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# Second-Trimester Uterine Artery Doppler in the Prediction of Stillbirths

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**Key Words**
Second-trimester screening · Uterine artery Doppler · Stillbirth · Pyramid of antenatal care

**Abstract**
***Objective:*** To examine the role of second-trimester uterine artery Doppler in the prediction of stillbirths. ***Methods:*** Uterine artery pulsatility index (PI) was measured at 20–24 weeks' gestation in 65,819 singleton pregnancies. The PI was converted to multiples of median (MoM) and compared in live births and stillbirths. Regression analysis was used to determine the significance of association between $\log_{10}$ uterine artery PI MoM and gestational age (GA) at delivery in cases of stillbirths. ***Results:*** There were 306 (0.46%) stillbirths and in 159 (52.0%) of these there was pre-eclampsia (PE), placental abruption and/or birthweight below the 10th percentile (small for gestational age, SGA). In the stillbirths, the uterine artery PI MoM was significantly higher than in live births and was inversely associated with GA at delivery. The uterine artery PI MoM was above the 90th percentile in 80.6% of stillbirths with PE, abruption and/or SGA delivering at <32 weeks' gestation, in 41.9% at 33–36 weeks and in 34.3% at ≥37 weeks, and the respective percentages for stillbirths without PE, abruption or SGA were 15.8, 25.0 and 12.4%. ***Conclusion:*** Second-trimester uterine artery PI is effective in identifying early stillbirths in association with PE, abruption or SGA but not late deaths in the absence of PE, abruption or SGA.



## Introduction

In developed countries the rate of stillbirth is about 5 per 1,000 births and an important contributing factor is impaired placentation manifested in pre-eclampsia (PE), fetal growth restriction and placental abruption [1–3]. In normal pregnancy the spiral arteries in the placental bed are invaded by trophoblast which becomes incorporated into the vessel wall and replaces the endothelium, muscular layer and neural tissue [4–7]. These physiological changes convert the spiral arteries from narrow muscular vessels to wide non-muscular channels independent of maternal vasomotor control. In pregnancies complicated by PE, placental abruption and birth of small for gestational age (SGA) neonates there is histological evidence of impaired trophoblastic invasion of spiral arteries [7–13]. Indirect evidence for impaired placental perfusion in such pregnancies has been provided by Doppler studies of the uterine arteries which showed an increased pulsatility index (PI) [13–16].

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In a study of 30,519 singleton pregnancies we found that the uterine artery PI at 20–24 weeks' gestation was increased in pregnancies with subsequent antepartum stillbirth and in particular when the death was associated with PE, SGA and placental abruption [15]. In this extended series of 65,819 singleton pregnancies, including 306 stillbirths, we examine the potential role of mid-trimester uterine artery Doppler in the prediction and prevention of stillbirths.

## Materials and Methods

*Study Population*

The study population consisted of singleton pregnancies undergoing a routine ultrasound examination at 20–24 weeks' gestation and delivering alive or dead phenotypically normal babies at or after 24 weeks' gestation. The scan included examination of the fetal anatomy and growth by transabdominal sonography and measurement of the uterine artery PI by transvaginal sonography. The sonographers who performed the Doppler studies had received the Certificate of Competence in Doppler of The Fetal Medicine Foundation (http://www.fetalmedicine.com).

We used two data sets. The first (data set A) consisted of 30,566 pregnancies examined between 1999 and 2002 at seven hospitals in and around London (Basildon Hospital; Greenwich Hospital; Harold Wood Hospital, Romford; King George Hospital, Ilford; King's College Hospital, London; Queen Mary's Hospital, Sidcup, and University Hospital Lewisham, London) that were collaborating in a multicentre randomized controlled trial using low-dose aspirin in the prevention of PE [17]. The study demonstrated that aspirin was not associated with a significant reduction in the rate of PE. In this data set GA was calculated from the measurement of the fetal head circumference at 20–24 weeks.

