Maternal and Fetal Resistin in Pre-gestational, Gestational and Non-Diabetic Pregnancies

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Abstract: *Objective*: To investigate possible differences in maternal and cord resistin between pregnancies affected by maternal gestational (GDM) and pre-gestational diabetes (PGDM) compared to non-diabetic pregnancies. *Design*: Prospective case control study. *Setting*: Tertiary level unit. *Methods*: Thirty-four women with PGDM (20 Type 1 diabetes and 14 Type 2 Diabetes) donated blood samples at 14, 20 and 36 weeks. Fourteen women with GDM donated blood samples at 36 weeks. Twelve control women in each trimester were matched on BMI to diabetic participants. Participants also consented for collection of matched cord samples after delivery. Resistin was measured by ELISA. *Main Outcome Measures*: Serum resistin, clinical measures (maternal age, parity, type of diabetes (non-diabetic, gestational diabetes, pre-gestational diabetes (type 1 diabetes (T1DM) or type 2 diabetes (T2DM)), maternal gylcaemia (HbA1c and fructosamine), gestation at delivery, method of delivery, and outcomes (birth weight, Apgars, cord pH, admission to neonatal intensive care (NICU), serum resistin concentration); comparison based on clinical group. *Results*: Maternal resistin was statistically significantly lower in T1DM compared to both non-diabetic and T2DM (maternal third trimester resistin in non-diabetic 37.5ng/ml (16-123), GDM 18.4 ng/ml (4.4-54.4), T2DM 40.5 ng/ml (5.7-109) and T1DM 3.7 ng/ml (1.7-10.6) ($p<0.01$); this difference held in cord samples. *Conclusions*: This is the first study investigating resistin in T1DM, T2DM and GDM maternal and cord blood. Despite the increase in insulin resistance with gestational diabetes and T2DM, there was no associated rise in maternal or cord resistin. The reduction in resistin in T1DM pregnancy may be protective as resistin also has a pro-inflammatory role.

Keywords: Resistin, diabetes, pregnancy.

INTRODUCTION

Resistin, an adipocytokine, was originally postulated to be the link between obesity and diabetes when first discovered. In mouse models serum resistin concentrations were higher in both genetic and diet induced obesity in mice, and was decreased on administration of the anti-diabetic drugs, thiazolidinediones. In addition, obese mice, given an antibody to resistin, had increased insulin stimulated glucose uptake [1].

Subsequent studies in rodents have differing results regarding the role for resistin in obesity associated with diabetes [2]. In humans the expression of resistin in adipocytes is low compared to that of rodents. Gene studies in humans have conflicting results [3], with some showing either an association with obesity alone [4], diabetes alone [5] or with neither obesity or diabetes [6]. Polymorphisms in the promoter of resistin gene expression have been shown to determine plasma resistin concentrations in humans, but are not in themselves associated with T2DM or obesity [7]. As a result of these studies, it appears that resistin is not the clear link between obesity and diabetes in humans as previously thought but may have a more complex role.

In pregnancy, insulin resistance increases. Understanding the changes in insulin resistance in pregnancy may open up more insights into insulin action and ultimately into understanding of T2DM [8].

Resistin is expressed in the human placenta, mostly in the syncytiotrophoblast but also in the extravillous cytotrophoblast cells in the decidua and the fetal membranes: furthermore resistin gene expression is higher in term placentae than first trimester chorionic villous samples [9]. Resistin levels in maternal serum increases in pregnancy and resistin is found in cord blood [10].

Much of the focus on resistin in diabetic pregnancy has focused on gestational diabetes. Studies in this area have had conflicting results, with some showing increased resistin [11-13], others no difference [13-16] and one a decrease in resistin [17] compared to non-diabetic controls.

To our knowledge, the only study to date investigating resistin in T1DM studied cord resistin in the infants of 12 women with T1DM and 38 women with insulin requiring GDM. Serum resistin was lower in infants of insulin dependent mothers than infants of

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E-ISSN: 2309-4400/14

non-diabetic and diet controlled GDM mothers (7.6ng/ml *vs*. 13.7ngml, 12.1ng/ml) [18]. We are unaware of any studies investigating resistin in T2DM pregnancy.

The aim of the study was to investigate resistin in diabetic pregnancy. Our hypothesis was that resistin would be increased in gestational and T2DM pregnancies compared to both non-diabetic and T1DM pregnancies as GDM and T2DM represent relative insulin resistance.

METHODS

This was a prospective cohort study.

