Gender, smoking during pregnancy and gestational age influence cord leptin concentrations in newborn infants

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Abstract

Background: Low birth weight (BW), small head circumference, reduced length, increased preterm births and neuro-endocrine dysfunctions are among known consequences of smoking during pregnancy. Few studies have linked leptin to clinical features of growth restriction associated with maternal smoking and explored interaction with other determinants of size at birth, such as gender.

Methods: Cord serum leptin concentrations were measured in 1215 term infants born to Caucasian mothers at completion of uneventful pregnancy. Serum concentrations were related to BW, gestational length, gender and maternal smoking and interaction with other determinants of size at birth evaluated.

Results: Smoking was more frequent in younger (P<0.001) and shorter mothers (P=0.03) from lower socio-economic groups (SEGPs) (P<0.001). Infants born to smokers were lighter (190 g less), shorter and with smaller head circumference. Cord serum leptin concentrations were higher in girls (9.8 s.d. 7.6 ng/ml) than in boys (7.05 s.d. 5.8 ng/ml) (P<0.001). Boys were heavier (BW 3.52 s.d. 0.49 kg) than girls (3.39 s.d. 0.44 kg) (P<0.001), but girls had greater skinfold thickness measurements (subscapular and quadriceps skinfold thicknesses 5.5 s.d. 1.6 mm and 7.6 s.d. 1.9 mm respectively; boys 5.3 s.d. 1.6 vs 7.24 ± 1.90 mm, P<0.001 respectively). Multivariate analyses showed gender (P<0.001), BW SDS (P<0.001), gestational length (P<0.001) and maternal smoking (P<0.042) as factors that influenced umbilical cord serum leptin concentrations in newborns.

Conclusion: Maternal smoking restrains foetal growth through placental vascular effects, and likely also via associated effects on leptin metabolism. More studies are needed to determine the influence that maternal smoking may have on placental syncytiotrophoblast and foetal adipose tissue.

Introduction

In 1957, Simpson described the association of maternal smoking with foetal growth restraint (1). Since then a series of studies have demonstrated a consistent effect of maternal smoking on foetal growth with reductions in birth weight (BW), length and head circumference. Moderate-to-heavy maternal smoking is responsible for an average reduction in BW of 90–200 g in infants whose mothers smoked during pregnancy (2). Foetal growth restriction is an important determinant of perinatal morbidity and mortality; and in the longer term, epidemiological studies suggest that intrauterine growth restriction predisposes to the development of the metabolic syndrome (the association of obesity, arterial hypertension, hyperlipidaemia, cardiovascular disease, impaired glucose tolerance and insulin resistance) (3).

Smoking during pregnancy has also been implicated in neurological endocrine as well as maturational modifications observed in infants born to smoking mothers (4).

The impact of maternal smoking on foetal growth arises in a number of ways either directly by reducing foetal growth as environmental toxin, by shortening gestational length (1, 5, 6), thus increasing the incidence of premature births, or by altering utero-placental and foetal blood flow, with consequent decrease in oxygen consumption, nutritional and energy supply to the foetus (7, 8). The classic measures of foetal growth, e.g. BW, are composites of a number of components each influenced to varying degrees by a series of growth factors. Longitudinal growth in utero is insulin-like growth factor-I (IGF-I) dependent and circulating concentrations of IGF-I are reduced in...
newborns born to mothers who have smoked during pregnancy (9). Other factors influence the development of adipose tissue, which is an important component of weight in the last 8 weeks of pregnancy.

Leptin, a 167 amino acid protein from the obese gene, is synthesized mostly in white adipose tissue but also in the placenta, and as a regulatory molecule of appetite it circulates at a concentration that is proportional to fat mass in both humans and rodents (10). A positive correlation between its cord concentrations, body weight and fat mass has been found in newborn infants (11), suggesting that leptin may play a role in the regulation of foetal adiposity.

The interaction of leptin with factors influencing foetal growth has not been determined and conflicting reports have been published on the impact of maternal smoking on cord serum leptin concentrations (12–15). In this report, we describe cord serum leptin concentrations in 1215 newborn infants born at term to Caucasian mothers and relate leptin values to BW, gestational age, gender and maternal smoking during pregnancy. Our aim was to answer the question of whether smoking during pregnancy, in addition to known mechanisms, also restricts foetal growth via its action on leptin metabolism.

