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Changes in Doppler flow velocity waveforms and fetal size at 20 weeks gestation among cigarette smokers

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Objectives To compare umbilical and uterine artery Doppler waveforms and fetal size at 20 weeks between smokers and nonsmokers.

Design Prospective cohort study.

Setting Auckland, New Zealand and Adelaide, Australia.

Population Nulliparous participants in the Screening for Pregnancy Endpoints (SCOPE) study.

Methods Self-reported smoking status was determined at 15 ± 1 weeks' gestation. At the 20 ± 1 week anatomy scan, uterine and umbilical Doppler resistance indices (RI) and fetal measurements were compared between smokers and nonsmokers.

Main outcomes measures Umbilical and mean uterine artery Doppler RI values, abnormal umbilical and uterine Doppler (RI > 90th centile) and fetal biometry.

Results Among the 2459 women, 248 (10%) were smokers. Smokers had higher umbilical RI [0.75 (SD 0.06) versus 0.73 (0.06), $P < 0.0001$] and mean uterine RI [0.59 (0.09) versus 0.56 (0.10), $P < 0.0001$]. They were twice as likely to have an abnormal umbilical Doppler at 20 weeks compared with nonsmokers [$n = 35$ (14.6%) versus $n = 156$ (7.2%), OR 2.21, 95% CI 1.49–3.27]. This effect remained significant after adjusting for age, ethnicity, marital status, employment and BMI (adjusted OR 1.62, 95% CI 1.03–2.54). Smokers were more likely to have an abnormal mean uterine RI [$n = 33$ (13.7%) versus $n = 198$ (9.2%), OR 1.57, 95% CI 1.06–2.33], but this association was not significant after adjusting for confounders. Fetuses of women who smoked had a small reduction in femur length and estimated weight compared with nonsmokers.

Conclusions At 20 weeks' gestation, women who smoke have higher umbilical artery RI, a surrogate measure for an abnormal placental villous vascular tree. This may contribute to later fetal growth restriction among smokers. Further research is needed to explore the clinical significance of these findings.

Keywords Doppler, fetal growth, small for gestational age, smoking.

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Introduction

From a population perspective maternal cigarette smoking is the most important cause of small for gestational age (SGA) babies in developed countries.[1] The mechanisms by which smoking influences fetal growth are multifactorial and include abnormal villous vascularisation within the placenta, and reduced cytotrophoblast proliferation and invasion.[2,3] Umbilical and uterine artery Doppler studies are surrogate measures of the feto-placental and uteroplacental circulations respectively. The impact of tobacco smoking on placental perfusion, as assessed by Doppler ultrasound, remains uncertain.[4–6] While two studies have documented elevated umbilical artery Doppler indices in the third trimester among smokers,[5,6] Doppler waveforms were not found to be abnormal in smokers in the second trimester.[4,6]

Despite the known association between maternal tobacco smoking and birth of SGA babies, it remains unclear whether the smoking effects on fetal growth are evident in

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the second trimester. Fetal size on ultrasound at 18 weeks of gestation can be reduced in babies born SGA.[7,8] To date, however, studies reporting the impact of smoking on fetal size early in pregnancy are inconsistent,[4,6,9,10] with the largest study reporting a reduction in femur length at 18–24 weeks' gestation.[9]

The aim of the current study was to determine the effect of maternal smoking on umbilical and uterine artery Doppler indices and fetal ultrasound biometry at 20 weeks gestation. We hypothesised that, women who smoked would have (i) increased resistance indices (RI) in the umbilical and/or uterine circulations and (ii) reduced fetal measurements on ultrasound at 20 weeks gestation compared with nonsmokers. Our secondary hypothesis was that among those who had SGA babies, smokers would have higher umbilical and/or uterine artery RI and reduced fetal measurements at 20 weeks gestation compared with nonsmokers.

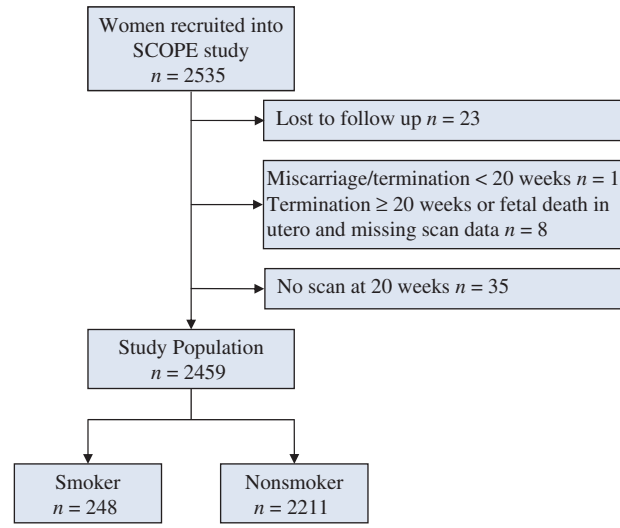

Figure 1. Flow chart of participants recruited.

