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Title page

Advanced maternal age and the risk of perinatal death due to intrapartum anoxia at term.

Dharmintra PASUPATHY, MSc,¹ Angela M WOOD, PhD,² Jill P PELL, MD,³ Michael FLEMING, BSc,⁴ and Gordon CS SMITH, MD PhD,⁵

¹Department of Obstetrics and Gynaecology, University of Cambridge, Cambridge, UK.

²Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK.

³Public Health Section, University of Glasgow, Glasgow, UK.

⁴Information and Statistics Division, Common Services Agency, Edinburgh, UK.

⁵Department of Obstetrics and Gynaecology, University of Cambridge; NIHR Cambridge Comprehensive Biomedical Research Centre, Cambridge UK.

Reprint requests and correspondence to:

Gordon CS Smith, MD PhD, Professor of Obstetrics and Gynaecology, The Rosie Hospital, Addenbrookes NHS Trust, Cambridge CB2 2SW, UK.

Tel: 01223 763888/763890; Fax: 01223 763889; E-mail: gcsm2@cam.ac.uk

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ABSTRACT

Background: Advanced maternal age is associated with higher risks of intrapartum complications. However the effect of maternal age on the risk of perinatal death due to these complications is unclear. Our aim was to determine the association between maternal age and delivery related perinatal death at term.

Methods: In this retrospective cohort study, we analysed birth records of 1,043,002 singleton term infants with cephalic presentation excluding anomalous and antepartum losses in Scotland between 1985 and 2004. We used linked Scottish national registries of pregnancy outcome data and perinatal death data. The event was delivery related perinatal death (i.e. intra-uterine fetal death during labour or death of the infant in the first four weeks of life), plus a sub-group ascribed to intrapartum anoxia.

Results: There were 803 delivery related perinatal deaths, with 490 due to intrapartum anoxia (4.7 per 10,000 births) and 313 (3.0 per 10,000 births) due to non-anoxic causes. Compared to women aged 25 to 34, women aged 40 and above had a two-fold risk of delivery related perinatal death at term (adjusted odds ratio [OR] 2.20, 95% confidence interval [CI] 1.42-3.40). The excess was explained by an increased risk of death due to intrapartum anoxia. Among women in labour at term, age greater than 40 was independently associated with the risk of anoxic death among both primiparous (adjusted OR 5.34, 95% CI 2.34-12.20) and multiparous women (adjusted OR 2.14, 95% CI 0.99-4.60).

Conclusions: Advanced maternal age is associated with an increased risk of death due to intrapartum anoxia at term.

Main text

INTRODUCTION

In industrialized countries, an increasing number of women are delaying childbirth.[1-4] It is well recognized that the incidence of adverse maternal outcomes, such as miscarriage, pre-eclampsia, gestational diabetes and antepartum stillbirth increases with increasing maternal age.[5-7] Increasing maternal age is also found to be associated with intrapartum complications, including dysfunctional labour and operative birth.[8,9] However the association between advanced maternal age and the risk of perinatal death due to these intrapartum complications is unclear. The aim of this study was to determine whether advanced maternal age was a risk factor for perinatal death due to intrapartum anoxia at term.

METHODS

Data sources

The Scottish Morbidity Record (SMR02) collects information on clinical and demographic characteristics and outcomes of patients discharged from Scottish maternity hospitals. The register is subjected to regular quality assurance checks and has been greater than 99% complete since the late 1970s.[10] The quality assurance exercise done in 1996-97 compared 5% of case records (n=1414) with the SMR02 database during a six month period. This exercise demonstrated that all fields used in the present study had less than 2% errors with the exception of maternal height (4.4%), estimated gestation (5.6%) and induction of labour (6.4%).[11]

Records of singleton births from the SMR02 between 1985 and 2004 inclusive, were identified and linked to the Scottish Stillbirth and Infant Death Survey (SSBIDS), a national registry that routinely classifies all perinatal deaths in Scotland. Coding of the cause of death is performed by a single medically qualified individual (the Scottish Coordinator) in the Information and Statistics Division of the National Health Service (NHS) on the basis of the clinical information obtained from the local coordinators and pathologists. Cases are identified through registration of stillbirths and neonatal deaths with the General Registrar's Office, which is a legal requirement following perinatal death. The register is 100% complete when compared with death certificate database and has been described in detail elsewhere.[12,13] Approval for the record linkage

was provided by the Privacy Advisory Committee of the Information and Statistics Division of the NHS Scotland.

