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First-trimester intrauterine hematoma and pregnancy complications

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KEYWORDS: adverse pregnancy outcome; first trimester; intrauterine hematoma; miscarriage; preterm birth

CONTRIBUTION

What are the novel findings of this work?
The presence of intrauterine hematoma (IUH) in the first trimester of pregnancy is not associated with first-trimester miscarriage; however, it is associated with an increased risk of preterm birth. These findings are independent of the presence of symptoms of pelvic pain and vaginal bleeding in the first trimester.

What are the clinical implications of this work?
Women with IUH in the first trimester can be informed that they are not at increased risk of first-trimester miscarriage. They should be counseled about their increased risk of preterm birth and possibly be offered increased surveillance during the course of their pregnancy.

ABSTRACT

Objective *To assess whether sonographic diagnosis of intrauterine hematoma (IUH) in the first trimester of pregnancy is associated with first-trimester miscarriage and antenatal, delivery and neonatal complications.*

Methods *This was a prospective observational cohort study of women with an intrauterine singleton pregnancy between 5 and 14 weeks' gestation recruited at Queen Charlotte's and Chelsea Hospital, London, UK, between March 2014 and March 2016. Participants underwent serial ultrasound examinations in the first trimester, and the presence, location, size and persistence of any IUH was evaluated. First-trimester miscarriage was defined as pregnancy loss before 14 weeks' gestation. Clinical symptoms, including pelvic pain and vaginal bleeding, were recorded at each visit using validated symptom scores. Antenatal, delivery and neonatal outcomes were obtained from hospital records. Logistic regression analysis and the chi-square test were used to assess the association between the presence and features of IUH and the incidence of adverse pregnancy outcome. Odds ratios (OR) were first adjusted for maternal age (aOR) and then further adjusted for the presence of vaginal bleeding or pelvic pain in the first trimester.*

Results *Of 1003 women recruited to the study, 946 were included in the final analysis and of these, 268 (28.3%) were diagnosed with an IUH in the first trimester. The presence of IUH was associated with the incidence of preterm birth (aOR, 1.94 (95% CI, 1.07–3.52)), but no other individual or overall antenatal, delivery or neonatal complications. No association was found between the presence of IUH in the first trimester and first-trimester miscarriage (aOR, 0.81 (95% CI, 0.44–1.50)). These findings were independent of the absolute size of the hematoma and the presence of vaginal bleeding or pelvic pain in the first trimester. When IUH was present in the first trimester, there was no association between its size, content or position in relation to the gestational sac and overall antenatal, delivery and neonatal complications. Diagnosis of a retroplacental IUH was associated with an increased risk of overall antenatal complications (*$P = 0.04$*).*

Conclusions *Our findings demonstrate that there is no association between the presence of IUH in the first*

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trimester and first-trimester miscarriage. However, an association with preterm birth, independently of the presence of symptoms of pelvic pain and/or vaginal bleeding, is evident. Women diagnosed with IUH in the first trimester should be counseled about their increased risk of preterm birth and possibly be offered increased surveillance during the course of their pregnancy.

INTRODUCTION

Intrauterine hematoma (IUH) is a term used for a sonographic diagnosis of a crescent-shaped hyperechoic or hypoechoic area between the chorionic membrane and the myometrium (Figure 1)[1,2]. The reported incidence of IUH varies from 1.7% to 18.2%[3,4], a variation due to differences in the inclusion criteria, definitions and resolution of the ultrasound equipment used.

The role of IUH in miscarriage remains controversial. Farrell and Owen suggested that the presence of IUH with vaginal bleeding in early pregnancy is associated with a greatly increased risk of miscarriage compared with vaginal bleeding alone[5]. However, similar studies have failed to support this finding[1,6]. A retrospective study of 144 women with IUH and 144 controls concluded that the presence of IUH did not increase the risk of pregnancy loss independent of vaginal bleeding[7].

Findings of studies evaluating how IUH might affect later pregnancy outcomes have been conflicting. Some have reported an association with a number of adverse pregnancy outcomes, including preterm birth (PTB), preterm prelabor rupture of membranes (PPROM), pre-eclampsia and stillbirth[8,9], while others have not[3,7,10]. A systematic review by Tuuli *et al.*[9] concluded that there was an association between IUH and adverse outcomes including miscarriage, stillbirth, preterm delivery and PPROM, but no association was found with other outcomes such as pre-eclampsia or small-for-gestational age. A large prospective cohort study concluded that pregnancies with IUH had an increased risk for a number of adverse outcomes, including preterm delivery, while the location, size and presence of vaginal bleeding did not have an impact on outcome[11].

These discrepant findings may be explained by the variation in inclusion and exclusion criteria as well as the design of these studies, with many lacking an adequate control group[9]. Few studies have taken into account the location, size and presence of symptoms associated with IUH[12], while IUH volume has often been calculated differently between studies[11,13–15]. A further limitation is that the majority of studies on IUH are retrospective and were carried out using small cohorts[6,8,16]. Many of the studies in the literature were conducted many years ago, using lower-quality ultrasound equipment and sometimes a transabdominal approach. As a result, current evidence is unable to provide clinicians with adequate information to best counsel women with an IUH.

