Associations of maternal age at the start of pregnancy with placental function throughout pregnancy: The Generation R Study

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Abstract

Objective—To examine the associations of maternal age at the start of pregnancy across the full range with second and third trimester uterine and umbilical artery flow indices, and placental weight.

Study design—In a population-based prospective cohort study among 8271 pregnant women, we measured second and third trimester uterine artery resistance and umbilical artery pulsatility indices and the presence of third trimester uterine artery notching using Doppler ultrasound.

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Ethical Standards
The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008, and has been approved by the institutional committees (MEC 198.782/2001/31)).

Authors Roles
JE and RG had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Study concept and design
JE, VJ, RGAnalysis and interpretation of data: JE,VJ, RGDrafting of the manuscript: JE, VJ, RGCritical revision of the manuscript for important intellectual content: All authors

Declaration of Competing Interest
None.

Results—Compared to women aged 25–29.9 years, higher maternal age was associated with a higher third trimester uterine artery resistance index (difference for women 30–34.9 years was 0.10 SD (95% Confidence Interval (CI) 0.02 to 0.17), and for women aged   40 years 0.33 SD (95% CI 0.08 to 0.57), overall linear trend 0.02 SD (95% CI 0.01 to 0.03) per year). Compared to women aged 25–29.9 years, women younger than 20 years had an increased risk of third trimester uterine artery notching (Odds Ratio (OR) 1.97 (95% CI 1.30–3.00)). A linear trend was present with a decrease in risk of third trimester uterine artery notching per year increase in maternal age (OR 0.96 (95% CI 0.94 to 0.98)). Maternal age was not consistently associated with umbilical artery pulsatility indices or placental weight.

Conclusions—Young maternal age is associated with higher risk of third trimester uterine artery notching, whereas advanced maternal age is associated with a higher third trimester uterine artery resistance index, which may predispose to an increased risk of pregnancy complications.

Keywords

1 Introduction

Young maternal age, defined as childbearing in women aged <20 years, and advanced maternal age, defined as childbearing in women aged   35 years, are associated with adverse pregnancy outcomes, including fetal growth restriction, preterm birth, and fetal and neonatal death [1–5]. Mechanisms underlying these observed associations are not fully understood but are likely multifactorial, including pre-existing medical conditions, obstetrical history and social characteristics [5,6]. Next to these factors, both young or advanced maternal age might affect placental vascular development and function throughout pregnancy, predisposing to an increased risk of pregnancy complications [2]. A better understanding of the role of maternal age in suboptimal placental development may aid screening for and early detection of symptoms associated with suboptimal placental development and the subsequent risk of pregnancy complications.

Placental function and growth can be assessed during pregnancy and at birth. Doppler ultrasound can be used to assess resistance and blood flow in uterine and umbilical arteries throughout pregnancy [7]. Utero-placental vascular resistance, measured in uterine arteries, is a parameter of downstream placental vascular resistance, and may increase as a result of impaired placentation. Feto-placental vascular resistance, measured in umbilical arteries, is a parameter of downstream placental vascular resistance at the fetal side, and may increase as result of suboptimal placentation or suboptimal fetal vascular development [8,9].

We hypothesized that both young and advanced maternal age leads to suboptimal placental development and function, which may subsequently lead to alterations in utero-placental and feto-placental blood flow and placental weight, predisposing to an increased risk of pregnancy complications. Therefore, in a population based, prospective cohort study among 8271 pregnant women, we assessed associations of maternal age across the full range with measures of placental vascular function throughout pregnancy and placental weight at birth.

2 Methods

2.1 Study design

This study was embedded in the Generation R Study, a population-based prospective cohort study from early pregnancy onwards in Rotterdam, the Netherlands [10] (MEC 198.782/2001/31). Written consent was obtained from all participating women. Pregnant women were enrolled between 2001 and 2005. Response rate at birth was 61%. 8879 women were enrolled during pregnancy. We excluded non-singleton live births ($n = 246$), and participants with no information available on placental measurements ($n = 362$). The population for analysis comprised 8271 pregnant women (**Figure 1**).

2.2 Maternal age

Maternal age was assessed at enrolment by questionnaire. We used maternal age as continuous variable and categorized in six groups: <20 years ($n = 338$); 20–24.9 years ($n = 1391$); 25–29.9 years ($n = 2256$); 30–34.9 years ($n = 3045$); 35–39.9 years ($n = 1102$); >40 years ($n = 139$) [11]. We used the 25–29.9 years age group as reference.