Methods

The participants were healthy nulliparous women with singleton pregnancies recruited to the Screening for Pregnancy Endpoints (SCOPE) study between November 2004 and July 2007 in Auckland, New Zealand and Adelaide, Australia. SCOPE is a prospective, multicentre cohort study with the main aim of developing screening tests to predict pre-eclampsia, SGA infants and spontaneous preterm birth. Women were recruited to the SCOPE study by 15 ± 1 week's gestation from a number of sources including: hospital antenatal clinics, obstetricians, general practitioners, independent midwives and self referral in response to advertisements or recommendations from friends. Women considered at high risk of pre-eclampsia, SGA or spontaneous preterm birth because of underlying medical conditions, gynaecological history, three or more previous miscarriages or terminations of pregnancy or who received interventions that may modify pregnancy outcome were excluded. For this study, women who participated in the SCOPE study, but did not have a 20-week ultrasound scan or had a fetal loss with incomplete 20-week scan data were also excluded (Figure 1). All women provided written informed consent.

Women who agreed to participate were interviewed and examined by a research midwife at 15 ± 1 and 20 ± 1 weeks' gestation and underwent ultrasound examination at 20 ± 1 weeks of gestation. Participants were followed prospectively by the research midwives, with pregnancy outcome data and baby measurements collected by research midwives, usually within 72 hours of birth. Pregnancy and birth clinical care was provided by the woman's maternity care provider (midwife, private obstetrician, hospital clinic or general practitioner).

Ultrasound examinations included fetal measurements (biparietal diameter, head circumference, abdominal circumference and femur length) and Doppler studies of the umbilical and uterine arteries. Estimated fetal weight was calculated using all four fetal growth measurements.[11] Umbilical and uterine artery Doppler studies were performed with women in a semi-recumbent position using colour flow pulsed Doppler in accordance with a standard operating procedure manual. The mid portion of the umbilical cord was identified and umbilical Doppler measurements obtained when the fetus was not breathing or moving. Colour Doppler was used to visualise the uterine arteries 1 cm distal to the apparent crossover with the external iliac artery and before any branching. The angles of isonation were adjusted to be as close to 0° as possible, and always <50°. A minimum of five waveforms was recorded for each measurement. In-built software calculated the RI. Mean RI, derived from the right and left uterine arteries, was calculated for uterine artery Doppler results. If only a left or right uterine RI result was available, this was used as 'mean RI' (n = 10). Sonographers did not have access to clinical data including smoking status.

Participants were divided into two smoking groups, according to self-reported maternal smoking status at 15 + 1 weeks of gestation: (i) smokers defined as smoking at 15 ± 1 weeks' gestation, n = 248; (ii) nonsmokers, n = 2211, comprised women who did not smoke during pregnancy (n = 1968, 89%) and women who had ceased smoking before 15 weeks' gestation (n = 243, 11%). Women who did not smoke and women who had ceased smoking before 15 weeks' gestation were grouped together as nonsmokers as we have previously shown that rates of SGA babies do not differ between these groups.[12]

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For consistency with a previous SCOPE Doppler publication, and future planned publications an umbilical artery RI > 90th centile or mean uterine artery RI > 90th centile were considered abnormal.[13] 'Any abnormal RI' was defined as either an abnormal umbilical or uterine Doppler RI. 'Abnormal umbilical and uterine RI' was defined as both an abnormal umbilical and an abnormal mean uterine artery Doppler waveform. SGA was defined as a birthweight <10th centile using customised birthweight centiles adjusted for maternal height, weight, parity and ethnicity.[14] Spontaneous preterm birth was spontaneous preterm labour or preterm premature rupture of the membranes resulting in preterm birth at <37 weeks' gestation. As fetal measurements (but not Doppler indices) increased significantly between each gestational week of scanning *z*-scores (which are independent of gestation) were used for comparison of all fetal measurements between cases and controls.