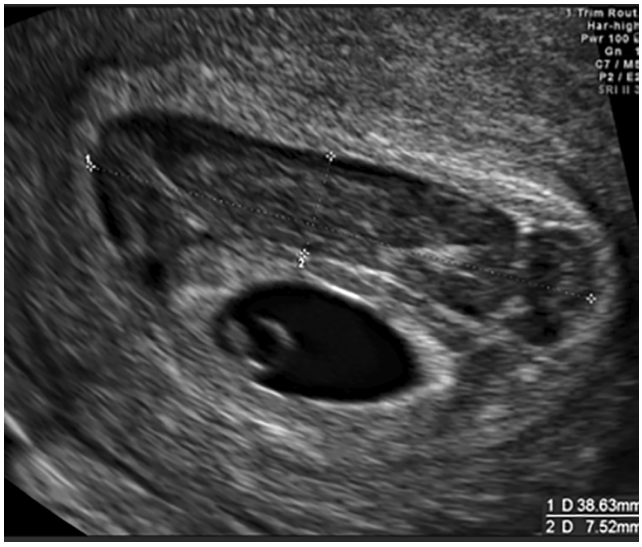

Figure 1 Ultrasound image showing intrauterine hematoma adjacent to viable pregnancy at 6 weeks' gestation.

In this study we aimed to evaluate prospectively the association of the first-trimester sonographic diagnosis of IUH with the incidence of first-trimester miscarriage and antenatal, delivery and neonatal complications. A secondary aim was to explore the effect of the size and location of the IUH, as well as gestational age and presence of vaginal bleeding and/or pelvic pain in the first trimester, on adverse pregnancy outcomes.

PATIENTS AND METHODS

Study design and inclusion criteria

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

Women in the first trimester of a singleton intrauterine pregnancy were recruited at a gestational age of between 5 and 14 weeks. The first trimester was defined as before 14 weeks' gestation according to the last menstrual period (LMP) or ultrasound-scan dating based on crown–rump length (CRL) measurement when LMP was not known[17]. 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 aged under 16 and over 50 years were excluded. Women were invited to participate via open advertisements (using posters) in local general practitioner surgeries, in local hospitals and at the university in which the study was being conducted (Imperial College London). The majority of women were recruited after attending the Ultrasound Department or Early Pregnancy Assessment Unit of Queen Charlotte's and Chelsea Hospital. The cohort described in the present study has been reported on before in a

previous study by our group evaluating the association between pelvic pain and/or vaginal bleeding occurring in the first trimester and the incidence of adverse pregnancy outcomes[18].

All study visits took place at Queen Charlotte's and Chelsea Hospital, London. Demographic information and past medical, gynecological and obstetric history were collected via a questionnaire. Pelvic pain and vaginal bleeding were assessed using validated symptom scores. Once recruited, participants attended for an ultrasound scan and review of their symptoms every 2 weeks. During the study, participants were seen between two and five times in the first trimester, depending on clinical need and gestational age at the time of recruitment. Data were collected from the routine dating scan at 11–14 weeks' gestation and the anomaly scan at 18–22 weeks. Participants 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 were invited to attend for an additional ultrasound scan if deemed necessary. Pregnancy outcomes were ascertained from hospital medical records.

The sample size needed was calculated based on the incidence of common pregnancy complications in a UK-based population. Using these known proportions and the predicted proportion in the cohort, an alpha of 0.05 and power of 80%, we estimated that a minimum of 861 participants would need to be recruited. Therefore, we aimed at recruiting 1000 participants to account for women lost to follow-up and missing data.

Ultrasound scans and assessment of symptoms

The mean gestational-sac diameter (MSD), yolk sac and embryo CRL were measured routinely at each visit. An IUH was diagnosed when a crescent-shaped hyperechoic or hypoechoic area between the chorionic membrane and myometrium was visualized (Figure 1). If present, IUH was measured in three orthogonal planes. The location of the IUH in relation to the gestational sac (anterior, posterior, above sac, below sac or surrounding the sac) was reported, as well as the site of pregnancy implantation. The IUH was then classified as retroplacental or non-retroplacental. The sonographers also reported their subjective impression of the percentage of the gestational sac surrounded by the IUH. The internal content of the IUH was described as homogeneous or heterogeneous. We also collected information on IUH persistence, which was defined as an IUH present on two ultrasound scans performed 10 days apart.

Validated tools were used to assess symptoms at each first-trimester study visit. 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[19]. The participants were asked to record the amount of vaginal bleeding they experienced on the day of their study visit, the worst vaginal bleeding experienced prior to their visit and the duration of bleeding in days.

Participants were asked to rate their pelvic pain on the day of the study visit and the worst pain they had experienced until that point, using a visual analog score (numerical scale of 0 (no pain) to 10 (maximum pain))[20]. They were also asked to document the duration of their pain in days.

Outcome measures

First-trimester miscarriage was defined as pregnancy loss before 14 weeks' gestation, and was diagnosed using the criteria outlined by Abdallah *et al.*[21] and Preisler *et al.*[22]. Late pregnancy outcome measures were defined as antenatal, delivery and neonatal complications.

Antenatal complications comprised: hypertensive disorders of pregnancy; gestational diabetes; antepartum hemorrhage; placental abruption; second-trimester miscarriage; PTB, preterm delivery and PPROM; fetal growth restriction (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 after 20 weeks' gestation in a woman with previously normal blood pressure, with proteinuria, quantified using a urine protein creatinine ratio (UPCR) of $>$ 0.3 mg/dL, or by 24-h urine collection ($>$ 3 g protein/24 h)[23]. A diagnosis of pre-eclampsia was also made in the case of eclampsia, if pregnancy-induced hypertension (PIH) with FGR but without proteinuria occurred, or in the case of PIH with deranged blood tests (thrombocytopenia $< 100 \times 10^9$/L, serum creatinine concentration $>$ 1.1 mg/dL or a doubling of this in the absence of renal disease, or elevated liver transaminases to twice the normal concentration)[23]. PIH was defined as blood pressure $\geq$ 140/90 mmHg without proteinuria, FGR and abnormal blood tests[23]. 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[23].

