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RESEARCH ARTICLE

Relation of antepartum stillbirth to birthweight and gestational age: Prospective cohort study

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Abstract

Objectives: To investigate the incidence of antepartum stillbirth in relation to the distribution of neonatal/fetal weight for different gestational ages.

Design: Prospective observational cohort study.

Setting: Obstetric ultrasound departments in two UK maternity hospitals.

Population: 168 966 women with singleton pregnancies attending for routine antenatal care.

Methods: We examined the incidence of antepartum stillbirths, within different birthweight and fetal weight percentile subgroups, conditioning for gestational age.

Main outcome measures: Incidence of antepartum stillbirth.

Results: The risk of stillbirth progressively increased for lower birthweight. Considering the 25–75th percentile as the reference category, the relative risks for stillbirth at <37 weeks' gestation were 7.6 (95% confidence interval [CI] 5.7–10.2) <1st percentile, 2.6 (95% CI 1.8–3.7) 1 to 10th percentile, 1.4 (95% CI 0.9–2.1) 10 to 25th percentile, 0.8 (95% CI 0.4–1.5) 75 to 90th percentile, 0.8 (95% CI 0.4–1.7) 90 to 99th percentile, 0.9 (95% CI 0.3–2.5) >99th percentile. The respective values for births at ≥37 weeks' gestation were 5.0 (95% CI 2.9–8.9), 2.1 (95% CI 1.4–3.3), 1.4 (95% CI 0.9–2.1), 1.2 (95% CI 0.7–1.8), 1.0 (95% CI 0.6–1.8) and 4.0 (95% CI 1.8–9.3). The incidence of stillbirth in ongoing low-risk singleton pregnancies gradually increases for smaller fetuses at any gestational point. The higher incidence (5.56%) was evident for fetal weight <1st percentile between 24 and 28 weeks' gestation.

Conclusion: Fetal weight and the weight of the stillborn have a continuous association with the incidence of antepartum stillbirth which is affected by gestational age.

KEYWORDS
birthweight, fetal growth restriction, incidence, small for gestational age, stillbirth

1 | INTRODUCTION

In a recent large prospective study, it was found that approximately 0.36% of singleton pregnancies end in stillbirth, 92.5% of which are antepartum and 7.5% intrapartum.[1] Placental dysfunction-related stillbirths accounted for 59% of all antepartum stillbirths and the remaining 41% were attributed to other causes or were considered to be unexplained.[1]

We have demonstrated that a small fetal size and high uterine artery pulsatility index (UtA-PI) at mid-trimester, increase the risk for placental-related stillbirth.[1,2] Published data suggest that prediction of small for gestational age (SGA) can be achieved by a competing risks approach that considers SGA a spectrum condition reflected in two dimensions, first, birthweight, and second, gestational age at birth.[2–6] The same continuous model can be effectively applied to predict placental-related stillbirths.[2] This new rationale explains previous findings suggesting a continuous association between birthweight percentile and the risk for stillbirth or perinatal death.[7–11] However, earlier reports have been restricted to term pregnancies and we have learnt that only about one-third of all stillbirths occur at term and the remaining are preterm and strongly associated with small fetal size.[1,2] On the other hand, a

recent review article suggested that most stillbirths at term occur in normal-sized fetuses.[12] Therefore, there is a need to study the continuous association between birthweight distribution and the incidence of stillbirth, including preterm pregnancies, after appropriate conditioning for gestational age.

The objective of this study was to examine the continuous association between the incidence of antepartum stillbirth and the distribution of birthweight and gestational age at delivery. We also aimed to quantify the incidence of antepartum stillbirth in ongoing pregnancies, in relation to the distribution of fetal weight and gestatonal age.

2 | METHODS

2.1 | Study population and design

The data for this prospective observational cohort study were derived from women attending for routine pregnancy care at King's College Hospital and Medway Maritime Hospital, UK, between March 2006 and November 2020. Gestational age was determined from measurement of fetal crown–rump length at 11–13 weeks and in <5% of cases, from fetal head circumference at 19–24 weeks.[13,14] Dating was always based on ultrasound except in cases of in vitro fertilisation.