The estimated date of delivery was calculated from a certain last menstrual period (LMP) date. The estimated date of delivery was only adjusted if either (i) a scan performed at <16 weeks' gestation found a difference of ≥7 days between the scan gestation and that calculated by the LMP or (ii) on 20-week scan a difference of ≥10 days was found between the scan gestation and that calculated from the LMP. If the LMP date was uncertain, then scan dates were used to calculate the estimated date of delivery.

Data are presented as mean (SD), median (10th, 90th centile) as appropriate. Student's *t*-test and chi-square test were used for comparison of continuous and categorical variables between cases and controls respectively. The *z*-score for each gestational week was derived by using the following formula: *z*-score = (actual value − mean for the gestational week)/SD (for the gestational week). Median *z*-score values combining all gestational weeks were then calculated. Statistical significance was defined as $P < 0.05$. Logistic regression was used to compare the odds of abnormal umbilical or uterine artery RI between smokers and nonsmokers, adjusting for: age, ethnicity, marital status, employment and body mass index. Pearson correlation was used to investigate the relationship between the number of cigarettes smoked and umbilical RI. All statistical tests were performed using SAS 9.1® (SAS Institute Inc., Cary, NC, USA). Data were available for >99% of all variables examined except for Doppler results (97% complete). Women who had missing Doppler results [umbilical RI $n = 58$ (2.4%); uterine RI $n = 65$ (2.6%)] were excluded from the respective multivariate logistic regression.

Results

Between November 2004 and July 2007, 2535 women were recruited to the SCOPE study in Auckland and Adelaide and follow up was complete in 99% of participants ($n = 2512$, Figure 1). A further 53 women were excluded as they either did not have a 20 week scan, had a miscarriage or termination <20 weeks or had fetal losses at ≥20 weeks resulting in missing ultrasound data. Ten percent ($n = 248$) of the 2459 eligible women reported they smoked at 15 ± 1 weeks and 2211 (90%) were nonsmokers. Among smokers, 119 (48.0%) smoked 1–5 cigarettes per day, 79 (31.9%) smoked 6–10 cigarettes per day and 50 (21.2%) smoked >10 cigarettes per day. Among the nonsmokers, 254 (11.5%) women ceased smoking before 15 weeks' gestation, half of whom had stopped smoking by 6 weeks gestation. Maternal demographic and physical characteristics as well as pregnancy outcomes are detailed in Table 1.

Umbilical RI and mean uterine RI values showed a significant shift in distribution between smokers and nonsmokers (Figures 2 and 3). Smokers had higher umbilical RI [0.75 (0.06) versus 0.73 (0.06), $P < 0.0001$] and mean uterine RI values [0.59 (0.09) versus 0.56 (0.10), $P < 0.0001$] compared with nonsmokers (Table 2). They

Table 1. Demographic and pregnancy outcomes

	Smoker ($n = 248$)	Nonsmoker ($n = 2211$)	*P* value
Age (year)	23.2 (5.6)	29.1 (5.4)	<0.0001
Ethnicity			
European	222 (89.5)	1917 (86.7)	0.0003
Asian	3 (1.2)	111 (5.0)	
Indian	0 (0)	66 (3.0)	
Polynesian	15 (6.1)	75 (3.4)	
Other	8 (3.2)	42 (1.9)	
Married/defacto	185 (74.6)	2093 (94.7)	<0.0001
Employed	142 (57.3)	1958 (88.6)	<0.0001
Primigravida	164 (66.1)	1671 (75.6)	0.001
BMI	25.9 (6.2)	25.3 (5.0)	0.20
Body mass index (kg/m^2)			
<20.0	40 (16.1)	153 (6.9)	<0.0001
20.0–24.9	94 (37.9)	1105 (50.0)	
25.0–29.9	56 (22.6)	625 (28.3)	
>=30.0	58 (23.4)	328 (14.8)	
Outcomes			
Spontaneous preterm birth	24 (9.7)	94 (4.3)	0.0002
Gestation at delivery	38.7 (3.3)	39.7 (2.0)	0.0002
Birthweight	3149.0 (733.0)	3426.1 (566.5)	<0.0001
Customised birthweight centile	41.6 (29.7)	49.2 (28.6)	<0.0001
SGA (<10th customised centile)	41 (16.5)	214 (9.7)	0.0008
<3rd customised centile	21 (8.5)	61 (2.8)	<0.0001
Male infants	123 (49.6)	1130 (51.1)	0.65

Data are mean (SD) or number (%) as appropriate. *P* values are for chi-square or Student' *t*-test as appropriate.

