Understanding care-seeking and subsequent pregnancy loss in the second trimester of pregnancy - A multicentre audit

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On behalf of the Tommy's Second Trimester Pregnancy Loss Group

Abstract

Words: 310

Objective:
This study aimed to increase understanding of the signs and symptoms that lead pregnant people to seek hospital care in the second trimester of pregnancy. In addition, we aimed to describe management and follow up, to record pregnancy outcomes, and to gather information about symptoms and signs related to second trimester pregnancy loss.

Methods:
This prospective audit in seven geographically dispersed sites across the UK collected data over two weeks (7th March–20th March 2022 inclusive) on all unscheduled secondary care attendances between 14 and 21 completed weeks' gestation. Data on the number of patients booked at each unit within this 8-week second trimester gestational age range were collected. Descriptive analyses identified common patterns and associations with second trimester pregnancy loss.

Results:
Of 8,585 patients in the second trimester of their pregnancy, 283 presented acutely at least once over the two-week period (3.3%) Of these, 19 patients experienced a second trimester pregnancy loss (7% of those presenting in the second trimester). There were a broad range of presentations and diagnoses and a lack of standardisation of investigation and management of patients. Logistic regression identified associations between previous first trimester miscarriage (OR 2.95 95% CI 1.15, 7.60), previous first trimester termination of pregnancy (OR 7.00 95% CI 2.45, 19.98), and presentation with increased vaginal discharge (OR 3.82 CI 1.24, 11.7) with second trimester pregnancy loss.

Conclusions:
This study has identified that a significant number of pregnant people attend hospital and reattend in the second trimester of pregnancy, with a worrying lack of standardisation of both investigation and management, and a broad range of presenting symptoms and diagnoses. Patients who present in the second trimester have a high rate of second trimester pregnancy loss and the preliminary associations identified would benefit from further research in a larger scale study.

Keywords
Stillbirth; Perinatal Death; Pregnancy Outcome; Second Trimester pregnancy loss; Vaginal discharge.

1. Introduction:

Over the last decade stillbirth has been a focus for research with two Lancet series highlighting the considerable impact of stillbirth on families and momentum to improve outcomes. This Increased focus and research into stillbirth has led to improvements in care in the UK, one example of this being the dropping stillbirth rate which fell by over 20% between 2013 and 2022.[1] However research around baby loss in the second (or mid) trimester of pregnancy, usually defined as a pregnancy loss between 14 and 24 completed weeks' gestation,[2] has not progressed to the same degree.

There is a paucity of research assessing the frequency of second trimester pregnancy loss. A US study estimated a rate of 1-5% for spontaneous loss between 14-19 weeks, dropping to 0.3% between 20-27 weeks.[3] The lack of data about the incidence of second trimester pregnancy loss prevents effective service planning and delivery of both clinical and bereavement care. An additional challenge is that patients experiencing second trimester pregnancy loss may "fall between" gynaecology and maternity services. This is often due to spontaneous baby loss occurring at less than 24 weeks' gestation being defined in the UK as a miscarriage[4], a condition generally managed within gynaecology services. However, patients experience of baby loss at this gestation are more aligned with stillbirth; this is reflected in qualitative studies which have highlighted significant issues around consent, choice, physical care, and psychological care[10 11] and a lack of legal recognition of baby loss in the second trimester.[11]

Efforts to identify patients at high risk of experiencing second trimester pregnancy loss are impaired by a paucity of evidence around the causes of, and symptoms preceding, loss. In some cases there are clear associations between specific conditions and second trimester loss, such as preterm prelabour rupture of membranes (PPROM). A national prospective observational study investigating PPROM before 23 weeks found significant association with second trimester pregnancy loss.[23] This is consistent with the significant risk of chorioamnionitis posed by PPROM; chorioamnionitis being the most common cause of second trimester pregnancy loss.[24] However not all presentations are as overt, and pregnant people experiencing second trimester pregnancy loss may present from 14 weeks with a diverse range of symptoms reflecting the multiple different fetal and maternal aetiologies.[5] Multiple presentations are mentioned in narrative reviews including abdominal pain, vaginal bleeding, vaginal discharge and open cervix on examination.[7 8 9] None of these have been demonstrated to be sufficiently sensitive nor specific for use in clinical practice and approximately 50-60% of second trimester losses remain unexplained.[6]

To broaden understanding of factors associated with hospital presentation in the second trimester of pregnancy we undertook a multi-centre audit across the UK. We aimed to extend knowledge in the field of second trimester care by describing the management and follow up of those who presented, to record the pregnancy outcome(s), and to gather preliminary information about symptoms and signs related to second trimester pregnancy loss.