The inclusion criteria for this study were singleton pregnancies that delivered a phenotypically normal livebirth or stillbirth at ≥24 weeks' gestation. We excluded pregnancies with known aneuploidies, major fetal abnormalities and those ending in a miscarriage or termination of pregnancy. There was no patient involvement in the design of the study. Participants gave their written informed consent and details of the ethical approval are given in the relative section.

2.2 | Outcome measures

Data on pregnancy outcome were obtained from the maternity hospital records or the general practitioners of women. Stillbirths were divided into those that occurred during pregnancy, prior to delivery and before the onset of labour (antepartum stillbirths) and those that occurred during labour in a fetus that was documented alive at the onset of labour (intrapartum stillbirths). We examined antepartum stillbirths for the purpose of our analysis. The Fetal Medicine Foundation fetal and neonatal population weight charts were used to convert birthweight and estimated fetal weight (EFW) to percentiles and *Z* scores.[15]

2.3 | Statistical analyses

Data were expressed as mean (standard deviation) for continuous variables and *n* (%) for categorical variables. Initially, we divided the population into birthweight percentile intervals and we examined the incidence of stillbirth with corresponding 95% confidence intervals (CIs), within the different percentile subgroups. We also obtained relative risks for stillbirth considering the 25–75th percentile subgroup as the reference category. The analysis was carried out separately for pregnancies delivered before and after 37 weeks' gestation. The next step was to obtain the bivariate joint distribution of birthweight *Z* scores and gestational age at delivery for the whole population and examine the location of stillbirth cases compared with the contours of this joint distribution. Subsequently, we described the risk of antepartum stillbirth for birthweight *Z* scores and gestational age at delivery with a logit model. We graphically depicted this association by constructing a series of curves joining up points of equal risk; every point on each line shows the coordinates of birthweight *Z* score and gestational age at delivery with the same risk.

The final step in our approach was to describe the incidence of antepartum stillbirth in ongoing pregnancies by the distribution of fetal weight and gestational age. This was feasible, as we knew the exact number of stillbirths per gestational period and the number of pregnancies that remained undelivered for the same period. The incidence of antepartum stillbirth was the ratio of the number of stillbirths per gestational period divided by the expected number of ongoing pregnancies within the examined percentile intervals. For our low-risk population, the percentiles can be translated to population proportions (i.e. 1st percentile means 1% of the population, 1st to 10th means 10% of the population, 10th to 25th means 25% of the population) and, provided we know the gestational age at delivery, the known total number of undelivered pregnancies can be converted to an estimated number of undelivered pregnancies within the given percentile interval. The last was the denominator for the incidence calculation. The statistical software package R was used for data analyses.[16]

3 | RESULTS

3.1 | Study population

The inclusion criteria were satisfied by 168 966 singleton pregnancies: 168 365 livebirths and 601 (0.36%) stillbirths, including 548 (0.32%) antepartum and 53 (0.03%) intrapartum stillbirths. The maternal and pregnancy characteristics for both stillbirths and live births are presented in Table S1.

3.2 | Incidence of antepartum stillbirth by birthweight

Figure 1 shows the incidence of antepartum stillbirth by birthweight percentile. For births that occurred at <37 weeks' gestation the incidence of stillbirth was highest below the 1st percentile (12.3%, 95% CI 10.6–14%), was reduced gradually until the 75–90th percentile (1.3%, 95% CI 0.5–2.0%) and remained constant for higher percentiles.