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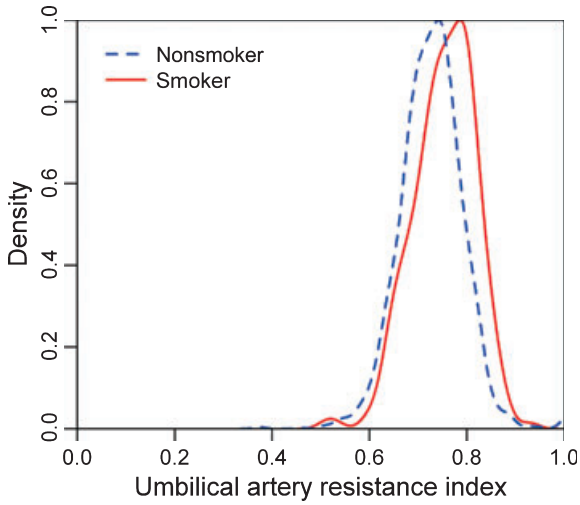

Figure 2. Distribution of umbilical artery resistance index (RI) among smokers and nonsmokers.

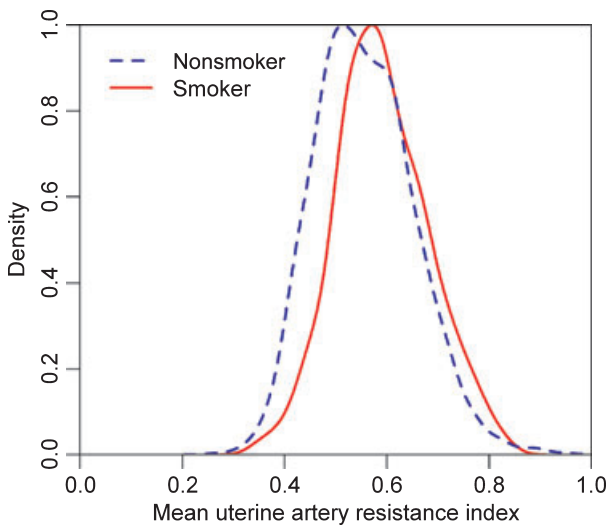

Figure 3. Distribution of mean uterine artery resistance index (RI) among smokers and nonsmokers.

were more likely to have an abnormal umbilical RI [n = 35 (14.6%) versus n = 156 (7.2%), unadjusted OR 2.21, 95% CI 1.49–3.27, $P < 0.0001$] or abnormal mean uterine RI [n = 33 (13.7%) versus n = 198 (9.2%), unadjusted OR 1.57, 95% CI 1.06–2.33, $P = 0.03$] at 20 weeks. After adjustment for maternal demographic characteristics, the relationship between smoking and abnormal umbilical Doppler RI remained significant (adjusted OR 1.62, 95% CI 1.03–2.54, $P = 0.04$), but was no longer significant for mean uterine RI (adjusted OR 1.21, 95% CI 0.78–1.89, $P = 0.39$). Smokers were also more likely to have both an abnormal umbilical as well as abnormal mean uterine RI [n = 9 (3.8%) versus n = 19 (0.88%), $P < 0.0001$] and 'any abnormal RI' [n = 59 (24.7%) versus n = 335 (15.6%), $P = 0.0003$) at 20 weeks compared with nonsmokers.

There were no differences in fetal head circumference, abdominal circumference or biparietal diameter (data not shown) between smokers and nonsmokers. Femur length and estimated fetal weight z-scores were slightly lower in the smoking group compared with nonsmokers (Table 2).

Among women who had SGA babies (n = 255), smokers (n = 41) had even lower customised birthweight centiles and birthweight compared with nonsmokers (Table 3). The 'SGA-smoker' group had higher umbilical RI values compared with the 'SGA-nonsmoker' group and were three times more likely to have an abnormal umbilical Doppler RI compared with the 'SGA-nonsmoker' group. There was no difference in uterine Doppler results or fetal biometry measurements between these two groups.

Two *post hoc* analyses were performed. Pearson correlation was used to investigate if there was a dose–response relationship between umbilical Doppler RI and the number of cigarettes smoked daily. A weak but nonsignificant correlation was found ($R^2 = 0.013$, $P = 0.08$). We also investigated whether smokers were more likely to have umbilical Doppler RI > 95th centile. Smokers were more than twice as likely to have an umbilical Doppler RI > 95th centile at 20 weeks compared with nonsmokers [n = 19 (8.0%) versus n = 72 (3.3%), OR 2.51, 95% CI 1.48–4.23].

