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Maternal age and adverse pregnancy outcome: a cohort study

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KEYWORDS: Cesarean section; gestational diabetes; pre-eclampsia; pregnancy complications; preterm delivery; stillbirth

ABSTRACT

Objective *To examine the association between maternal age and a wide range of adverse pregnancy outcomes after adjustment for confounding factors in obstetric history and maternal characteristics.*

Methods *This was a retrospective study in women with singleton pregnancies attending the first routine hospital visit at 11 + 0 to 13 + 6 weeks' gestation. Data on maternal characteristics, and medical and obstetric history were collected and pregnancy outcomes ascertained. Maternal age was studied, both as a continuous and as a categorical variable. Regression analysis was performed to examine the association between maternal age and adverse pregnancy outcome including pre-eclampsia, gestational hypertension, gestational diabetes mellitus (GDM), preterm delivery, small-for-gestational age (SGA) neonate, large-for-gestational age (LGA) neonate, miscarriage, stillbirth and elective and emergency Cesarean section.*

Results *The study population included 76 158 singleton pregnancies with a live fetus at 11 + 0 to 13 + 6 weeks. After adjusting for potential maternal and pregnancy confounding variables, advanced maternal age (defined as ≥ 40 years) was associated with increased risk of miscarriage (odds ratio (OR), 2.32 (95% CI, 1.83–2.93); P < 0.001), pre-eclampsia (OR, 1.49 (95% CI, 1.22–1.82); P < 0.001), GDM (OR, 1.88 (95% CI, 1.55–2.29); P < 0.001), SGA (OR, 1.46 (95% CI, 1.27–1.69); P < 0.001) and Cesarean section (OR, 1.95 (95% CI, 1.77–2.14); P < 0.001), but not with stillbirth, gestational hypertension, spontaneous preterm delivery or LGA.*

Conclusions *Maternal age should be combined with other maternal characteristics and obstetric history when calculating an individualized adjusted risk for adverse pregnancy complications. Advanced maternal age is a risk factor for miscarriage, pre-eclampsia, SGA, GDM and Cesarean section, but not for stillbirth, gestational hypertension, spontaneous preterm delivery or LGA.*

INTRODUCTION

A rising trend in advanced maternal age has been observed over the last few decades, particularly in high-income countries[1–7]. A commonly accepted definition of advanced maternal age is 35 years or more. Several studies have examined the association between advanced maternal age and adverse pregnancy outcome, including miscarriage, stillbirth, pre-eclampsia, gestational hypertension, gestational diabetes mellitus (GDM), preterm birth, delivery of a small- (SGA) or large- (LGA) for-gestational-age neonate and elective or emergency Cesarean section; these studies have reported contradictory findings[8–15]. Such discordance could be attributed to differences in the populations studied and in the definition of outcomes, with some studies failing to distinguish between pre-eclampsia and gestational hypertension, iatrogenic and spontaneous preterm birth or elective and emergency Cesarean section. Additionally, many studies failed to adjust for potential confounders.

The aim of this study was to examine the association between maternal age and a wide range of adverse pregnancy outcomes after adjustment for confounding factors in maternal characteristics and obstetric history.

METHODS

This was a retrospective study in women attending for their first routine hospital antenatal visit at three UK hospitals: King's College Hospital, London; University College London Hospitals, London; and Medway Maritime Hospital, Kent. This visit, which was held at 11 + 0

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to 13 + 6 weeks' gestation, included recording maternal demographic characteristics and obstetric and medical history, measurement of maternal weight and height, ultrasound examination for the measurement of fetal crown–rump length and to determine gestational age[16], measurement of fetal nuchal translucency thickness[17], and examination of the fetal anatomy for the diagnosis of major fetal defects[18]. Data on pregnancy outcome were collected from the hospital maternity records and the women's general medical practitioners.

Participants completed a questionnaire on their age, racial origin (Caucasian, Afro-Caribbean, South Asian, East Asian or mixed), method of conception (spontaneous or assisted), cigarette smoking during pregnancy, history of chronic hypertension, history of Type 1 or Type 2 diabetes mellitus and obstetric history, including the outcome of each previous pregnancy. The questionnaire was then reviewed by a doctor and the woman together.

Outcome measures included miscarriage, stillbirth, pre-eclampsia, gestational hypertension, GDM, spontaneous and iatrogenic preterm delivery before 34 weeks' gestation, delivery of an SGA or LGA neonate and delivery by elective or emergency Cesarean section.

We excluded pregnancies with fetal aneuploidies or major defects diagnosed either prenatally or in the neonatal period, and pregnancies ending in termination for psychosocial reasons.

Miscarriage included spontaneous miscarriage and fetal death after screening at 11 + 0 to 13 + 6 weeks and before 24 weeks' gestation. Stillbirth was defined as fetal death at or after 24 weeks. The diagnosis of pre-eclampsia and gestational hypertension was made according to the guidelines of the International Society for the Study of Hypertension in Pregnancy[19]. Gestational hypertension was defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg on at least two occasions 4 h apart, developing after 20 weeks' gestation in a previously normotensive woman in the absence of significant proteinuria. Pre-eclampsia was defined as gestational hypertension with proteinuria of ≥ 300 mg in 24 h, or two readings of at least ++ on dipstick analysis of midstream or catheter urine specimen, if no 24-h collection was available. We also subdivided pre-eclampsia according to gestational age at delivery into early pre-eclampsia (< 34 weeks) and late pre-eclampsia (≥ 34 weeks). In the investigation of the relationship between maternal age and pre-eclampsia or gestational hypertension we excluded pregnancies ending in miscarriage or fetal death before 24 weeks' gestation.