2.3 Placental vascular function and placental weight at birth

Ultrasound examinations were carried out in two dedicated research centers in first trimester (median 13.2 weeks gestational age, interquartile range (IQR) 12.2–14.8), second trimester (median 20.5 weeks gestational age, IQR 19.9–21.3) and third trimester (median 30.3 weeks gestational age, IQR 29.8–30.9)[12]. We established gestational age by using data from the first ultrasound examination [13]. In second and third trimester, uterine artery resistance indices were measured in the uterine arteries near the crossover with the external iliac artery and umbilical artery pulsatility indices were measured in a free-floating loop of the umbilical cord as described previously [8]. The mean of three measurements was used for further analysis. Third trimester uterine artery notching was diagnosed if a notch was present uni- or bilaterally, as a result from increased blood flow resistance, which is a sign of placental insufficiency [14]. Placental weight was obtained from medical records and measured according to standard protocols [15]. Birth weight:placental weight ratio was calculated, as indicator of the ability of the placenta to maintain adequate nutrient supply to the fetus, and is associated with neonatal morbidity and mortality [16]. Small-size for gestational age (SGA) was defined as gestational age adjusted birth weight <10th percentile. Large-size for gestational age (LGA) is defined as gestational age adjusted birth weight >90th percentile.

2.4 Covariates

Maternal height (cm) and weight (kg) were measured without shoes and heavy clothing at enrolment. Body mass index (BMI, kg/m^2) was calculated and categorized: normal weight (BMI <25 kg/ m^2), overweight (BMI 25.0–30.0 kg/ m^2) and obese (BMI 30.0 kg/ m^2) [17]. Information about ethnicity (European/non-European), education (higher education yes/no), folic acid supplementation (yes/no) and parity (nulliparous/multiparous), was obtained at enrolment by questionnaire [18]. Smoking status was assessed by questionnaires

and categorized into non-smoking, early-pregnancy only and continued smoking during pregnancy [13].

2.5 Statistical analyses

First, we used linear and logistic regression models to assess the associations of maternal age categories with second and third trimester uterine artery resistance indices and umbilical artery pulsatility indices, uterine artery notching, placental weight, birth weight and birth weight:placental weight ratio. P-values for trend were obtained by entering maternal age to the models as a continuous instead of a categorical variable. These models were adjusted for gestational age at each measurement, maternal education, ethnicity, parity, smoking, BMI, folic acid supplementation and fetal sex. These covariates were selected based on previous studies and their associations with the outcomes [11,19,20].As a secondary analysis, we took forward significant associations of maternal age with placental vascular resistance and explored whether changes in placental vascular resistance partly explained the already established association of maternal age with birth weight [20]. We therefore additionally added placental vascular resistance parameters to linear regression models focused on the associations of maternal age with birth weight, and to logistic regression models focused on the associations of maternal age with risk of delivering an SGA newborn. We used multiple imputation for missing values according to Markov Chain Monte Carlo method [21]. Five imputed datasets were created and pooled for the analyses. Analyses were performed using the Statistical Package of Social Sciences version 24.0 for Windows (IBM Corp., Armonk, NY, USA).

3 Results

3.1 Population characteristics

Table 1 shows population characteristics according to maternal age categories. Younger women were more likely to be of non-Dutch or European ethnicity, to smoke, to have a lower BMI, and to deliver an SGA newborn. Older women were more likely to be of Dutch or European ethnicity and parous, and to deliver an LGA newborn.

3.2 Maternal age and placental vascular function

Maternal age was not associated with second trimester uterine artery resistance index (Table 2). Compared to women aged 25–29.9 years, higher maternal age was associated with a higher third trimester uterine artery resistance index (difference for women 30-34.9 years was 0.10 SD (95% Confidence Interval (CI) 0.02;0.17), and for women aged 40 years 0.33 SD (95%CI 0.08;0.57), overall linear trend 0.02 SDS (95%CI 0.01;0.03) per year). As compared to women aged 25–29.9 years, women younger than 20 years had an increased risk of third trimester uterine artery notching (Odds Ratio 1.97 (95%CI 1.30;3.00)). A linear trend was present with a decrease in risk of third trimester uterine artery notching per year increase in maternal age (OR 0.96 (95%CI 0.94;0.98)).We did not observe associations of maternal age with second or third trimester umbilical artery pulsatility index (Table 3).