Study cohort

This retrospective cohort study comprised of all singletons with cephalic presentation delivered between 1985 and 2004. The study exclusion criteria were multiple pregnancy, antepartum stillbirth, perinatal death due to congenital abnormality or rhesus isoimmunisation, delivery outside 37-43 weeks gestation, records with unknown mode of delivery and deliveries in units with less than 10 deliveries per annum.

Definitions

Maternal and obstetric characteristics

Maternal age was defined as the age of the mother at the time of birth. Five-year categories of maternal age were created, with the youngest age category of 20 and below and the oldest age category of 40 and above. The risk of delivery related perinatal death was compared between the age categories. We adjusted the risk of delivery related perinatal death for maternal parity, height, socioeconomic deprivation, gestational age, fetal sex, birth weight percentile corrected for sex and gestational age, induction of labour, hospital throughput and year of delivery. All these characteristics except the following were defined as previously described.[14] Hospital throughput was defined as the total number of births recorded in the SMR02 database for the given hospital over the given

year. Hospital throughput was categorised into equal and above or below the median (3000 births).

Perinatal deaths

There were two main outcomes (pre-specified in the grant application supporting this work), namely, delivery related perinatal death **and a subgroup of these events where the cause was** ascribed to intrapartum anoxia. Delivery related perinatal death was defined as intrapartum stillbirth or neonatal death, excluding deaths due to congenital abnormality or rhesus isoimmunisation. Intrapartum stillbirth was defined as a stillbirth where intra-uterine fetal death occurred following the onset of labour but prior to birth. Neonatal death was defined as death during the first four weeks **after birth** in a liveborn baby. Early neonatal death was defined as death of a liveborn infant between day 1 and day 7 (inclusive) of life where the day of birth is counted as day 1. Late neonatal death was defined as death of a life born infant between day 8 and 28 (inclusive) of life. Both early and late neonatal deaths were included in the analysis, as deaths due to events in labour may occur beyond the early neonatal period.[15]

The cause of stillbirth and neonatal death was coded using a modification of the Wigglesworth classification.[12,16] Deaths were classified according to direct obstetric causes (in order): congenital abnormality, isoimmunisation, toxemia (pre-eclampsia/eclampsia), haemorrhage (antepartum), mechanical, maternal, miscellaneous and unexplained. It is a hierarchical system which dictates that a

perinatal death where there was severe pre-eclampsia complicated by abruption would be ascribed to toxemia since toxemia is above haemorrhage in the hierarchy. Deaths were also classified according to paediatric causes (in order): congenital abnormality, isoimmunisation, intra-uterine anoxia (sub-divided into antepartum or intrapartum), birth trauma, pulmonary complications of prematurity, intra-cranial haemorrhage, infection, haemorrhage (other than intra-cranial), miscellaneous) and unexplained (sudden infant death syndrome). Deaths ascribed to congenital abnormality was defined as “any structural or genetic defect incompatible with life or potentially treatable but causing death”. Hence classification as deaths ascribed to intrapartum anoxia was on the basis of the paediatric classification and could be associated with a variety of obstetric antecedents. The definition of anoxia in this classification is broad and includes hypoxia, acidosis and asphyxia.

Statistical analyses

Observed continuous variables were summarized by the median and interquartile range, and comparisons between groups were made by the Kruskal-Wallis test. Univariate comparisons of dichotomous data were made by the use of the chi-square test and chi-square test for trend as appropriate. Since missing covariates were likely to be missing at random, and to avoid a loss in efficiency, missing covariate values were imputed using multiple imputation by chain equations.[17] Five imputations were created using a set of appropriate imputation models constructed from all covariates and outcome variables in their raw scale

(maternal age was subsequently categorised). Logistic regression analysis on the imputed data was used to estimate crude and adjusted odds ratios for each age category. The referent category was age between 25 and **34, inclusive** which contained the median age of the population. Similar results were obtained from multivariate models using (i) the complete-cases, (ii) missing indicator variables for height and socioeconomic deprivation category and (iii) multiple imputed data (comparison not shown). The Wald test was used to test the interaction between maternal age and parity and between maternal age and year of delivery. Clustered analysis at hospital and maternal level was performed on the crude logistic model on the complete-cases to allow for clustering of deliveries in maternity units and repeated deliveries to the same individual. The P value for all the hypotheses were two sided and the statistical significance was set at $p < 0.05$. Univariate and multivariate analysis were performed using STATA, version 10.0, software (StataCorp LP, College Station, Texas). Multiple imputation was performed using the ICE package [18-20] and clustered analysis was performed using xtmelogit.