2. Methods:

A prospective audit was conducted in seven tertiary UK maternity units in Birmingham, Edinburgh, Leeds, London (three units) and Manchester, between 7th and 20th March 2022

inclusive. Service users' data were included if they presented to the hospital with an unplanned attendance between 14 weeks' and 21 weeks 6 days' gestation. The lower threshold was chosen to be 21+6 rather than the usual 24 completed weeks following expert opinion and new UK guidance that resuscitation could be offered for neonates born from 22 weeks' gestation[22]which may have altered the management of the pregnancy. Data were recorded for all Pregnant people presenting to Accident and Emergency (A&E), Early Pregnancy Assessment Units (EPAU), Emergency Gynaecology Units (EGU), Maternity Triage and Antenatal Assessment Units (AAU). Examples of such presentations include: acute attendances to the A&E department with any presentation; onward referrals following routine appointments to Maternity Triage or AAU with acute problems such as hypertension, bleeding or no fetal heart beat identified on scan; acute attendances to Maternity Triage with problems such as pain and bleeding including those who were un-booked or were rapidly transferred to the labour ward; acute attendances to EPAU and EGU with symptoms such as pain, bleeding or no FH identified on early scan (<16 weeks).

Data were collected prospectively from records by local clinicians and entered into a secure Research Electronic Data Capture (REDcap) data capture form. Clinicians followed up each eligible attendee to ascertain whether their pregnancy was still ongoing at 22 completed weeks. Re-attendances were documented within the original attendance noting whether their re-attendance was for the same or different complaint, thereby avoiding duplicate data entry. All data entered were anonymised with individual participants given an anonymous database number.

Data collected included maternal age, gravidity, parity, history of pregnancy loss, date and time of attendance, gestation, location seen, grade and profession of healthcare staff attending, presenting complaint, examination, investigations, maternal risk factors for second trimester loss, presumed diagnosis, management, follow up, and pregnancy outcome at 22 weeks.

Data on the number of patients booked at each unit within this eight-week second trimester gestational age range was collected to provide a denominator for the total number of potential attendances.

2.1 Statistical analysis:

Data were analysed using STATA software (Version 14.0, STATA Corp, College Station, TX). Descriptive statistics were performed to summarize the characteristics of the cohort. Possible association with second trimester pregnancy loss was assessed using two-way frequency tables using Pearson's Chi-Squared for larger sample sizes and Fisher's Exact Test for smaller samples (<6). We assessed individual variables (n=46) for an association with second trimester pregnancy loss to see if there was any statistically significant association in clinical presentation, diagnosis, or maternal characteristics. Variables with a larger data spread, such as parity and maternal age, were grouped prior to logistic regression. Logistic regression was conducted to estimate the odds for variables on the risk of second trimester pregnancy loss. Odds ratios (OR) with 95% confidence interval (CI) were reported. A *p*-value of 0.05 or less was considered statistically significant.

3. Results:

Across the seven sites there were 8,585 patients between 14 weeks and 21 weeks 6 days pregnant during our audit period. Of this cohort, 283 patients had unplanned attendances during the audit period (3.3% of the total population within this second trimester gestational age range, 95% CI 2.9-3.7%) (see Table 1). Of these 14 had incomplete data entry with no documented pregnancy outcome and were excluded from statistical analysis assessing association with second trimester pregnancy loss.. Of the remaining 269 patients with complete data, 250 were still pregnant at 22 weeks' gestation, 19 experienced a second trimester pregnancy loss. The incidence of second trimester pregnancy loss among patients presenting to maternity services in the second trimester was 7%. Based on this total cohort of patients pregnant at this gestation, the rate of second trimester pregnancy loss across all seven sites was 0.22%.

Most pregnant people presented only once during the second trimester (73%) but seventy-two (27%) presented to maternity services more than once during this time. Of the 19 Pregnant people who experienced a second trimester pregnancy loss, 8 (42%) presented to maternity services on more than one occasion.