Gestational diabetes was diagnosed if fasting plasma glucose levels were $>$ 5.6 mmol/L or if a 2-h plasma glucose level was $>$ 7.8 mmol/L after an oral glucose tolerance test[24]. Antepartum hemorrhage was described when vaginal bleeding occurred after 24 weeks' gestation and before delivery[25]. Placental abruption was defined as the placenta shearing away from the uterine lining, antenatally or during delivery[25]. Second-trimester miscarriage was defined as miscarriage after 14 weeks and before 23 completed weeks of gestation, as defined by the 11–14-week dating scan[26].

PTB was described as any delivery after 24 weeks and before 37 completed weeks of gestation, and included both iatrogenic preterm delivery and spontaneous preterm labor. Preterm delivery was defined as iatrogenic delivery before 37 completed weeks' gestation (as dated by the routine dating scan)[27]. Preterm labor was defined as the spontaneous onset of labor before 37 weeks' gestation (as dated by the routine dating scan)[27]. PPROM was defined

as rupture of membranes before 37 weeks' gestation (as defined by the routine dating scan) occurring more than 24 h before delivery[27].

The term FGR was used to describe an ultrasound-based antenatal diagnosis of estimated fetal weight $< 10^{th}$ centile for gestational age with abnormal umbilical artery Doppler results (pulsatility index $> 95^{th}$ percentile with or without reversed or absent end-diastolic flow)[28]. LBW was defined in accordance with World Health Organization (WHO) criteria and WHO centiles as delivery weight $< 10^{th}$ percentile for gestational age, where the final gestational age was estimated using the dating scan as a reference[29].

Intrauterine death or stillbirth was described when there was intrauterine fetal demise and the fetus was born dead after 24 weeks' gestation[30].

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 (forceps and ventouse) delivery. Information as to the indication for delivery was collected, and included 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 UK National Institute for Health and Care Excellence (NICE) intrapartum guideline[31].

The amount of bleeding at delivery was recorded. For a vaginal delivery (including SVD, forceps and ventouse delivery), estimated blood loss of > 500 mL was classified as postpartum hemorrhage (PPH). At Cesarean section (emergency and elective), an estimated blood loss of > 1000 mL was recorded as PPH. Any delivery with an estimated blood loss of > 1500 mL was characterized as massive obstetric hemorrhage (MOH)[32]. The cause of bleeding was documented as atony, trauma, retained placenta or morbidly adherent placenta. Manual removal of the 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 the placenta.

Neonatal complications recorded were admission to the neonatal unit and 1-min and 5-min Apgar scores < 7.

Statistical analysis

Python 3.6.2 (Python Software Foundation, DE, USA) was used for statistical analysis. Comparison of the cohort characteristics with regard to the presence or absence of IUH during the first trimester was performed using the chi-square test, Student's *t*-test or the Mann–Whitney *U*-test, as appropriate.

Logistic regression analysis and the chi-square test were used to evaluate the association between IUH features and adverse pregnancy outcomes. For this purpose, pregnancy outcomes were assessed individually as well as grouped into antenatal, delivery and neonatal complications. In addition, antenatal complications of similar etiology were grouped together, for example PTB and PPROM. Results were reported as odds ratios (OR) with 95% CIs. All OR analyses were first adjusted for maternal age and then were further adjusted for the presence of vaginal bleeding or the presence of pelvic pain in the first trimester. Additionally, we performed analyses adjusting further for the highest bleeding score and the total number of bleeding days recorded during the first trimester as potential confounders, but adjustment for these parameters did not significantly affect the OR values and therefore the analyses are not reported.

The main variable was the presence or absence of IUH at any assessment during the first trimester. Secondary variables evaluated were the size, content, location and persistence of the IUH.

The impact of the absolute IUH size on pregnancy complications was evaluated using three different quantification measures: the maximum IUH diameter (in mm) measured during the first trimester; the maximum product of the three orthogonal diameters of the IUH ($(a \times b \times c)/1000$; in cm^3) recorded during the first trimester; and a scaled version of this product obtained by calculating its cube root ($\sqrt[3]{(a \times b \times c)}$; in mm), which relates to the original unit of measurement. It should be noted that our aim was not to measure precisely the volume of the IUH, but to develop a proxy measurement that is potentially useful for further assessment. For that reason, we did not use the scaling factor derived from the study of Stabile *et al.*[33], which is a simple linear constant that would only affect the scale of the OR.

An additional variable was also created to explore the relative size of the IUH compared with that of the gestational sac. To this end, we examined the ratio of the maximum diameter of the IUH divided by the MSD measured at the corresponding scan.

When assessing the impact of IUH on first-trimester miscarriage, data from only the first available scan were used in order to avoid introducing a selection bias, since some of these women progressively dropped out of the study during the first trimester as they miscarried. The IUH content (homogeneous *vs* heterogeneous) and IUH location in relation to the gestational sac (anterior, posterior, above sac, below sac or surrounding the sac) were evaluated using the first ultrasound scan when the IUH was diagnosed. The association of persistence of IUH with overall antenatal, delivery and neonatal complications was also explored. We defined IUH as persistent if it was still present on ultrasound more than 10 days after the previous scan. The position of the IUH in relation to the placenta (retroplacental *vs* non-retroplacental) and its association with overall antenatal, delivery and neonatal complications, were also assessed.

The potential association of the IUH content, location and persistence with adverse outcomes was tested using the chi-square test.