The National Maternity Hospital is one of three tertiary level units serving the city of Dublin and surrounding areas. Approximately 9,000 women deliver in the hospital per annum, of which 50 would be women with a diagnosis of pre-gestational diabetes and one hundred with gestational diabetes.

Women were included if they consented to the study and did not smoke. Women with pre-gestational and gestational diabetes attend a dedicated multidisciplinary clinic and are seen every one to two weeks during pregnancy with regular ultrasound assessment. All women with T2DM (White's Class A) required oral hypoglycaemics and diet to maintain euglycaemia prior to pregnancy, but were converted to subcutaneous insulin at the beginning of pregnancy (mean 7 weeks (range 5-9)).

Diagnosis of gestational diabetes (GDM) (two raised values) was made only at GTT, using the criteria outlined by the National Diabetes Data Group [19]. Treatment commenced with a low glycaemic diet. Patients with abnormal glucose values whilst on diabetic diet were commenced on insulin. Women with gestational diabetes treated with insulin, have the same ultrasound monitoring as detailed for the pre-gestational diabetic patients.

Non-diabetic controls were recruited from routine low risk clinics staffed by midwives and obstetricians. All controls had screened negative for gestational diabetes.

Maternal samples were obtained from consenting women in the first (14 weeks), second (20 weeks) and third trimester (36 weeks) and from cord blood following delivery in women with T1DM, T2DM and non-diabetic controls. In addition samples were obtained from women with gestational diabetes in the third trimester (36 weeks) and cord blood obtained after delivery.

Clinical data on normal, GDM and PGDM pregnancies was obtained prospectively from the labour 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 as well as infant outcomes. In addition, women with PGDM and GDM underwent the routine third trimester ultrasound examinations, assessing fetal wellbeing and fetal growth. Macrosomia was defined by birth weight greater than the 90th centile for gestation and gender.

Resistin was measured by enzyme linked immunoassay (Human Resistin Enzyme Immunoassay, BioVendor Laboratorní Medicína a.s, Brno, Czech Republic) according to manufacturer instructions. The intra-assay precision was 3.2% and inter-assay precision was 6%. The minimal detectable level of resistin is 0.033ng/ml in this assay.

Statistical Analysis

Statistical analysis was performed using SPSS version 16; non-parametric data was compared using Mann Whitney, Kruskal Wallis or tests for trend (median/range).

Ethical Approval

This study was approved by the Ethics Committee of the National Maternity Hospital.

RESULTS

Twenty women with T1DM and 14 women with T2DM consented to take part in the study and donated samples at 14, 20 and 36 weeks. Fourteen women with gestational diabetes consented to the study and donated blood samples at 36 weeks and cord samples after delivery. All diabetic women were matched to controls based on BMI.

In the control groups, 12 women in the first trimester, 12 women in the second trimester and 12 women in the third trimester consented to participate in the study. Third trimester participants also consented for collection of matched cord samples after delivery. Patient characteristics are shown in Table **1**.

Table 1: Background Characteristics of the Participants, Age, Parity, BMI, Birth Weight, Birth Weight Centile and Gestational Age Recorded as Median (range); CS (caesarean section, admission to general postnatal infant and female infant recorded as proportion (%)

	First Trimester Non Diabetic (n=12)	Second Trimester Non-Diabetic (n=12)	Third Trimester Non-Diabetic (n=14)	T2DM All Trimesters (n=14)	Gestational Diabetes (n=14)	Type 1 Diabetes (n=20)	p
Age (years)	32 (24-42)	35 (28-41)	34 (21-40)	35 (29-39)	34 (27-44)	34 (24-39)	0.73
Parity	0 (0-2)	1 (0-2)	0 (0-1)	1 (0-6)	0 (0-3)	0 (0-3)	0.18
BMI	29.6 (22.9-39)	27.8 (21.7-30.3)	25.8 (21-35)	26.4 (23-44)	26.6 (20-38)	25.4 (19-35)	0.76
Birth Weight (g)	3450 (2300-4480)	3422 (3030-4900)	3490 (2890-4280)	3850 (2635-4170)	3870 (2940-4600)	3560 (2830-4140)	0.049
Birth Weight Centile*	50 (25-92)	50 (20-100)	60 (9-99)	85 (4-99)	86 (28-99)	70 (9-99)	0.027
GA at delivery (weeks)*	39^{+1} (34^{+1} - 42)	39^{+3} (36^{+5}-42)	39^{+2} (37^{+1}-42)	39^{+1} (38-40)	38^{+6} (35^{+5}-41^{+1})	38 (37-39)	0.002
% Caesarean Section	8/12	9/12	8/14	5/14	9/14	10/20	0.22
% General postnatal ward admission	12/12	12/12	14/14	14/14	13/14	16/20	0.007*
Female infant	6/12	8/12	7/14	8/15	7/14	11/20	0.88

BMI: Basal Metabolic Index; GA: Gestational Age; CS: Caesarean Section

Of the 20 women with T1DM, seven were Whites Class B, six Class C and six Class D. There was one woman with diabetic proliferative retinopathy in this group, but none with diabetic nephropathy.