RESULTS

The SMR02 contained 1,163,914 records of singleton births between 1985 and 2004. We excluded 69,492 (6.0%) records where gestation was outside 37-43 weeks and 3,677 (0.3%) with missing values for gestation. Of the term deliveries, we excluded 899 (0.1%) perinatal deaths due to congenital abnormality or rhesus isoimmunisation, 1,776 (0.2%) antepartum stillbirths and 44,016 (4.1%) non-cephalic deliveries. We further excluded 333 (0.03%) records with unknown mode of delivery, 714 (0.1%) records where the deliveries were documented to have taken place in hospitals delivering less than 10 women per year and 5 records with inconsistent perinatal death classification. This resulted in a study cohort of 1,043,002 pregnancies which was 95.6% of all singleton term births in Scotland between 1985 and 2004. There were 803 (0.08%) intrapartum and neonatal deaths, of which 490 (61.0%) were anoxic and 313 (39.0%) were non-anoxic.

The demographic, maternal and obstetric characteristics are reported by categories of maternal age (Table1). The median maternal age in the population was 27 (inter-quartile range 23 to 31). Increasing maternal age was associated with increasing parity, prostaglandin induction or augmentation of labour, caesarean delivery and delivery in larger obstetric units. Higher maternal age was associated with lower deprivation scores and incidence of assisted vaginal delivery. Median birth weight increased with increasing maternal age up to the

age of 39, with a decrease from the age of 40. Women aged less than 20 were shorter than the rest of the cohort (Table 1).

The incidence of delivery related perinatal death in the population was 7.7 per 10,000 births (95% confidence interval [CI] 7.2-8.3). **The incidence of delivery related perinatal death was higher only in women age 40 and above.** Across most age groups, the absolute risk of anoxic cause delivery related perinatal death (4.7 per 10,000 births; 95% CI 4.3-5.1) was higher than the risk of non-anoxic deaths (3.0 per 10,000 births; 95 % CI 2.7-3.4) ($p=0.007$) (Table 1). Compared to women age 25 to 34, the risk of delivery related perinatal death was significantly increased among women aged 40 and older (crude odds ratio [OR] 1.99; 95% CI 1.30-3.05). There were 22 delivery related perinatal deaths in women aged 40 and older (14.7 per 10,000 births) and 16 (72.7%) of these were due to intrapartum anoxia (Table 1). The two-fold risk of delivery related perinatal death in women aged 40 and older was due to the increased risk of anoxic death (10.7 per 10,000 births) (Table 2). Adjustment for year of delivery and range of maternal, fetal and obstetric characteristics strengthened this association (adjusted OR 2.76; 95% CI 1.65-4.61). There was no association between advanced maternal age and non-anoxic cause death (Table 2).

There was a significantly increased incidence of both planned and emergency caesarean delivery with increasing maternal age (Table 1). The rate of caesarean section in women aged 40 and above was 25%, with elective procedures

accounting for approximately 50% of caesarean deliveries. There was only one anoxic death amongst women delivered by elective caesarean delivery. Excluding women delivered by elective caesarean section and confining the analysis to women in labour, strengthened the association between maternal age greater than 40 and the risk of anoxic cause delivery related perinatal death (adjusted OR 3.05; 95% CI 1.72-5.41). The rest of the analysis is restricted to this cohort of women in labour.

Primiparous women were at an increased risk of anoxic death (adjusted OR 1.58; 95% CI 1.28-1.96). Amongst multiparous women there was no association between number of previous births and the risk of delivery related perinatal death due to intrapartum anoxia. There was a non-significant trend towards a stronger association between maternal age greater than 40 (interaction term, $p=0.1$) and the risk of anoxic death in primiparous women (adjusted OR 5.34; 95% CI 2.34-12.20) compared to multiparous women (adjusted OR 2.14; 95% CI 0.99-4.60). Confining the analysis to multiparous women with no previous caesarean delivery, women aged 40 and above still remained at increased risk of anoxic death (adjusted OR 2.57; 95% CI 1.12-5.91).