All analyses were performed on complete cases only. The proportion of missing values among IUH variables were: presence/absence of IUH, 0% ($n = 0$); maximum IUH diameter, 1.9% ($n = 5$); product of three diameters,

1.9% ($n = 5$); IUH location in relation to the gestational sac at first scan, 8.6% ($n = 23$); IUH content on first scan, 18.3% ($n = 49$); IUH diameter/MSD ratio, 7.1% ($n = 19$); location of IUH in relation to the placenta, 6.7% ($n = 18$); and retroplacental status, 10.8% ($n = 29$). The later missing numbers are mostly explained by the absence of available MSD measurements.

There were no missing values for the majority of pregnancy outcomes, except for: LBW, which had < 3% ($n = 20$) missing values, mostly owing to the birth weight being unavailable; PPH and MOH, which had 5% ($n = 39$) missing data each, owing to the absence of blood-loss quantification; meconium, which had < 1% ($n = 6$) missing data; and Apgar score, which had < 2% ($n = 16$) missing data for 1-min Apgar score and < 3% ($n = 18$) for 5-min Apgar score.

Analyses of antenatal complications were performed on all pregnancies that were viable at the end of the first trimester. Delivery and neonatal complication analysis was performed on pregnancies resulting in a live birth. Analysis of PPH and MOH were performed on a subset of patients excluding those who experienced traumatic PPH ($n = 53$) and traumatic MOH ($n = 10$). Results were not corrected for multiple comparisons owing to the exploratory nature of this study.

RESULTS

Of 1242 consecutive women with a singleton pregnancy seen during the study period, 1003 were recruited (Figure 2). Following the exclusion of patients who underwent termination of pregnancy ($n = 20$), withdrew from the study ($n = 5$) or were lost to follow-up ($n = 32$), 946 women were included in the final analysis. Of these, 268 (28.3%) had an IUH in the first trimester (Figure 2). Table 1 shows the patient characteristics of our cohort according to whether IUH was diagnosed in the first trimester. Participants with an IUH, compared with those without, were more likely to experience vaginal bleeding in the first trimester ($P < 0.0001$) and have a higher bleeding score ($P < 0.0001$). However, there was no difference between the two groups with respect to the presence of pelvic pain ($P = 0.896$) and the maximum pain score reported ($P = 0.826$) (Table 1). Table 2 shows the incidence of individual adverse pregnancy outcomes in the whole cohort and in women with and those without IUH.

There was no association between the presence of IUH and first-trimester miscarriage (adjusted OR (aOR), 0.81 (95% CI, 0.44–1.50)) (Figure 3a, Table 3). This finding was independent of the presence of pelvic pain or vaginal bleeding (Table 3) and adjustment for gestational age at