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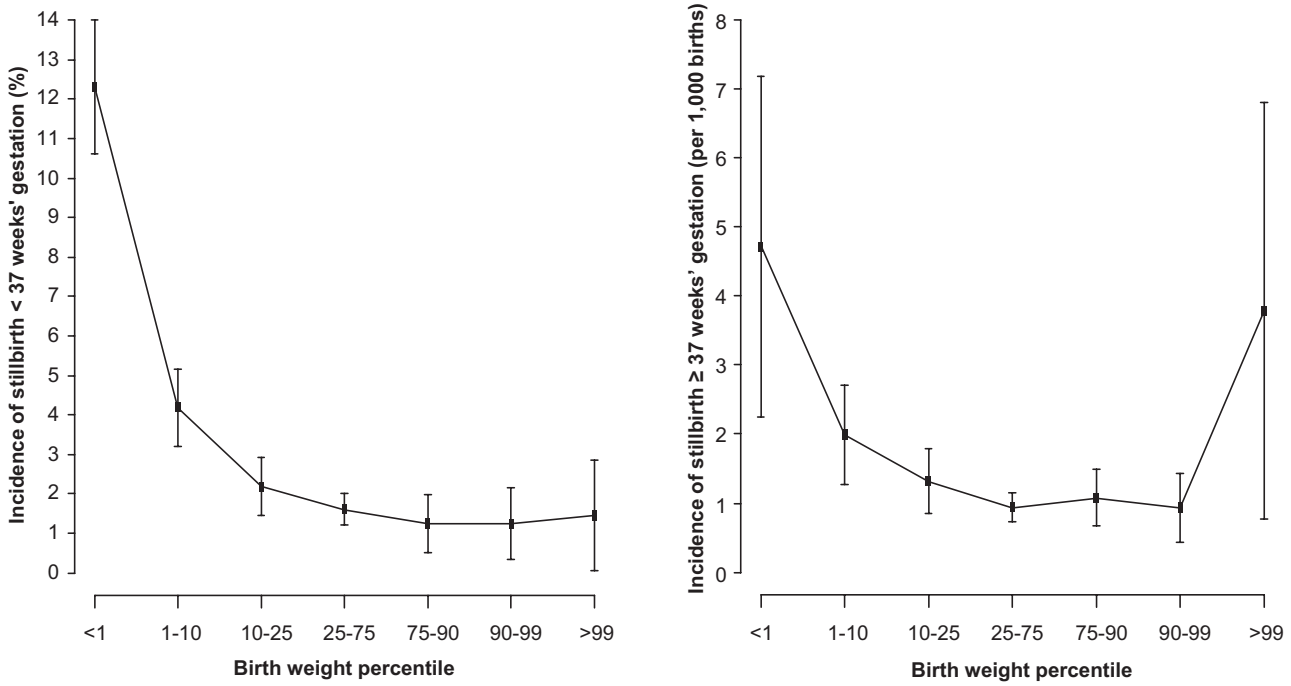

FIGURE 1 Incidence of antepartum stillbirth by birthweight percentile for deliveries before and after 37 weeks' gestation.

Considering the 25–75th percentile as the reference category, the relative risks for stillbirth at <37 weeks' gestation for the different birthweight percentile subgroups were 7.6 (95% CI 5.7–10.2) <1st percentile, 2.6 (95% CI 1.8–3.7) 1st to 10th percentile, 1.4 (95% CI 0.9–2.1) 10th to 25th percentile, 0.8 (95% CI 0.4–1.5) 75th to 90th percentile, 0.8 (95% CI 0.4–1.7) 90th to 99th percentile, 0.9 (95% CI 0.3–2.5) >99th percentile.

For births that occurred at ≥37 weeks' gestation the incidence of antepartum stillbirth was highest below the 1st percentile (4.7‰, 95% CI 2.3–7.2‰), was reduced gradually until the 25th–75th percentile (0.9‰, 95% CI 0.7–1.2‰), remained constant until the 99th percentile and then increased at >99th percentile (3.8‰, 95% CI 0.8–6.8‰). Considering the 25–75th percentile as the reference category the relative risks for stillbirth at ≥37 weeks' gestation for the different birthweight percentile subgroups were 5.0 (95% CI 2.9–8.9) <1st percentile, 2.1 (95% CI 1.4–3.3) 1st to 10th percentile, 1.4 (95% CI 0.9–2.1) 10th to 25th percentile, 1.2 (95% CI 0.7–1.8) 75the to 90th percentile, 1.0 (95% CI 0.6–1.8) 90th to 99th percentile, 4.0 (95% CI 1.8–9.3) >99th percentile.

3.3 | Incidence of antepartum stillbirth by gestational age at delivery

The incidence of antepartum stillbirth in relation to gestational age at delivery was 25.9% (155/598 deliveries) at 24–28 weeks' gestation, 8.6% (89/1033 deliveries) at 28–32 weeks, 1.4% (112/8256 deliveries) at 32–37 weeks and 0.12% (192/159 079 pregnancies) at 37–43 weeks.