Subjects and methods

Study group

The study cohort and our inclusion and exclusion criteria have been described elsewhere (9). The present study was confined to term-born infants (gestational age > 37 weeks; gestational age was determined according to last menstrual date and/or the first obstetrical ultrasound). Maternal cigarette smoking was categorized as: never smoked (group 1, n = 870), stopped on becoming pregnant (group 2, n = 117), smoked less than 10 cigarettes/day (group 3, n = 115), smoked 10–20 cigarettes/day (group 4, n = 90) and smoked more than 20 cigarettes/day (group 5, n = 26). Socio-economic status was determined from age at which full-time education was completed, marital status, occupation and partner’s occupation, and social class assignment was made using the classification of the United Kingdom Office of Population Census and Statistics (Standard Occupational Classification Volume 3. OPCS 1991). Pregnancy complications were noted and infants excluded from analysis from those mothers who developed complications of pregnancy.

Complete perinatal outcome and anthropometric data (BW, length, head and mid-arm circumference) were available in 1484 babies. BW was measured using self-calibrating electronic scales (Seca, Birmingham, UK), length was measured using Infantometer (Child Growth Foundation, London, UK) and head circumference with a metal tape (Holtain, Crymych, UK). Ponderal index was calculated as weight/length³ and skinfolds (triceps, sub-scapular and quadriceps) were measured using skinfold callipers (Holtain); three separate measurements were taken and the mean recorded. The coefficient of variation of the measurement error for length was 0.15% based on ten infants, each having been measured five times by three observers. Blood sample was collected after birth and before completion of the third stage of labour into EDTA from the umbilical vein. The sample was centrifuged, after cord blood pH was measured, separated and plasma stored immediately at −20°C until leptin assays were performed within 3 months of collection. The study received approval from the Research Ethics Committee of University College London Hospitals, and written informed consent for participation obtained from the mothers both for own participation and that of their newborn child after its birth.

Leptin assay

Serum assay leptin concentration was measured by commercial RIA (Linco Research Inc., St Charles, MO, USA). The within-assay coefficients of variation (CV) were 8.3, 3.9 and 3.4 at 4.9, 10.4 and 25.6 ng/ml respectively. The between-assay CV values were 5.6 and 6.3 at 3.5 and 15.5 ng/ml respectively. The calibrants in the assay were from purified recombinant human leptin. The minimum detection limit was 0.5 ng/ml.

Statistical analysis

Anthropometric measures (BW, length and head circumference) were expressed as SDS using the 1990 British growth reference (16). Correlations between hormonal data and anthropometrics measures were estimated using Pearson’s correlation coefficient. \( \chi^2 \) was used to compare the distribution of frequencies between groups. One-way ANOVA was used to determine differences between the mean values of the groups with Student–Newman–Keuls post hoc test to determine significance between groups. Multiple linear regression analysis was used to explore the effects of maternal smoking, infant’s gender (male 1, female 2), BW (SDS), placental weight and gestational length on cord serum leptin concentration.

Results

General

In the study, 1650 mothers were enrolled and 1484 live infants were delivered, of whom 70 were preterm infants. Of the remaining 166 who did not deliver, 127 did not complete the study either because they had moved away or because they were lost to follow-up, 28 patients pregnancies were terminated either into
miscarriage or by medical termination and 11 simply withdrew from the study. Analysis is therefore confined to 1215 term infants (gestational age > 37 weeks) born to mothers whose pregnancies were uncomplicated by gestational diabetes, utero-placental hypoxia–ischaemia–antepartum haemorrhage, pregnancy-induced hypertension and pre-eclampsia. Clinical and anthropometric characteristics of mothers enrolled for this study are summarized in Table 1 and show that mothers who smoked heavily were younger (one-way ANOVA $F=27.4; P<0.001$) and shorter ($F=2.64; P=0.003$) and from SEGPs 4 and 5 (SEGP 1. 96% non-smokers versus 56% in SEGP 5; $P<0.001$). Maternal body mass index was not significantly different between smokers and non-smokers. Smoking habit was not influenced by parity. No significant differences were found between groups with regard to maternal pre-gestation weight, weight gain during pregnancy (data not shown), gestation at first antenatal attendance, gestational age at delivery and blood pressure at first antenatal attendance or maternal haemoglobin.

