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CLINICAL ARTICLE

# Fetal and maternal leptin in pre-gestational diabetic pregnancy

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ABSTRACT

*Objective:* To compare maternal and fetal leptin among women without diabetes, women with type 1 diabetes, and women with type 2 diabetes. *Methods:* In a prospective study at the National Maternity Hospital, Dublin, 40 women with type 1 diabetes, 10 with type 2 diabetes, and 30 without diabetes were enrolled between July 2006 and July 2008. Maternal (36-week) and cord blood leptin was measured by enzyme-linked immunoassay. *Results:* No difference was found in maternal leptin among the groups: without diabetes (mean, range): 325 pg/mL, 36–1492 pg/mL; type 1 diabetes: 343.2 pg/mL, 55.5–1108.2 pg/mL; type 2 diabetes: 202.2 pg/mL, 35.1–1553.3 pg/mL ($P>0.05$). Leptin levels were higher among fetuses of women with type 1 (223 pg/mL, 25.7–810 pg/mL) and type 2 (447.2 pg/mL, 136.3–679 pg/mL) diabetes than among women without diabetes (80.3 pg/mL, 27.3–623.1 pg/mL; $P<0.05$). The single significant predictor of fetal leptin for the whole cohort was maternal body mass index (BMI; $r=0.39$, $P=0.01$). Only third-trimester glycosylated hemoglobin (HbA1c) was significantly related to fetal leptin after controlling for maternal BMI among women with diabetes ($r=0.28$, $P=0.04$). *Conclusion:* Fetuses of women with diabetes might have some degree of leptin resistance. This might be important in appetite regulation in extrauterine life.


## 1. Introduction

Leptin is involved in the regulation of body weight through suppression of appetite and stimulation of energy expenditure [1]. Conversely, leptin levels are increased in obesity [2], which is considered to be a state of leptin resistance. Leptin is higher among pregnant women than among non-pregnant women, and correlates strongly with maternal body mass index (BMI, calculated as weight in kilograms divided by the square of height in meters) [3]. Raised maternal leptin in pregnancy is due to both an increase in maternal adipose tissue [4] and greater placental production [5].

In type 1 diabetes and gestational diabetes, maternal plasma leptin concentrations have not been shown to be significantly different from controls. In their infants, both fetal and placental leptin concentrations are higher compared with controls [1]. Up to 3–5-fold higher leptin protein and mRNA levels are found in the placentae of women with insulin-treated diabetes compared with control women [6]. This suggests that the changes elicited by diabetes mellitus may be confined to the fetoplacental unit [7]. Umbilical leptin levels are higher again among pregnancies with diabetes and fetal macrosomia [6,8]. Although data are available for pregnancies in women with type 1 diabetes, there is no information on maternal and fetal leptin for pregnancies in women with type 2 diabetes.

The aim of the present study was to examine maternal and fetal leptin levels among pregnancies in women with type 1 and type 2 diabetes and to compare the data with those from pregnant women without diabetes. The hypothesis was that maternal leptin would be higher among women with type 2 diabetes compared with type 1 diabetes, because evidence indicates that insulin resistance plays a role in leptin production [9,10], and type 2 diabetes is a state of insulin resistance.

## 2. Materials and methods

In a prospective cohort study, pregnant women attending the National Maternity Hospital, Dublin, Ireland, were recruited between July 2006, and July 2008. Institutional ethics approval was obtained for the study, and all participants provided informed written consent.

Women with pre-gestational and gestational diabetes were invited to participate in the study. Women without diabetes were recruited from routine low-risk clinics staffed by midwives and obstetricians. All non-diabetic control women had screened negative for gestational diabetes.

Pregnant women with pre-gestational and gestational diabetes were managed by predefined multidisciplinary guidelines, which have been defined previously [11]. All women with type 2 diabetes required oral hypoglycemic drugs to maintain a state of euglycemia prior to pregnancy. At the beginning of pregnancy, the medication of the women was converted to subcutaneous insulin at a mean of 7 weeks (range 5–9 weeks).

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Blood was obtained from the participants at 36 weeks of gestation. One woman delivered at 35 weeks of gestation and was excluded from the study. After delivery of the neonate but before delivery of the placenta, cord blood was obtained from the umbilical vein. Blood was centrifuged in the hospital laboratory and plasma stored at −20 °C.

Clinical data were obtained prospectively from the labor ward database, ultrasound department database, and patient records. Participant characteristics such as maternal age, parity, gestational age at delivery, and type of delivery were recorded, in addition to neonatal outcomes such as birth weight, birth weight centile, and Apgar score at 1 and 5 minutes. Macrosomia was defined as a birth weight greater than the 90th centile for gestation and gender. Poor perinatal outcome was defined as any of the following: an Apgar score at 1 or 5 minutes of less than 7, a cord pH of less than 7.2, or admission to the neonatal intensive care unit (NICU) for an indication other than hypoglycemia. In addition, measurements of glycemic control (glycosylated hemoglobin, HbA1c) at early pregnancy (first visit) and at 36 weeks of gestation were recorded for women with diabetes. Full data were obtained for all participants.

Women with pre-gestational diabetes (type 1 and type 2 diabetes) underwent a routine third-trimester ultrasound examination, assessing fetal wellbeing and fetal growth. Ultrasound measurements were performed transabdominally by 1 of 3 trained operators (M.F.H., N.M.R., F.M.M.) using either a Voluson 730 Expert (GE Medical Systems, Munich, Germany) or Toshiba Xario (Toshiba Medical Systems, Minato, Japan) instrument.