3.3 Maternal age and placental weight, birth weight and birth weight: placental weight ratio

Compared to women aged 25–29.9 years, women aged 35–39.9 years had a lower placental weight (−12 g (95% CI −24.0; −0.17) and gave birth to newborns with a lower birth weight (−34 g (95% CI −66; −1.3)), and a higher birth weight: placental weight ratio (ratio difference 0.12 (95% CI 0.03;0.22)) (Table 4). Women aged 40 gave birth to newborns with a lower birth weight (p-value<0.05), but no difference in placental weight was present. A decreasing trend for birth weight was present across the full range of maternal age (−2.5 g per additional year (95% CI −4.7;0.3)), but not for placental weight. As higher maternal age was significantly associated with higher third trimester uterine artery vascular resistance and lower birth weight, we explored whether third trimester uterine artery vascular resistance partly explained this observed association of higher maternal age with a lower birth weight and the risk of delivering an SGA newborn. **Table S1 and S2** show that additional adjustment for third trimester uterine artery vascular resistance partly attenuated the association of maternal age with birth weight, and the risk of delivering an SGA newborn.

4 Discussion

4.1 Principal findings

We observed that after adjustment for socio-demographic and lifestyle factors, young maternal age was associated with an increased risk of third trimester uterine artery notching, whereas advanced maternal age was associated with an increased third trimester uterine artery resistance index. Maternal age was not associated with second trimester uterine artery resistance index or second and third trimester umbilical artery pulsatility indices. Advanced maternal age tended to be associated with lower placental and birth weight and higher birth weight:placental weight ratio, but this association was not consistent across the full range of maternal age.

4.2 Results

Both young and advanced maternal age are associated with an increased risk of pregnancy complications [2]. Suboptimal placental function may play a key role in the pathophysiology of these placenta-related complications, but studies focusing on pathophysiological mechanisms are scarce [22,23]. Obtaining a better insight into potential placenta-related pathophysiological mechanisms underlying the observed associations of young and advanced maternal age with pregnancy complications is important to develop future prevention, screening and treatment strategies for a population that is increasingly of advanced maternal age during pregnancy.

For young maternal age, previous studies have only focused on the associations of young maternal age with placental weight and showed conflicting findings [24,25]. In a study among 31 adolescent pregnancies, young maternal age had no effect on placental weight, morphometry or cell turnover [25]. A study among 552 mothers and their healthy singleton newborns, found no association of young maternal age with placental weight [26]. However, a study among 431 uncomplicated singleton near-term deliveries, showed that young

maternal age was associated with a low birth weight:placental weight ratio [27].We observed that the risk of third trimester uterine artery notching was increased among women aged <20 years, but we did not observe associations with uterine artery resistance or umbilical artery pulsatility indices across the full range. There were no associations of young maternal age with placental weight or placental weight:birth weight ratio. Thus, our findings seem to suggest that young maternal age may specifically be associated with a suboptimal third trimester utero-placental vascular function. Normally, in early pregnancy, trophoblast invasion and spiral artery remodeling takes place to ensure adequate blood flow to the placenta, leading to larger vessels with lower resistance and increased end diastolic flow [28]. If these processes are inadequate, abnormal uterine artery flow patterns with higher resistance indices and notching may be observed, which is strongly associated with the risk of pregnancy complications. This may be the case in biologic immaturity among adolescent pregnancies [29]. It might be that young maternal age mostly affects placentation leading to an increased risk of notching, but due to overall adequate vascular quality and dynamics of young women, small changes in utero-placental flow and resistance can be more easily compensated. The lack of associations with other placental vascular function markers and placental weight might be due to the relatively high (19 years) young maternal age in our study.

