

**Role of Adiponectin in Matching of Fetal and Placental Weight in Mothers with Type 1 Diabetes**

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Received for publication 19 November 2007 and accepted in revised form 10 March 2008

*Objective:* To assess the association of fetal hormones with placental growth and fetal:placental weight ratio (FPI) in pregnancies complicated by maternal diabetes.

*Research Design and Methods:* Prospective study using umbilical venous blood samples taken at birth from 122 offspring of mothers with type 1 diabetes (OT1DM) and 46 controls.

*Results:* Placental weight ( $p=0.009$ ) and gestation-adjusted birthweight ( $p<0.001$ ) were increased in OT1DM, but FPI was unaltered ( $p=0.33$ ). Placental weight correlated with birthweight ( $p<0.001$ ) and cord leptin ( $p<0.001$ ) in controls and OT1DM, with further relationships to cord insulin, IGF-1, IGFBP-3, triceps and subscapular thickness in OT1DM. FPI was associated with adiponectin in both groups, even after adjustment for confounders.

*Conclusions:* Placental and fetal growth show a parallel increase in mothers with type 1 diabetes. The possible role of adiponectin in matching of fetal and placental growth merits further study.

Placental weight is strongly associated with birthweight, with experimental and epidemiological studies demonstrating associations of reduced fetal:placental index (FPI) with hypertension, later glucose intolerance and coronary heart disease, suggesting in-utero programming of adult disease(1). Fetal adiponectin, an adipokine with insulin sensitising and anti-inflammatory effects, has been identified as the first biomarker associated with FPI(2). In this study we examined FPI and its relation to hormonal indices, in particular insulin and adiponectin, in offspring born to mothers with type 1 diabetes (OT1DM) - a group observed to exhibit reduced FPI(3) and adiponectin(4), and to be subject to *in-utero* programming of glucose intolerance(5).

#### RESEARCH DESIGN AND METHODS

A comprehensive description of prospective recruitment and exclusion criteria are available in previous publications(4;6). 122 OT1DM and 46 control offspring were available for analysis. FPI, [birthweight (grams) divided by placental weight (grams)] was calculated for each delivery. Maternal HbA1c and cord plasma insulin, leptin, IGF-1, IGFBP-3, adiponectin, CRP, ICAM-1 were assayed centrally(4;6). Hemoglobin and hematocrit (available in 32 controls and 81 OT1DM) were measured locally by routine clinical hematological analysers. HbA1c was included when assessed between weeks 26 and 34 of pregnancy (available in 90 OT1DM).

Results are presented as mean±standard deviation or unadjusted median (interquartile range). Pearson correlations, general linear models, and stepwise logistic regression ( $p \leq 0.15$  for inclusion of predictors) on log transformed variables were used to assess relationships.

#### Results

Birthweight [controls 3553±520g; OT1DM 3778±701g;  $p < 0.001$ ] and placental weight [controls 627g (551-700); OT1DM 700g

(600-800);  $p < 0.001$ ] were increased in OT1DM, with no difference in FPI [controls 5.73±0.9; OT1DM 5.55±1.12;  $p = 0.33$ ], even after adjustment for gestational-at-delivery or sex. Maternal diabetes was associated with increased cord insulin [controls 22.5pmol/l (15.4-37.7); OT1DM 111.0pmol/l (64.9-220.8),  $p < 0.001$ ], leptin [controls 9.0ng/ml (4.1-17.2); OT1DM 33.3ng/ml (14.1-58.0),  $p < 0.001$ ] and CRP [controls 0.14mg/l (0.12-0.16); OT1DM 0.17mg/l (0.13-0.22),  $p < 0.001$ ] and a reduction in adiponectin [controls 21.9±5.3µg/ml; OT1DM 19.7±6.2µg/ml,  $p = 0.039$ ]. All differences remained significant after adjustment for sex, mode of delivery, placental weight and birthweight.

Placental weight was strongly correlated with birthweight [controls  $r = 0.63$ ,  $p < 0.001$ ; OT1DM  $r = 0.66$ ,  $p < 0.001$ ] and fetal leptin [controls  $r = 0.42$ ,  $p = 0.004$ ; OT1DM  $r = 0.37$ ,  $p < 0.001$ ]. In OT1DM placental weight was also associated with insulin ( $r = 0.46$ ,  $p < 0.001$ ), IGF-I ( $r = 0.54$ ,  $p < 0.001$ ), IGFBP-3 ( $r = 0.50$ ,  $p < 0.001$ ), maternal HbA1c ( $r = 0.45$ ,  $p < 0.001$ ). FPI was associated with adiponectin ( $r = 0.43$ ,  $p = 0.002$ ) and CRP ( $r = -0.32$ ,  $p = 0.03$ ) in controls and maternal HbA1c ( $r = -0.28$ ,  $p = 0.006$ ), insulin ( $r = -0.18$ ,  $p = 0.04$ ), IGF-1 ( $r = -0.21$ ,  $p = 0.02$ ) and IGFBP3 ( $r = -0.20$ ,  $p = 0.03$ ) in OT1DM. FPI was not related to birthweight in either controls or OT1DM but showed negative relationships with placental weight in both groups (controls:  $r = -0.69$ ,  $p < 0.001$ ; OT1DM:  $r = -0.66$ ,  $p < 0.001$ ).