Screening for GDM was based on a two-step approach. In all women, random plasma glucose was measured at 24–28 weeks' gestation and, if the concentration was > 6.7 mmol/L, an oral glucose tolerance test was carried out within 2 weeks. A diagnosis of GDM was made if the fasting plasma glucose level was at least 6 mmol/L or the plasma glucose level 2 h after oral administration of 75 g glucose was ≥ 7.8 mmol/L[20]. In women with a normal random blood glucose level, an oral glucose tolerance test was performed if they had persistent glycosuria or developed polyhydramnios or the fetus became macrosomic. In the investigation of the relationship between maternal age and GDM we excluded pregnancies with prepregnancy diabetes mellitus Type 1 or 2 and those ending in miscarriage or delivery before 30 weeks because they might not have had screening and diagnosis of GDM.

Spontaneous preterm delivery included those with spontaneous onset of labor and those with preterm prelabor rupture of membranes occurring before 34 completed weeks (238 days) of pregnancy. In the investigation of the relationship between maternal age and spontaneous preterm delivery, we excluded pregnancies ending in miscarriage or stillbirth and those with iatrogenic delivery before 34 weeks. The commonest causes of iatrogenic preterm delivery in our cohort were pre-eclampsia and fetal growth restriction. In the investigation of the relationship between maternal age and iatrogenic preterm delivery, we excluded pregnancies ending in miscarriage or stillbirth and those with spontaneous delivery before 34 weeks.

SGA and LGA neonates were defined as those with birth weight below the 5th percentile or above the 95th percentile for gestation, respectively[21]. In the investigation of the relationship between maternal age and SGA or LGA, we excluded pregnancies ending in miscarriage or fetal death before 24 weeks.

Emergency Cesarean section included all cases in which such delivery was undertaken after the onset of labor, usually for failure to progress, fetal distress or intrapartum hemorrhage. This group also included cases of antepartum hemorrhage requiring Cesarean section. Elective Cesarean section was performed before the onset of labor for obstetric or medical indications or at the request of the mother. In the investigation of the relationship between maternal age and elective or emergency Cesarean section, we excluded pregnancies ending in miscarriage or fetal death before 24 weeks.

Statistical analysis

We examined the association between maternal age, both as a continuous and as a categorical variable, with each pregnancy complication. Women were categorized into three age groups: < 35 years, 35–39.9 years and ≥ 40 years. First, univariable logistic regression analysis was performed to examine the association between maternal age and each of the adverse pregnancy outcomes by likelihood ratio test. Odds ratios with their respective confidence intervals were calculated for the 35–39.9-year and ≥ 40-year groups, using the group aged less than 35 years as a reference. The risk for each of the pregnancy outcomes was then calculated from the formula: odds/(1 + odds), where odds = e^Y, and Y was derived from the univariable logistic regression analysis. Second, in those variables for which there was a significant association, in order to assess the trend of this association, another logistic regression analysis was

carried out with orthogonal polynomial contrast, using the center of each interval for the metric (24.6, 37.5 and 47.7, respectively).

Multivariable logistic regression analysis was performed for the prediction of each pregnancy outcome by maternal age, weight, height, racial origin, mode of conception, smoking, history of chronic hypertension or diabetes, history of adverse outcome in a previous pregnancy or family history of pre-eclampsia. Before performing the multivariable regression analysis, continuous variables were centered by subtracting the mean from each measured value (69 for maternal weight in kg, 1.64 for maternal height in meters and 30 for maternal age in years). The statistical software package SPSS Statistics 20.0 (SPSS Inc., Chicago, IL, USA) was used for data analysis.

RESULTS

During the study period, first-trimester combined screening for aneuploidies was carried out in 79 694 singleton pregnancies. We excluded from further analysis 3533 (4.4%) women because there were no or incomplete data on pregnancy outcome ($n = 2407$), because of the prenatal or postnatal diagnosis of aneuploidy or major defect or because of pregnancy termination for psychosocial reasons ($n = 1126$).

In the remaining 76 161 singleton pregnancies, there were 75 104 live births, 764 (1.0%) miscarriages and 293 (0.4%) stillbirths. In three of the stillbirths, fetal death was the consequence of maternal death (car accident in two and eclampsia in one), and these were excluded from further analysis.

In the 76 158 cases included in the study, the median maternal age was 31.3 (interquartile range (IQR), 26.8–35.2) years, median height was 164 (IQR, 160.0–168.0) cm and median weight was 65.5 (IQR, 59.0–75.6) kg; 7651 (10.0%) women were cigarette smokers, 870 (1.1%) had a history of chronic hypertension and 545 (0.7%) had a history of Type 1 or Type 2 diabetes. The racial origin was Caucasian in 57 564 (75.6%), Afro-Caribbean in 11 395 (15.0%), South Asian in 3645 (4.8%), East Asian in 1793 (2.4%) and mixed in 1761 (2.3%). Out of the 76 158 cases included in the study, 55 772 (73.2%) were under 35, 16 325 (21.4%) were between 35 and 39 and 4061 (5.3%) were 40 or more.

Pregnancy complications

The frequency of pregnancy outcomes according to the maternal age group is described in Table 1. Univariable logistic regression analysis demonstrated that maternal age at 11–13 weeks' gestation was significantly associated with miscarriage, pre-eclampsia, GDM, delivery of an SGA or LGA neonate and both elective and emergency Cesarean section, but not stillbirth, gestational hypertension, or spontaneous preterm delivery (Table 2, Figure 1). There was a significant quadratic trend towards increased miscarriage, pre-eclampsia, GDM requiring insulin, SGA and elective Cesarean section, but not towards emergency Cesarean section (Table 3).