The effects of advanced maternal age on placental function have been studied in larger populations. A study among 536,954 singleton births showed that older women had larger placentas [30]. It was suggested that this enlargement represents a biological compensatory mechanism for suboptimal placental function, to secure a threatened pregnancy [30]. Possibly, other maternal characteristics which influence placental weight and are strongly related to maternal age, such as parity, may be responsible for the larger placentas among older women [30]. A observational prospective study among 24,152 singleton live-births, found that after correction for maternal characteristics, such as parity, BMI, cigarette use, socio-economic status and race, higher maternal age was associated with lower placental weight [31]. A cross-sectional study among 884 pregnant women showed that after adjustment for gestational age and parity, advanced maternal age was associated with an increased uterine artery pulsatility index in the second half of pregnancy [32]. We observed that after correction for socio-demographic and lifestyle factors, higher maternal age was associated with an increased third trimester uterine artery resistance index, and that the effect of maternal age on uterine artery vascular resistance is already visible from 30 years onwards. These effects of advanced maternal age on third trimester uterine artery vascular resistance were small and within the normal range. However, several studies have shown that small increases in utero-placental vascular resistance, even within the normal range, is associated with pregnancy complications [33–36]. Importantly, the direction of the normal changes in hemodynamics during pregnancy seems to be opposite to the changes that occur in ageing [37]. Previous studies have shown that with ageing, uterine blood flow diminishes, uterine blood vessels are less compliant, and endothelium-dependent function is altered [32,37,38]. The increased uterine artery vascular resistance may indeed be explained by general reduced vascular compliance among older women, whereas newly constructed fetal vasculature is not affected by the effects of advanced maternal age on vascular quality, which could explain lack of effect on feto-placental vascular function

in our study. As differences in third trimester uterine artery vascular resistance were within the normal range and we observed no associations with the risk of third trimester notching, our findings may suggest that not suboptimal placentation explains these observed associations, but rather overall reduced vascular quality due to advanced maternal age. We further observed that higher maternal age was associated with a lower birth weight, and an increased risk of delivering an SGA newborn, and that this association attenuated after considering third trimester uterine artery vascular resistance. This suggests that even this small difference in third trimester utero-placental vascular function among older women may play a pathophysiological role in the established associations of advanced maternal age with an increased risk of pregnancy complications, such as an abnormal birth weight.

Our findings provide insight into potential pathophysiological mechanisms explaining observed associations of young and advanced maternal age with pregnancy complications. From a clinical perspective, measurement of utero-placental vascular function among pregnant women with a young or advanced maternal age could possibly aid in screening for those pregnancies at risk of adverse pregnancy outcomes. However, the additional value of using utero-placental vascular function for screening for adverse pregnancy outcomes may depend upon specific populations and pregnancy outcomes of interest. We have previously shown within the same study population that among low-risk, multi ethnic women combined second and third trimester utero-placental vascular function ultrasound results in addition to maternal characteristics improved screening for pre-eclampsia but not for gestational hypertension [39]. A systematic review has shown that model performance for screening for gestational hypertensive disorders varies with the use of different maternal, fetal and placental characteristics among low-risk and high-risk populations [40]. A meta-analysis comprising seventeen observational studies showed that among SGA fetuses and newborns, which is considered a high-risk population, concluded that an increased UtA-PI increased the risk of adverse perinatal outcomes, but because of limited predictive capacity as a standalone test, UtA-PI should be combined in combination with other tests [41]. Although causality cannot be established in observational research, these findings suggest that maternal age may, through suboptimal utero-placental vascular function, influence pregnancy outcomes. Among young maternal age pregnancies, impaired placental development may be due to biologic immaturity, whereas among advanced maternal age pregnancies, reduced vascular quality due to ageing may play a key role. Further mechanistic studies are needed to obtain a better understanding of these potential pathways, by using more advanced placental imaging techniques from early pregnancy onwards, placental biomarkers or detailed assessments of placental vasculature at birth through placental biopsy. Large meta-analyses on patient level data are necessary to enable assessment of associations at the extremes of the maternal age spectrum where numbers are smaller and to enable identification of the optimal maternal age at pregnancy for various pregnancy outcomes.

4.3 Strengths and limitations

Bias due to nonresponse at baseline is unlikely because biased estimates in large cohort studies mainly arise from loss to follow-up rather than from nonresponse at baseline [42]. Selection of a healthy population might affect the generalizability of results to higher-risk

populations. As clinical practice guidelines during the inclusion period of the current study (2001–2006) did not recommend Aspirin prophylaxis, we do not have information on Aspirin use available. Although we do not think that the use Aspirin prophylaxis, or rather the lack thereof, has biased the results of the current study, it may limit the generalizability of our results to contemporary populations. Finally, we had a relatively small number of women in the age group 40 years and older and these results should be interpreted with caution. Although we adjusted for a number of potential confounders, residual confounding by other lifestyle factors might still be present.