The second (data set B) consisted of 35,253 pregnancies in which the scan at 20–24 weeks was preceded by combined screening for aneuploidies at 11–13 weeks' gestation between 2006 and 2011 at three hospitals in and around London (King's College Hospital; University College London Hospital, and Medway Maritime Hospital, Kent) [18]. In this data set the GA at screening was calculated from the measurement of the fetal crown-rump length at 11–13 weeks [19].

Participant characteristics including maternal age, racial origin (Caucasian, African, South Asian, East Asian or mixed), cigarette smoking (yes or no), parity (number of previous pregnancies ending at or after 24 weeks), maternal weight and height were recorded.

Written informed consent was obtained from the women agreeing to participate in either the multicentre randomized controlled trial on aspirin or the first-trimester screening study on adverse pregnancy outcomes, both of which were approved by the Ethics Committee of each participating hospital.

The women with a mean uterine artery PI greater than 1.6 were followed up with growth scans, blood pressure measurements and urinalysis for protein at 28, 32 and 36 weeks. Women with normal uterine artery Doppler received routine antenatal care.

*Outcome Measures*

Data on pregnancy outcome were collected from the hospital maternity records or from general medical practitioners. Stillbirths were divided into three groups: antepartum, intrapartum and placental abruption. Antepartum stillbirth was defined as fetal death before the onset of labour and in such cases the diagnosis was essentially made by ultrasonography in women presenting with reduced or absent fetal movements. Intrapartum stillbirth was defined as fetal death after the onset of labour and before birth and in these cases there was ultrasonographic or cardiotocographic evidence that the fetus was alive at the onset of labour. Placental abruption was defined retrospectively by the presence of a retroplacental clot at the delivery of a stillbirth that was either alive or dead at presentation with abdominal pain either with or without vaginal bleeding.

The newborn was considered to be SGA if the birthweight was less than the 10th percentile after correction for gestation at delivery [20].

The definition of PE was that of the International Society for the Study of Hypertension in Pregnancy [21].

*Statistical Analysis*

Comparisons of maternal characteristics between the outcome groups were by $\chi^2$ test or Fisher's exact test for categorical variables and the Mann-Whitney U test for continuous variables. The measured uterine artery PI was converted to multiples of the expected normal median (MoM) corrected for GA in weeks and racial origin. Comparisons of uterine artery PI MoM between live birth and stillbirth groups were by Mann-Whitney U test with post hoc Bonferroni correction (critical statistical significance, $p < 0.004$). Linear regression analysis was used to determine the significance of association between $\log_{10}$ uterine artery PI MoM and GA at delivery in the cases of stillbirths. The proportion of stillbirths (with or without PE, SGA or placental abruption) with uterine artery PI MoM above the 90th percentile was determined.

The statistical software package SPSS 20.0 (SPSS Inc., Chicago, Ill., USA) was used for the data analyses.

## Results

*Study Population*

In the total population of 65,819 singleton pregnancies, there were 65,513 live births and 306 (0.46%) stillbirths. The characteristics of the pregnancies in the total population, data set A and data set B, are presented in table 1. In the group with stillbirths, compared to those with live births, there was a higher prevalence of women of African racial origin and the weight of the women was higher. The GA distribution at delivery of stillbirths and live births is shown in figure 1.

In the stillbirths the death was antepartum in 228 (74.5%) cases, intrapartum in 62 (20.3%) and in association with placental abruption in 16 (5.2%). The stillbirth was antepartum in 80.2% (105 of 131) in those delivered