Discussion

In this large cohort of healthy nulliparous women, we found that smokers had higher umbilical artery RI and were more likely to have abnormal umbilical artery Doppler studies at 20 weeks gestation compared with nonsmokers. Women who smoked also had higher mean uterine artery RI and were more likely to have an abnormal mean uterine artery Doppler result, but the relationship between smoking and abnormal uterine Doppler was no longer significant after adjustment for confounding factors.

This is the first study to report that maternal smoking increases umbilical artery Doppler indices in the mid-trimester of pregnancy. Two previous studies did not find a relationship between umbilical or uterine artery Doppler results and smoking.[4,6] Newnham *et al.*[4] performed serial scans in a cohort of 535 women and found that umbilical artery and uteroplacental systolic/diastolic ratios at 18 and 24 weeks were similar in smoking and nonsmoking women. Their study was smaller, used old technology with a spectral analyser with a bi-directional Doppler rather than pulsed colour Doppler and obtained uterine Doppler measurements from the placental bed rather than the uterine arteries. Pringle and co-workers used similar Doppler methodology to ours, but sub-divided the smoking groups according to number of cigarettes smoked.[6] They reported

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Table 2. Ultrasound measurement at 20 weeks among smoker versus nonsmoker

	Smoker (*n* = 248)	Nonsmoker (*n* = 2211)	*P* value
Gestation at scan	19.8 (0.73)	19.6 (0.73)	<0.0001
Doppler studies*			
Umbilical RI	0.75 (0.06)	0.73 (0.06)	<0.0001
Abnormal umbilical RI	35 (14.6)	156 (7.2)	<0.0001
Mean uterine RI	0.59 (0.09)	0.56 (0.10)	<0.0001
Abnormal mean uterine RI	33 (13.7)	198 (9.2)	0.03
Fetal measurements**			
Head circumference	−0.06 (−1.27, 1.42)	0.05 (−1.27, 1.29)	0.74
Abdominal circumference	−0.05 (−1.19, 1.24)	−0.03 (−1.12, 1.32)	0.33
Femur length	−0.21 (−1.61, 0.89)	−0.11 (−1.22, 1.30)	0.0005
Estimated fetal weight	−0.21 (−1.20, 1.10)	−0.05 (−1.21, 1.35)	0.02

Data are mean (SD) or number (%) median (10th, 90th centile) as appropriate. *P* values are for chi-square or Student's *t*-tests as appropriate.
RI, resistance index.
*Denominators varied slightly due to small amount of missing data.
**Expressed as '*z*-scores'.

Table 3. Ultrasound measurements at 20 weeks among small for gestational age (SGA) infants stratified by smoking status

	SGA-smoker (*n* = 41)	SGA-nonsmoker (*n* = 214)	*P* value
Gestation at delivery	38.0 (4.7)	38.5 (3.1)	0.50
Birthweight	2380.3 (691.8)	2615.9 (525.2)	0.04
Customised birthweight centile	3.2 (2.9)	4.9 (2.9)	0.0005
Doppler studies*			
Umbilical RI	0.78 (0.05)	0.74 (0.07)	<0.0001
Abnormal umbilical RI	11 (27.5)	20 (9.5)	0.002
Mean uterine RI	0.63 (0.09)	0.60 (0.10)	0.15
Abnormal mean uterine RI	11 (27.5)	47 (22.6)	0.5
Fetal measurements**			
Head circumference	−0.32 (−1.27, 0.88)	−0.46 (−1.54, 0.62)	0.27
Abdominal circumference	−0.61 (−1.30, 0.83)	−0.55 (−1.53, 1.0)	0.79
Femur length	−0.21 (−1.22, 0.80)	−0.51 (−1.61, 0.89)	0.62
Estimated fetal weight	−0.42 (−1.59, 0.77)	−0.55 (−1.46, 0.86)	0.62

Data are mean (SD) or number (%) or median (10th, 90th centile) as appropriate. *P* values are for chi-square or Student's *t*-tests as appropriate.
RI, resistance index.
SGA is defined as <10th customised centile.
*Denominators varied slightly due to missing data.
**Expressed as '*z*-scores'.

there was no association between uterine or umbilical artery Doppler pulsatility index and smoking status at 20 weeks gestation, but found the umbilical artery pulsatility index at 30 weeks gestation was increased among smokers. In combination, these data suggest the predominant effect of smoking is on the vasculature in placental villi, with a lesser impact on the uteroplacental blood supply.