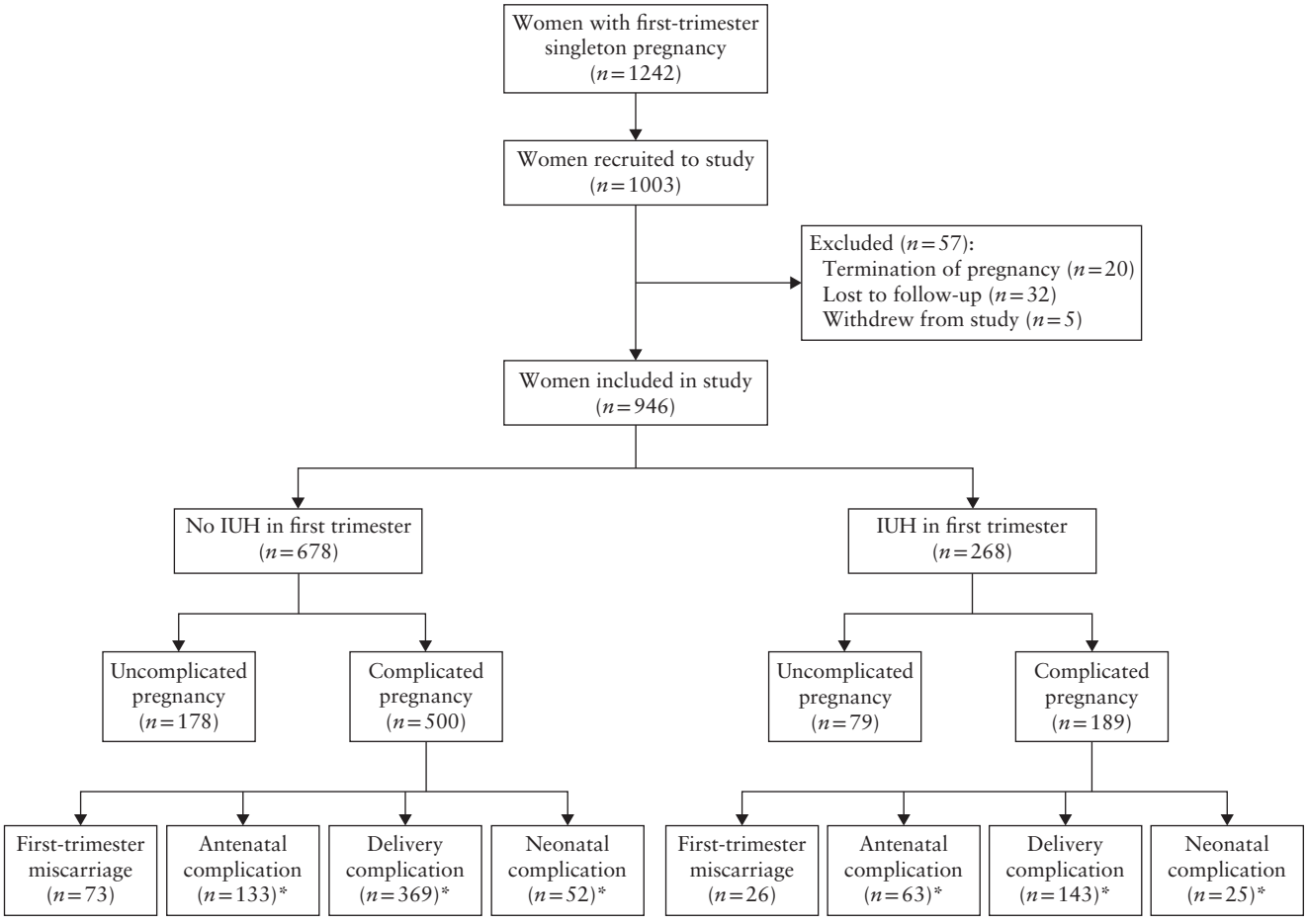

Figure 2 Flowchart showing inclusion in study of women with singleton pregnancy, and incidence of pregnancy complications according to whether intrauterine hematoma (IUH) was seen on first-trimester ultrasound. *Some pregnancies experienced more than one type of complication.

Table 1 Background and clinical characteristics of 946 women with singleton pregnancy included in study cohort, according to whether they were diagnosed with intrauterine hematoma (IUH) in first trimester

Characteristic	*IUH (n = 268)*	*No IUH (n = 678)*	P
Maternal age (years)	32 (17–48)	33 (17–48)	0.1165
Maternal ethnicity			0.5135
White	182 (67.9)	450 (66.4)	
Asian	27 (10.1)	91 (13.4)	
Black	32 (11.9)	82 (12.1)	
Mixed	8 (3.0)	20 (2.9)	
Other	19 (7.1)	34 (5.0)	
Unknown	0 (0.0)	1 (0.1)	
BMI (kg/m^2)*	23.4 (17.4–44.5)	24.1 (15.8–53.9)	0.0218
Parity			0.0442
0	135 (50.4)	350 (51.6)	
1	93 (34.7)	231 (34.1)	
2	34 (12.7)	59 (8.7)	
3	4 (1.5)	20 (2.9)	
≥ 4	1 (0.4)	18 (2.7)	
Unknown	1 (0.4)	0 (0.0)	
Previous first-trimester miscarriage			0.0134
None	163 (60.8)	346 (51.0)	
1	73 (27.2)	198 (29.2)	
2	24 (9.0)	86 (12.7)	
3	4 (1.5)	29 (4.3)	
≥ 4	3 (1.1)	19 (2.8)	
Unknown	1 (0.4)	0 (0.0)	
Previous second-trimester miscarriage			0.2835
None	261 (97.4)	649 (95.7)	
1	6 (2.2)	27 (4.0)	
≥ 2	0 (0.0)	2 (0.3)	
Unknown	1 (0.4)	0 (0.0)	
Cervical surgery			0.5404
No	255 (95.1)	654 (96.5)	
Yes	12 (4.5)	23 (3.4)	
Unknown	1 (0.4)	1 (0.1)	
Smoker			0.8005
No	231 (86.2)	592 (87.3)	
Yes	33 (12.3)	78 (11.5)	
Unknown	4 (1.5)	8 (1.2)	
Pregnancy outcome			0.6401
Live birth	235 (87.7)	594 (87.6)	
First-trimester miscarriage	26 (9.7)	73 (10.8)	
Second-trimester miscarriage	6 (2.2)	8 (1.2)	
Stillbirth	1 (0.4)	3 (0.4)	
GA at birth (days)†	278 (181–295)	276 (170–302)	0.0801
Birth weight (g)‡	3340 (850–4640)	3340 (700–4830)	0.5527
First-trimester vaginal bleeding			< 0.0001
Yes	199 (74.3)	350 (51.6)	
No	69 (25.7)	328 (48.4)	
Highest vaginal-bleeding score§			< 0.0001
0	67 (25.0)	323 (47.6)	
1	75 (28.0)	195 (28.8)	
2	67 (25.0)	105 (15.5)	
3	31 (11.6)	27 (4.0)	
4	27 (10.1)	24 (3.5)	
Unknown	1 (0.4)	4 (0.6)	
First-trimester pelvic pain			0.896
Yes	164 (61.2)	418 (61.7)	
No	104 (38.8)	260 (38.3)	
Highest pelvic-pain score¶			0.826
0	105 (39.2)	265 (39.1)	
1–2	36 (13.4)	77 (11.4)	
3–4	39 (14.6)	86 (12.7)	
5–6	38 (14.2)	103 (15.2)	
7–8	30 (11.2)	91 (13.4)	
9–10	19 (7.1)	52 (7.7)	
Unknown	1 (0.4)	4 (0.6)	

Data are given as median (range) or *n* (%). Data are missing for: *Nine cases with and 22 without IUH; †one case with and three without IUH (only cases with live birth were considered); ‡three cases without IUH (only cases with live birth were considered). §Assessed on numerical scale of 0 (no bleeding) to 4 (heavy bleeding) based on modified pictorial blood assessment chart[19]. ¶Assessed using visual analog scale from 0 (no pain) to 10 (maximum pain)[20]. BMI, body mass index; GA, gestational age.

