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Causes of antepartum stillbirth in women of advanced maternal age

Kate F. Walker [a,*], Lucy Bradshaw [b], George J. Bugg [c], Jim G. Thornton [a]

[a] Maternity Department, Nottingham City Hospital, Nottingham University Hospitals NHS Trust, Nottingham NG5 1PB, UK
[b] Nottingham Clinical Trials Unit, University of Nottingham, UK
[c] Maternity Department, Queen's Medical Centre, Nottingham University Hospitals NHS Trust, Nottingham NG7 2UH, UK

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ABSTRACT

Objectives: To breakdown the causes of antepartum stillbirth by maternal age.
Study design: Observational study.
Setting: UK.
Sample: Anonymised national data on 2850 cases of antepartum stillbirth in 2009.
Statistical analysis: The association between cause of stillbirth and maternal age was examined using an adjusted multinomial logistic regression model. Risk ratios were calculated relative to stillbirth due to haemorrhage.
Main outcome measures: Antepartum stillbirths classified by the Centre for Maternal and Child Enquiries (CMACE) classification.
Results: Stillbirths in women aged 35 years and over are more likely to be due to major congenital anomalies (relative risk ratio (RRR) 2.0, 95% CI 1.3–3.0), mechanical causes (RRR 1.6, 95% CI 1.0–2.6), maternal disorders (RRR 2.1, 95% CI 1.2–3.6) or associated obstetric factors (RRR 2.1, 95% CI 1.1–3.9) than women less than 35. Women aged 35 years and over have a statistically significant increased risk of stillbirth due to major congenital anomalies (OR relative to live birth 1.6, 95% CI 1.3–1.9) and maternal disorders (OR 1.7, 95% CI 1.2–2.4) than younger women. Women aged 35 years and over were 30% more likely to experience a term stillbirth than women <35 years (OR 1.3, 95% CI 1.1–1.5). Stillbirth due to congenital anomaly was statistically significantly more likely in women ≥35 years.
Conclusions: Advanced maternal age is a significant risk factor for antepartum stillbirth particularly at term. Attention should be given to stillbirth due to mechanical causes, maternal disorders and associated obstetric factors in such women.

Introduction

The average age at childbirth in the UK is increasing, and babies delivered to women aged 35 and over are at a higher risk of perinatal death [1]. The main cause of this is an increased risk of antepartum stillbirth at term which starts at 39 weeks and peaks at 41 weeks [2]. Maternal age 35 years and over is associated with a 65% increase in the odds of stillbirth and accounts for over 4000 stillbirths in high income countries each year [3]. The increasing average age at first childbirth may be contributing to the static rates of antepartum stillbirth in the UK over the last 20 years [4]. Are particular causes of antepartum stillbirth more common in women of advanced maternal age?

Traditional methods of classifying the cause of stillbirth (for example the Wigglesworth approach) leave two thirds of cases 'unexplained' [5–7]. In 2008, the Centre for Maternal and Child Enquiries (CMACE) who report on perinatal deaths in the United Kingdom introduced a new classification system which reduced the proportion of 'unexplained' stillbirths to 23% [1]. They found the most common causes were haemorrhage (13%), intrauterine growth restriction (IUGR) (10%) and placental (9%). They found that women aged 35 and over were less likely to experience a stillbirth due to IUGR.

A study of 715 cases of stillbirth by Fretts et al. examined whether particular causes of stillbirth were more common in women aged 35 and over. The authors found that stillbirths to women aged over 35 were more likely to be due to infection (odds ratio, OR 2.8), 'unusual causes' such as cord pathology (OR 2.0) or be 'unexplained' (OR 2.2) [8]. Another study of 76 cases of unexplained antepartum stillbirth found that the chance of

* Corresponding author. Tel.: +44 0115 823 1893.
E-mail address: katefwalker@doctors.org.uk (K.F. Walker).

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experiencing an unexplained stillbirth without IUGR increased by 16% for each year increase in maternal age [9].

The objective of this study is to breakdown the main causes of antepartum stillbirth by maternal age, and identify if specific causes are more common in older mothers.

Materials and methods

Anonymised data were extracted from the CMACE national database of all cases of antepartum stillbirth in the UK in 2009. As CMACE data captures details of perinatal deaths in the UK, population denominators were obtained from an alternative source [1]. The total number of stillbirths reported in 2009 was 4125. Multiple pregnancies and intrapartum stillbirths were excluded. Cases of antepartum stillbirth were transferred securely by the National Perinatal Epidemiology Unit in June 2014.

CMACE and its predecessors (Confidential Enquiry into Stillbirth and Death in Infancy and Confidential Enquiries into Maternal and Child Health) have produced reports on perinatal deaths in the UK between 2002 and 2009. In 2009 CMACE changed the system that was used for classifying the cause of stillbirth, this makes comparison with earlier data problematic and hence only data from 2009 was selected for this study.

Causes of antepartum stillbirth were coded using the CMACE maternal and fetal classification (2008). CMACE have a data collection form which asks notifiers to identify all conditions that arose during pregnancy, caused or were associated with the death and to specify which condition was the main condition causing or associated with the death. CMACE regional managers will then use this information plus any post mortem and placental histology reports to classify the one primary cause or associated factor and up to three other causes or associated factors.