5 Conclusions

Young maternal age is associated with higher risk of third trimester uterine artery notching, whereas advanced maternal age is associated with higher third trimester uterine artery resistance index, which may predispose to an increased risk of pregnancy complications. These associations are not explained by maternal socio-demographic or lifestyle characteristics.

Acknowledgements

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Table 1

Characteristics of women (n = 8271).

Characteristics	<20 years *n* = 338	20–24.9 years *n* = 1391	25–29.9 years *n* = 2256	30–34.9 years *n* = 3045	35–39.9 years *n* = 1102	40 years *n* = 139
Maternal characteristics						
Age, years (median, IQR)	19.0 (18.2–19.5)	22.8 (21.6–24.0)	27.8 (26.4–28.9)	32.4 (31.2–33.6)	36.6 (35.7–37.9)	41.2 (40.5–42.3)
Height, mean (SD) (cm)	165.1 (6.4)	165.3 (7.1)	166.4 (7.4)	168.3 (7.3)	168.2 (7.5)	167.9 (8.2)
Weight, mean (SD) (kg)	65.3 (13.4)	67.8 (13.8)	69.7 (14.2)	69.6 (12.5)	71.0 (12.1)	72.3 (13.6)
Body Mass Index, mean (SD) (kg/m^2)	23.9 (4.6)	24.8 (4.7)	25.1 (4.9)	24.6 (4.3)	25.1 (4.1)	25.6 (4.6)
Parity, No. nulliparous (%)	295 (88.9)	985 (71.9)	1341 (60.1)	1538 (51.0)	370 (33.9)	49 (36.0)
Education, No. higher education (%)	2 (0.7)	101 (8.2)	718 (35.1)	1686 (59.2)	611 (58.9)	73 (57.1)
Race / Ethnicity, No. (%)						
Dutch or European, No. (%)	75 (25.0)	389 (30.3)	1107 (51.8)	2105 (71.6)	725 (67.9)	81 (60.0)
Surinamese, No. (%)	61 (20.3)	192 (15.0)	210 (9.8)	165 (5.6)	74 (6.9)	9 (6.7)
Turkish, No. (%)	32 (10.6)	236 (18.4)	253 (11.8)	155 (5.3)	49 (4.6)	6 (4.4)
Moroccan, No. (%)	19 (6.3)	157 (12.2)	192 (9.0)	118 (4.0)	50 (4.7)	12 (8.9)
Cape Verdian or Dutch Antilles, No. (%)	72 (23.9)	190 (14.8)	154 (7.2)	132 (4.6)	49 (4.6)	6 (4.4)
Smoking, No. (%)						
None, No. (%)	161 (55.9)	747 (61.8)	1454 (73.8)	2110 (78.0)	717 (73.8)	89 (77.4)
Early-pregnancy only, No. (%)	27 (9.4)	102 (8.4)	172 (8.7)	238 (8.8)	74 (7.4)	7 (6.1)
Continued, No. (%)	100 (34.7)	360 (29.8)	343 (17.4)	358 (13.2)	181 (18.6)	19 (16.5)
Folic acid use No. used (%)	71 (30.5)	809 (83.4)	1156 (70.0)	1942 (82.1)	637 (76.7)	73 (71.6)
2nd trimester uterine artery RI, mean (SD)	0.56 (0.09)	0.54 (0.09)	0.54 (0.09)	0.54 (0.09)	0.55 (0.09)	0.56 (0.09)
2nd trimester umbilical artery PI, mean (SD)	1.24 (0.19)	1.23 (0.19)	1.21 (0.18)	1.19 (0.18)	1.18 (0.19)	1.17 (0.19)
3rd trimester uterine artery RI, mean (SD)	0.48 (0.08)	0.48 (0.07)	0.48 (0.08)	0.48 (0.08)	0.50 (0.08)	0.51 (0.07)
3rd trimester umbilical artery PI, mean (SD)	0.99 (0.16)	0.99 (0.17)	0.99 (0.17)	0.98 (0.17)	0.98 (0.17)	0.97 (0.19)
3rd trimester uterine artery notching, No. (%)	40 (22.5)	113 (14.8)	137 (10.8)	146 (7.9)	50 (7.6)	6 (8.1)
Birth characteristics						
Males, No.(%)	164 (48.5)	713 (51.3)	1131 (50.1)	1536 (50.4)	572 (51.9)	72 (51.8)
Gestational age at delivery, weeks (IQR)	39.9 (38.7–40.8)	40.0 (39.1–40.9)	40.1 (39.0–41.0)	40.1 (39.4–41.0)	40.3 (39.3–41.0)	40.3 (38.7–41.1)
Birth weight, mean (SD) grams	3184 (516)	3315 (522)	3399 (551)	3461 (576)4	3487 (549)	3424 (656)
Small-size for gestational age, No. (%)	53 (15.7)	191 (13.7)	214 (9.5)	254 (8.3)	97 (8.8)	13 (9.4)
Large-size for gestational age, No. (%)	16 (4.7)	75 (5.4)	209 (9.3)	379 (12.4)	122 (11.1)	20 (14.4)
Preterm birth	27 (8.0)	65 (4.7)	128 (5.7)	153 (5.0)	50 (4.5)	9 (6.5)
Assisted vaginal delivery	29 (9.8)	156 (12.4)	301 (14.6)	409 (14.7)	128 (12.7)	10 (7.7)