**Table 1.** Maternal characteristics in the study population

| Variables | Total population | | Data set A | | Data set B | |
|---|---|---|---|---|---|---|
| | live births (n = 65,513) | stillbirths (n = 306) | live births (n = 30,410) | stillbirths (n = 156) | live births (n = 35,103) | stillbirths (n = 150) |
| Maternal age, years | 30.4 (26.1–34.3) | 30.9 (26.0–34.9) | 30.0 (25.8–33.7) | 31.4 (27.0–34.5)* | 30.9 (26.3–34.8) | 29.8 (24.9–35.3) |
| Weight, kg | 65.5 (58.7–76.0) | 70.0 (62.5–82.0)* | 65.7 (58.5–75.9) | 70.0 (63.0–81.5)* | 65.5 (58.9–76.0) | 70.0 (61.4–83.0)* |
| Height, cm | 163 (160–168) | 163 (157–167) | 163 (158–168) | 163 (157–168) | 164 (160–169) | 164 (158–168) |
| Racial origin, n | | | | | | |
| Caucasian | 46,301 (70.7) | 158 (51.6)* | 22,023 (72.4) | 82 (52.5)* | 24,278 (69.2) | 76 (50.7)* |
| African | 12,924 (19.7) | 129 (42.2)* | 5,502 (18.1) | 65 (41.7)* | 7,422 (21.1) | 64 (42.6)* |
| South Asian | 3,974 (6.1) | 16 (5.2) | 2,339 (7.7) | 9 (5.8) | 1,635 (4.7) | 7 (4.7) |
| East Asian | 1,188 (1.8) | 1 (0.3) | 332 (1.1) | 0 (0.0) | 856 (2.4) | 1 (0.7) |
| Mixed | 1,126 (1.7) | 2 (0.7) | 214 (0.7) | 0 (0.0) | 912 (2.6) | 2 (1.3) |
| Parity, n | | | | | | |
| Nulliparous | 34,035 (52.0) | 153 (50.0) | 15,462 (50.8) | 73 (46.8) | 18,573 (52.9) | 80 (53.3) |
| Parous | 31,478 (48.0) | 153 (50.0) | 14,948 (48.2) | 83 (53.2) | 16,530 (47.1) | 70 (46.7) |
| Cigarette smoker, n | 7,834 (12.0) | 41 (13.4) | 4,513 (14.8) | 24 (15.4) | 3,321 (9.5) | 17 (11.3) |

Maternal age, weight and height are median values with interquartile ranges in parentheses. All other values in parentheses are percentages. Comparisons between live births and stillbirths within each data set were by $\chi^2$ or Fisher's exact test for categorical variables and Mann-Whitney U test for continuous variables. * $p < 0.05$ was considered significant.