There was no evidence that the **association between maternal age and the risk of anoxic related perinatal death** changed over the period of study (interaction term, $p=0.1$). The nature and statistical significance of associations

were not affected by analytic methods which corrected standard errors for clustering at maternal and hospital level (data not shown).

DISCUSSION

The risk of intrapartum stillbirth and neonatal death amongst women in Scotland between 1985 and 2004 with cephalic presentation at term was 7.7 per 10,000 births. More than 60% of these deaths were due to intrapartum anoxia. Women aged 40 and above had greater than a two-fold increased risk of delivery related perinatal death. This was secondary to an increased risk of intrapartum anoxia. This association was not explained by year of delivery, maternal height, parity, socio-economic deprivation, gestational age, fetal sex, birth weight percentile, onset of labour and hospital throughput. The association was observed among both primiparous and multiparous women but there was a non-significant trend towards a strong association in the former group. These associations did not change over the period of study.

Many previous studies had shown that advanced maternal age was associated with the risk of stillbirth. Approximately 90% of stillbirths follow death of the infant prior to the onset of labour. The clinical implications of an association with stillbirth clearly differ in relation to whether the increased risk of death is present before the onset of labour, during labour or both. Furthermore, complications of labour at term also lead to an increased risk of neonatal death. Hence, it has been suggested that studies of the association between intrapartum complications and the risk of perinatal death utilize a composite outcome, namely intrapartum stillbirth and neonatal death excluding deaths due to congenital anomaly.[21] Hence, definition of this outcome requires detailed information on

both the timing and the cause of death. Few databases combine this level of detail on perinatal death with high quality information on the denominator. The few previous studies that have addressed the relationship between maternal age and the risk of intrapartum stillbirth have failed to demonstrate an association.[22,23] Our observation most likely reflects the relative advantages of both the data source and our analytic approach.

This research question has important public health implications. In the UK, pregnancies and labour are classified as either low or high risk depending on the presence of prenatal, ante-natal or intra-partum risk factors. This risk status dictates the appropriate place of delivery and care in labour, including the need for continuous electronic fetal heart rate monitoring. There are also national incentives to increase women's choice of place of labour including home delivery, midwifery led birthing units and obstetric units. A recent guideline by the UK National Institute of Clinical Excellence on the intrapartum care of women in labour at term stated that there were no high quality studies which identified risk factors to inform assessment of eligibility for home delivery. However, maternal age greater than 40 was identified as one of the factors that required individual assessment when planning the place of birth.[24] This guideline and a further national report on the use of electronic fetal monitoring in labour did not identify maternal age greater than 40 as a risk factor requiring continuous fetal monitoring.[25] The present data demonstrate that these women have a significantly increased risk of death of the infant due to intrapartum anoxia and

we propose that this should be considered when planning the place and monitoring of labour.

The biological basis of this association is unclear. Abnormal placental function in labour may increase the risk of anoxic related events. Older women may have coexisting medical conditions, which increases the risk of placental insufficiency. However recent evidence has demonstrated that after exclusion of deaths due to congenital anomalies, the increased risk of antepartum stillbirth in older women are largely unexplained.[26] Some studies suggest that there is no association between clinical markers of utero-placental insufficiency and advanced maternal age.[27] Collectively, this would suggest that suboptimal placental function is unlikely to be mediating the association between advanced maternal age and anoxic cause perinatal death. A recent report using data from in-vitro studies and epidemiological analysis, demonstrated that increasing maternal age is associated with dysfunctional myometrial contractility, longer duration of labour and increased risk of operative delivery.[4] This adverse effect of age on uterine function in labour may mediate the association between maternal age and the risk of anoxic cause perinatal death. However, the association with operative delivery is a continuum across the range of maternal age. In contrast, we found a threshold effect among women of very advanced age and the risk of delivery related perinatal death. This suggests that the biological basis of these associations may differ.