Characteristics	<20 years n = 338	20–24.9 years n = 1391	25–29.9 years n = 2256	30–34.9 years n = 3045	35–39.9 years n = 1102	40 years n = 139
Cesarean delivery	28 (9.5)	111 (8.8)	249 (12.1)	363 (13.0)	142 (14.0)	32 (24.6)
Gestational hypertension	13 (4.1)	42 (3.2)	80 (3.8)	117 (4.1)	41 (3.9)	4 (3.1)
Preeclampsia	10 (3.2)	23 (1.8)	58 (2.8)	57 (2.0)	15 (1.5)	3 (2.3)
APGAR <7 after 5 min, No. (%)	5 (1.6)	18 (1.3)	27 (1.2)	38 (1.3)	11 (1.0)	1 (0.7)
Placental weight (grams) median (IQR)	600 (500–695)	600 (520–700)	620 (540–713)	630 (545–725)	619 (530–724)	650 (530–732)

Abbreviation: IQRinter quartile range. Values are observed data and represent means (SD), medians (IQR) or number of subjects (valid%).

Table 2

Associations of maternal age with uterine artery resistance indices and notching.

	Difference in uterine artery resistance index[a]		Uterine artery notching[b]
	Second trimester $n = 4578$ SDS difference (95% CI)	Third trimester $n = 4479$ SDS difference (95% CI)	Third trimester $n = 4762$ Odds ratio (95% CI)
Maternal age			
<20 years	0.12 (–0.05 to 0.29) $n = 159$	–0.02 (–0.19 to 0.15) $n = 169$	1.97 (1.30–3.00)[*] $n = 178$
20–24.9 years	–0.02 (–0.05 to 0.08) n = 715	–0.00 (–0.10 to 0.09) n= 717	1.25 (0.994–1.66) $n = 755$
25–29.9 years	reference $n = 1268$	Reference $n = 1179$	Reference $n = 1272$
30–34.9 years	–0.00 (–0.08 to 0.07) $n = 1760$	0.10 (0.02 to 0.17)[*] $n = 1745$	0.79 (0.61–1.03) $n = 1826$
35–39.9 years	0.04 (–0.07 to 0.14) $n = 611$	0.18 (0.08 to 0.29)[*] $n = 601$	0.77 (0.54–1.11) $n = 657$
40 years	0.18 (–0.07 to 0.44) $n = 65$	0.33 (0.08 to 0.57)[*] $n = 68$	0.85 (0.36–2.01) $n = 74$
Trend[c]	*0.00 (–0.00 to 0.01)*	*0.02 (0.01 to 0.03)*[*]	*0.96 (0.94 to 0.98)*[*]

CI: Confidence Interval; SDS: Standard deviation score; Models are adjusted for maternal age at intake, smoking, parity, education, BMI, ethnicity, folic acid intake, fetal sex and gestational age at ultrasound measurement.

[*] Significant value ($p < 0.05$).