The results of multivariable logistic regression analysis for the prediction of miscarriage, pre-eclampsia, GDM, delivery of an SGA or LGA neonate, iatrogenic preterm delivery and elective or emergency Cesarean section, by maternal age, weight, height, ethnic origin, smoking history, history of chronic hypertension or diabetes and previous obstetric history, are summarized in Tables 4–6.

Multiple logistic regression analysis demonstrated that, in women whose pregnancy was complicated by

Table 1 Frequency of pregnancy complications according to maternal age group

		Maternal age group		
Pregnancy outcome	*Total*	*< 35 years (n = 55 772)*	*35–39 years (n = 16 325)*	*≥ 40 years (n = 4061)*
Fetal loss	1054	684 (1.2)	262 (1.6)	108 (2.7)
Miscarriage	764	489 (0.9)	187 (1.1)	88 (2.2)
Stillbirth	290	195 (0.3)	75 (0.5)	20 (0.5)
Hypertensive disorder*	3505	2517 (4.6)	743 (4.6)	245 (6.2)
Pre-eclampsia	1698	1191 (2.2)	377 (2.3)	130 (3.3)
Gestational hypertension	1807	1326 (2.4)	366 (2.3)	115 (2.9)
Gestational diabetes*	1355	839 (1.5)	392 (2.4)	124 (3.1)
Abnormal growth*				
LGA (> 95th centile)	4495	3071 (5.6)	1124 (7.0)	300 (7.6)
SGA (< 5th centile)†	3866	2900 (5.4)	740 (4.7)	226 (5.9)
Delivery before 34 weeks*	1281	897 (1.6)	293 (1.8)	91 (2.3)
Spontaneous	768	549 (1.0)	167 (1.0)	52 (1.3)
Iatrogenic	513	348 (0.6)	126 (0.8)	39 (1.0)
Cesarean section*	19 523	12 727 (23.0)	5284 (32.7)	1512 (38.1)
Elective	8785	5207 (9.4)	2755 (17.1)	823 (20.7)
Emergency	10 738	7520 (13.6)	2529 (15.7)	689 (17.3)

Data given as *n* (%). *Pregnancies complicated by miscarriage were excluded from analysis of hypertensive disorders, gestational diabetes, abnormal growth, delivery before 34 weeks and Cesarean section. †From the SGA group, pregnancies affected with pre-eclampsia were also excluded. LGA, large-for-gestational age; SGA, small-for-gestational age.

Table 2 Univariable logistic regression analysis of the association between maternal age at 11 + 0 to 13 + 6 weeks' gestation and pregnancy complications

		Age as continuous variable		*Age as categorical variable*		
Pregnancy outcome	n	*OR (95% CI)*	P	*35–39 years OR (95% CI)*	*≥ 40 years OR (95% CI)*	P*
Fetal loss						
Miscarriage	764	1.03 (1.02–1.04)	< 0.001	1.31 (1.11–1.55)	2.51 (1.99–3.15)	< 0.001
Stillbirth	290	1.00 (0.98–1.02)	0.748	1.32 (1.01–1.72)	1.43 (0.90–2.27)	0.068
Hypertensive disorder						
Pre-eclampsia	1698	1.01 (1.00–1.01)	0.175	1.08 (0.96–1.22)	1.54 (1.29–1.86)	< 0.001
Early (delivery < 34 weeks)	260	1.01 (0.99–1.03)	0.349	1.30 (0.97–1.72)	1.89 (1.22–2.93)	0.012
Intermediate (delivery at 34–37 weeks)	435	1.02 (1.00–1.03)	0.056	1.13 (0.90–1.42)	1.65 (1.16–2.34)	0.027
Late (delivery > 37 weeks)	1003	1.00 (0.99–1.01)	0.959	1.02 (0.87–1.19)	1.42 (1.11–1.81)	0.027
Gestational hypertension	1807	1.00 (1.00–1.01)	0.315	0.95 (0.84–1.06)	1.23 (1.01–1.49)	0.063
Gestational diabetes	1355	1.06 (1.05–1.07)	< 0.001	1.62 (1.43–1.83)	2.10 (1.74–2.55)	< 0.001
Gestational diabetes on insulin	586	1.06 (1.05–1.08)	< 0.001	1.81 (1.52–2.17)	1.96 (1.45–2.65)	< 0.001
Abnormal growth						
LGA (> 95th centile)	4495	1.03 (1.02–1.03)	< 0.001	1.27 (1.19–1.37)	1.39 (1.23–1.57)	< 0.001
SGA (< 5th centile)	3866	0.98 (0.97–0.98)	< 0.001	0.87 (0.80–0.94)	1.10 (0.96–1.27)	0.001
Delivery before 34 weeks						
Spontaneous	768	1.00 (0.99–1.01)	0.984	1.04 (0.88–1.24)	1.33 (1.00–1.77)	0.170
Iatrogenic	513	1.00 (0.99–1.02)	0.656	1.24 (1.01–1.52)	1.57 (1.13–2.19)	0.010
Cesarean section						
Elective	8785	1.09 (1.08–1.09)	< 0.001	2.07 (1.97–2.18)	2.73 (2.51–2.97)	< 0.001
Emergency	10 738	1.03 (1.03–1.04)	< 0.001	1.32 (1.25–1.39)	1.58 (1.45–1.73)	< 0.001

*Likelihood ratio test. LGA, large-for-gestational age; OR, odds ratio; SGA, small-for-gestational age.

