the results. TB, MA, DT, TV, PB and BVC drafted the manuscript and all authors were involved in its critical review and final approval.

Details of Ethics Approval: The study had been approved by NHS National Research Ethics Service (NRES) Riverside Committee London (REC 14/LO/0199) on 12th February 2014.

Funding: TB is supported by the National Institute for Health Research (NIHR) Biomedical Research Centre based at Imperial College Healthcare NHS Trust and Imperial College London. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health. DT is a Senior Clinical Investigator of the Research Foundation–Flanders (FWO). MAM is funded by the Tommy's National Centre for Miscarriage Research. TV is a SB PhD fellow at FWO, Research Foundation Flanders (project 1S93918N). SB is supported by NIHR

References

1. Everett C. Incidence and outcome of bleeding before the 20th week of pregnancy: prospective study from general practice. *Bmj* 1997; **315**: 32-34.
2. Hasan R, Baird DD, Herring AH, Olshan AF, Jonsson Funk ML, Hartmann KE. Association between first-trimester vaginal bleeding and miscarriage. *Obstet Gynecol* 2009; **114**: 860-867. DOI: 10.1097/AOG.0b013e3181b79796.
3. van Oppenraaij RH, Jauniaux E, Christiansen OB, Horcajadas JA, Farquharson RG, Exalto N. Predicting adverse obstetric outcome after early pregnancy events and complications: a review. *Hum Reprod Update* 2009; **15**: 409-421. DOI: 10.1093/humupd/dmp009.
4. Saraswat L, Bhattacharya S, Maheshwari A, Bhattacharya S. Maternal and perinatal outcome in women with threatened miscarriage in the first trimester: a systematic review. *Bjog* 2010; **117**: 245-257. DOI: 10.1111/j.1471-0528.2009.02427.x.
5. Johns J, Hyett J, Jauniaux E. Obstetric outcome after threatened miscarriage with and without a hematoma on ultrasound. *Obstet Gynecol* 2003; **102**: 483-487.
6. Mulik V, Bethel J, Bhal K. A retrospective population-based study of primigravid women on the potential effect of threatened miscarriage on obstetric outcome. *J Obstet Gynaecol* 2004; **24**: 249-253. DOI: 10.1080/01443610410001660724.
7. Wijesiriwardana A, Bhattacharya S, Shetty A, Smith N, Bhattacharya S. Obstetric outcome in women with threatened miscarriage in the first trimester. *Obstet Gynecol* 2006; **107**: 557-562. DOI: 10.1097/01.AOG.0000199952.82151.de.
8. Arafa M, Abdel-Fataah M, Zeid HA, el-Khouly A. Outcomes of pregnancies complicated by early vaginal bleeding. *East Mediterr Health J* 2000; **6**: 457-464.
9. Hossain R, Harris T, Lohsoonthorn V, Williams MA. Risk of preterm delivery in relation to vaginal bleeding in early pregnancy. *Eur J Obstet Gynecol Reprod Biol* 2007; **135**: 158-163. DOI: 10.1016/j.ejogrb.2006.12.003.
10. Sipila P, Hartikainen-Sorri AL, Oja H, Von Wendt L. Perinatal outcome of pregnancies complicated by vaginal bleeding. *Br J Obstet Gynaecol* 1992; **99**: 959-963.