The small differences we found in umbilical artery Doppler RI, between smokers and nonsmokers in this study at 20 weeks, may not seem clinically important. However, mathematical models of the umbilical placental circulation have shown that at least 20–30% of small placental vessels need to be obliterated before detectable changes occurred in the pulsatility index.[15] The small differences in RI between smokers and nonsmokers in our study, could therefore be associated with significant vascular pathology, especially if the changes become more pronounced in smokers as gestation advances.

Our data are also consistent with the spectrum of placental changes which have been associated with smoking in

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pregnancy. Cigarette smoke contains hundreds of toxic compounds many of which are capable of inducing direct cellular damage.[16] Maternal smoking alters human placental development in numerous ways, recently reviewed by Jauniaux and Burton.[3] Smoking is associated with narrowing of the terminal villous capillaries with consequent reduced volume density of fetal vessels in the terminal villi.[17] Stem villous arteries of heavy smokers have been reported to have a greater vasoconstrictive response to endothelin 1 than do those from nonsmokers.[18] A very recent publication has also demonstrated that smokers had reduced eNOS activity in the umbilical vein implying reduced vasodilatory capacity, which is also consistent with the increased umbilical artery Doppler indices in the current study.[19] Hence altered structural development of the villous vascular tree, together with modification of the vascular biology of villous arterioles and small arteries to vasoactive substances, are likely to contribute to the increased umbilical artery Doppler RI we observed in smokers at 20 weeks' gestation.

Smoking also impacts on trophoblast invasion in early pregnancy and development of the uteroplacental blood supply. In the first trimester, the number of anchoring villi is reduced[2] and cell islands (trophoblasts with fibrinoid material) that fail to make uterine attachments are increased in placentae from smokers.[20] Reduced cytotrophoblast proliferation and impaired invasion is evident in explant cultures of first trimester placenta from smokers and seen in placental explant cultures following nicotine exposure *in vitro*.[2,20] These smoking and nicotine induced changes in early placentation could impair trophoblast invasion and remodelling of the spiral arteries. The increased uterine artery Doppler RI we found associated with continuing smoking in pregnancy is consistent with defective development of uteroplacental blood supply. However, after adjusting for maternal demographic characteristics, the odds of having an abnormal uterine artery Doppler waveform among smokers was no longer increased.

Among SGA infants, women who smoked were three times more likely to have an abnormal umbilical RI and had SGA babies with lower birthweight centiles and mean birthweight 200 g less than in those with SGA babies who did not smoke. These data suggest that smokers may have babies with more severe fetal growth restriction and that an important difference between smokers and nonsmokers with SGA babies is the effect of smoking on the umbilical placental circulation which can be detected as early as 20 weeks gestation.

Compared with nonsmokers, fetuses of smokers had a small reduction in femur length at 20 weeks' gestation but not abdominal or head circumference, consistent with two previous studies.[9,21] Although the absolute reduction in these fetal measurements at 20 weeks was minimal, these data suggest that the earliest effect of smoking is on longitudinal rather than visceral fetal growth, whereas at birth both femur length as well as abdominal circumference are reduced in infants born to women who smoke.[22]

A potential limitation of this study is that self-reported smoking status, as is usual in clinical practice, was not validated by measurement of cotinine levels. As cotinine measurements are highly correlated with self-reported smoking status,[23,24] we consider it unlikely that under reporting of smoking will have significantly impacted our results.

We were not able to demonstrate a dose–response relationship between umbilical Doppler RI and the number of cigarettes smoked daily. This may be because of limited power, with only 248 smokers, and also that only 21% of women smoked >10 cigarettes per day. A study with a larger number of smokers is required to further explore this relationship.

Our data suggest that smoking is associated with alteration of the umbilical-placental circulation as early as 20 weeks of gestation. Further among SGA infants, women who smoked were more likely to have an abnormal umbilical artery Doppler waveform at 20 weeks. Impaired development of the umbilical-placental vasculature may be a mechanism contributing to fetal growth restriction among women who smoke in pregnancy.

Disclosure of interest

No conflict of interest.

Contribution to authorship

All authors participated in the conception and design of the study and drafting the manuscript. EC provided statistical analysis. EMK, RN, PRS, GD and LM contributed to the interpretation of data. All authors approved the final version.

Details of ethical approval

Ethical approval was gained from local ethics committees (New Zealand AKX/02/00/364 and Australia REC 1712/5/2008).

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