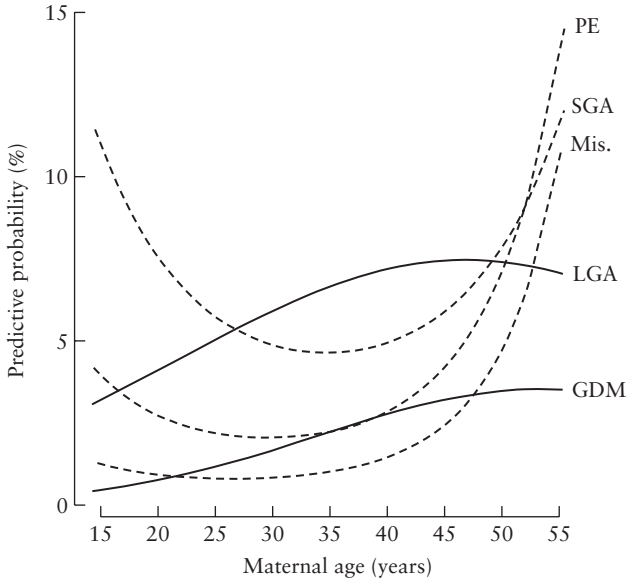

Figure 1 Predictive probability of miscarriage (Mis.), pre-eclampsia (PE), small-for-gestational age (SGA) fetus, gestational diabetes mellitus (GDM) and large-for-gestational age (LGA) fetus plotted against maternal age.

miscarriage, there were significant contributions from maternal age between 35 and 39.9 years, maternal age of 40 years or more, weight, height, Afro-Caribbean and mixed racial origin, assisted conception using ovulation drugs, cigarette smoking and Type 2 diabetes (Table 4) (Nagelkerke $R^2 = 0.093$, $P < 0.001$).

In the prediction of pre-eclampsia, there were significant contributions from maternal age between 35 and 39.9 years, maternal age of 40 years or more, weight, height, Afro-Caribbean and South Asian racial origin, assisted conception using *in-vitro* fertilization (IVF), chronic hypertension, Type 1 diabetes, previous pre-eclampsia and family history of pre-eclampsia (Table 4) (Nagelkerke $R^2 = 0.112$, $P < 0.001$).

In the prediction of GDM, there were significant contributions from maternal age between 35 and 39.9 years, maternal age of 40 years or more, weight, height, and Afro-Caribbean, South Asian and East Asian racial origin (Table 5) (Nagelkerke $R^2 = 0.073$, $P < 0.001$). Risk factors for delivering an SGA neonate included maternal age between 35 and 39.9 years, maternal age of 40 years or more, all non-Caucasian racial origins, assisted conception using ovulation drugs, smoking, chronic hypertension and Type 2 diabetes mellitus. Maternal weight, height, multiparity and Type 1 diabetes mellitus were associated with reduced risk of SGA (Table 5) (Nagelkerke $R^2 = 0.074$, $P < 0.001$). Maternal weight, height and both Type 1 and Type 2 diabetes mellitus were associated with an increased risk of delivering an LGA neonate, while Afro-Caribbean, South Asian and mixed racial origin, cigarette smoking and chronic hypertension were associated with a reduced risk, and maternal age was not significantly associated with LGA (Table 5) (Nagelkerke $R^2 = 0.092$, $P < 0.001$).

Risk factors for iatrogenic preterm delivery included maternal age between 35 and 39.9 years, maternal age of 40 years or more, weight, Afro-Caribbean, South Asian and mixed racial origin, assisted conception, cigarette smoking, chronic hypertension and Type 1 diabetes

Table 3 Logistic regression analysis of the association between maternal age at 11 + 0 to 13 + 6 weeks' gestation and pregnancy complications with orthogonal polynomial contrast

	Linear trend		*Quadratic trend*	
Pregnancy outcome	*Coefficient*	P	*Coefficient*	P
Hypertensive disorder				
Pre-eclampsia	0.300	< 0.001	0.131	0.028
Early (delivery < 34 weeks)	0.447	0.003	0.079	0.557
Intermediate (delivery at 34–37 weeks)	0.345	0.005	0.129	0.262
Late (delivery > 37 weeks)	0.239	0.005	0.079	0.066
Gestational hypertension	—	—	—	—
Gestational diabetes	0.530	< 0.001	−0.055	0.360
Gestational diabetes on insulin	0.489	< 0.001	−0.179	0.048
Fetal loss				
Miscarriage	0.639	< 0.001	0.197	0.013
Stillbirth	—	—	—	—
Abnormal growth				
LGA (> 95th centile)	0.236	< 0.001	−0.047	0.209
SGA (< 5th centile)	0.059	0.225	0.158	< 0.001
Delivery before 34 weeks				
Spontaneous	—	—	—	—
Iatrogenic	0.318	0.006	0.028	0.791
Cesarean section				
Elective	0.722	< 0.001	−0.138	< 0.001
Emergency	0.327	< 0.001	−0.016	0.546

LGA, large-for-gestational age; SGA, small-for-gestational age.