Site	**Number of patients with an unplanned hospital attendance in the second trimester**	**Total number of patients in the second trimester during the 2-week audit period**	**Percentage of patients with an unplanned hospital attendance**
Edinburgh	41	1537	2.7%
Kings	11	775	1.4%
GSTT	21	1194	1.8%
Leeds	75	1719	4.7%
Birmingham	38	1159	3.2%
UCLH	42	1015	4.1%
Manchester	55	1186	4.6%

Table 1 – Number of presenting Pregnant people and total number of pregnancies in the second trimester by site. GSTT = Guys and St Thomas's Hospital, UCLH – University College Hospital, London.

The age of participants was distributed across the normal reproductive lifespan (median age 30 years, range 15-43, Table 2). The median parity was 1; 38% of attendees were nulliparous. The median gestation for first presentation was 17 weeks and 6 days with a range between 14 weeks and 21 weeks and 6 days. Pregnant people presented to a range of secondary care services (Table 2) the commonest of which was Maternity Triage (an assessment area for pregnant people with acute obstetric complications) with 75% of presentations. Of those who experienced a second trimester pregnancy loss 31% (6) pregnant people were seen in the Early Pregnancy Assessment Unit and 68% (13) were seen in Maternity Triage. None of those who experienced a second trimester pregnancy loss presented to the Accident and Emergency Department, Emergency Gynaecology Unit or Antenatal Admissions Unit.

Demographic	**Median (range) or n (%)**	**Data for those experiencing loss**
Maternal age	30 (15-43)	32 (24-40)

Gravidity	2 (1-14)	3 (1-9)
Parity	1 (0-5)	1 (0-3)
Gestation at presentation	17+6 (14+0-21+6)	17+1 (14+2-21+5)
Service / Location of presentation	**Number presenting at this service**	**Data for those experiencing loss**
Adult Emergency Department	3 (1%)	0 (0%)
Early Pregnancy Assessment Unit	20 (7.4%)	6 (32%)
Emergency Gynaecology Unit	14 (5.2%)	0 (0%)
Maternity triage	201 (75%)	13 (68%)
Antenatal Assessment unit	8 (2.9%)	0 (0%)

Table 2 – Characteristics of Pregnant people presenting in the second trimester of pregnancy and the location/service they presented to.

The location in which pregnant people were seen varied by gestation although the largest proportion in both the 14-17 week and 18-21 week gestation range were seen in Maternity Triage (91 [66%] and 114 [95%] respectively). Pregnant people were seen most frequently by Midwives (66% n=179), 47% by Specialty Trainee (ST) doctors with 1-2 years of Obstetrics & Gynaecology (O&G) experience (n=127), 20% by ST doctors with 3-7 years' O&G experience (n=53), 6% by Consultants (n=18) and 9.6% by Nurses and Advanced Nurse Practitioners (n=26). 46% (n=126) were seen by more than one type of clinician.

Pregnant people presented with a variety of symptoms that could be associated with a second trimester loss (Table 3), the most common being abdominal pain comprising 43% of those who presented, followed by vaginal bleeding in 24%. Other presenting symptoms included: chest pain, shortness of breath (SOB), skin rash and other maternal medical conditions. 28% (76) presented with more than one symptom.

Presenting symptom	**Number of patients presenting with this symptom n (%)**	**Number of pregnancy losses with this presentation n (%)**
Vaginal bleeding	68 (24%)	8 (31%)
Fever/Unwell	13 (4%)	1 (4%)
Abdominal pain	122 (43%)	7 (27%)
Pelvic Pressure	6 (2%)	1 (4%)
Reduced movements	23 (8%)	0 (0%)
Vaginal Discharge	26 (9%)	5 (19%)
Nause and vomiting	28 (10%)	0 (0%)
Headache	16 (5%)	0 (0%)
Other (including chest pain, SOB, skin rashes)	72 (25%)	4 (15%)

Table 3 – Presenting symptoms, number of presentations, number of second trimester pregnancy losses with this presentation

Pregnant people presenting in the second trimester had a range of investigations which were not mutually exclusive. 83% had observations recorded and a modified early warning score

(MEWS) calculated (n=235), 63% had abdominal palpation (n=181), 41% had a vaginal speculum examination (n=118), 44% had a urine dipstick (n=126),
15% had an ultrasound scan (n=45), 14% had blood tests, most commonly a full blood count or C-Reactive Protein (n=41), 30% had other investigations (n=86) such as chest X-rays, venous Doppler of the lower limb and other non-obstetric tests. No fetal fibronectin (fFN) tests were performed. Whilst cumulatively 63% (n=180) of patients presented with either vaginal bleeding, discharge or abdominal pain only 60% (n=109) of these had a speculum examination.