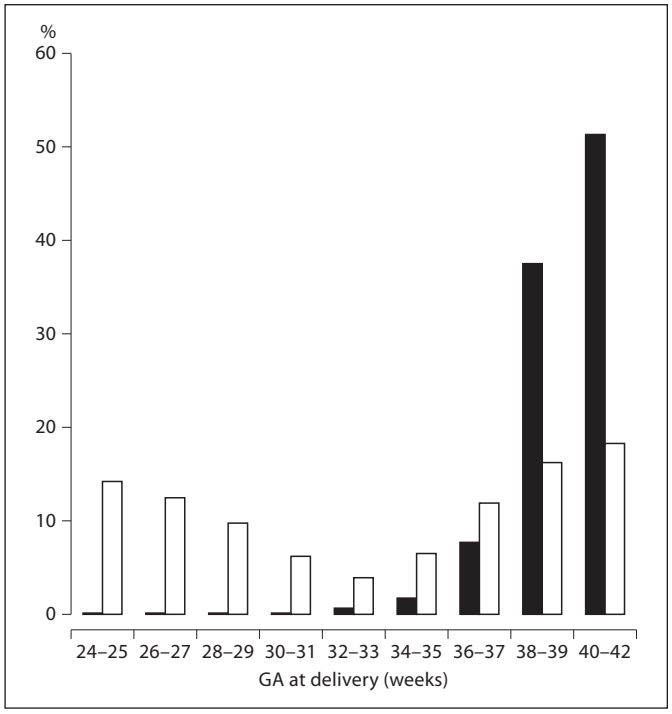


**Fig. 1.** GA distribution at delivery of stillbirths (white bars) and live births (black bars).

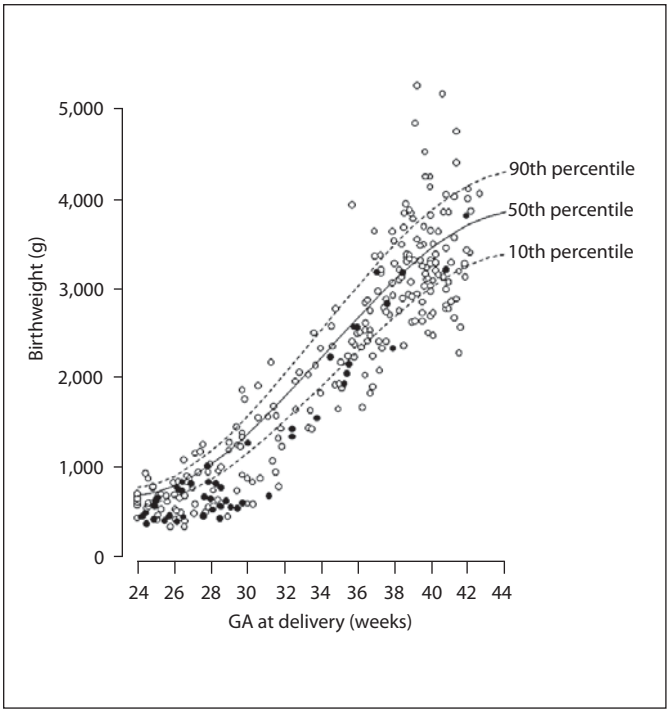


**Fig. 2.** Birthweight with GA at delivery in pregnancies complicated by stillbirth in the presence (●) or absence (○) of PE, plotted on the 10th, 50th and 90th percentiles of the normal range [20].

**Table 2.** Median and interquartile range (in parentheses) of second-trimester uterine artery PI in the live births and stillbirths

| Outcomes | n | Median | p value | Correlation of $log_{10}$ uterine artery PI MoM with GA | |
|---|---|---|---|---|---|
| | | | | r | p value |
| Live births | 65,513 | 1.018 (0.862–1.210) | | –0.114 | <0.001 |
| Stillbirths | | | | | |
| Total | 306 | 1.263 (0.953–1.646) | <0.001* | –0.373 | <0.001 |
| SGA | 128 | 1.602 (1.215–1.972) | <0.001* | –0.398 | <0.001 |
| PE | 51 | 1.873 (1.589–2.236) | <0.001* | –0.597 | <0.001 |
| SGA and/or PE | 143 | 1.603 (1.220–1.983) | <0.001* | –0.430 | <0.001 |
| No SGA or PE | 163 | 1.077 (0.884–1.317) | 0.008 | –0.052 | 0.512 |
| Antepartum | 228 | 1.323 (0.966–1.760) | <0.001* | –0.450 | <0.001 |
| SGA and/or PE | 137 | 1.606 (1.224–2.005) | <0.001* | –0.430 | <0.001 |
| No SGA or PE | 91 | 1.019 (0.884–1.302) | 0.592 | 0.047 | 0.659 |
| Intrapartum | 62 | 1.113 (0.876–1.270) | 0.170 | –0.019 | 0.881 |
| SGA and/or PE | 6 | 1.353 (1.013–1.676) | 0.069 | –0.143 | 0.787 |
| No SGA or PE | 56 | 1.064 (0.873–1.265) | 0.396 | –0.040 | 0.767 |
| Placental abruption | 16 | 1.472 (1.209–1.643) | <0.001* | –0.585 | 0.017 |
| Abruption, PE and/or SGA | 159 | 1.584 (1.220–1.940) | <0.001* | –0.440 | <0.001 |
| No abruption, PE or SGA | 147 | 1.025 (0.877–1.280) | 0.197 | 0.011 | 0.890 |

Comparisons between live births and stillbirths were by Mann-Whitney U test, with post hoc Bonferroni correction. * $p < 0.004$ was considered significant.