Table 4 Multivariable logistic regression analysis for prediction of miscarriage and pre-eclampsia by maternal factors and obstetric history

	Miscarriage		*Pre-eclampsia*	
Independent variable	*OR (95% CI)*	P	*OR (95% CI)*	P
Maternal age				
<35 years (reference)	1		1	
35–39 years	1.36 (1.15–1.62)	< 0.001	1.19 (1.05–1.35)	0.006
≥ 40 years	2.32 (1.83–2.93)	< 0.001	1.49 (1.22–1.82)	< 0.001
Maternal weight – 69 (kg)*	1.01 (1.01–1.02)	< 0.001	1.02 (1.02–1.03)	< 0.001
Maternal height – 1.64 (m)*	0.35 (0.12–0.99)	0.047	0.06 (0.03–0.12)	< 0.001
Ethnic origin				
Caucasian (reference)	1		1	
Afro-Caribbean	3.17 (2.70–3.72)	< 0.001	2.60 (2.32–2.92)	< 0.001
South Asian	1.37 (0.95–1.96)	0.092	1.76 (1.42–2.19)	< 0.001
East Asian	1.20 (0.70–2.05)	0.517	1.13 (0.79–1.63)	0.499
Mixed	2.33 (1.60–3.42)	< 0.001	1.29 (0.92–1.80)	0.137
Conception				
Spontaneous (reference)	1		1	
Ovulation drugs	2.99 (2.11–4.24)	< 0.001	1.15 (0.79–1.68)	0.459
In-vitro fertilization	1.16 (0.72–1.88)	0.536	1.68 (1.28–2.19)	< 0.001
Cigarette smoking	1.33 (1.05–1.68)	0.018	0.90 (0.75–1.08)	0.261
History of chronic hypertension	1.45 (0.94–2.22)	0.091	4.69 (3.82–5.74)	< 0.001
History of pre-existing diabetes mellitus				
None (reference)	1		1	
Type 1	2.02 (0.89–4.57)	0.091	2.08 (1.25–3.45)	0.005
Type 2	2.31 (1.20–4.46)	0.012	0.97 (0.52–1.80)	0.918
Obstetric history				
No pregnancy >16 weeks (reference)	1		—	—
Previous pregnancy > 16 weeks			—	—
Previous pregnancy with live birth	0.99 (0.85–1.15)	0.867	—	—
Previous pregnancy with miscarriage/stillbirth	1.21 (0.71–2.06)	0.48	—	—
Parity				
Nulliparous (reference)	—	—	1	
Parous without previous pre-eclampsia	—	—	0.31 (0.28–0.35)	< 0.001
Parous with previous pre-eclampsia	—	—	2.19 (1.86–2.59)	< 0.001
Family history of pre-eclampsia	—	—	1.59 (1.32–1.92)	< 0.001

OR, odds ratio. *Continuous variables were centered by subtraction of mean values (69 kg for maternal weight and 1.64 m for maternal height).

Table 5 Multivariable logistic regression analysis for the prediction of gestational diabetes and small- or large-for-gestational age neonates by maternal factors and obstetric history

	Gestational diabetes		*Large-for-gestational age*		*Small-for-gestational age*	
Independent variable	*OR (95% CI)*	P	*OR (95% CI)*	P	*OR (95% CI)*	P
Maternal age						
< 35 years (reference)	1		1		1	
35–39 years	1.62 (1.43–1.83)	< 0.001	1.06 (0.98–1.14)	0.127	1.15 (1.05–1.25)	0.002
≥ 40 years	1.88 (1.55–2.29)	< 0.001	1.10 (0.97–1.25)	0.133	1.46 (1.27–1.69)	< 0.001
Maternal weight – 69 (kg)*	1.04 (1.04–1.04)	< 0.001	1.03 (1.03–1.03)	< 0.001	0.98 (0.98–0.98)	< 0.001
Maternal height – 1.64 (m)*	0.01 (0.01–0.02)	< 0.001	24.66 (15.92–38.20)	< 0.001	0.03 (0.02–0.05)	< 0.001
Ethnic origin						
Caucasian (reference)	1		1		1	
Afro-Caribbean	1.43 (1.25–1.64)	< 0.001	0.52 (0.47–0.57)	< 0.001	2.33 (2.14–2.54)	< 0.001
South Asian	2.66 (2.17–3.25)	< 0.001	0.55 (0.45–0.68)	< 0.001	2.31 (2.04–2.60)	< 0.001
East Asian	2.85 (2.16–3.76)	< 0.001	0.84 (0.65–1.09)	0.181	1.50 (1.24–1.81)	< 0.001
Mixed	1.16 (0.80–1.68)	0.429	0.66 (0.52–0.84)	0.001	1.68 (1.39–2.03)	< 0.001
Conception						
Spontaneous (reference)	1		1		1	
Ovulation drugs	1.55 (1.09–2.20)	0.015	1.08 (0.85–1.36)	0.527	1.52 (1.20–1.91)	< 0.001
In-vitro fertilization	1.22 (0.86–1.72)	0.264	0.92 (0.73–1.16)	0.461	1.12 (0.89–1.40)	0.343
Cigarette smoking	0.88 (0.72–1.08)	0.224	0.47 (0.41–0.53)	< 0.001	2.96 (2.72–3.23)	< 0.001
History of chronic hypertension	1.35 (0.97–1.89)	0.075	0.64 (0.48–0.86)	0.003	2.03 (1.53–2.68)	< 0.001
History of pre-existing diabetes mellitus						
None (reference)	—	—	1		1	
Type 1	—	—	7.12 (5.53–9.16)	< 0.001	0.34 (0.14–0.83)	0.018
Type 2	—	—	1.61 (1.07–2.42)	0.023	1.82 (1.09–3.05)	0.022
Parous	0.97 (0.87–1.09)	0.628	1.82 (1.70–1.94)	< 0.001	0.56 (0.52–0.59)	< 0.001

OR, odds ratio. *Continuous variables were centered by subtraction of mean values (69 kg for maternal weight and 1.64 m for maternal height).

mellitus, while maternal height and multiparity reduced the risk (Table 6) (Nagelkerke $R^2 = 0.053$, $P < 0.001$).