Mothers (26%, two in the first trimester group and four each in the second and third trimester groups), seven babies of T2DM mothers (50%) and seven babies of GDM mothers (50%) were macrosomic.

Differences in resistin concentrations are shown in Figures **1** and **2**. Maternal resistin was statistically significantly lower in T1DM compared to both non-diabetic and T2DM (maternal third trimester resistin in non-diabetic 37.5ng/ml (16-123), GDM 18.4 ng/ml (4.4-54.4), T2DM 40.5 ng/ml (5.7-109) and T1DM 3.7 ng/ml (1.7-10.6) ($p<0.01$). On individual group analysis, maternal third trimester resistin concentration was lower in GDM mothers compared to both T2DM ($p<0.01$) and non-diabtetic groups ($p<0.01$). Cord resistin concentration was statistically lower in infants of T1DM mothers compared to the non diabetic, T2DM and GDM groups (36.4ng/ml (8.8-130) in non diabetic group, 48.3ng/ml (1.2-121) in infants of T2DM mothers, 24.8ng/ml (3.9-47.03) in infants of GDM mothers and 13.9ng/ml (3.2-38.8) in infants of T1DM mothers ($p<0.003$). On individual group analysis, cord resistin concentration was lower in infants of GDM mothers compared to both T2DM ($p<0.01$) and non-diabtetic groups ($p<0.01$).

Maternal Resistin

There was no statistical correlation between maternal and cord resistin levels. There was no overall correlation between maternal resistin and maternal BMI ($r=-0.005$, $p=0.95$). There was no correlation between maternal resistin and birth weight or birth weight centile. There was no difference in maternal resistin between those whose infants were admitted to the ward after delivery compared to those whose infants were admitted to NICU either in the group as a whole or as individual groups. With regards maternal glycaemic control, there was no correlation between maternal resistin and HbA1c (early, first, second and third trimester). Neither was there any correlation between maternal resistin and length of diabetes.

Cord Resistin

Cord resistin did not correlate with either birth weight or birth weight centile; neither was there any statistical relationship found with gestational age at delivery. There was no difference in cord resistin based on infant gender, parity of mother or mode of delivery Neither was there any difference found on individual group analysis. There was no difference in cord resistin

