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Translational

Markers of endothelial cell dysfunction are increased in human omental adipose tissue from women with pre-existing maternal obesity and gestational diabetes

*Martha Lappas**

Obstetrics, Nutrition and Endocrinology Group, Department of Obstetrics and Gynaecology, University of Melbourne, Victoria, Australia
Mercy Perinatal Research Centre, Mercy Hospital for Women, Heidelberg, Victoria, Australia

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ABSTRACT

Objective. To determine the effect of maternal obesity and gestational diabetes mellitus (GDM) on the expression and release of genes involved in endothelial cell dysfunction in human placenta and omental adipose tissue.

Materials/Methods. Human placenta and omental adipose tissue were obtained from non-obese and obese normal glucose tolerant (NGT) women and women with GDM at the time of Caesarean section. Quantitative RT-PCR was performed to determine the level of expression. Tissue explants were performed to determine the release of proteins of interest.

Results. There was no effect of pre-existing maternal obesity or GDM on placental gene expression or secretion of members of the VEGF family members (PLGF and VEGF-A expression and secretion; sFlt-1 release; VEGFR1 and VEGFR2 mRNA expression); FGFR1 mRNA expression, FGF2 mRNA expression and secretion; endoglin mRNA expression and secretion (sEng); and the adhesion molecules ICAM-1 and VCAM-1. On the other hand, in omental adipose tissue, pre-existing maternal obesity and GDM were associated with increased gene expression of PLGF, endoglin and ICAM-1 and increased secretion of PLGF, sFlt-1, FGF2, sEng and sICAM-1. There was, however, no effect of maternal pre-existing obesity and GDM on VEGF-A, VEGFR1, VEGFR2, FGFR1 and VCAM-1 expression or secretion.

Conclusions. This study demonstrated the presence of abnormal expression and secretion of angiogenic proteins and adhesion molecules in omental adipose tissue, but not placenta, from pregnant women with GDM and pre-existing maternal obesity. Increased angiogenic and adhesion molecules released from adipose tissue may affect angiogenesis, inflammation and or lipid and glucose metabolism in both mum and her offspring.

Abbreviations: GDM, gestational diabetes mellitus; NGT, normal glucose tolerant; qRT-PCR, quantitative RT-PCR; sICAM, soluble intracellular adhesion molecule; sVCAM, soluble vascular cell adhesion molecule; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; Flt-1, fms-like tyrosine kinase 1; sFlt-1, soluble fms-like tyrosine kinase 1; sEng, soluble endoglin; PLGF, placental growth factor; FGF2, basic fibroblast growth factor; FGFR1, fibroblast growth factor receptor 1.

* *Corresponding author at:* Department of Obstetrics and Gynaecology, University of Melbourne, Mercy Hospital for Women, Level 4/163 Studley Road, Heidelberg, 3084, Victoria, Australia. Tel.: +61 3 8458 4370; fax: +61 3 8458 4380.
E-mail address: mlappas@unimelb.edu.au.

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1. Introduction

The prevalence of gestational diabetes mellitus (GDM) and maternal obesity during pregnancy is increasing; affecting up to 20% of all pregnancies [1–4]. These metabolic disturbances are associated with increased risk of adverse pregnancy and infant outcomes [5–7]. Additionally, there is an increased risk of developing obesity, type 2 diabetes and cardiovascular disease later in life for both mother and child [5–7]. The economic costs associated with GDM and maternal obesity during pregnancy are substantial and extend well into adulthood [5,8]. There is now increasing evidence that the obese and diabetic environment may induce a number of changes in both placenta and maternal adipose tissue which may play an important role in the growth and development of the fetus [9–11].