Regarding the mode of delivery, 19 523 (25.6%) delivered by Cesarean section, 8785 (11.5%) of which were elective and 10 738 (14.1%) were emergency Cesarean sections. In the group under 35 years old, 12 727 (23.0%) delivered by Cesarean section, compared with 5284 (32.7%) in the group aged 35–39 and 1512 (38.1%) in the group aged ≥ 40 years old ($P < 0.001$). Risk factors for elective Cesarean section included maternal age between 35 and 39.9 years, maternal age of 40 years or more, maternal weight, assisted conception using IVF, chronic hypertension, pre-existing diabetes mellitus and multiparity, while Afro-Caribbean and mixed racial origin, maternal height and cigarette smoking were associated with a reduced risk (Table 6) (Nagelkerke $R^2 = 0.075$, $P < 0.001$).

Risk factors for emergency Cesarean section included maternal age between 35 and 39.9 years, maternal age of 40 years or more, maternal weight, Afro-Caribbean and South Asian racial origin, assisted conception using IVF, chronic hypertension and pre-existing diabetes mellitus. Taller and parous women were less likely to have an emergency Cesarean section (Table 6) (Nagelkerke $R^2 = 0.093$, $P < 0.001$).

Odds ratios for the risk of pregnancy complications according to maternal age, after adjustment for maternal characteristics and obstetric history, are shown in Figure 2.

DISCUSSION

The results of this study demonstrate that advanced maternal age, after adjustment for other maternal characteristics and obstetric history, is associated with increased risk for a wide range of adverse pregnancy outcomes, including miscarriage, pre-eclampsia, SGA, GDM and Cesarean section, but not stillbirth, gestational hypertension, spontaneous preterm delivery or LGA. These findings are of particular interest to both the women themselves and healthcare professionals because of the rising trend to delayed childbearing secondary to improving access to education, career opportunities, contraception and assisted reproductive techniques.

The strengths of this study include the large number of subjects from a multiracial inner-city population, prospective collection of data, accurate assessment of gestational age and recording of maternal weight and height, examination of a wide range of adverse pregnancy outcomes and the use of multivariable logistic regression analysis to control for risk factors associated with each adverse outcome. Additionally, we present results for both the traditionally used arbitrary age thresholds of 35 and 40 years to allow comparison with the findings of previous studies, but we have also examined maternal age as a continuous variable. A limitation of our study is the lack of data on level of education and socioeconomic class of the women.

Our results are in general agreement with those of previous studies that examined advanced maternal age

Table 6 Multivariable logistic regression analysis for the prediction of iatrogenic preterm delivery before 34 weeks' gestation and elective and emergency Cesarean section by maternal factors and obstetric history

	Iatrogenic preterm delivery		*Elective Cesarean section*		*Emergency Cesarean section*	
Independent variable	*OR (95% CI)*	P	*OR (95% CI)*	P	*OR (95% CI)*	P
Maternal age						
< 35 years (reference)	1		1		1	
35–39 years	1.28 (1.03–1.59)	0.023	1.80 (1.71–1.90)	< 0.001	1.62 (1.54–1.71)	< 0.001
≥ 40 years	1.35 (0.95–1.92)	0.09	2.17 (1.99–2.37)	< 0.001	1.95 (1.77–2.14)	< 0.001
Maternal weight – 69 (kg)*	1.01 (1.01–1.02)	< 0.001	1.02 (1.02–1.02)	< 0.001	1.02 (1.02–1.02)	< 0.001
Maternal height – 1.64 (m)*	0.03 (0.01–0.12)	< 0.001	0.04 (0.03–0.06)	< 0.001	0.01 (0.01–0.01)	< 0.001
Ethnic origin						
Caucasian (reference)	1		1		1	
Afro-Caribbean	2.42 (1.97–2.98)	< 0.001	0.84 (0.79–0.90)	< 0.001	1.41 (1.33–1.50)	< 0.001
South Asian	1.59 (1.08–2.34)	0.019	1.08 (0.97–1.21)	0.142	1.22 (1.11–1.35)	< 0.001
East Asian	1.19 (0.64–2.19)	0.583	0.97 (0.83–1.13)	0.70	1.04 (0.91–1.20)	0.559
Mixed	1.78 (1.07–2.96)	0.025	0.82 (0.70–0.97)	0.019	0.94 (0.81–1.09)	0.396
Conception						
Spontaneous (reference)	1		1		1	
Ovulation drugs	2.07 (1.25–3.45)	0.005	1.08 (0.90–1.28)	0.413	0.98 (0.83–1.16)	0.835
In-vitro fertilization	2.25 (1.45–3.47)	< 0.001	2.01 (1.75–2.31)	< 0.001	1.40 (1.23–1.60)	< 0.001
Cigarette smoking	1.83 (1.41–2.36)	< 0.001	0.76 (0.70–0.83)	< 0.001	0.93 (0.87–1.01)	0.073
History of chronic hypertension	5.66 (4.04–7.93)	< 0.001	1.23 (1.01–1.50)	0.039	1.81 (1.52–2.14)	< 0.001
History of pre-existing diabetes mellitus						
None (reference)	1		1		1	
Type 1	6.44 (3.73–11.13)	< 0.001	3.92 (2.93–5.25)	< 0.001	4.42 (3.36–5.80)	< 0.001
Type 2	2.11 (0.94–4.70)	0.069	2.15 (1.53–3.01)	< 0.001	1.69 (1.18–2.42)	0.004
Parous	0.65 (0.54–0.78)	< 0.001	1.89 (1.80–1.99)	< 0.001	0.35 (0.33–0.37)	< 0.001

OR, odds ratio. *Continuous variables were centered by subtraction of mean values (69 kg for maternal weight and 1.64 m for maternal height).