3.4 | Incidence of antepartum stillbirth and distribution of birthweight and gestational age at delivery

The joint birthweight and gestational age distribution of the antepartum stillbirths in relation to the joint distribution of birthweight and gestational age at delivery of the whole population is shown in Figure S1: 81.4% (446/548) of antepartum stillbirths occurred in the 50% contour of the more extreme combinations of birthweights and gestational ages and 59.3% (325/548) of antepartum stillbirths in the 95% contour of more extreme combinations of birthweights and gestational ages (Figure S1). The equal-risks curves in Figure 2 show that the smaller the size at birth and the earlier the delivery, the higher the risk for stillbirth.

3.5 | Incidence of antepartum stillbirth in ongoing pregnancies and distribution of fetal weight and gestational age

The incidence of antepartum stillbirth in relation to gestational age for ongoing pregnancies was 0.09% (155/168 966 pregnancies) at 24–28 weeks' gestation, 0.05% (89/168 368 pregnancies) at 28–32 weeks, 0.07% (112/167 335 pregnancies) at 32–37 weeks and 0.12% (192/159 079 pregnancies) at 37–43 weeks.

Figure 3, shows the incidence of antepartum stillbirth in ongoing pregnancies in relation to fetal weight percentile and gestational age. The incidence of antepartum stillbirth for ongoing pregnancies with fetal weight <1st percentile

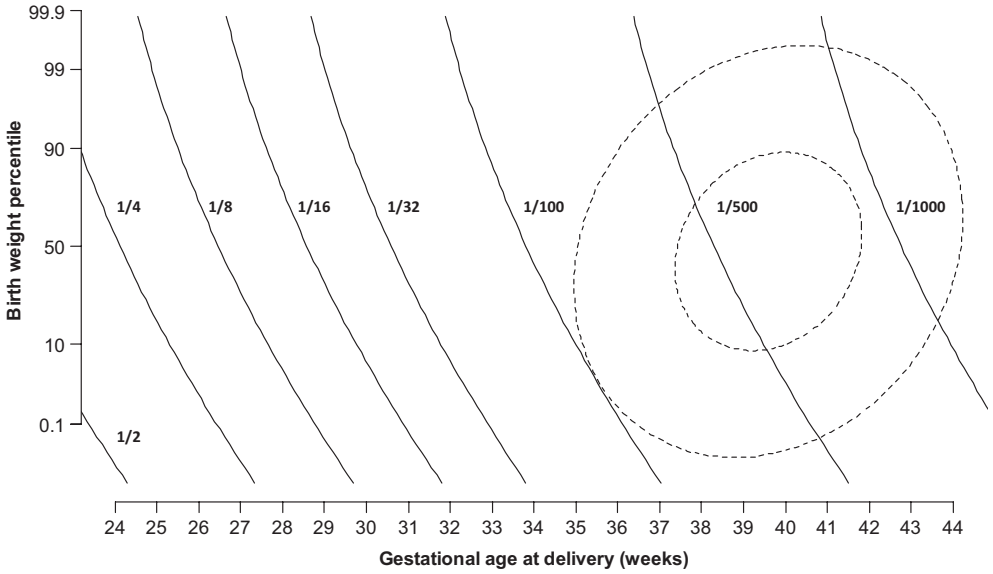

FIGURE 2 Joint distribution of birthweight and gestational age at delivery for the whole study population (50% and 95% contours) and a series of equal-risk curves. Any point on each line shows the respective coordinates of birthweight percentile and gestational age at delivery with the same risk.