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11. Tongsong T, Srisomboon J, Wanapirak C, Sirichotiyakul S, Pongsatha S, Polsrisuthikul T. Pregnancy outcome of threatened abortion with demonstrable fetal cardiac activity: a cohort study. *J Obstet Gynaecol (Tokyo 1995)* 1995; **21**: 331-335.
 12. Williams MA, Mittendorf R, Lieberman E, Monson RR. Adverse infant outcomes associated with first-trimester vaginal bleeding. *Obstet Gynecol* 1991; **78**: 14-18.
 13. Weiss JL, Malone FD, Vidaver J, Ball RH, Nyberg DA, Comstock CH, Hankins GD, Berkowitz RL, Gross SJ, Dugoff L, Timor-Tritsch IE, D'Alton ME. Threatened abortion: A risk factor for poor pregnancy outcome, a population-based screening study. *Am J Obstet Gynecol* 2004; **190**: 745-750. DOI: 10.1016/j.ajog.2003.09.023.
 14. Johns J, Jauniaux E. Threatened miscarriage as a predictor of obstetric outcome. *Obstet Gynecol* 2006; **107**: 845-850. DOI: 10.1097/01.AOG.0000206186.91335.9a.
 15. Strobino B, Pantel-Silverman J. Gestational vaginal bleeding and pregnancy outcome. *Am J Epidemiol* 1989; **129**: 806-815.
 16. Yang J, Hartmann KE, Savitz DA, Herring AH, Dole N, Olshan AF, Thorp JM, Jr. Vaginal bleeding during pregnancy and preterm birth. *Am J Epidemiol* 2004; **160**: 118-125. DOI: 10.1093/aje/kwh180.
 17. Robinson HP, Fleming JE. A critical evaluation of sonar "crown-rump length" measurements. *Br J Obstet Gynaecol* 1975; **82**: 702-710.
 18. Higham JM, O'Brien PM, Shaw RW. Assessment of menstrual blood loss using a pictorial chart. *Br J Obstet Gynaecol* 1990; **97**: 734-739.
 19. Hawker GA, Mian S, Kendzerska T, French M. Measures of adult pain: Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF-36 BPS), and Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP). *Arthritis Care Res (Hoboken)* 2011; **63 Suppl 11**: S240-252. DOI: 10.1002/acr.20543.
 20. Koren G, Boskovic R, Hard M, Maltepe C, Navioz Y, Einarson A. Motherisk-PUQE (pregnancy-unique quantification of emesis and nausea) scoring system for nausea and vomiting of pregnancy. *Am J Obstet Gynecol* 2002; **186**: S228-231.
 21. Williams D, Craft N. Pre-eclampsia. *Bmj* 2012; **345**: e4437. DOI: 10.1136/bmj.e4437.
 22. Jacklin PB, Maresh MJ, Patterson CC, Stanley KP, Dornhorst A, Burman-Roy S, Bilous RW. A cost-effectiveness comparison of the NICE 2015 and WHO 2013 diagnostic criteria for women with gestational diabetes with and without risk factors. *BMJ Open* 2017; **7**: e016621. DOI: 10.1136/bmjopen-2017-016621.
 23. Giordano R, Cacciatore A, Cignini P, Vigna R, Romano M. Antepartum Haemorrhage. *J Prenat Med* 2010; **4**: 12-16.

24. Edlow AG, Srinivas SK, Elovitz MA. Second-trimester loss and subsequent pregnancy outcomes: What is the real risk? *Am J Obstet Gynecol* 2007; **197**: 581.e581-586. DOI: 10.1016/j.ajog.2007.09.016.
25. Tucker J, McGuire W. Epidemiology of preterm birth. *Bmj* 2004; **329**: 675-678.
26. Unterscheider J, Daly S, Geary MP, Kennelly MM, McAuliffe FM, O'Donoghue K, Hunter A, Morrison JJ, Burke G, Dicker P, Tully EC, Malone FD. Optimizing the definition of intrauterine growth restriction: the multicenter prospective PORTO Study. *Am J Obstet Gynecol* 2013; **208**: 290.e291-296. DOI: 10.1016/j.ajog.2013.02.007.
27. Hadlock FP, Harrist RB, Sharman RS, Deter RL, Park SK. Estimation of fetal weight with the use of head, body, and femur measurements--a prospective study. *Am J Obstet Gynecol* 1985; **151**: 333-337.
28. McCowan LM, Roberts CT, Dekker GA, Taylor RS, Chan EH, Kenny LC, Baker PN, Moss-Morris R, Chappell LC, North RA. Risk factors for small-for-gestational-age infants by customised birthweight centiles: data from an international prospective cohort study. *Bjog* 2010; **117**: 1599-1607. DOI: 10.1111/j.1471-0528.2010.02737.x.
29. Blencowe H, Cousens S, Jassir FB, Say L, Chou D, Mathers C, Hogan D, Shiekh S, Qureshi ZU, You D, Lawn JE. National, regional, and worldwide estimates of stillbirth rates in 2015, with trends from 2000: a systematic analysis. *Lancet Glob Health* 2016; **4**: e98-e108. DOI: 10.1016/s2214-109x(15)00275-2.
30. Delgado Nunes V, Gholitabar M, Sims JM, Bewley S. Intrapartum care of healthy women and their babies: summary of updated NICE guidance. *Bmj* 2014; **349**: g6886. DOI: 10.1136/bmj.g6886.
31. Amelia Banks AN. Massive Haemorrhage in Pregnancy. *Continuing Education in Anaesthesia Critical Care & Pain* 2005; **5**: 195-198. DOI: <https://doi.org/10.1093/bjaceaccp/mki052>.
32. Bender R, Lange S. Adjusting for multiple testing--when and how? *J Clin Epidemiol* 2001; **54**: 343-349.
33. Velez Edwards DR, Baird DD, Hasan R, Savitz DA, Hartmann KE. First-trimester bleeding characteristics associate with increased risk of preterm birth: data from a prospective pregnancy cohort. *Hum Reprod* 2012; **27**: 54-60. DOI: 10.1093/humrep/der354.
34. Sarri G, Davies M, Gholitabar M, Norman JE, Guideline Development G. Preterm labour: summary of NICE guidance. *Bmj* 2015; **351**: h6283. DOI: 10.1136/bmj.h6283.