Table 2 Incidence of pregnancy complications in 946 women with singleton pregnancy, overall and according to whether they were diagnosed with intrauterine hematoma (IUH) in first trimester

Complication	*All women (n = 946)*	*IUH (n = 268)*	*No IUH (n = 678)*
Miscarriage following diagnosis of IUH on initial first-trimester scan*	99/946 (10.5)	13/146 (8.9)	86/800 (10.7)
Miscarriage following diagnosis of IUH at any time in first trimester	99/946 (10.5)	26/268 (9.7)	73/678 (10.8)
Antenatal complications†	196/827 (23.7)	63/236 (26.7)	133/591 (22.5)
APH and placental abruption	57/847 (6.7)	19/242 (7.9)	38/605 (6.3)
Low birth weight	51/827 (6.2)	18/236 (7.6)	33/591 (5.6)
Preterm birth	47/847 (5.5)	20/242 (8.3)	27/605 (4.5)
Gestational diabetes	44/847 (5.2)	13/242 (5.4)	31/605 (5.1)
Pre-eclampsia	25/847 (3.0)	7/242 (2.9)	18/605 (3.0)
PPROM	23/847 (2.7)	9/242 (3.7)	14/605 (2.3)
Fetal growth restriction	21/847 (2.5)	10/242 (4.1)	11/605 (1.8)
Pregnancy-induced hypertension	16/847 (1.9)	4/242 (1.7)	12/605 (2.0)
Second-trimester miscarriage	14/847 (1.7)	6/242 (2.5)	8/605 (1.3)
Stillbirth	4/847 (0.5)	1/242 (0.4)	3/605 (0.5)
Gestational proteinuria	4/847 (0.5)	0/242 (0.0)	4/605 (0.7)
Delivery complications‡	512/789 (64.9)	143/227 (63.0)	369/562 (65.7)
Operative delivery	411/829 (49.6)	101/235 (43.0)	310/594 (52.2)
Operative delivery for fetal distress	153/685 (22.3)	36/196 (18.4)	117/489 (23.9)
Postpartum hemorrhage§	159/727 (21.9)	45/208 (21.6)	114/519 (22.0)
Meconium staining	92/823 (11.2)	28/234 (12.0)	64/589 (10.9)
Sepsis in labor	41/829 (4.9)	13/235 (5.5)	28/594 (4.7)
Massive obstetric hemorrhage§	33/727 (4.5)	11/208 (5.3)	22/519 (4.2)
Neonatal complications‡	77/810 (9.5)	25/230 (10.9)	52/580 (9.0)
1-min Apgar score < 7	59/813 (7.3)	18/232 (7.8)	41/581 (7.1)
5-min Apgar score < 7	7/811 (0.9)	1/231 (0.4)	6/580 (1.0)
Admission to neonatal unit	37/828 (4.5)	12/234 (5.1)	25/594 (4.2)

Data are given as *n*/*N* (%). Analysis performed only in cases with complete data. *146 pregnancies had IUH on initial scan. †Antenatal complications are reported for pregnancies that were viable at end of first trimester ($n = 847$). ‡Delivery and neonatal complications are reported for pregnancies with live birth ($n = 829$). §Excluding cases with trauma. APH, antepartum hemorrhage; PPROM, preterm prelabor rupture of membranes.

first scan (Table S1). If IUH was present, its content, absolute size and location did not impact on the risk of miscarriage (Table S1).

There was no association between the presence of IUH in the first trimester and overall antenatal, delivery or neonatal complications (Figure 3b, Table 3). There was a general trend towards an association between the presence of IUH and individual antenatal complications, with PTB reaching significance (aOR, 1.94 (95% CI, 1.07–3.52)) (Figure 3c). There was also an association between the presence of IUH and PTB and PPROM when these two outcomes were grouped together (aOR, 1.84 (95% CI, 1.03–3.28)). This association was independent of the presence or absence of vaginal bleeding or pelvic pain in the first trimester (Table 3). No association was seen between the presence of an IUH and individual delivery and neonatal complications (Table 3).

When IUH was present in the first trimester, there was no association between the size, content or location of the IUH in relation to the gestational sac and overall antenatal, delivery and neonatal complications (Tables S2–S4). Retroplacental hematomas were associated with a greater risk of antenatal complications ($P = 0.0395$) but not delivery or neonatal complications. Persistence of the IUH for more than 10 days ($n = 66$) was not associated with an increased risk of overall antenatal, delivery or neonatal complications (Tables S2–S4).

DISCUSSION

Our findings show that the presence of an IUH in the first trimester of pregnancy was associated with an increased risk of PTB, but IUH was not associated with an increased likelihood of first-trimester miscarriage. These findings were independent of the presence or absence of vaginal bleeding or pelvic pain in the first trimester. In addition, the size and content of the IUH did not affect pregnancy outcomes; however, the presence of a retroplacental IUH appeared to be associated with an increased risk of overall antenatal complications. Although associations between presence of IUH and other individual antenatal complications were observed, these did not reach significance.

The incidence of IUH in our study was greater than that previously reported[11,12]. This is probably the result of using more advanced ultrasound equipment that provided higher-quality images and the fact that recruitment was conducted in a dedicated early-pregnancy assessment unit. Our finding that there is an overall increased risk of PTB in pregnancies with first-trimester IUH is consistent with those of other studies[11], including a systematic review[9]. Another systematic review reported that retroplacental location and persistence of the hematoma are highly predictive of adverse outcomes[12]. In our study, IUH size, location, sonographic appearance and persistence did not have any significant association with pregnancy