**Size at birth** Neonatal anthropometric measures are summarized in Table 2. Overall, there were significant sex differences in BW, length and head circumference, with male infants being heavier, longer and leaner, and having larger heads than females. Infants born to mothers who smoked showed BW (a reduction of 190 g), length and head circumference that were lower, compared with those of infants of non-smoking mothers ($P<0.05$ for groups 1 and 2 versus groups 3–5); differences between groups (smoking and non-smoking) in these three parameters were not dose dependent.

Although no statistically significant differences could be observed between infants of smokers and those of non-smokers in skinfold thickness and mid-arm circumference, male infants had greater mid-arm circumference but smaller skinfolds than females. Fine analysis and comparison of BW between infants born to smoking mothers and those of non-smokers showed that frequency of babies with BW comprised between the third and the tenth centile born to smoking mothers when compared with non-smokers (19% vs 7%; $\chi^2 33.2; P<0.001$).

**Cord serum leptin concentration** Table 3 compares cord serum leptin concentration, BW, ponderal index, triceps, sub-scapular and quadriceps skinfold thicknesses between sexes. Cord serum leptin concentrations were higher in girls than boys ($P<0.001$); although the latter had higher BWs, girls had higher skinfold thickness measurements.

The effects of maternal smoking on cord serum leptin concentrations are shown in Fig. 1. There was no significant difference between the groups. The $P$ value for comparison of cord leptin concentrations in non-smokers with the other groups is summarized in Table 4. Multiple regression analyses were then performed with umbilical cord serum leptin concentration as dependent variable, and infant’s gender, BW (SDS), gestational length and maternal smoking during pregnancy as independent variables. BW ($P<0.001$), gender ($P<0.001$), gestational length and maternal smoking were of significant importance. Multivariate analyses with maternal smoking, placental weight, gender, gestational length and BW (SDS) showed that gender ($P<0.001$), BW SDS ($P<0.001$), gestational length ($P<0.001$) and maternal smoking ($P<0.042$) were the important factors that were associated with umbilical cord serum leptin concentration in newborns.

**Discussion**

This study was designed to assess the effects of maternal smoking during pregnancy on foetal cord serum leptin concentration at birth, in term infants, and hence answer the question of whether foetal growth restriction secondary to maternal smoking during gestation could result from the action of the latter on foetal leptin metabolism (Table 5).

Our results show effectively that factors associated with cord serum leptin concentrations in newborns are gender, gestational age, as well as smoking during pregnancy. Inaccuracy of self-reported smoking habits in comparison with cotinine assay by our study population is a likely criticism that may be made of this study. Biological assays, although more accurate, often provide

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**Table 1** Clinical and anthropometric details of mothers enrolled in the study.

| Age (years) | Non-smokers ($n=868$) | Stopped ($n=117$) | <10/day ($n=114$) | 10–20/day ($n=90$) | >20/day ($n=26$) |
|------------|-----------------------|------------------|------------------|-------------------|-----------------|
|            | 31.8 (5.3)            | 31.2 (5.1)       | 27.6 (5.7)       | 27.9 (5.8)        | 27.5 (5.3)      |
| Height (cm)| 164.8 (6.9)           | 165.2 (6.6)     | 163.9 (6.5)      | 162.9 (6.0)       | 162.5 (6.6)     |
| Weight (kg)| 63.8 (11.1)           | 64.1 (9.2)      | 63.2 (10.4)      | 62.2 (11.8)       | 65.8 (17.7)     |
| BMI (kg/m²)| 23.6 (4.2)            | 23.6 (3.9)      | 23.2 (3.4)       | 23.4 (4.3)        | 24.7 (6.0)      |
| Gestation at delivery (weeks) | 39.7 (1.3) | 40.0 (1.3) | 39.6 (1.4) | 39.7 (1.2) | 39.5 (1.4) |

Data shown as mean with s.o. in parenthesis.
no precise information regarding quantities or timing of exposure. Moreover, some studies have reported good correlation between self-reporting versus cotinine assay and smoking effects on foetal growth (17, 18).