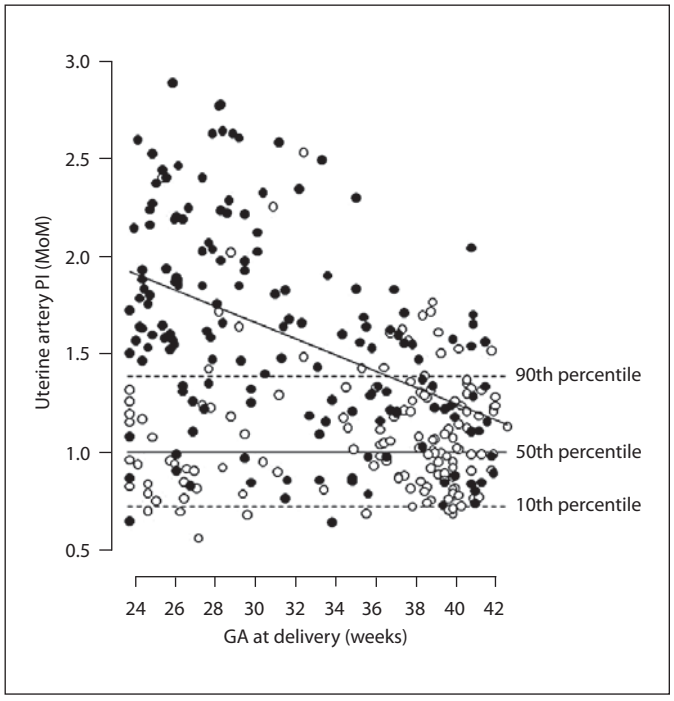


**Fig. 3.** Uterine artery PI MoM with GA at delivery in pregnancies complicated by stillbirth with PE, placental abruption or SGA (●) and stillbirth without PE, abruption or SGA (○).

<32 weeks, in 74.5% (38 of 51) at 32–36 weeks and in 68.5% (85 of 124) at ≥37 weeks.

The stillbirth was intrapartum in 16.0% (21 of 131) in those delivered <32 weeks, in 9.8% (5 of 51) at 32–36 weeks and in 29.0% (36 of 124) at ≥37 weeks. In 13 of the 21 intrapartum stillbirths at <32 weeks there was spontaneous labour at 24–25 weeks and the underlying cause was thought to be cervical incompetence.

*Pre-Eclampsia and Small for Gestational Age*

The incidence of PE was 16.7% (51 of 306) in the stillbirths and 2.5% (1,629 of 65,721) in the live births ($p < 0.001$). The birthweight was below the 10th percentile in 41.8% (128 of 306) of the stillbirths (fig. 2) and in 12.1% (7,972 of 65,721) of the live births ($p < 0.001$).

In all the stillbirths there was PE and/or SGA in 67.2% (88 of 131) of those delivered <32 weeks, in 45.1% (23 of 51) at 32–36 weeks and in 25.8% (32 of 124) at ≥37 weeks. In the antepartum stillbirths there was PE and/or SGA in 82.9% (87 of 105) of those delivered <32 weeks, in 57.9% (22 of 38) at 32–36 weeks and in 32.9% (28 of 85) at ≥37 weeks.

**Table 3.** Proportion of stillbirths with uterine artery PI MoM above the 90th percentiles

| Stillbirths | All stillbirths | | <32 weeks | | 32–36 weeks | | >37 weeks | |
|---|---|---|---|---|---|---|---|---|
| | total | n | total | n | total | n | total | n |
| All cases | 306 | 122 (39.9) | 131 | 81 (61.8) | 51 | 18 (35.3) | 124 | 23 (18.5) |
| SGA | 128 | 81 (63.3) | 81 | 64 (79.0) | 20 | 9 (45.0) | 27 | 8 (29.6) |
| PE | 51 | 45 (88.2) | 36 | 35 (97.2) | 9 | 7 (77.8) | 6 | 3 (50.0) |
| SGA and/or PE | 143 | 90 (62.9) | 88 | 70 (79.5) | 23 | 10 (43.5) | 32 | 10 (31.3) |
| No SGA or PE | 163 | 32 (19.6) | 43 | 11 (25.6) | 28 | 8 (28.6) | 92 | 13 (14.1) |
| Antepartum | 228 | 104 (45.6) | 105 | 72 (68.6) | 38 | 15 (39.5) | 85 | 17 (20.0) |
| SGA and/or PE | 137 | 87 (63.5) | 87 | 69 (79.3) | 22 | 10 (45.5) | 28 | 8 (28.6) |
| No SGA or PE | 91 | 17 (18.7) | 18 | 3 (16.7) | 16 | 5 (31.3) | 57 | 9 (15.8) |
| Intrapartum | 62 | 8 (12.9) | 21 | 4 (19.0) | 5 | – | 36 | 4 (11.1) |
| Placental abruption | 16 | 10 (62.5) | 5 | 5 (100) | 8 | 3 (37.5) | 3 | 2 (66.7) |
| Abruption, PE and/or SGA | 159 | 100 (62.9) | 93 | 75 (80.6) | 31 | 13 (41.9) | 35 | 12 (34.3) |
| No abruption, PE or SGA | 147 | 22 (15.0) | 38 | 6 (15.8) | 20 | 5 (25.0) | 89 | 11 (12.4) |