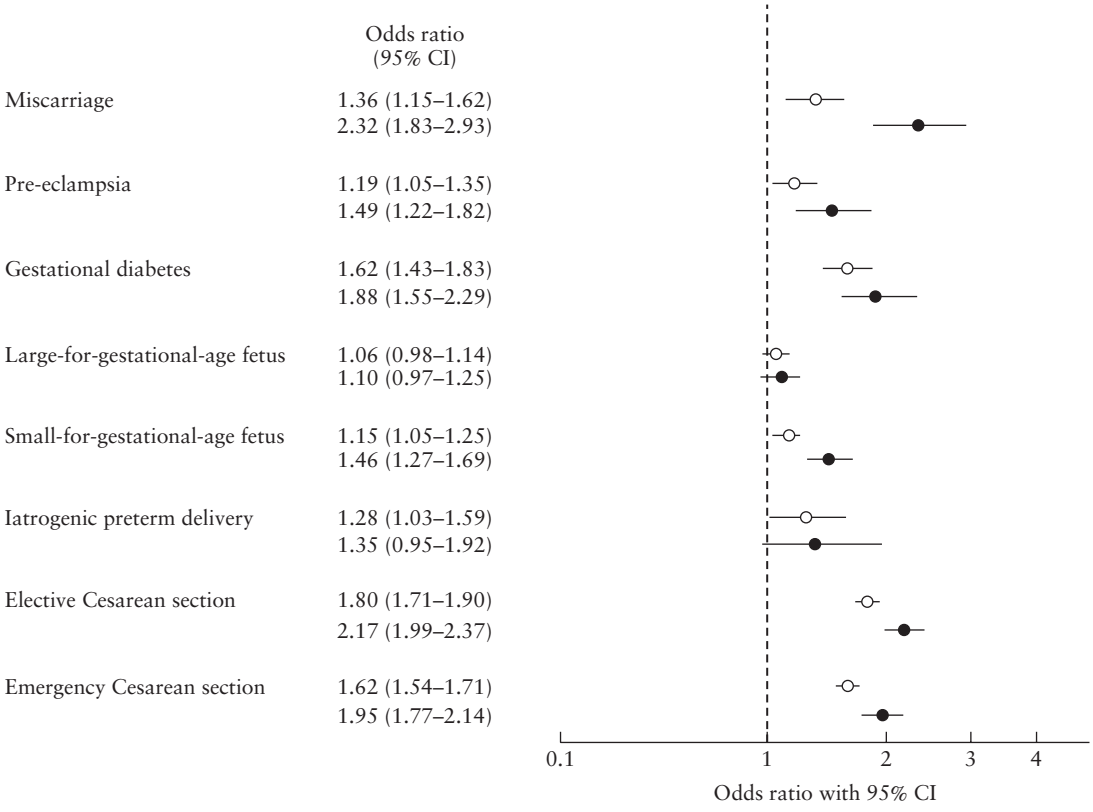

Figure 2 Forest plot of odds ratios with 95% CIs, after adjustment for maternal characteristics and obstetric history, for the risk of pregnancy complications according to maternal-age group (35–39 years (○) or ≥ 40 years (●)), compared with maternal age group < 35 years.

in its relation to pregnancy complications as a categorical variable[11,13,15,22–35]. Although such analysis does not allow accurate estimation of patient-specific risks, it highlights the concerns raised in earlier studies associated with delaying childbearing[11,13,15,22–35]. It seems that there is a stepwise increase in the risk of pregnancy complications with increasing maternal age. Cleary-Goldman *et al.*[22] examined the association between advanced maternal age and adverse pregnancy outcome in 36 056 women included in the FASTER multicenter trial and reported a significant association with rates of miscarriage, GDM, Cesarean section, low birth weight and iatrogenic preterm delivery. Consistent with our findings, these authors demonstrated no significant association between advanced maternal age and gestational hypertension or spontaneous preterm delivery. The authors adjusted for potential confounders and concluded that increasing age is independently associated with specific pregnancy complications in a continuous rather than a stepwise fashion[22].

The risk of miscarriage increased exponentially with maternal age, and compared to women under the age of 35 years the risk for those aged 35–39 years was 1.3 times higher and for those aged 40 years or more the risk was 2.5 times higher. Since women in our study were recruited at 11–13 weeks' gestation when the fetus had been shown to be alive, most of the miscarriages occurred in the second trimester. The likely causes for such late miscarriages are fetal death secondary to extreme placental impairment and extreme early spontaneous delivery of a fetus that died during labor and/or delivery. In this respect, miscarriage cases in our study could be considered to represent the extreme end of the spectrum of impaired placentation, resulting in pre-eclampsia, SGA, stillbirth and spontaneous preterm delivery. In previous studies reporting on the association of maternal age with miscarriage the majority of fetal losses occurred in the first trimester, and these could be attributed to aneuploidies[22,23].