Older women were more likely to be multiparous and to have had a previous caesarean section. Multiparous women were at lower risk of anoxic cause perinatal death overall, although those with previous caesarean delivery are at an increased risk of delivery related perinatal death secondary to uterine rupture.[14,28] There was a trend toward a stronger association between advanced maternal age and the risk of perinatal death due to intrapartum anoxia among primiparous women. However, maternal age greater than 40 was still associated with the risk of anoxic perinatal death when confined to multiparous women without a previous caesarean delivery. Hence, these observations suggest that women aged 40 and above should be regarded as being at increased risk of anoxic cause delivery related perinatal death irrespective of parity. **The present study lacked data on some other maternal characteristics which are associated with advanced age, such as body mass index and use of assisted reproductive technology.[29-31] Further studies addressing this question using other data sources may be able to take these factors into account. However, given the strength of the associations observed, we think that the present findings are unlikely to be explained by an effect of unmeasured maternal confounders.**

Finally, over the period of study much of obstetrics and neonatal care has changed. This includes rising rates of caesarean delivery, changes in maternal, fetal and obstetric demographics and the declining rates of perinatal

mortality.[4,9,32] These changes do not appear to mediate the observed association with maternal age over 40 as it persisted in multivariate analysis.

In summary, our findings demonstrate that the risk of intrapartum stillbirth and neonatal death at term is increased in women aged 40 and older. This is due to the increased risk of perinatal deaths due to intrapartum anoxia. These findings should be discussed when planning the location and conduct of labour with women aged 40 and above.

What this paper adds

Advanced maternal age is associated with increased risk of adverse pregnancy outcome including perinatal mortality. However, the risk of perinatal death at term due to complications of labour and delivery is unknown.

At term, women who are 40 and older are at increased risk of perinatal death due to complications of labour and delivery.

Statements

Competing interest

All authors have no competing interests to declare.

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Table1. Characteristics of Cohort by Categories of Maternal Age, Scotland, 1985 – 2004.

Characteristics	Maternal age, years (No;%)					P value*
	<20	20-24	25-34	35-39	>39	
	88,193 (8.5)	237,950 (22.8)	605,016 (58.0)	96,870 (9.3)	14,953 (1.4)	
Maternal						
Height, cm (median; IQR)	161 (157-165)	162 (157-166)	162 (158-167)	162 (158-167)	162 (157-167)	<0.001
Missing value (No;%)	12,099 (13.7)	26,562 (11.2)	72,884 (12.1)	15,802 (16.3)	2,723 (18.2)	<0.001
Parity (No;%) ^a						
0	76,076 (86.3)	132,170 (55.6)	226,504 (37.5)	22,608 (23.4)	2,965 (19.9)	
1-2	12,067 (13.7)	101,230 (42.6)	335,634 (55.5)	57,609 (59.5)	7,789 (52.3)	<0.001
>2	49 (0.06)	4,525 (1.9)	42,711 (7.1)	16,547 (17.1)	4,136 (27.8)	
Deprivation category (No; %) ^a						
1 (Least deprived)	1,247 (1.4)	5,395 (2.3)	40,979 (6.8)	9,678 (10.0)	1,368 (9.2)	
2	5,147 (5.8)	20,053 (8.4)	91,361 (15.1)	17,632 (18.2)	1,593 (17.3)	
3	12,458 (14.1)	41,395 (17.4)	133,048 (22.0)	22,845 (23.6)	3,634 (24.3)	
4	21,820 (24.7)	60,492 (25.4)	144,537 (23.9)	21,096 (21.8)	3,386 (22.6)	<0.001
5	18,421 (20.9)	44,733 (18.8)	86,167 (14.2)	11,301 (11.7)	1,718 (11.5)	
6	14,646 (16.6)	34,640 (14.6)	64,135 (10.6)	8,905 (9.2)	1,351 (9.0)	
7 (Most deprived)	13,220 (15.0)	27,208 (11.4)	37,762 (6.2)	4,677 (4.8)	792 (5.3)	
Missing value (No;%)	1, 234 (1.4)	4,034 (1.7)	7,027 (1.2)	736 (0.8)	111 (0.7)	
Infant						
Gestational age (median; IQR) ^a	40 (39-41)	40 (39-41)	40 (39-41)	40 (39-40)	40 (40-41)	<0.001
Male (No;%) ^a	45,508 (51.6)	122,249 (51.4)	309,321 (51.1)	49,582 (51.2)	7,554 (50.5)	0.002
Birth weight, g (median; IQR) ^a	3340	3380	3460	3490	3460	
	(3040-3650)	(3080-3700)	(3150-3790)	(3170-3820)	(3120-3800)	<0.001