Values are presented as numbers with percentages in parentheses.

*Uterine Artery Pulsatility Index*

The uterine artery PI MoM was significantly higher in the stillbirths than in the live births (table 2). In the stillbirths associated with PE, SGA or placental abruption there was a significant association between $\log_{10}$ uterine artery PI MoM and GA at delivery (table 2; fig. 3).

The uterine artery PI MoM was above the 90th percentile in 80.6% of stillbirths with PE, abruption and/or SGA delivering at <32 weeks' gestation, in 41.9% at 33–36 weeks and in 34.3% at ≥37 weeks (table 3). The respective percentages for stillbirths without PE, abruption or SGA were 15.8, 25.0 and 12.4%.

## Discussion

The findings of this study demonstrate that impaired placentation, reflected in high uterine artery PI at 20–24 weeks' gestation, was observed in antepartum stillbirths associated with PE and/or SGA and in cases of placental abruption but not in intrapartum stillbirths or in antepartum stillbirths without SGA or PE. In the stillbirths with PE, placental abruption or SGA, uterine artery PI was inversely associated with GA at delivery.

The rate of stillbirth in this study was 0.46%, which is similar to the UK national rate of 0.47% in 2009 [22]. The study has confirmed the known associations of African racial origin and high maternal weight with increased risk for stillbirth. Large population-based studies reported that the risk of stillbirth is twice as high in African women compared to Caucasians [22, 23] and the risk increases with maternal weight [24–26].

*Stillbirths before 32 Weeks' Gestation*

In more than 40% of our stillbirths death occurred at less than 32 weeks and in two thirds of these cases the birthweight was below the 10th percentile for GA. In view of the early gestation and severe growth restriction, a strategy based on the identification of the high-risk group, close monitoring and early delivery is unlikely to improve the outcome in such pregnancies but may convert some of the stillbirths into postnatal deaths.

An alternative strategy for the avoidance of such early stillbirths should focus on the early identification of high-risk pregnancies and the undertaking of the necessary measures to improve placentation [27]. Algorithms combining maternal characteristics and biophysical and biochemical tests at 11–13 weeks could identify most pregnancies delivering preterm SGA neonates in the presence or absence of PE [28, 29]. Furthermore, evidence from meta-analyses of randomized studies utilizing the prophylactic use of low-dose aspirin in pregnancies at high risk of PE reported that such therapy initiated before 16 weeks' gestation can substantially reduce PE, fetal growth restriction and perinatal death [30, 31].

In 20% of the stillbirths in this group the death was intrapartum or in association with placental abruption and in half of the cases delivery was at 24–25 weeks. It is

likely that in at least some of the cases the death may have been the consequence of a decision by the attending obstetricians in consultation with the parents to avoid emergency caesarean section because of the perceived high risk of neonatal death or severe handicap in survivors. Avoidance of some of the early intrapartum stillbirths should be based on a strategy of early screening for spontaneous preterm delivery by a combination of maternal characteristics and sonographic measurement of the cervical length followed by the prophylactic administration of progesterone and/or cervical cerclage in the high-risk groups [32–36].