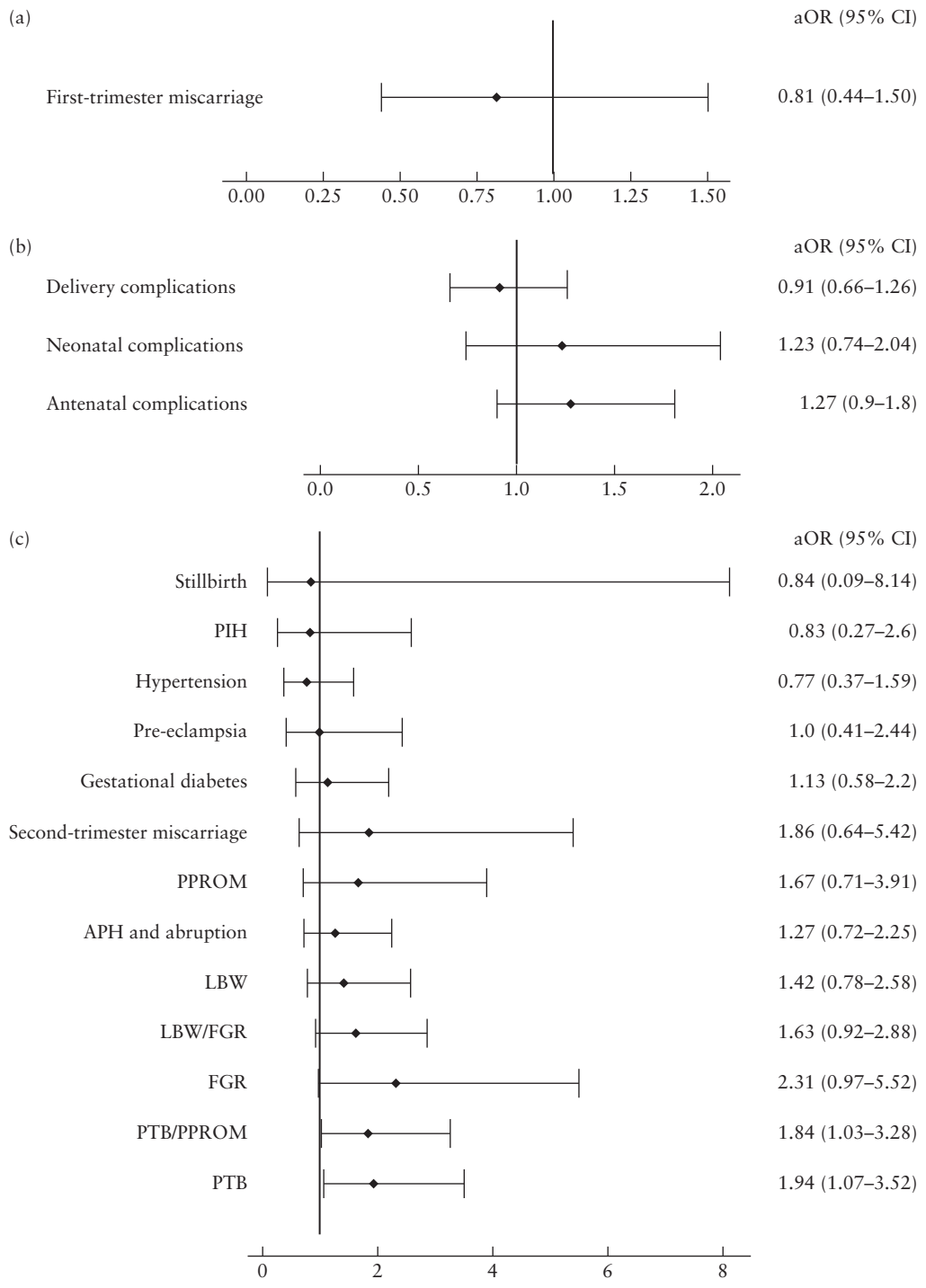

Figure 3 Forest plots showing association between presence of intrauterine hematoma (IUH) on initial first-trimester scan and first-trimester miscarriage (a), and between presence of IUH at any point in first trimester and overall antenatal, delivery and neonatal complications (b) and individual antenatal complications (c). aOR, odds ratio adjusted for maternal age; APH, antepartum hemorrhage; FGR, fetal growth restriction; LBW, low birth weight; PIH, pregnancy-induced hypertension; PPROM, preterm prelabor rupture of membranes; PTB, preterm birth.

complications. This may be because of the limited number of the various types of IUH in pregnancies with an adverse outcome.

A number of mechanisms have been proposed to explain how IUH may cause PTB, such as the hypothesis that IUH may hamper implantation and development of the placenta[34]. A retrospective cohort study evaluating the relationship between IUH, sonographic cervical length and PTB, found an association between PTB and IUH even when adjusting for cervical length, the presence of vaginal bleeding and use of progesterone[35]. This suggests that another mechanism for PTB, other than cervical shortening, exists in women with an IUH. A candidate mechanism is subclinical infection. Seki *et al.*[36]. found that chorioamnionitis was more common in women with a persistent IUH.

Table 3 Association of presence of intrauterine hematoma adjusted for maternal age (MA), and MA plus presence of bleeding or pelvic pain in first trimester, with individual antenatal, delivery and neonatal complications and first-trimester miscarriage