Endothelial cell dysfunction is a feature of obese and GDM pregnancies. For example, maternal obesity is associated with impaired endothelial function [12], and non-branching angiogenesis is evident in the placentas from obese women [13]. Women with GDM develop endothelial dysfunction during pregnancy [14], and despite returning to normal glucose tolerance, endothelial dysfunction is still evident in women 1 year post GDM pregnancy [15]. Indeed, women with GDM have increased circulating levels of the adhesion molecules soluble intracellular adhesion molecule (sICAM)-1 and soluble vascular cell adhesion molecule (sVCAM)-1 levels [16]. The angiogenic markers vascular endothelial growth factor (VEGF), fms-like tyrosine kinase 1 (Flt-1), endoglin, placental growth factor (PLGF), and basic fibroblast growth factor (FGF2), and the adhesion molecules ICAM-1 and VCAM-1 play an important role in the development of endothelial dysfunction [17–22]. In preeclampsia, a systemic syndrome of pregnancy characterised by widespread maternal endothelial dysfunction [23], placental trophoblast cells produce significantly more sEng, sFlt-1, and PLGF compared with those from normal placenta [24,25]. There is, however, a paucity of data on the effect of GDM and maternal obesity on the expression and secretion of these markers in placenta and adipose tissue.

Thus, the aim of this study was to determine the effect of maternal obesity and GDM on the (i) gene expression of PLGF, FGF2 and FGF receptor 1 (FGFR1), VEGF-A and its receptors VEGFR1 (also known as Flt-1), VEGFR2, endoglin, ICAM-1 and VCAM-1 and (ii) release of PLGF, FGF2, soluble Flt-1 (sFlt-1), VEGF, soluble endoglin (sEng), sICAM-1 and sVCAM-1 from human placenta and omental adipose tissue.

2. Materials and methods

2.1. Tissue collection and preparation

Approval for this study was obtained from the Mercy Hospital for Women's Research and Ethics Committee and written informed consent was obtained from all participating subjects. Human placenta and omental adipose tissue were obtained from a total of 60 pregnant women (28 NGT and 32 GDM). Tissues were obtained within fifteen minutes of delivery.

Women were invited to provide samples on the day of admission for surgery. Sample collection occurred between November 2011 and July 2013. All tissues were obtained at the time of term Caesarean section in the absence of labour. Indications for Caesarean section included repeat Caesarean section or breech presentation. Women with any adverse underlying medical condition (i.e. including asthma, preeclampsia and pregestational diabetes) were excluded. Samples were collected from non-obese (BMI between 18 and 29 kg/m^2) and obese (BMI ≥30 kg/m^2) subjects. The women were classified as non-obese or obese based on their pre-pregnancy BMI. Women with GDM were diagnosed according to the criteria of the Australasian Diabetes in Pregnancy Society (ADIPS) by either a fasting venous plasma glucose level of ≥5.5 mmol/l glucose, and/or ≥8.0 mmol/l glucose 2 h after a

Table 1 – Characteristics of the study group.

	NGT Non-obese (n = 12)	NGT Obese (n = 16)	GDM Non-obese (n = 17)	GDM Obese (n = 15)
Maternal age (years)	31.7 ± 0.6	30.9 ± 1.2	30.5 ± 1.0	32.2 ± 1.0
Pre-pregnancy BMI (kg/m^2)	24.3 ± 0.9**	38.0 ± 2.0*	24.1 ± 0.7	37.0 ± 1.1#
Maternal BMI at delivery (kg/m^2)	29.3 ± 1.2**	39.7 ± 1.8*	28.5 ± 0.7	38.8 ± 0.9#
Gestational age at birth (weeks)	38.6 ± 0.2	38.6 ± 0.3	38.7 ± 0.2	38.4 ± 0.2
Fetal birth weight (g)	3315 ± 105	3395 ± 85	3360 ± 66	3575 ± 61
Fetal Gender	5 Female 7 Male	10 Female 6 Male	7 Female 10 Male	8 Female 7 Male
OGTT at ~28 weeks' gestation				
Fasting plasma OGTT (mmol/l)	4.5 ± 0.1	4.5 ± 0.1	4.9 ± 0.2	5.4 ± 0.3**
1 h plasma OGTT (mmol/l)	6.4 ± 0.4#	6.9 ± 0.4	9.2 ± 0.4	9.5 ± 0.4**
2 h plasma OGTT (mmol/l)	5.6 ± 0.4#	5.5 ± 0.2	8.7 ± 0.3	8.0 ± 0.4**

Values represent mean ± SEM.
OGTT, oral glucose tolerance test.
* $P < 0.05$ vs. NGT non-obese; ** $P < 0.05$ vs. NGT obese; #$P < 0.05$ vs. GDM non-obese (one-way ANOVA).