Leptin was measured by enzyme-linked immunoassay (Human Leptin Immunoassay, R&D Systems, Minneapolis, MN, USA) with an inter-assay and intra-assay precision of 4.2% and 3.2%, respectively. For this assay, the detection limit of this assay was 7.8 pg/mL of leptin.

Statistical analysis was performed via SPSS version 16 (IBM, Armonk, NY, USA). Non-parametric data were compared using test for trend, Mann–Whitney test (median/range), or Kruskal–Wallis test. Spearman correlation was used for non-parametric continuous data. Multiple linear analysis using forward stepwise analysis was performed. Statistical significance was set at a $P$ level of less than 0.05.

## 3. Results

During the study period, 40 women with type 1 diabetes, 10 women with type 2 diabetes, and 30 women without diabetes were recruited and completed the study. Patient characteristics are shown in Table 1. None of the patients had diabetic nephropathy or proliferative retinopathy. The degree of glycemic control and the time from diagnosis of diabetes among the participants with diabetes are shown in Table 2.

No difference in maternal leptin levels were found at 36 weeks of gestation. Fetal leptin was higher among neonates of both women with type 1 diabetes and women with type 2 diabetes than among neonates of women without diabetes (Fig. 1). No correlation between maternal and fetal leptin levels was found ($r=-0.01$; $P=0.88$). A significant correlation between maternal leptin and maternal BMI ($r=0.293$, $P=0.01$) was identified.

Regarding macrosomia, 21 neonates of women with type 1 diabetes (52.5%), 3 neonates of women with type 2 diabetes (30%), and 5 neonates of women without diabetes (16.66%) were macrosomic. Within the group as a whole, maternal leptin did not correlate with birth weight, birth weight centile, maternal age, or gestational age at delivery. No significant correlation with any of these parameters was found when the groups were divided into women without diabetes, women with type 1 diabetes, or women with type 2 diabetes. There was no difference within the group as a whole, or among the study groups, when maternal leptin was compared on the basis of gender of neonate, mode of delivery, or poor perinatal outcome.

No significant difference in maternal leptin was found between women whose infants were admitted to the postnatal ward after delivery and those whose infants were admitted to NICU either for the whole cohort or for the group of neonates of mothers with type 1 diabetes. Only 1 neonate from the control group and 1from the type 2 diabetes group was admitted to NICU. With regard to maternal glycemic control, no relationship between maternal leptin and HbA1c (first and third trimester) was identified; nor was there a significant difference between maternal leptin and duration of diabetes.

Among the whole cohort, fetal leptin correlated with both birth weight centile ($r=0.304$, $P=0.06$) and birth weight ($r=0,3$, $P=0.007$). No relationship was found with gestational age at delivery ($r=-0.17$, $P=0.12$). Across the cohort, there was no difference in fetal leptin on the basis of gender of neonate, mode of delivery, or composite perinatal outcome. No difference in fetal leptin was identified between neonates admitted to NICU and those admitted to the postnatal ward. The relationship between fetal leptin and ultrasonic and blood markers of glycemic control is shown in Table 3.

**Table 2**
Glycemic control, duration of diabetes, and prenatal ultrasound markers of adiposity in pre-gestational diabetes.

| | Type 1 diabetes (n=40)[a] | Type 2 diabetes (n=30)[a] | $P$ value |
|---|---|---|---|
| Duration of diagnosis, y | 13 (0–34) | 3 (2–4) | 0.001 |
| Early HbA1c, % | 7.3 (5.2–13) | 6.3 (4.9–7.3) | 0.002 |
| 36-week HbA1c, % | 5.9 (4.9–7.5) | 5.8 (4.4–6.3) | 0.28 |
| 36-week fetal abdominal circumference, mm | 336 (296.8–401) | 334 (305.5–358) | 0.89 |
| 36-week fetal anterior abdominal wall thickness, mm | 5.2 (3.0–8.1) | 5.4 (3.5–7.8) | 0.47 |

[a] Values are given as mean (range).

**Table 1**
Patient demography and leptin levels according to group.[a]

| | Without diabetes (n=30) | Type 1 diabetes (n=40) | Type 2 diabetes (n=10) | $P$ value |
|---|---|---|---|---|
| Age, y | 33 (19–42) | 34 (26–42) | 37 (32–40) | 0.08 |
| Primiparous | 8 (26.6) | 13 (32.5) | 2 (20.0) | 0.74 |
| BMI | 24.56 (19.05–31.2) | 24.4 (18–47) | 26 (23–36) | 0.18 |
| Cesarean delivery | 22 (73.3) | 22 (55.0) | 7 (70.0) | 0.16 |
| Apgar >7 at 1 min | 30 (100) | 40 (100) | 10 (100) | 0.50 |
| Apgar >7 at 5 min | 30 (100) | 40 (100) | 10 (100) | 0.48 |
| Birth weight, g | 3535 (2715–4280) | 3625 (2870–4875) | 3715 (2635–4170) | 0.30 |
| Birth weight, centile | 60 (3–99) | 90 (10–99) | 75 (10–99) | 0.04 |
| Admission to NICU | 1 (3.3) | 12 (30) | 1 (10) | 0.01 |
| Gestational age, wk+d | 39+0 (37+6 to 41+0) | 38+2 (36 to 40+0) | 38+6 (38+0 to 40+0) | 0.004 |
| Maternal leptin, pg/mL | 325 (36–1492) | 343.2 (55.5–1108) | 202.2 (35.1–1553) | 0.41 |
| Fetal leptin, pg/mL | 80 (27–623) | 223 (26–810) | 447 (136–679) | <0.001 |

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); NICU, neonatal intensive care unit.
[a] Values are given as mean (range) or number (percentage) unless stated otherwise.