The risk of pre-eclampsia increased exponentially with maternal age, especially after the age of 40 years, when the risk was 1.5 times higher than in women under the age of 35 years. This is consistent with the findings of a systematic review examining several risk factors for pre-eclampsia and reporting that age over 40 years is associated with a doubling in risk[29]. Nationwide data from the USA have shown that the risk of pre-eclampsia does not appear to be affected by age before 35 years but increases thereafter by 30% per year[36]. In a study examining the maternal risk factors for hypertensive disorders in pregnancy, we showed that the risk for late-onset pre-eclampsia increases by 4% for every year over the age of 32 years[37]. Increasing age is associated with glucose intolerance due to a reduction in insulin sensitivity and abnormal lipid profile with increased levels of triglycerides and cholesterol[38,39]. In the case of SGA there is a U-shaped relationship with maternal age, with an increased risk for women under the age of 30 years and for those over 40 years. In a study involving 33 602 women investigating the prediction of SGA at 11–13 weeks' gestation, increased maternal age was associated with 1.7 times the risk for SGA, when age was analyzed as a continuous variable[40]. In a case–control study including 824 cases and 1648 controls randomly selected from the same population during the same study period, Odibo *et al.*[10] reported a positive dose–response association between increasing maternal age and increasing risk for growth restriction. Maternal age greater than 35 and greater than 40 years was independently associated with intrauterine growth restriction, with odds ratios of 1.4 and 3.2, respectively. The mechanism of the association between advanced maternal age and SGA has not yet been established. Possible confounders include chronic hypertension, diabetes and increased risk of aneuploidy. However, even after adjusting for these factors, there remains an independent significant association. A similar phenomenon has also been described in animal studies[41]. Some authors have proposed a role for poor oxygen exchange as a possible cause of the increased risk of SGA associated with advanced maternal age[26,42].

The risk of iatrogenic, but not spontaneous, early preterm delivery increased with maternal age. This is not surprising because the main indications for iatrogenic delivery before 34 weeks' gestation are pre-eclampsia and SGA, both of which increased exponentially with advancing maternal age. The observed difference between spontaneous and iatrogenic preterm delivery in their relationship to maternal age may offer an explanation for the contradictory results of previous studies that did not differentiate between the two types of deliveries[11–14,22,23,28,32,34,35,43–47]. Similarly, studies varied in their results because of differences in the threshold for gestational age in the classification of preterm delivery, including 37-, 34- or 32-week deliveries[11–14,22,23,28,32,34,35,43–47] and failure to correct for confounding variables[23,34,46].

We found that the incidence of GDM increases with maternal age, reaching a plateau at around 40 years, an increase that is consistent with the findings of previous studies[11,22,25,27,31–35] and could be explained by the association between aging and progressive vascular endothelial damage[11,26,48]. The risk of GDM was higher in older women, even after adjusting for confounding factors associated with decreased insulin sensitivity such as ethnicity and obesity in the logistic regression model. Fulop *et al.*[38] reported a reduction in insulin sensitivity with age, and in individuals with impaired glucose tolerance, pancreatic β-cell function deteriorates with age[49]. In the univariable regression analysis we found an increase in the risk of delivery of LGA infants with maternal age, which was similar to the relationship of age with GDM and reached a plateau at around 40 years. However, after adjusting for potential confounding factors in a multivariate regression model, advanced maternal age was no longer significantly associated with LGA. Our results are in agreement with those of other studies[12,22,27,35].

In our study, which excluded cases with aneuploidy and structural abnormalities from the analysis, there was no significant association between maternal age

and stillbirth. This finding is in agreement with that of a recent study involving 45 033 nulliparous women with singleton gestations, which reported that advanced maternal age was not an independent risk factor for perinatal mortality[50]. A systematic review investigating the risk of stillbirth in relation to maternal age reported that the risk was not increased in 7 of 16 hospital-based cohort studies and, although the overall risk was increased, a pooled relative risk could not be calculated because of extreme methodological heterogeneity among the individual studies[8]. However, a significant association between advanced maternal age and the risk of stillbirth has been reported previously[8,11,50]. This difference could be explained by the fact that we excluded cases with aneuploidy or structural abnormalities. Alternatively our cohort might not have been adequately powered to address a potentially weak association.

The rates of both elective and emergency Cesarean section increased linearly with maternal age, a finding that is consistent with those of previous studies. A systematic review of 29 studies, including 15 that adjusted for potential confounders, reported an increased rate of Cesarean section among older women in all the individual studies[30]. However, the authors did not calculate a pooled estimate of the risk because of the extreme heterogeneity among the studies. Proposed causes for the increase in rate of Cesarean section with age include inefficiency of the aging myometrium, decreased number of oxytocin receptors[22,51–54], increased rates of chronic medical diseases and maternal complications such as pre-eclampsia and GDM[9,24,55,56], lower clinical threshold for obstetric interventions[51,54] and closer monitoring[54].

Early identification of women at increased risk of developing a pregnancy complication is likely to facilitate targeted surveillance and early intervention. In order to develop a clinically useful screening test, algorithms should be derived from multivariable logistic regression analysis combining maternal characteristics and biophysical and biochemical markers in order to develop an individualized adjusted risk for each adverse pregnancy outcome. We therefore propose a new approach to antenatal care, whereby the patient-specific risk for a wide variety of pregnancy complications is estimated at a first hospital visit at 11–13 weeks' gestation, followed by an individualized patient- and disease-specific approach, in terms of both the schedule and content of subsequent antenatal care[57].

In summary, advanced maternal age is a risk factor for miscarriage, pre-eclampsia, SGA, GDM and Cesarean section. We propose that maternal age should be combined with other maternal characteristics and obstetric history when calculating an individualized adjusted risk for adverse pregnancy complications.

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