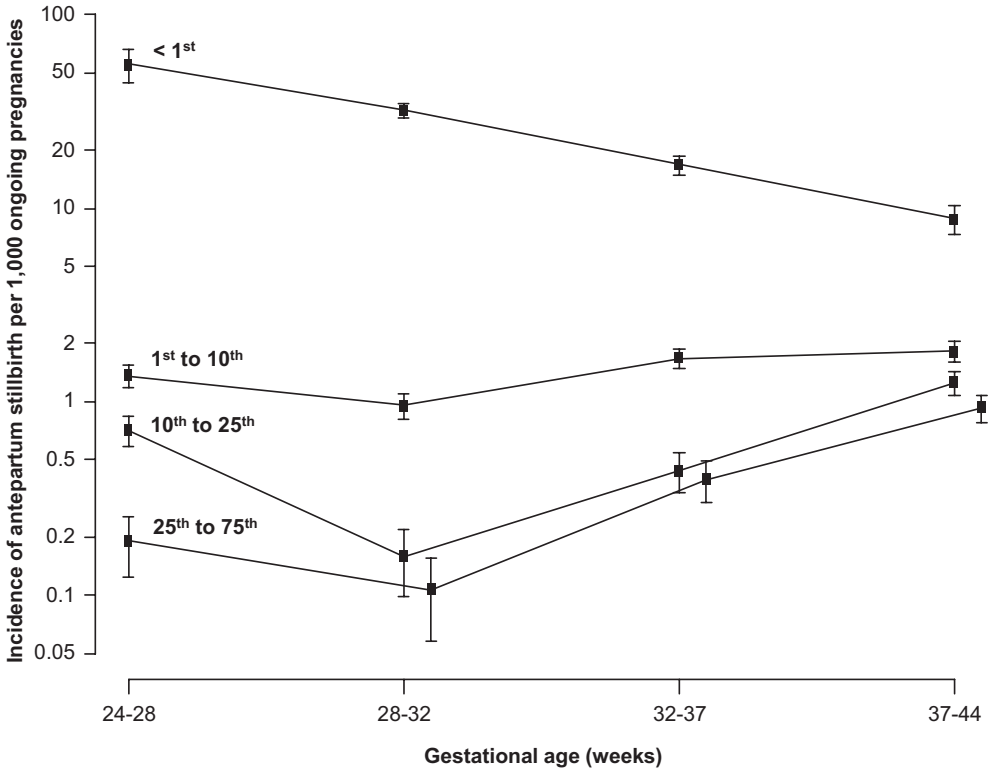

FIGURE 3 Incidence of antepartum stillbirth in ongoing pregnancies by fetal weight and gestational age.

was 5.56%, 3.21%, 1.67% and 0.88% for ongoing pregnancies at 24–28, 28–32, 32–37 and 37–43 weeks' gestation, respectively. The respective values for fetal weight for the 1st to 10th percentile were 0.14%, 0.10%, 0.17% and 0.18%, for the 10th–25th percentile 0.07%, 0.02%, 0.04% and 0.13%, and for the 25th–75th percentile 0.02%, 0.01%, 0.034% and 0.09%.

4 | DISCUSSION

4.1 | Main findings

There are four principal findings of this large prospective observational study on the incidence of antepartum stillbirth. First, birthweight has a continuous and non-linear

association with the incidence of antepartum stillbirth in both term and preterm pregnancies; the smaller the neonate, the higher the risk (Figure 1). The overall risk is lower in term pregnancies but the pattern of the association is similar. Secondly, about 60% of antepartum stillbirths lie outside the 95% contour of the joint distribution of birthweight and gestational age at delivery (Figure S1). Specifically, almost two-thirds of the antepartum stillbirths occur in the 5% of the population with the more extreme birthweights and gestational ages and therefore in pregnancies delivered either prematurely or with a small neonate or both. Thirdly, the association of the weight of the stillborn with the incidence of stillbirth at delivery, should be considered relative to gestational age at delivery. A two-dimensional approach allows the reflection of stillbirth incidence in the combination of the weight of the stillborn and the gestational age at birth. Increasingly smaller size and earlier gestational age at birth rapidly increases the risk for stillbirth (Figure 2). Our modelling proves that growth restriction has two correlated elements: smallness and prematurity. Fourthly, we investigated the incidence of stillbirth in ongoing low-risk singleton pregnancies. At any gestational point the risk of stillbirth gradually increases for smaller fetuses (Figure 3). Fetuses at the lower percentiles of fetal weight have progressively lower risk for increasing gestation, whereas fetuses at higher percentiles have progressively higher risk for increasing gestation (Figure 3). Therefore, we see a pattern that leads to a less deviated incidence between lower and upper fetal weight percentiles for increasing gestation.

4.2 | Strengths and limitations

The strengths of the study are: large sample size with prospectively collected data; we adopted a two-dimensional approach to account for the effect of gestational age at delivery in the association between birthweight and the incidence of stillbirth; we were able to model the in utero risk for ongoing pregnancies. An important strength is that the large sample size allowed us to exclude intrapartum stillbirths because obstetrical complications and potential mismanagement during labour may have interfered with the association between birthweight, gestational age and stillbirth incidence.