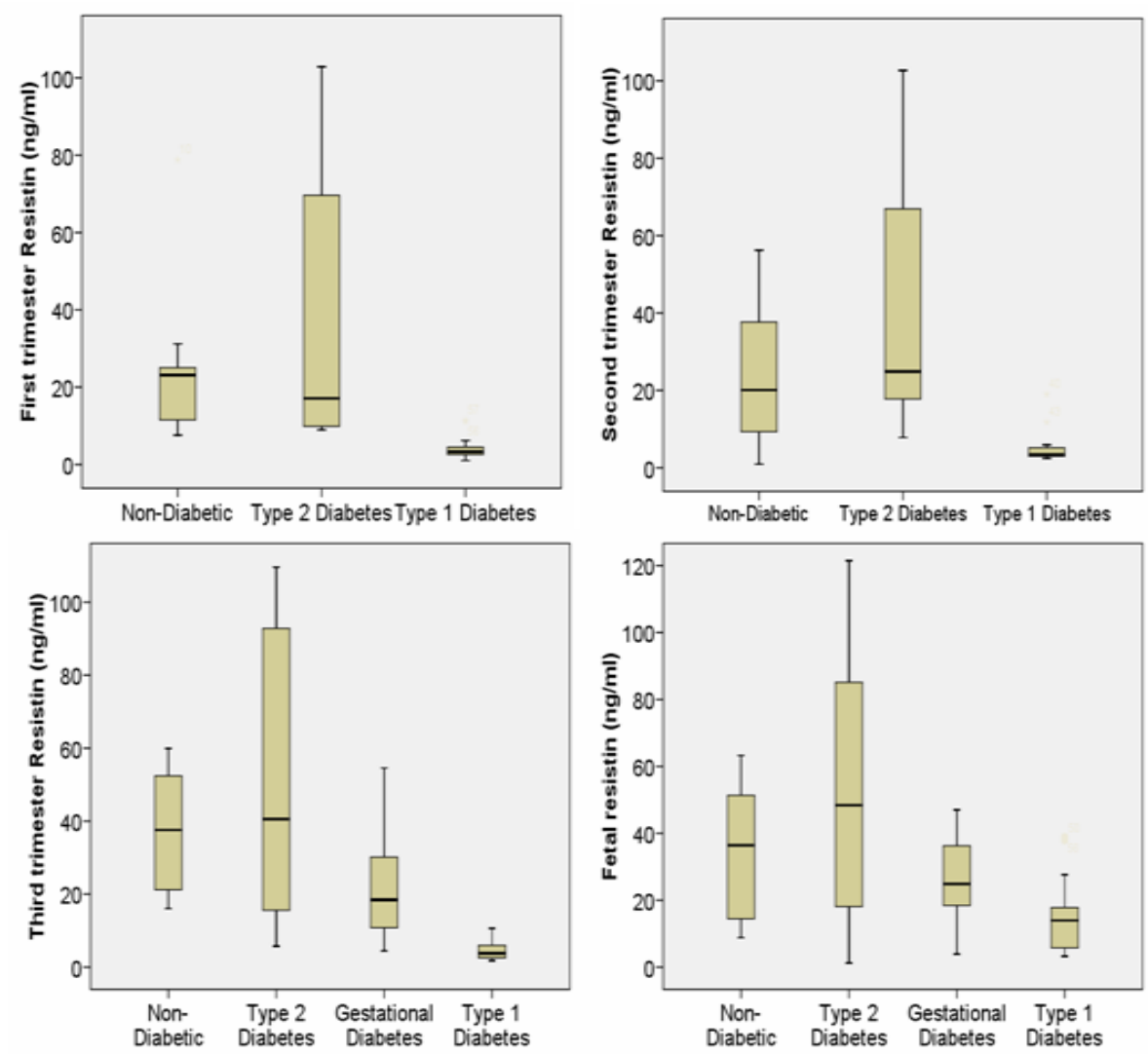

Figure 1: Resistin concentration based on gestational age at sampling (median, range).

in infants admitted to NICU compared to those admitted to the postnatal ward. Cord resistin did not correlate with maternal HbA1c.

DISCUSSION

This study investigates, for the first time, the effect of maternal diabetes on maternal and cord resistin in diabetic pregnancy. Women with gestational diabetes requiring insulin for stabilization, pre-existing type 1 (T1DM) and type 2 (T2DM) diabetes all consented to the study so that the effect of different types of diabetes in pregnancy on resistin could be studied. This is in contrast to previous studies, which have largely concentrated on gestational diabetes [11, 12, 14-17].

The most striking finding is the statistically lower serum resistin in both maternal and cord serum in Type 1 diabetic pregnancy. A previous study investigating serum resistin in infants of diabetic mothers also showed a lower serum resistin in infants of insulin dependent mothers [18]. The researchers postulated that the cord serum hyperinsulinemia also found in infants of insulin dependent diabetic mothers might thus suppress resistin. This hypothesized effect of insulin on resistin is controversial, though insulin has been shown to suppress resistin mRNA expression in 3T3-L1 adipocytes [20]; thus resistin may play a pivotal role in inhibiting adipocyte differentiation and reduction in insulin may thus eliminate a constraint on the development of new adipocytes and increase fetal macrosomia. In contrast, we have not found any correlation between maternal or cord insulin with current markers for maternal glycaemia or with antenatal ultrasound markers for fetal growth or birth weight or birth weight centile.