**Leptin and gender**

The gender difference in serum leptin concentrations previously reported by several other studies (13, 14, 17) was also found in our study. Cord serum leptin concentrations were higher in girls than boys. It is tempting to speculate that, boys being heavier than girls, their body weight likely reflects heavier muscle bulk and skeleton, whereas higher leptin concentrations in girls are correlated with more subcutaneous fat. As this gender difference in body fat distribution is present as early as during antenatal life, we consider, like Jaquet et al. (19) that body weight at birth does not reflect body fat mass alone.

There are several explanations to the gender difference in cord serum leptin concentrations: for Tome et al. (20), the sex-based differences are not attributable to any growth-related differences between boys and girls, but may simply reflect a sex-based difference in the regional adipose tissue regulation of leptin production. For Bennet et al. (21), however, sexual dimorphism is probably the result of regional distribution of adipose tissue. Van Harmelen et al. (22) suggested that gender difference in leptin concentration was a consequence of variation in leptin secretion present in women and not in men. Like Nagy et al. (23), we think that the sexual dimorphism in cord serum leptin concentration is likely to be due to both relative body composition and fat distribution, which are different in male and female infants. The gender differences in cord leptin concentrations reported here are, however, not a constant finding in the literature, some studies have reported similar concentrations in boys and girls (13). The reasons for these discrepancies are yet to be elucidated.

**Effects of maternal smoking on placental circulation and foetal growth**

**Effects of maternal smoking on placental morphology and function**

Active maternal smoking during gestation induces morphological changes with consequent reduction in both volume of maternal intervillous space and surface area of foetal capillaries (24), these changes lead to reduced oxygen diffusion across the placenta. Metabolites of cigarette smoke cross the placenta, passing from mother to foetus, and act as vasoconstrictors that reduce uterine blood flow by up to 38% (25). Of note is the fact that smoking hypoxia is not exclusively pre-placental in origin, but is complicated by both blood flow problems and cadmium toxicity that act at trophoblastic as well as other placental sites (26). Maternal smoking, therefore, places the foetus under chronic hypoxic stress, and hence contributes to restriction in weight gain, reduced length and small head circumference. Based on the model classifying the origins of hypoxia by Kingdom et al. (26), three principal classes are recognized: pre-placental, utero-placental

### Table 2

Newborn infants’ anthropometric measures in relation to maternal smoking status.

| Measure | Non-smokers | Stopped | <10/day | 10–20/day | >20/day | P     |
|---------|-------------|---------|---------|-----------|---------|-------|
|         | (n=868)     | (n=117) | (n=114) | (n=90)    | (n=26)  |       |
| BW (g)  | 0.18 (0.96) | 0.04 (0.87) | -0.28 (0.99) | -0.23 (0.95) | -0.29 (1.25) | <0.001 |
| BL (cm) | -0.08 (1.11) | 0.03 (1.24) | -0.33 (1.23) | -0.48 (1.16) | -0.61 (1.16) | 0.001 |
| HC (cm) | 0.01 (1.10) | 0.04 (1.10) | 0.28 (1.10) | 0.33 (1.02) | 0.29 (1.37) | 0.001 |
| TS (cm) | 5.8 (1.5)   | 6.2 (1.7)  | 5.7 (1.6)  | 5.8 (1.6)  | 5.8 (1.8)  | 0.06  |
| SS (cm) | 5.4 (1.6)   | 5.5 (1.4)  | 5.2 (1.7)  | 5.3 (1.5)  | 5.5 (2.2)  | 0.62  |
| QS (cm) | 7.5 (1.9)   | 7.6 (1.8)  | 7.2 (2.1)  | 7.3 (2.0)  | 7.1 (2.3)  | 0.47  |
| MC (cm) | 10.6 (1.0)  | 10.6 (1.0) | 10.3 (1.0) | 10.4 (1.0) | 10.5 (1.3) | 0.11  |

Data are presented as mean with S.D. in parentheses, skinfold thicknesses expressed in mm. BW, birth weight; BL, birth length; HC, head circumference; TS, triceps skinfold; SS, sub-scapular skinfold; QS, quadriceps skinfold; MC, mid-arm circumference.