	Adjusted for:		
Complication	*MA*	*MA + first-trimester vaginal bleeding*	*MA + first-trimester pelvic pain*
Antenatal complication	1.27 (0.90–1.80)	1.19 (0.84–1.71)	1.27 (0.90–1.81)
APH and placental abruption	1.27 (0.72–2.25)	1.36 (0.76–2.45)	1.28 (0.72–2.27)
Low birth weight	1.42 (0.78–2.58)	1.38 (0.75–2.54)	1.42 (0.78–2.58)
Preterm birth	1.94 (1.07–3.52)	1.93 (1.04–3.56)	1.95 (1.07–3.55)
Gestational diabetes	1.13 (0.58–2.2)	1.04 (0.53–2.07)	1.11 (0.57–2.17)
Pre-eclampsia	1.00 (0.41–2.44)	0.91 (0.37–2.24)	1.00 (0.41–2.44)
PPROM	1.67 (0.71–3.91)	1.74 (0.72–4.18)	1.67 (0.71–3.92)
Fetal growth restriction	2.31 (0.97–5.52)	2.11 (0.87–5.13)	2.31 (0.97–5.52)
Pregnancy-induced hypertension	0.83 (0.27–2.60)	0.71 (0.22–2.24)	0.84 (0.27–2.63)
Second-trimester miscarriage	1.86 (0.64–5.42)	1.68 (0.56–5.02)	1.83 (0.63–5.35)
Gestational proteinuria	N/A	N/A	N/A
Stillbirth	0.84 (0.09–8.14)	1.59 (0.16–15.72)	0.85 (0.09–8.19)
Low birth weight or fetal growth restriction	1.63 (0.92–2.88)	1.57 (0.88–2.82)	1.63 (0.92–2.87)
Hypertension	0.77 (0.37–1.59)	0.69 (0.33–1.44)	0.77 (0.37–1.58)
Preterm birth or PPROM	1.84 (1.03–3.28)	1.84 (1.02–3.33)	1.85 (1.04–3.30)
Delivery complication	0.91 (0.66–1.26)	0.86 (0.62–1.20)	0.91 (0.66–1.26)
Operative delivery	0.71 (0.52–0.97)	0.67 (0.49–0.91)	0.71 (0.52–0.97)
Operative delivery for fetal distress	0.73 (0.48–1.12)	0.69 (0.45–1.06)	0.74 (0.48–1.12)
Postpartum hemorrhage*	1.00 (0.67–1.47)	0.96 (0.64–1.43)	0.99 (0.67–1.47)
Meconium staining	1.11 (0.69–1.78)	1.18 (0.73–1.92)	1.11 (0.69–1.78)
Sepsis in labor	1.21 (0.61–2.38)	1.19 (0.59–2.39)	1.20 (0.61–2.36)
Massive obstetric hemorrhage*	1.35 (0.64–2.85)	1.30 (0.60–2.81)	1.34 (0.63–2.83)
Neonatal complication	1.23 (0.74–2.04)	1.09 (0.65–1.83)	1.23 (0.74–2.04)
1-min Apgar score < 7	1.12 (0.63–1.99)	1.02 (0.56–1.83)	1.12 (0.63–1.99)
5-min Apgar score < 7	0.41 (0.05–3.43)	0.31 (0.04–2.63)	0.41 (0.05–3.44)
Admission to neonatal unit	1.18 (0.58–2.41)	1.09 (0.53–2.25)	1.20 (0.59–2.45)
First-trimester miscarriage†	0.81 (0.44–1.50)	0.81 (0.43–1.52)	0.88 (0.44–1.51)

Data are given as odds ratios (OR) (95% CI). *Excluding cases with trauma. †Adjusted for MA, MA plus vaginal bleeding at initial first-trimester scan, and MA plus pelvic pain at initial first-trimester scan. APH, antepartum hemorrhage; N/A, no OR available because of complete separation owing to small number of cases; PPROM, preterm prelabor rupture of membranes.

The findings of studies assessing the association between first-trimester miscarriage and IUH are conflicting, with some showing no increased risk[1,7] and others an increased risk of miscarriage[5,6,37]. Previous studies have also suggested that the presence of IUH before 7 or 8 weeks' gestation is associated with a higher risk of miscarriage[8,38]. Our findings did not show an increased risk of miscarriage in pregnancies with an IUH, even when adjusting for the presence of vaginal bleeding, pelvic pain or gestational age at the time of diagnosis. When present, the size, location and content of the IUH did not impact on the risk of miscarriage. This finding is similar to that of a recent meta-analysis aiming to assess predictors of miscarriage in viable pregnancy, which also found that IUH was not associated with miscarriage[39].

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 thoroughly assessed in a prospective manner. This allowed us to reliably explore the association between IUH, clinical symptoms of pelvic pain and/or vaginal bleeding and pregnancy complications.

There are some limitations of the study that need to be acknowledged. Even though we recruited more than 1000 women, the relatively small incidence of each individual adverse outcome in our cohort made it difficult to establish statistically significant associations. Most of our 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[40], whereas in our population the incidence was 5.7%. During follow-up, an unavoidable bias common to all observational studies in this field is that some participants received treatment to prevent an adverse outcome as part of their standard clinical care. For example, cervical cerclage was placed in 18 women in the study, which may have led to fewer preterm deliveries in our cohort, so the overall impact of IUH may have been underestimated. It is also possible that we underestimated the prevalence of IUH in our cohort, as hematomas could have developed and resolved in the time period between the serial ultrasound examinations. Furthermore IUH may have been present and persisted prior to recruitment but resolved by the time of recruitment to the study.

In conclusion, our study shows that women with an IUH in the first trimester are at increased risk of PTB. These pregnancies should potentially be managed as high-risk pregnancies and undergo additional antenatal surveillance. The presence of an IUH was not associated with an increased risk of first-trimester miscarriage irrespective of the location or size of the hematoma, and women should therefore be counseled accordingly.

Future research should focus on identifying subgroups of women who are most at risk of PTB. In addition, further work is required to address the possible mechanisms by which IUH may be associated with PTB.

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SUPPORTING INFORMATION ON THE INTERNET

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

Tables S1–S4 Association of presence and features of intrauterine hematoma (IUH) assessed on initial first-trimester scan with risk of first-trimester miscarriage (Table S1), antenatal complications (Table S2), delivery complications (Table S3) and neonatal complications (Table S4)