Obstetric & Service						
Onset of labour (No;%) ^a						
Spontaneous onset	66,467 (75.4)	179,245 (75.4)	454,522 (75.2)	71,878 (74.2)	10,484 (70.1)	<0.001
Amniotomy (± oxytocin)	9,541 (10.8)	26,660 (11.2)	64,989 (10.8)	10,318 (10.7)	1,826 (12.2)	0.04
Prostaglandin (± oxytocin)	12,156 (13.8)	31,984 (13.4)	85,296 (14.1)	14,634 (15.1)	2,637 (17.6)	<0.001
Mode of delivery						
Spontaneous vaginal delivery	69,705 (79.0)	186,937 (78.6)	447,405 (74.0)	66,937 (69.1)	9,615 (64.3)	<0.001
Assisted vaginal delivery	12,056 (13.7)	29,072 (12.2)	77,346 (12.8)	11,091 (11.5)	1,599 (10.7)	<0.001
Emergency caesarean delivery	5,800 (6.6)	16,993 (7.1)	52,943 (8.8)	10,542 (10.9)	1,954 (13.1)	<0.001
Elective caesarean delivery	632 (0.7)	4,948 (2.1)	27,322 (4.5)	8,300 (8.6)	1,785 (11.9)	<0.001
Hospital throughput						
No of deliveries/year (No;%)						
<1000	5,340 (6.1)	18,880 (7.9)	46,116 (7.6)	7,051 (7.3)	1,100 (7.4)	
1000 - 1999	18,688 (21.2)	52,104 (21.9)	123,327 (20.4)	16,909 (17.5)	2,498 (16.7)	
2000 - 2999	19,156 (21.7)	50,934 (21.4)	132,478 (21.9)	21,391 (22.1)	3,209 (21.5)	<0.001
3000 - 3999	21,264 (24.1)	53,254 (22.4)	134,953 (22.3)	22,080 (22.8)	3,550 (23.7)	
≥4000	23,745 (26.9)	62,778 (26.4)	168,142 (27.8)	29,439 (30.4)	4,596 (30.7)	
Perinatal death (PND)						
Delivery related PND	71 (0.08)	192 (0.08)	448 (0.07)	70 (0.07)	22 (0.15)	>0.99
Anoxic cause PND	41 (0.05)	97 (0.04)	293 (0.05)	43 (0.04)	16 (0.11)	0.08
Non-anoxic cause PND	30 (0.03)	95 (0.04)	155 (0.03)	27 (0.03)	6 (0.04)	0.04

* Two sided *P* value; Kruskal-Wallis and chi-squared test for trend. ^a Small numbers of missing values in other variables as follows:

maternal age 20 (0.002%), parity (0.04%), sex 24 (0.002%), birth weight 316 (0.03%) and onset of labour 345 (0.03%). IQR – inter-quartile range.

Table 2. Crude and Adjusted Odds Ratio for Delivery Related Perinatal Death During the Study Period by Categories of Maternal Age (n=1,043,002), Scotland, 1985 to 2004.

Maternal age	All cause PND (n=803)		Anoxic cause PND (n=490)		Non-anoxic cause PND (n=313)	
	Crude OR (95% CI)	Adjusted OR ^a (95% CI)	Crude OR (95% CI)	Adjusted OR ^a (95% CI)	Crude OR (95% CI)	Adjusted OR ^a (95% CI)
<20	1.09 0.85-1.40	0.91 0.70-1.18	0.96 0.69-1.33	0.71 0.50-1.00	1.33 0.90-1.96	1.35 0.90-2.05
20-24	1.09 0.92-1.29	0.98 0.82-1.16	0.84 0.67-1.06	0.70 0.55-0.88	1.56 1.21-2.01	1.57 ^b 1.21-2.05
25-34	Referent		Referent		Referent	
35-39	0.98 0.76-1.26	1.07 0.83-1.39	0.92 0.67-1.26	1.11 0.80-1.53	1.09 0.72-1.64	1.03 0.68-1.56
>39	1.99 1.30-3.05	2.20 1.42-3.40	2.21 1.34-3.66	2.76 1.65-4.61	1.57 0.69-3.54	1.40 0.62-3.17

^a Adjusted for year of birth, maternal height, parity, socio-economic deprivation status, gestational age, birth weight percentile, fetal sex, onset of labour and hospital throughput. ^b Excess deaths due to Sudden Infant Death Syndrome (SIDS). PND – perinatal death, OR – odds ratio, CI – confidence interval.