### Table 3

Comparisons between boys and girls of anthropometric measures and cord serum leptin concentrations.

| Sex | BW (SDS) | Pondind. | Triceps SF | SSSF | Quad SF | Cord leptin |
|-----|----------|----------|-----------|------|---------|-------------|
| Male | 3.52 (0.49) | 27.34 (3.25) | 5.77 (1.60) | 5.28 (1.54) | 7.24 (1.90) | 7.05 (5.84) |
| (n=632) | (n=613) | (n=577) | (n=576) | (n=573) | (n=474) |
| Female | 3.39 (0.44) | 27.57 (3.14) | 5.86 (1.50) | 5.48 (1.60) | 7.62 (1.87) | 9.77 (7.60) |
| (n=586) | (n=575) | (n=527) | (n=527) | (n=521) | (n=442) |
| P value | <0.001 | 0.236 | 0.348 | 0.032 | 0.001 | <0.001 |

BW, birth weight; Pondind, ponderal index; Triceps SF, triceps skinfold thickness; SSSF, sub-scapular skinfold thickness; Quad SF, quadriceps skinfold thickness. Skinfold thickness in mm and cord leptin in ng/ml. Data shown as mean with S.D. in parentheses.
Table 4 Cord leptin concentrations in relation to maternal smoking or non-smoking status.

| Smoking status         | N  | Mean cord leptin (s.d.) | P value |
|------------------------|----|-------------------------|---------|
| Never smoked           | 657| 8.53 (6.90)             |         |
| Stopped smoking        | 85 | 7.63 (5.43)             | 0.79    |
| Smoked <10 cigarettes  | 82 | 8.03 (7.20)             | 0.97    |
| 10–20 cigarettes       | 74 | 7.60 (6.26)             | 0.81    |
| >20 cigarette          | 18 | 10.63 (11.72)           | 0.70    |
is not possible to differentiate the two. Further research is needed to clarify this.

Several studies have analysed the effects of maternal smoking on cord serum leptin concentration, with discordant results (11–14). In the study by Helland et al. (13), children of smoking mothers were lighter than those of non-smokers, plasma leptin concentrations were, however, similar between the two groups. For these authors, reduced BW in neonates of smoking mothers is not consequent to altered leptin concentration. Pardo et al. (12) also studied the effect of maternal smoking on leptin concentrations in term appropriate-for-gestational-age newborns, and reported similar leptin concentrations between infants of smoking and those of non-smoking mothers. Mantzoros et al. (11) have, however, reported that maternal smoking during pregnancy was associated with decreased cord leptin concentrations of both full-term and preterm newborns. For these authors, smoking during pregnancy induces reduction in foetal cord serum leptin concentration through depletion of foetal energy stores directly via substances present in tobacco smoke or indirectly by compromising nutrient supply consequent to induced placental changes. Another pathway through which smoking could influence leptin concentrations in neonates may be through decreased energy stores in foetal adipose tissue, probably via an increase in foetal catecholamine level. The later phenomenon is known to increase lipolysis. In another recent study by Ozkan et al. (14), maternal smoking has been shown to lower foetal plasma leptin concentration independently of BW. In our study, although comparison of cord serum leptin concentrations between infants born to smokers and those of non-smokers did not reach statistical significance (univariate analysis), multiple regression analysis performed with cord serum leptin concentration as dependent variable tends to suggest that infant’s gender, BW, gestational length and maternal smoking during gestation were the more significant independent variables that influenced cord serum leptin concentrations. We have shown that BW SDS is significantly different between infants of smokers when compared with those of non-smokers; we could not, however, find statistically significant difference in cord serum leptin concentrations between the two groups (smokers versus non-smokers). Infants born to heavy smokers (>20 cigarettes/day) had cord serum leptin concentrations that were slightly higher; the reason for this discrepancy remains unexplained. The likely, but speculative explanations could be that these infants who were also the smallest (severe SGA), could have had enhanced endogenous steroidogenesis (secondary to chronic hypoxia) leading to an increase in leptin synthesis (37). Whether maternal smoking also restrains foetal growth by altering foetal leptin metabolism is not established with certainty, but this hypothesis cannot totally be ruled out.