The first objective of the study was to breakdown the main causes of antepartum stillbirth for those women who experienced a stillbirth by maternal age. The causes of antepartum stillbirth were plotted as frequency counts and percentages. The association between cause and maternal age was first examined by cross tabulation, then by using multinomial logistic regression, with primary cause of stillbirth as the outcome and maternal age as the exposure. Maternal age was categorised as <35 years and ≥35 years as traditionally women who are pregnant over the age of 35 have been labelled as 'advanced maternal age' [10]. This is historically based on the increased antepartum, intrapartum and postpartum risks associated with maternal age of 35 years or older. A further adjustment in the model for parity, pre-existing medical conditions, BMI, ethnicity and smoking status was made. Results were expressed as relative risk ratios (RRR) relative to stillbirth due to haemorrhage with 95% confidence intervals. Haemorrhage was chosen as the reference group as the odds ratio for haemorrhage as a cause of stillbirth in women ≥35 years was less than one.

The second objective was to determine the risk of a particular cause of antepartum stillbirth for all women of advanced maternal age. Odds ratios for the 12 main causes of antepartum stillbirth by maternal age relative to a live birth were obtained using population denominators from Perinatal Mortality 2009. This was to obtain a crude risk of having a stillbirth due to a particular cause in women over 35 years of age. The multinomial logistic regression model used to obtain relative risk ratios presents the risk of a particular cause of stillbirth in women who had experienced a stillbirth, not for all women in the general population.

Odds ratios for the 12 main causes of antepartum stillbirth at ≥37 weeks gestation by maternal age relative to a live birth were obtained using population denominators. This was to obtain a crude risk of having a stillbirth due to a particular cause at 37 weeks or beyond in women over 35 years of age.

Results

There were 2850 cases of antepartum stillbirth in singleton pregnancies the UK in 2009, of which 2206 (78%) occurred in women under 35 years and 637 (22%) in women over 35 years. Using a population based denominator of live births by maternal age [11] the rate of antepartum stillbirth in women <35 years was 3.5 per 1000 live births and in women ≥35 years was 4.0 per 1000 live births (OR 1.2, 95% CI 1.1–1.3, p 0.001). Cause of death was available for 2823 cases.

A post-mortem was performed in 1143 cases (40%) and placental histology obtained in 2373 (83%). Table 1 shows the main causes for 2823 cases by maternal age group and the results of the multinomial logistic regression model adjusted for BMI, parity, ethnicity and pre-existing medical problems.

For the four primary causes of antepartum stillbirth shown to be more common in women over 35 years of age in the adjusted multinomial logistic regression model Table 2 shows a further breakdown into subgroups.

The crude analysis of causes of antepartum stillbirth in women by maternal age is shown in Table 3.

Table 4 shows the main causes of antepartum stillbirth by the gestational age at which the death was confirmed for women aged <35 years and women aged ≥35 years.

Overall, women ≥35 years were 30% more likely to experience a term stillbirth than women <35 years (OR 1.3, 95% CI 1.1–1.5). The only cause of term stillbirth that was statistically significantly more likely in women ≥35 years was congenital anomaly (Table 5).

Table 1
A multinomial logistic regression model with main cause of antepartum stillbirth as the outcome and maternal age (<35 years or ≥35 years) as the exposure.

Main cause of death	<35 years n (%)	≥35 years n (%)	RRR	95% CI	p-Value
No antecedent or associated obstetric factors	646 (29)	157 (25)	1.2	0.82–1.8	0.33
Antepartum and intrapartum haemorrhage	231 (11)	48 (7.6)	Reference group		
Intra-uterine growth restriction	128 (5.8)	36 (5.7)	1.4	0.84–2.5	0.18
Specific placental conditions	256 (12)	66 (10)	1.5	1.0–2.4	0.07
Major congenital anomaly	312 (14)	122 (19)	**2.0**	**1.3–3.0**	**0.01**
Mechanical	165 (7.5)	52 (8.2)	**1.6**	**1.0–2.6**	**0.04**
Infection	97 (4.4)	23 (3.7)	1.3	0.73–2.4	0.33
Associated obstetric factors	65 (3.0)	22 (3.5)	**2.1**	**1.1–3.9**	**0.02**
Hypertensive disorders of pregnancy	123 (5.6)	38 (6.0)	1.7	1.0–2.9	0.07
Specific fetal conditions	52 (2.4)	20 (3.2)	1.8	1.0–3.6	0.06
Maternal disorder	103 (4.7)	44 (7.0)	**2.1**	**1.2–3.6**	**0.01**
Unclassified	14 (0.64)	3 (0.48)	1.5	0.28–7.8	0.62

Adjusted for BMI (<25 and ≥25), ethnicity (white as the reference group), parity (nulliparous and multiparous), presence of pre-existing medical problems, smoking (non-smoker and smoker). Statistically significant results (p-value less than 0.05) are shown in bold.