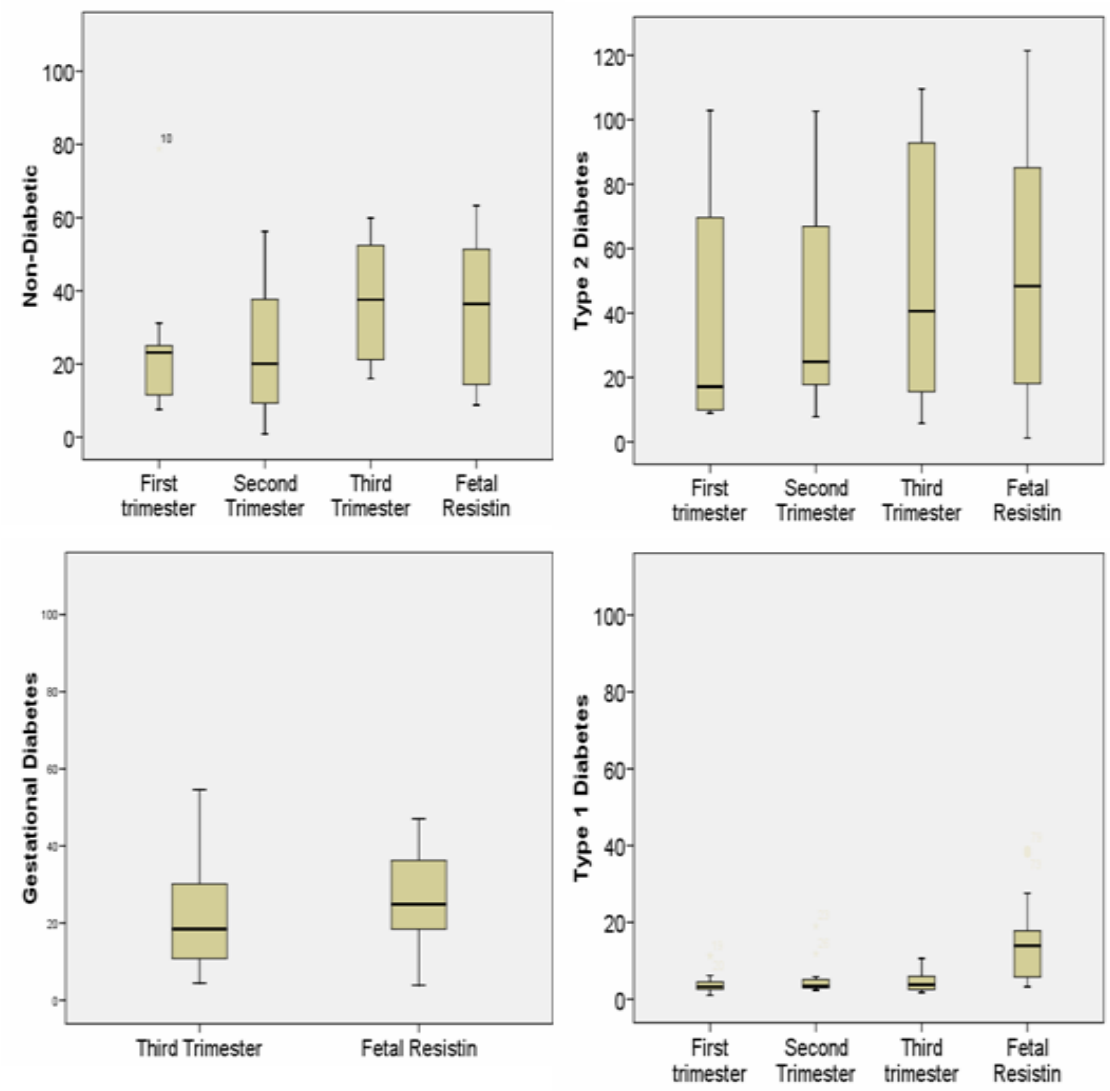

Figure 2: Resistin concentration based on participant group (median, range).

In analyzing infants of "insulin dependent diabetic mothers", one study [18] included infants of 12 mothers with Type 1 diabetes and 26 mothers with gestational diabetes requiring insulin. These two groups are comparable based on the requirement for insulin but in causative factors for their hyperglycaemia are fundamentally different. A more homogenous comparison, such as in this study, shows that in fact there are fundamental differences in serum resistin in pregnancies affected by gestational diabetes and pre-gestational diabetes and that these may not be explained by insulin alone.

Another interesting finding is the reduction in resistin also seen in maternal and cord blood in gestational diabetic pregnancy. Pregnancy is characterized by a progressive rise in insulin resistance and this is further exaggerated in GDM pregnancy. Resistin is expressed in the human placenta, increases in the third trimester and has been suggested to play a role in insulin resistance in pregnancy. Previous studies investigating resistin in GDM pregnancy have shown differing results. How can these differences in GDM pregnancy be explained? Is there a difference in resistin in GDM based on whether the GDM was controlled by diet alone or using exogenous insulin? One study comparing resistin in diet controlled GDM (n=13) to insulin controlled GDM (n=10) found no difference [17], but analysed samples obtained at the time of testing for GDM and therefore prior to treatment.