It is likely that in some occasions the birthweight of the stillborn babies could be lower than the weight at the time of actual death because intrauterine retention may result in a reduction in birthweight and a possible overestimation of small neonatal size in stillbirth cases.[17] We did not correct the gestational age at delivery for the possible retention interval because the structured antenatal care of this cohort would have probably lower the retention interval and because any correction would have been vague and arbitrary.

4.3 | Comparison with results of previous studies

Previous studies reported a similar pattern to that of our study for the association between birthweight distribution and incidence of stillbirth (Figure 1).[7–11] However, we have made several significant contributions. First, we extended the association between birthweight distribution and incidence of stillbirth to preterm pregnancies, which is clinically important, considering the link with the potentially avoidable placental dysfunction related stillbirths. Secondly, we adopted two-dimensional modelling so that the incidence of stillbirth is quantified in relation to the joint distribution of birthweight and gestational age at delivery (Figures 2 and 3). Finally, we describe the pattern of the incidence of stillbirth for ongoing low-risk pregnancies (Figure 3).

4.4 | Interpretation

This study demonstrates that birthweight has a continuous association with the incidence of stillbirth. An important element that affects this association is gestational age at delivery. Interestingly, our data also show a continuous association between fetal size of ongoing pregnancies and stillbirth at any stage between 24 and 44 weeks' gestation. These findings may change our clinical thinking; examining a tangible outcome such as stillbirth proves that growth restriction is a spectrum condition; and estimated fetal weight by ultrasound scan at any stage could be a continuous proxy for stillbirth. We should be moving beyond fixed arbitrary definitions that hinder an efficient management in accordance with the true nature of the condition. We must use estimated fetal weight as a continuous biomarker and not as a fixed criterion.[18] The varying degree of stillbirth risk for different fetal/neonatal sizes and gestational ages requires a continuous stratification with varying intensities of monitoring according to a personalised risk assessment.[6]

The incidence of antepartum stillbirth in ongoing pregnancies shows that smaller fetuses are in greater danger and the difference between lower and higher percentiles becomes progressively less for advancing gestation (Figure 3). This observation has two major ramifications. The first is that we need efficient strategies focused on the very high-risk preterm small babies. In other words, we need to address the clinical questions of which pregnancies should be seen again, and at what point until 37 weeks' gestation. The combination of maternal risk factors, EFW and uterine artery pulsatility index at mid-trimester identifies a high-risk group that contains a high proportion of placental dysfunction related antepartum stillbirths.[4,6] The next step is a personalised stratification.[6] The second implication of our findings is how to prevent term stillbirths where incidence differences among percentiles are smaller. If stillbirth prevention at term were based solely on fetal size estimation, it would be possible that many unnecessary

deliveries of otherwise healthy small neonates will take place. On the other hand, our findings highlight the fact that fetuses/neonates above the traditional thresholds for smallness could have a substantial risk for stillbirth. The clinical solution is applying a personalised stratification at 35–37 weeks' gestation combining maternal factors, EFW and biomarkers of impaired placentation.[5] This way we can examine many more cases using minimum resources. Pregnancies at risk for stillbirth will probably benefit from stratified intensive monitoring, including repeating fetal growth, biophysical profile, fetal heart rate patterns and Doppler studies.

5 | CONCLUSION

Overall, the incidence of stillbirth increases continuously for both smaller fetal size and lower gestational age. Therefore the severity of growth restriction as defined by fetal size should be considered relative to gestational age. Growth restriction is a spectrum condition and fixed arbitrary criteria do not capture the dynamic association between smallness and stillbirth throughout gestation.[2–6] Continuous stratification of pregnancy care may prevent stillbirth related to placental dysfunction.[6] The timing and the intensity of monitoring should be adapted to the varying incidence of stillbirth for fetal/neonatal size and gestational age.

AUTHOR CONTRIBUTIONS

KHN and IP conceptualized and designed the study. KHN oversaw the study. IP and KHN wrote the paper. GA, AS and RA were involved in the sample collection. All authors revised and contributed to the intellectual content of the paper.

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CONFLICT OF INTEREST STATEMENT

None declared.

DATA AVAILABILITY STATEMENT

Research data have not been shared.

ETHICS APPROVAL

Women gave written informed consent to take part in the study, which was carried out in compliance with the 1975 Declaration of Helsinki Guidelines. The study was approved by the NHS Research Ethics Committee (REC reference 2 March 2033, date of approval 11 March 2003).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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