Figure legends

Figure 1 Study flowchart

Figure 2 Forest plot showing odds ratios adjusted for maternal age for first trimester pain and/or bleeding and risk of antenatal, delivery and neonatal complications

Figure 3 Forest plot of odds ratio adjusted for maternal age for pain and/or bleeding in the first trimester and individual antenatal complications

Table 1. Table showing patient cohort characteristics.

Patient characteristic	N (%), or Median (range)
Maternal Age in years, median (range)	32 (17-48)
Paternal Age in years, median (range)	34 (17-55)
Maternal Ethnicity, n (%)	
Caucasian	555 (65.5)
Asian	114 (13.5)
Afro-Caribbean	105 (12.4)
Other	72 (8.5)
Unknown	1 (0.1)
BMI, mean (range)	23.67 (15.84-53.9)
Parity, n (%)	
0	437 (51.6)
1	285 (33.6)
2	87 (10.3)
3	22 (2.6)
>4	16 (1.9)
Caesarean Section, n (%)	
0	715 (84.4)
1	106 (12.5)
2	20 (2.4)
>3	6 (0.7)
1 st Trimester Miscarriage, n (%)	
0	464 (54.8)
1	244 (28.8)
2	95 (11.2)
>3	44 (5.2)
2nd Trimester Miscarriage, n (%)	
0	817 (96.5)
1	29 (3.4)
>2	1 (0.1)
History of surgery, n (%)	
Cervix	27 (3.2)
Uterus	328 (38.7)
Live birth information	
Final GA in days, median (range)	276 (170-302)
Baby Weight in grams, median (range)	3340 (700-4830)

BMI = Body Mass index, GA = gestational age

Table 2. Descriptive statistics of first trimester symptoms

First trimester symptom	N (%), or Median (range)
Any episode of bleeding or pain, n (%)	662 (78.2)
Any episode of bleeding, n (%)	477 (56.3)
Any episode of pain, n (%)	510 (60.2)
Total bleeding days, median (range)	1 (0 to 50)
Worst bleeding score (scale 0-4), median (range)	1 (0 to 4)
Total pain days, median (range)	1 (0 to 39)
Worst pain score (scale 0-10), median (range)	2 (0 to 10)
Worst PUQE score (scale 3-15), median (range)	6 (3 to 15)
GA discrepancy between LMP and USS at first visit, median (days)	1.35 (-13 to 14)

Table 3. Adjusted odds ratios (with 95% confidence intervals) for the association between antenatal, delivery and neonatal complications and each first trimester symptom.

First trimester symptom	Odds ratio scale	Antenatal Complications (n=826)	Delivery Complications (n=789)	Neonatal Complications (n=810)
Any episode of pain and/or 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 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 pain	Yes vs no	1.69 (1.20 - 2.38)	1.04 (0.77 - 1.41)	1.17 (0.71 - 1.90)
Total bleeding days	Per day	1.04 (1.02 - 1.06)	1.00 (0.98 - 1.03)	1.02 (0.98 - 1.05)
Worst bleeding score reported	Per unit	1.18 (1.02 - 1.37)	1.04 (0.90 - 1.19)	1.27 (1.03 - 1.55)
Total pain days	Per day	1.03 (1.00 - 1.06)	0.99 (0.96 - 1.02)	0.98 (0.93 - 1.03)
Worst pain score reported	Per unit	1.07 (1.02 - 1.12)	1.03 (0.99 - 1.08)	1.0 (0.93 - 1.08)
Worst 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 1st visit	Per day	0.98 (0.94 - 1.02)	0.99 (0.95 - 1.03)	1.04 (0.97 - 1.10)