There were a broad range of working diagnoses (see Figure 1), notably the commonest diagnosis was 'none' representing 24% of attendances, 5% were given a diagnosis of fetal death/loss. Due to limitations with data collection some of the diagnostic categories are non-specific. Cervical conditions included ectropion, cervical polyp or suspicious lesions. Infection includes all sources of infection including genital tract, urinary, respiratory etc. Those with uncomplicated RFM had reassuring monitoring. Urogynaecology conditions included prolapse, urinary incontinence and retention. The working diagnosis was documented at discharge by midwifery, nursing or medical staff.

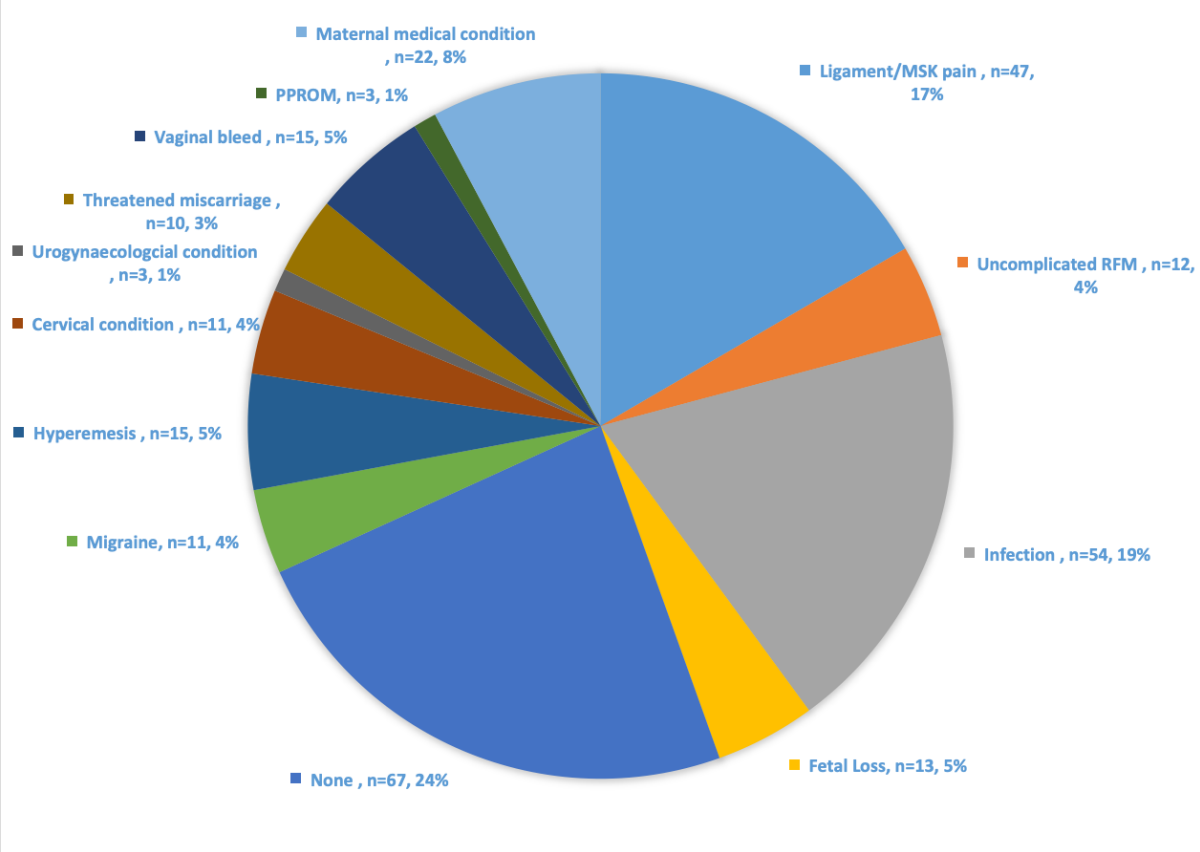

Figure 1 – Working 'diagnosis' of those who presented in the second trimester.