[a] Values are regression coefficients (95% confidence interval) that reflect the difference in SDS score or odds ratio per measurement per maternal age-group compared to the reference group of women aged between 25 and 29.9 years. Tests for trend were based on multiple linear regression models with maternal age as a continuous variable. The trends are differences in measurements per additional maternal year.

[b] Values are odds ratios (95% confidence interval) compared to the reference group of women aged between 30 and 34.9 years. Tests for trend were based on logistic regression models with maternal age as a continuous variable.

[c] Tests for trend were based on multiple linear and logistic regression models with maternal age as a continuous variable. The trends are differences in regression coefficients and odds ratio per additional maternal year.

Table 3

Associations of maternal age with umbilical artery pulsatility indices.

	Difference in umbilical artery pulsatility index	
	Second trimester n = 6141 SDS difference (95% CI)	Third trimester *n* = 6668 SDS difference (95% CI)
Maternal age		
<20 years	0.04 (–0.10 to 0.18) *n* = 228	–0.08 (–0.21 to 0.06) *n* = 259
20–24.9 years	0.06 (–0.02 to 0.14) *n* = 978	–0.01 (–0.09 to 0.07) *n* = 1104
25–29.9 years	*reference* *n* = 1693	*reference* *n* = 1804
30–34.9 years	–0.00 (–0.07 to 0.06) *n* = 2333	–0.03 (–0.09 to 0.07) *n* = 2502
35–39.9 years	–0.01 (–0.09 to 0.08) *n* = 821	0.02 (–0.07 to 0.10) *n* = 888
40 years	–0.03 (–0.24 to 0.18) *n* = 88	0.02 (–0.17 to 0.21) *n* = 111
Trend	*–0.00 (–0.01 to 0.00)*	*0.00 (–0.00 to 0.01)*

CI: Confidence Interval; SDS: Standard deviation score;

Models are adjusted for maternal age at intake, smoking, parity, education, BMI, ethnicity, folic acid intake, fetal sex and gestational age at ultrasound measurement. Values are regression coefficients (95% confidence interval) that reflect the difference in SDS per measurement per maternal age-group compared to the reference group of women aged between 25 and 29.9 years. Tests for trend were based on multiple linear regression models with maternal age as a continuous variable. The trends are differences in SDS per additional maternal year.

Table 4

Associations of maternal age with placental weight, birth weight and birth weight:placental weight ratio.

	Placental weight at birth	Birth weight	Birth weight:Placental weight ratio
	n = 6197 Difference in grams (95% CI)	*n* = 8224 Difference in grams (95% CI)	*n* = 6197 Difference in ratio (95% CI)
Maternal age			
<20 years	–6 (–25 to 13) *n* = 249	–23(–74 to 29) *n* = 332	0.04 (–0.10 to 0.19) *n* = 249
20–24.9 years	–1 (–12 to 10) *n* = 1064	0 (–30 to 30) *n* = 1381	0.00 (–0.08 to 0.09) *n* = 1064
25–29.9 years	*reference* *n* = 1707	*Reference* *n* = 2247	*reference* *n* = 1707
30–34.9 years	–0.0 (–9 to 9) *n* = 2230	–1 (–25 to 23) *n* = 3029	0.00 (–0.07 to 0.07) *n* = 2230
35–39.9 years	–12 (–24 to –0)[*] *n* = 833	–34 (–66 to –1.3)[*] *n* = 1096	0.12 (0.03 to 0.22)[*] *n* = 833
40 years	–9 (–35 to 18) *n* = 114	–80 (–155 to –6)[*] *n* = 139	0.01 (–0.20 to 0.22) *n* = 114
Trend	*-0 (–1 to 0)*	*–2.5 (–4.7 to–0.3)*[*]	*0.00 (–0.00 to 0.01)*

CI: Confidence Interval. Models are adjusted for maternal age at intake, smoking, parity, education, BMI, ethnicity, folic acid intake, fetal sex and gestational age at birth. Values are regression coefficients (95% confidence interval) that reflect the difference in grams or ratio per maternal age-group compared to the reference group of women aged between 25 and 29.9 years. Tests for trend were based on multiple linear regression models with maternal age as a continuous variable. The trends are differences in grams or ratio per additional maternal year.

[*] Significant value ($p < 0.05$).