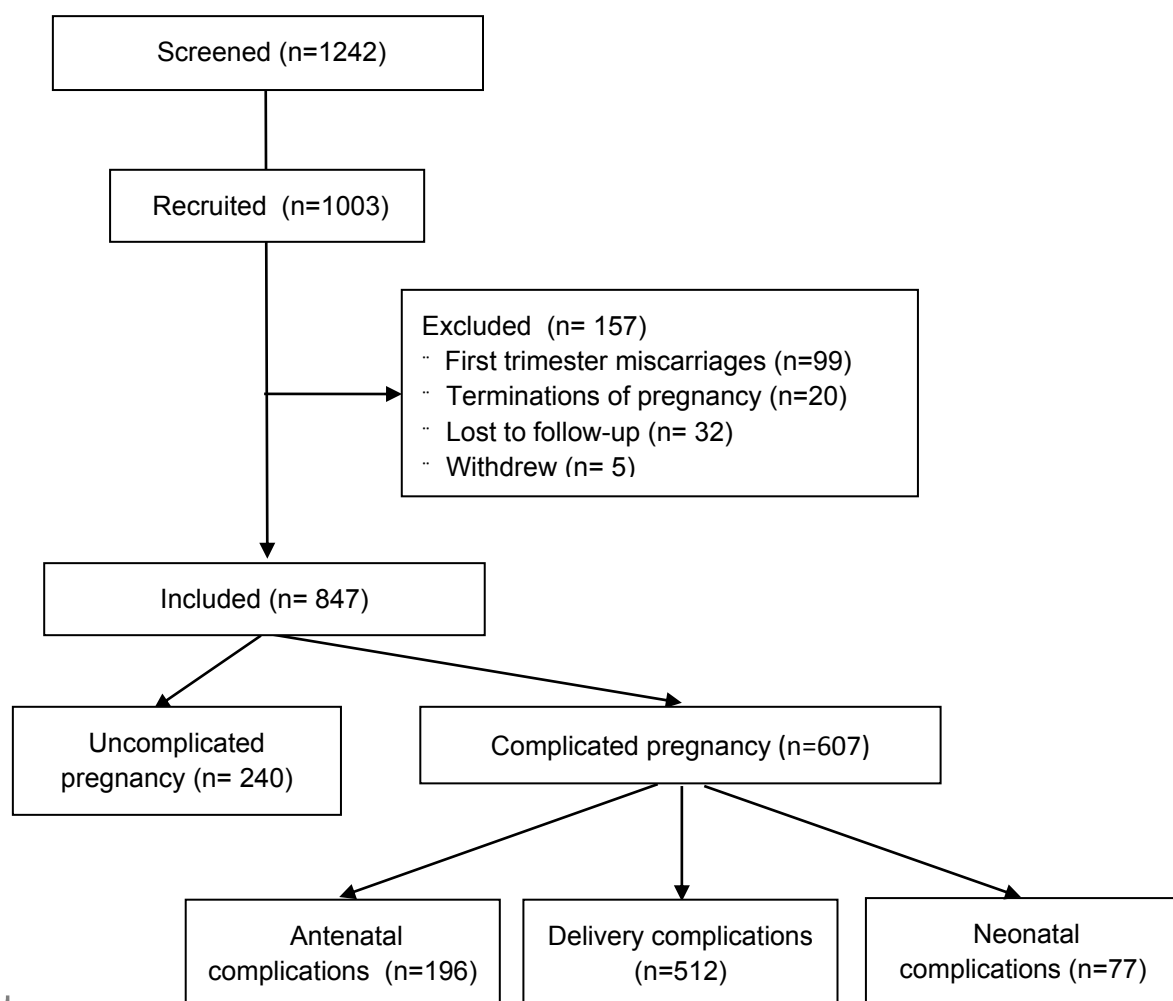
Table 4. Any pain and/or bleeding in the first trimester and the percentage risk of each individual antenatal, neonatal and delivery complication.