Of the patients who were subsequently diagnosed with a second trimester pregnancy loss, the commonest presenting complaint was vaginal bleeding (31%), followed by abdominal pain (27%), vaginal discharge (19%) or other (15%), less common were fever (4%) and pelvic pressure (4%).

There were no statistically significant associations between maternal age, gravidity or parity and pregnancy loss identified in this sample. A history of previous first trimester miscarriage (OR 2.95 95% CI 1.15, 7.60) and previous first trimester termination of pregnancy (TOP) (OR 7.00 95% CI 2.45, 19.98) were significantly associated with second trimester pregnancy loss (see Table 4). Notably, history of previous second trimester pregnancy loss approached statistical significance (OR 4.47 95% CI 0.84, 23.85).

History of:	Ongoing pregnancy (n=250)	Pregnancy loss (n=19)	Odds Ratio	95% Confidence Interval	P value
1st trimester miscarriage	***64 (25.6)***	***10 (52.6)***	***2.95***	***1.15, 7.60***	***0.03***
2nd trimester pregnancy loss	6 (2.4)	2 (10.5)	4.47	0.84, 23.85	0.08
1st trimester TOP	***18 (7.2)***	***7 (36.8)***	***7***	***2.45, 19.98***	***<0.001***
2nd trimester TOP	2 (0.8)	1 (5.2)	6.44	0.57, 74.52	0.14

Table 4 – Maternal risk factors associated with second trimester pregnancy loss. Percentages are shown in parentheses

Presentation with vaginal discharge/loss of mucous plug (OR 3.82 CI 1.24, 11.7,) was associated with second trimester pregnancy loss (p=0.019). Of those who presented with vaginal discharge/loss of mucous plug (n=26, 9.6% total presentations), 3 (11.5%) had a final diagnosis of preterm prelabour rupture of membranes. Of these 3 pregnant people, 2 were still pregnant at 22 weeks' gestation with one experiencing second trimester pregnancy loss. No other presenting complaints were found to be associated with second trimester pregnancy loss (see Table 5). There was no association between presentations of reduced fetal movements and second trimester pregnancy loss.

Symptom	Ongoing pregnancy (n=250)	Pregnancy loss (n=19)	Odds Ratio	95% Confidence Interval	P value
PV spotting/bleeding	57 (22.8)	8 (42.1)	2.25	0.86, 5.88	0.096
Vaginal discharge/ mucus plug lost	***20 (8)***	***5 (26.3)***	***3.82***	***1.24, 11.7***	***0.019***
Abdo pain/contractions	102 (40.8)	7 (36.8)	0.75	0.28, 1.98	0.57
Sensation of pressure	6 (2.4)	1 (5)	2.11	0.24, 18.5	0.50
Fever/malaise	10 (4)	1 (5)	1.24	0.15, 10.2	0.84
Other symptoms	65 (26)	4 (21)	0.69	0.22, 2.16	0.53

Table 5 – Presenting symptoms associated with second trimester pregnancy loss. Percentages are shown in parentheses

4. Discussion:

4.1 Main findings:

This multicentre audit demonstrated that 3.3% of pregnant people presented to secondary care in the second trimester of pregnancy-with unplanned hospital attendance. There were a wide range of symptoms with the most common being abdominal pain.

Of those who presented acutely in the second trimester, 7% experienced a second trimester loss, representing a population rate of approximately 0.22% which is consistent with estimates of between 0.3% to 1-5% dependent on gestation.[3] Our audit did not include those who presented with a second trimester loss at a planned contact, so this figure is likely an underestimate.

Our data also suggest that those pregnant people with a previous first trimester miscarriage, a previous first trimester termination of pregnancy, or those who present with loss of mucous plug/increased vaginal discharge had a higher incidence of second trimester pregnancy loss.

4.2 Strengths and limitations:

This study was strengthened by its multicentre approach with centres geographically distributed across the UK allowing a diverse population to be included, making results more generalisable to the UK population. Importantly, this study also demonstrates the feasibility of data collection for a larger study of this nature, and provides valuable preliminary data regarding factors potentially associated with second trimester loss to inform future work.