*Stillbirths at 32–36 Weeks' Gestation*

In 17% of our stillbirths death occurred at 32–36 weeks and in 75% of the cases the death was antepartum. In 58% of the antepartum stillbirths there was SGA and/or PE and at least some of these deaths could have been avoided by iatrogenic delivery. Failure to do so reflects the inadequacy of current antenatal care in the detection of severe fetal growth restriction. The extent to which a routine ultrasound examination at 32 weeks' gestation could have identified these cases leading to timely delivery and the prevention of stillbirth requires further investigation. It is possible that a scan at 32 weeks, which was performed in many of the cases with high uterine artery PI at 20–24 weeks, may have prevented some of the potential stillbirths at 32–36 weeks, offering a possible explanation for the bimodal distribution in the GA of our stillbirths.

The alternative to a routine scan at 32 weeks would be third-trimester monitoring of the cases identified by uterine artery Doppler at 20–24 weeks as having increased PI. However, the uterine artery PI was above the 90th percentile in only 35% of all stillbirths at 32–36 weeks.

*Stillbirths at or after 37 Weeks' Gestation*

In about 40% of our stillbirths death occurred at ≥37 weeks and in one third of these cases the death was intrapartum or was associated with placental abruption. Most of the intrapartum deaths could have been prevented by better obstetric care. The UK confidential enquiry on perinatal death has reported that a high proportion of intrapartum deaths were associated with avoidable factors [22].

In the group of antepartum stillbirths there was SGA and/or PE in one third of the cases and although these could have potentially been avoided by iatrogenic delivery it is uncertain how the impaired fetal growth would have been identified. It is likely that a routine scan at 32 weeks would identify some but certainly not all of the cases with SGA at 37–43 weeks. It is also uncertain whether the effectiveness of a routine scan at 32 weeks in identifying and preventing potential late stillbirths could be improved if, in addition to basic biometry, the scan includes the assessment of fetal Doppler. A meta-analysis of five trials of Doppler ultrasound for the investigation of umbilical artery and fetal vessel waveforms at 26–36 weeks in unselected and low-risk pregnancies, compared to no Doppler ultrasound, reported that the intervention was not associated with a beneficial effect on perinatal death [37].

An alternative strategy to a routine scan at 32 weeks for the prevention of late stillbirth is the induction of labour at 37 weeks' gestation in women with second-trimester abnormal uterine artery Doppler indices. This was suggested by the authors of a uterine artery Doppler study at 19–23 weeks' gestation in 15,796 singleton pregnancies in nulliparous women and in those with a previous pregnancy complicated by fetal growth restriction, PE or stillbirth [38]. The incidence of antepartum stillbirth was 9 per 1,000 and the uterine artery impedance to flow at 19–23 weeks was above the 90th percentile in 47% of the stillbirths [38].

In our study, which included all pregnancies attending for routine pregnancy care, uterine artery PI was above the 90th percentile in 40% of the stillbirths, but the incidence of abnormal Doppler decreased with GA at death from 62% at <32 weeks to 19% at ≥37 weeks. This reflects the decreasing contribution of impaired placentation to stillbirth with gestation, with the incidence of PE, placental abruption or SGA in stillbirths being 71% at <32 weeks and decreasing to 28% at ≥37 weeks. Consequently, a strategy of induction of labour at 37 weeks' gestation in the 10% of pregnancies with high uterine artery PI at 20–24 weeks is likely to increase the rate of caesarean section but unlikely to result in a significant reduction in late stillbirth.

A study requiring further investigation is the potential value of a routine ultrasound examination at 36 weeks' gestation in the reduction of late stillbirth due to fetal growth restriction but also macrosomia and malpresentation.

## Conclusion

The measurement of uterine artery PI at 20–24 weeks can identify a high proportion of subsequent stillbirths. However, in most of these cases the stillbirth may not be avoidable because it is associated with severe early-onset fetal growth restriction and it should, therefore, be aimed

at identifying high-risk pregnancies in the first trimester when therapeutic interventions may improve placentation. The avoidance of stillbirth at or after 32 weeks should focus, firstly, on the antenatal detection of fetal growth restriction and, secondly, on improved intrapartum care. The potential value of an ultrasound scan performed routinely at 32 or 36 weeks to detect fetal compromise and prevent stillbirth by timely delivery remains to be determined.


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