In multivariate analysis (Table 1), birthweight was positively associated with male sex, gestation-at-delivery, insulin and leptin in both controls and OT1DM with additional relationships to IGF-1 and CRP in OT1DM. Placental weight showed similar relations to the fetal cord measures with addition of a borderline negative relationship with adiponectin ( $P = 0.03$ ) in both OT1DM and controls. By contrast, only adiponectin was significantly related to

FPI in both controls (contribution to variance: CTV 20.3%, $p=0.005$ ) and OT1DM (CTV 3.9%, $p=0.03$ ) with additional effects of sex, IGF-1 and gestation-at-delivery in OT1DM.

The contribution of hypoxia and maternal glycaemia in the relationship of FPI and adiponectin were assessed by inclusion of cord hematocrit or maternal HbA1c as predictors. Hematocrit was weakly associated with FPI (CTV 3.5%, $p=0.09$ ) in OT1DM independent of other predictors with the association with adiponectin maintained (CTV 4.4%, $p=0.05$ ). Maternal HbA1c was a negative predictor of FPI (CTV 7.4%, $p=0.01$ ), however, again associations of FPI with adiponectin were maintained (CTV 5.1%, $p=0.03$ ).

## **DISCUSSION**

We demonstrate that although both fetal and placental sizes are increased in the presence of maternal diabetes, their respective weights remain highly correlated and FPI is not significantly reduced in our series. Lower FPI is driven primarily by higher placental weight in both controls and OT1DM and is also associated with poorer maternal glycaemic control in OT1DM. Finally we confirm recent findings that lower FPI is associated with lower adiponectin concentrations in controls(2) and show a similar, albeit weaker relationship in OT1DM.

The contribution of fetal hormonal axes in matching fetal and placental growth in OT1DM is largely unknown. Birth and placental weight are positively associated with cord blood levels of IGF-1, IGFBP-3, and IGF-2:IGF-2 receptor ratios(7;8). We observe similar relationships in OT1DM and in addition a relationship of insulin to birthweight and placental weight. In accordance with this placental insulin receptors undergo temporospatial shifts to fetal endothelium across gestation enabling fetal insulin to drive fetal and potentially placental growth(9).

Adiponectin has recently been reported as an associate of FPI independent

of fetal adiposity(2). The authors speculated that this might reflect effects of adiponectin to augment insulin sensitivity and thus increase fetal growth(2). By contrast while confirming the relationships of adiponectin and FPI, we do not show a correlation of adiponectin to birthweight suggesting that other mechanisms are responsible. Direct effects of fetal adiponectin on the placenta also appear unlikely, given the localisation of adiponectin receptors to syncytiotrophoblast(10).

Adiponectin and FPI might also be related secondary to hypoxia, given the association of hypoxia with reduced FPI and diminished adipocyte adiponectin secretion. However, inclusion of hematocrit into our models did not alter the association between adiponectin and FPI in controls or OT1DM. Furthermore the lack of relationship between adiponectin and cord hematological indices would suggest that the low adiponectin levels of OT1DM are unlikely to be due to hypoxia. Similarly although adiponectin is inversely correlated with systemic indices of inflammation, the lack of attenuation of the relationship between adiponectin and FPI in controls by inclusion of CRP in multivariate analysis, and the absent relationship in OT1DM, suggests that FPI and adiponectin are not linked via inflammatory pathways. The role of adiponectin in the linkage of fetal and placental growth merits further study.

## **ACKNOWLEDGEMENTS:**

Chief Scientist Office (K/MRS/50/C2726) and GRI Endowment (05REF007).

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**Table 1** Multivariate analysis of predictors of birthweight, placental weight and fetal:placental index. †Stepwise regression model for birthweight, placental weight and fetal:placental index included the predictors; log insulin, log leptin, adiponectin, IGF-I, log CRP, sex and gestational age. Predictors shown where P<0.10.

	Offspring of Control Mothers				Offspring of Mothers with type 1 Diabetes			
	Associates	$\beta$	% variance	P	Associates	$\beta$	% variance	P
<b>Birth weight</b> <sup>†</sup>	log Leptin (ng/ml)	169	24.2%	01	IGF-I (nmol/l)	89	27.6%	<0.001
	Sex	Male higher	22.2%	0.001	Gestational age (weeks)	173	10.3%	<0.001
	Gestational age (weeks)	221	9.7%	0.0002	log Leptin (ng/ml)	140	10.0%	0.001
	log Insulin (pmol/l)	105	6.6%	0.01	Sex	Male higher	5.4%	0.001
				log Insulin (pmol/l)	128	2.8%	0.008	
				log CRP (mg/ml)	158	1.6%	0.050	
<b>Placental weight</b> <sup>†</sup>	log Leptin (ng/ml)	60	15.3%	0.004	IGF-I (nmol/l)	27	31.1%	<0.001
	Adiponectin ( $\mu$ g/ml)	-8	6.0%	0.03	log Insulin (pmol/l)	45	6.0%	0.002
	Sex	Male higher	6.5%	0.07	log CRP (mg/ml)	59	3.3%	0.014
					Adiponectin ( $\mu$ g/ml)	-4	1.6%	0.06
<b>Fetal:Placental Index</b> <sup>†</sup>	Adiponectin ( $\mu$ g/ml)	0.07	20.3%	0.005	Gestational age (weeks)	0.18	4.7%	0.02
	CRP (log mg/ml)	-0.56	6.0%	0.08	IGF-I (nmol/l)	-0.06	5.2%	0.07
					Sex	Male higher	2.7%	0.001
					Adiponectin ( $\mu$ g/ml)	0.04	3.9%	0.03