However, due to the constraints of an audit approach we were not able to record personal or sensitive data, and therefore were not able to obtain data on ethnicity or postcode (to facilitate calculation of area level deprivation indices) meaning that the impact of health inequalities in second trimester pregnancy loss cannot be reported here. Furthermore, this was a snapshot of practice within the participating units which may not be representative of presentations in other services or at different times of year (for example it was not undertaken at a time of high rates of seasonal influenza). In addition, the audit was undertaken at sites who expressed an interest in participation when contacted, introducing a potential for bias with larger and more research-oriented hospitals participating in data collection. We were not able to calculate case ascertainment for this audit and therefore data may be incomplete. Our audit only looked at secondary care services and thus we have no information available on presentations to primary care. Finally, within secondary care services our audit only covered unplanned attendances so data on pregnancy losses diagnosed at planned antenatal appointments such as the anomaly ultrasound scan are not included. This may have resulted in an underestimate of the rate of second trimester loss.

4.3 Interpretation:

Our audit indicates there are many acute hospital presentations in the second trimester. In 2022 in the UK there were 607,912 total births.[1] Utilising our data we can extrapolate that there are 20,039 encounters per year in the second trimester in the UK, increasing up to almost 25,449 when re-attendance is considered (27% re-attendance rates in our audit data). This represents a significant burden of attendance throughout the second trimester,

for which there is a paucity of evidence or clinical guidance available to inform care. This is reflected in our audit findings, which identified variation in the location of assessment, grade of clinician, examination and investigations undertaken in those presenting in the second trimester. This emphasizes the need for further studies to inform clinical guidance and advice to improve the management of pregnant people presenting in the second trimester.

This audit has identified some associations with second trimester pregnancy loss which would benefit from further exploration in larger scale study. The association between a history of one or more previous first trimester miscarriages and subsequent second trimester pregnancy loss is consistent with a study undertaken by Westin *et al.* that identified an odds ratio of 1.34 (95% CI 1.07–1.68), and that risk increased with the number of previous miscarriages.[13] A further study also observed increased rate of second trimester pregnancy loss of both a live fetus (OR 9.5 95% CI 4.6-19.8) and a dead fetus (OR 2.9 95% CI 2.0-4.0) in patients with a history of first trimester loss.[15]

We also identified an association between previous first trimester termination of pregnancy (TOP) and second trimester pregnancy loss. Since our data on, the indication for the previous TOP, and method is incomplete this association is equivocal. The existing literature around the association between first and second trimester TOP and second trimester pregnancy loss is scarce and conflicting. The EPIPAGE study identified previous induced abortion as a significant risk factor for extremely pre-term delivery between 22-27 weeks (OR 1.7 95% CI 1.2-2.5) with the strength of the association increased with decreasing gestational age.[14] Similarly, P-Y Ancel *et al.* identified previous induced termination as a risk factor for second trimester pregnancy loss of a live fetus (OR 3.6 95% CI 1.3-9.9).[15] The mechanism of termination may be of significance with some authors suggesting that surgical procedures increase the risk of subsequent preterm birth.[16] This argument is supported by a case control study by Winer *et al.* who examined the use of misoprostol for first or second trimester induced abortion and found no increased risk of second trimester pregnancy loss or pre-term birth.[17] Raatikainen *et al.* analysed a Finnish population-based data base of 26,976 singleton pregnancies and identified no association between previous TOP and subsequent adverse pregnancy outcome.[18] The uncertainty regarding this association merits further exploration in a larger-scale study and highlights the need to include information about the indication and method of termination.

4.4 Future work:

This study emphasises the need for the development of guidance for the investigation and management of presentations in the second trimester. To provide evidence for clinical guidance, larger scale studies are required to identify factors associated with second trimester pregnancy loss. In addition, studies of the aetiology of second trimester loss are needed to understand the underlying causes in order that appropriate tests (e.g. fetal fibronectin, ultrasound assessment) can be applied in this context.

5. Conclusion:

This study demonstrates there are many pregnant people attending and reattending in the second trimester of pregnancy with a broad range of presenting symptoms and ultimate diagnoses. Those who had acute unscheduled attendances had a higher proportion of second

trimester pregnancy loss than the population rate. The audit has identified some interesting preliminary associations which would benefit from a larger study to properly investigate and has emphasised the need for ongoing research into the second trimester.

6. *Ethical approval:*

As this was an audit ethical approval was not required, however the audit was appropriately registered at each site and data collection was compliant with the local clinical governance policies at each participating hospital.

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