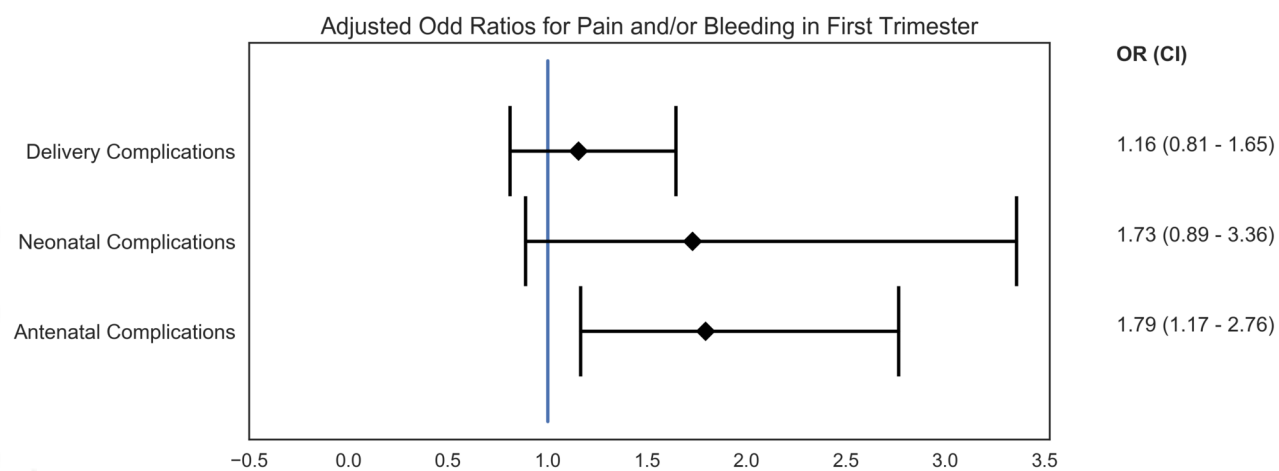
Complication	All women, % (n/N)	Any pain and/or bleeding, % (n/N)	No pain and/or bleeding, % (n/N)
Antenatal Complications	24% (196/826)	26% (166/645)	17% (30/181)
APH and Abruptio	7% (57/847)	7% (47/662)	5% (10/185)
LBW	6% (51/826)	6% (40/645)	6% (11/181)
PTB	6% (47/847)	6% (41/662)	3% (6/185)
Gestational diabetes	5% (44/847)	6% (39/662)	3% (5/185)
PET	3% (25/847)	3% (20/662)	3% (5/185)
PPROM	3% (23/847)	3% (21/662)	1% (2/185)
FGR	2% (21/847)	3% (18/662)	2% (3/185)
PIH	2% (16/847)	2% (14/662)	1% (2/185)
2nd trimester miscarriage	2% (14/847)	2% (11/662)	2% (3/185)
Gestational Proteinuria	<1% (4/847)	1% (4/662)	0% (0/185)
Stillbirth	<1% (4/847)	1% (4/662)	0% (0/185)
Delivery Complications	65% (512/789)	65% (402/615)	63% (110/174)
Operative Delivery	50% (411/829)	51% (327/647)	46% (84/182)
PPH (trauma excluded)	22% (159/727)	22% (125/567)	21% (34/160)
OD for fetal distress	22% (153/685)	23% (120/529)	21% (33/156)
Meconium	11% (92/823)	11% (70/642)	12% (22/181)
Sepsis in labour	5% (41/829)	5% (35/647)	3% (6/182)
MOH (trauma excluded)	5% (33/727)	5% (27/567)	4% (6/160)
Neonatal Complications	10% (77/810)	10% (66/634)	6% (11/176)
Abnormal Apgar 1 min	7% (59/813)	8% (49/635)	6% (10/178)
Admission to NNU	4% (37/828)	5% (32/647)	3% (5/181)
Abnormal Apgar 5 min	1% (7/811)	1% (7/634)	0% (0/177)

Analysis performed on completed cases only.