Another interesting result is the finding that there was very little difference in resistin levels in T2DM

pregnancy compared to non diabetic controls, especially in the context that resistin was decreased in gestational diabetic pregnancies. We had hypothesized that gestational and T2DM pregnancies would be very similar in measurement of resistin as both reflect relative insulin resistance and resistin is postulated to be related to insulin sensitivity. In further investigating the possible differences between the two groups it may have been useful to measure possible differences in insulin resistance and sensitivity between the groups. Insulin sensitivity can be measured by homeostasis model assessment (HOMA) and quantitative insulin sensitivity check index (QUICKI); insulin resistance may be evidenced by increases in fasting insulin and C-peptide concentrations. Regrettably these measurements were not performed in this study and therefore we cannot comment further in this area.

Insulin has both stimulatory and inhibitory effects on the release of resistin in both animal and human studies [21, 22]. In 3T3-L1 and mouse adipocytes insulin inhibits resistin release [20, 23] whereas in streptozotocin diabetic mice and zucker diabetic rats [24, 25] insulin stimulates resistin release. In humans, insulin has been shown to have a biphasic effect, with levels of 0.1μm to 1 μm increasing resistin release from the placenta and levels of 10 μm insulin resulting in a reduction of resistin to basal levels [26]. Resistin has an influence on glucose transport across the placental trophoblasts. Stimulation of intracellular pathways by resistin resulted in the synthesis of glucose transporter (GLUT-1) and increasing glucose uptake by trophoblasts. At higher levels of resistin (50-100ng/ml) glucose uptake was affected, presumably by decreasing the transporter [27]. Therefore insulin appears to affect glucose uptake to the placenta, mediated by resistin, at low levels but inhibit uptake at higher insulin levels.

Insulin is not the only factor influencing release of resistin: progesterone, dexamethasone and estrogen decrease the release of resistin from the placenta. There is also an association between resistin and inflammation: PMA, a potent activator of protein kinase C and thus TNF alpha and IL6 activation, stimulated resistin release [26]. Resistin stimulates pro-inflammatory cytokines and immune cells [28] and also stimulates human mononuclear cells to secrete TNF alpha and IL6 [29]. Resistin is related to CRP and IL6 [12]. Resistin may also have a role in the immune response to intra-amniotic infection [30]. It may be that the reduction in serum resistin found in T1DM pregnancy may actually be protective to an already high-risk pregnancy for maternal and fetal morbidity and mortality.

Genetic polymorphisms in the resistin promoter have also been shown to determine plasma resistin concentrations in humans; those with haplotypes A-G (including the allele -420G and -537A) had significantly higher resistin concentrations than others. These genotypes remained significant for determining plasma resistin concentration even after adjustment for diabetes or not, sex, age, BMI, fasting glucose, HOMA and triglyceride concentration [7]. Therefore, there may be significant heterogeneity for resistin within the population even before comparing based on diabetes or not. Added to these differences in genotypes, there are also differences in the definition of gestational diabetes, which have been further challenged with the publication of the HAPO trial [31].

This study investigates for the first time the influence of different types of diabetes on resistin in maternal and cord blood. Previous studies have concentrated on gestational diabetes as resistin may have a role in insulin resistin, though this is controversial. The incidence of T2DM is increasing worldwide so it is of increasing importance to study the effect of T2DM on growth factors, which may influence fetal growth. Resistin is decreased in T1DM, a condition that has significant fetal and maternal morbidity and mortality. Resistin is associated with a pro-inflammatory state so reduction in resistin in pregnancy may be beneficial to the neonate.

KEY MESSAGE

Resistin, originally hypothesized as the link between obesity and diabetes, is secreted from the placenta. This study investigated the concentration of resistin in diabetic pregnancies. Intrigingly, resistin was significantly lower in type 1 diabetic and GDM pregnancies compared to controls.

ACKNOWLEDGEMENT

To the participating mothers and the midwives of the National Maternity Hospital Dublin

FUNDING

This project was funded by a grant from the Health Research Board, Dublin, Ireland

ABBREVIATIONS

BMI = Body Mass Index

CS = Caesarean section

GDM = Gestational diabetes

PGDM = Pre-gestational diabetes mellitus

T1DM = Type 1 diabetes mellitus

T2DM = Type 2 diabetes mellitus

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Received on 04-04-2014 Accepted on 24-04-2014 Published on 30-06-2014

DOI: http://dx.doi.org/10.14205/2309-4400.2014.02.01.3