Smoking during pregnancy deprives the foetus of nutrients and oxygen, resulting in episodic foetal hypoxia–ischemia and malnutrition. Smoking-induced foetal stress has been shown to be associated with raised amniotic fluid catecholamine concentrations, but studies have reported conflicting results in this regard, with some reporting increased amniotic levels (38) and others reporting lower cord catecholamine concentrations (39). That cigarette smoking during pregnancy could also impair foetal growth via leptin metabolism seems feasible, this would probably result from increased foetal lipolysis secondary to raised catecholamine concentrations. Systemic nicotine treatment in healthy men has, indeed, been shown to stimulate human adipose tissue lipolysis through local cholinergic and catecholaminergic receptors (40).

Table 5 Placental weight and mother’s body mass index (BMI) according to smoking status.

| Smoking status | N  | Mean | s.d. | Std. error | 95% Confidence interval for mean | Minimum | Maximum |
|----------------|----|------|-----|-----------|-------------------------------|---------|---------|
| placwt         |    |      |     |           |                               |         |         |
| 1              | 778| 673.23|129.240|6.333     | 664.13–682.32                 | 320     | 1240    |
| 2              | 99 | 668.37|135.743|13.643    | 641.30–695.45                 | 400     | 1100    |
| 3              | 89 | 667.03|120.568|12.780    | 641.64–692.43                 | 400     | 990     |
| 4              | 79 | 669.94|115.821|13.031    | 643.99–695.88                 | 380     | 1000    |
| 5              | 24 | 667.71|169.090|34.515    | 596.31–739.11                 | 410     | 1160    |
| Total          | 1069| 671.90|129.000|4.160     | 664.15–679.64                 | 320     | 1240    |
| BMI            |    |      |     |           |                               |         |         |
| 1              | 803| 23.599|4.2150|0.1487    | 23.307–23.891                 | 16.0    | 52.6    |
| 2              | 113| 23.620|3.8848|0.3654    | 22.896–24.344                 | 18.2    | 45.7    |
| 3              | 104| 23.167|3.3893|0.3323    | 22.508–23.826                 | 16.7    | 34.3    |
| 4              | 84 | 23.371|4.2493|0.4636    | 22.449–24.294                 | 18.0    | 44.8    |
| 5              | 25 | 24.710|5.9604|1.1921    | 22.250–27.170                 | 17.7    | 40.4    |
| Total          | 1129| 23.569|4.1607|0.1238    | 23.326–23.812                 | 16.0    | 52.6    |

1, never smoked; 2, stopped smoking; 3, smoked <10 cigarettes/day; 4, smoked 10–20 cigarettes/days; 5, smoked >20 cigarettes/day.
Contribution of maternal smoking during pregnancy to foetal growth restriction, therefore, implies multifactorial physio-pathological mechanisms, some of which have been elucidated (IGF-I, placental changes, blood flow effects, etc). Nicotine-induced hypoxia has been extensively studied, cadmium toxicity acts at trophoblastic as well as other placental sites (26) and leptin is produced in large amounts by the syncytiotrophoblast (36); whether nicotine and/or cadmium toxicity impairs the expression of leptin mRNA here, needs to be studied further.

Conclusion

We have shown that maternal smoking during pregnancy restraints foetal growth, with infants born to heavy smoking mothers being the smallest. Our study also confirms the gender difference in cord serum leptin concentrations between boys and girls. Cord serum leptin concentrations, although slightly elevated in infants of heavy smokers, could not reach the level of significance. Multivariate analysis, however, points out gender, BW, gestational length and maternal smoking as most significant independent variables that influence cord leptin concentrations. We, therefore, think that maternal smoking also likely impairs foetal growth via its effects on leptin metabolism, in addition to well-known placental vascular effects. Studies are awaited to analyse the effects of maternal smoking on both placental syncytiotrophoblast and foetal adipose tissue.

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