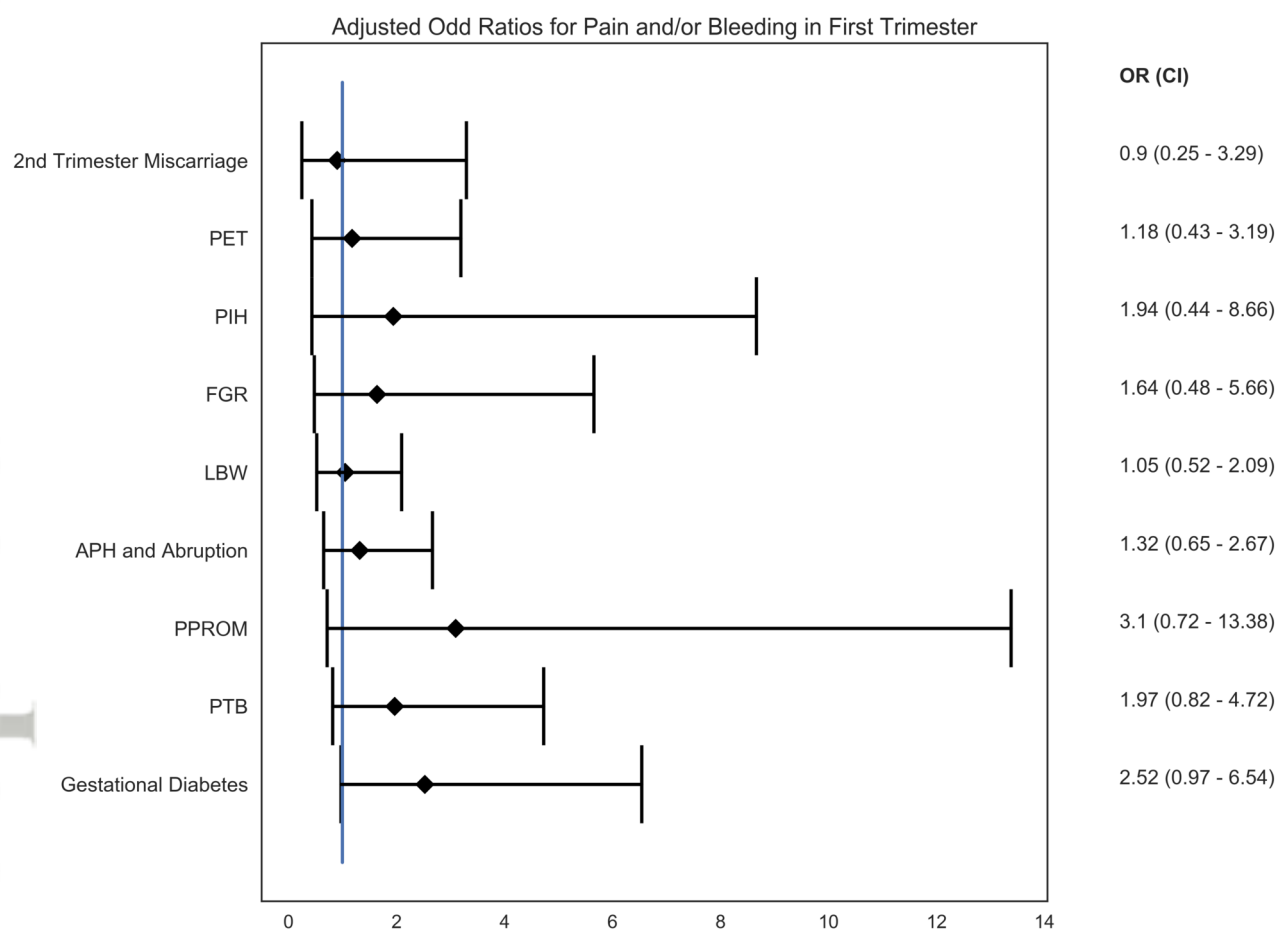
*Hypertensive disorders of pregnancy is a group comprised of PIH, PET and gestational proteinuria.

APH = antepartum haemorrhage, LBW = low birth weight, FGR=fetal growth restriction, PTB =preterm birth, PPRM = preterm prelabour rupture of membranes, PET=preeclampsia, PIH=pregnancy induced hypertension, OD=operative delivery, PPH = postpartum haemorrhage, MOH = massive obstetric haemorrhage, NNU = Neonatal unit





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UOG_20262_Fig3-Antenatal Complications_PainAndOrBleeding .tiff