Association between gestational diabetes and biomarkers: A role in diagnosis

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Abstract

Background:

We investigated the association between markers of insulin resistance, chronic inflammation, and adipokines and GDM.

Methods:

In our case-cohort study in Johannesburg we included women with GDM and controls. We tested the ability of biomarkers to identify women at high risk of GDM.

Results:

Of the 262 pregnant women, 83 (31.7%) had GDM. Women with GDM were heavier ($p = 0.04$) and had more clinical risk factors ($p = 0.008$). We found a significant difference in fasting insulin ($p < 0.001$), adiponectin ($p = 0.046$), HOMA ($p < 0.001$) and QUICKI ($p < 0.001$). HOMA (AUROC = 0.82) or QUICKI (AUROC = 0.82) improved the ability of risk factors to identify women at high risk of GDM.

Conclusions:

Insulin sensitivity markers are promising tools to identify women at high risk of GDM.

Keywords: Biomarkers, gestational diabetes, adiponectin, insulin

Introduction:

The International Diabetes Federation (IDF) reports that the incidence of gestational diabetes (GDM) is increasing at an alarming rate with recent studies reporting an incidence as high as 30% [1]. This increase parallels the obesity epidemic. Furthermore, the diagnosis of GDM infers the long-term risk of developing type 2 diabetes mellitus (T2DM) on the pregnant women [2]. In addition, the offspring of a mother with GDM has an increased risk of developing glucose intolerance and obesity in later life [3].

The two-hour-seventy-five-grams oral glucose tolerance test (OGTT) remains the gold-standard for the diagnosis of GDM. Universal screening for GDM is now recommended by most international organisations [4]. This means that all pregnant women will require this unpleasant time-consuming test. The associated nausea, vomiting and bloating will make it more likely that women will not complete the test [5]. It is advised that the OGTT be conducted at twenty-four to twenty-eight weeks of gestation. At this gestation GDM has already developed and the hyperglycaemia may have already caused adverse effects [6]. Thus there is a need for a simpler more effective test that can either identify women at high risk of developing GDM or diagnose GDM earlier in pregnancy.

Pregnancy is a progressively hyperglycaemic period. It is characterised by increasing insulin resistance from mid-gestation. The relative hyperglycaemia of pregnancy is an important source of nutrition and is vital for the development of the fetus. In women with GDM insulin secretion is inadequate to compensate for the characteristic insulin resistance of pregnancy. This insulin resistance exists before pregnancy in women who develop GDM. Thus GDM is partly a result of chronic insulin resistance [2].

GDM and T2DM have similar predisposing factors leading to dysglycaemia. Obesity is a major risk factor and it may contribute to the pathogenesis of both conditions via chronic subclinical inflammation, low grade activation of the acute phase response and the dysregulation of adipokines [7].

The use of markers of insulin resistance, chronic inflammation, and adipokines has been investigated as a tool for the prediction of GDM [8-12]. However, it has been illustrated that there are differences in these markers between ethnic groups [13]. Data regarding gestational diabetes and especially the related biomarkers in an African population is sparse. However, the incidence of obesity, T2DM, and GDM in Africa continues to increase [14, 15]. The aim of this study was to investigate the association between the concentrations of biomarkers associated with glucose homeostasis and GDM in a South African population.

Methods:

This paper forms part of a larger prospective cohort observational study investigating screening strategies for GDM in a South African population. Informed consent was obtained from all participants prior to enrolment into the study. The protocol for this study was approved by the University of Pretoria Health Sciences Ethics Committee (180/2012).

We recruited one thousand pregnant women less than twenty-six weeks pregnant. Women known to have diabetes mellitus were excluded. The women completed a demographic questionnaire and had a random glucose and

glycated haemoglobin (HbA1c) measured at the first visit. They returned within two weeks and had a fasting glucose measurement. At this time serum and whole blood were stored for future testing. The blood was centrifuged at 4000rpm for 15 minutes and serum was extracted. The samples were stored at -40ºC. An OGTT was scheduled between twenty-four and twenty-eight weeks of gestation. GDM was diagnosed based on the criteria recommended by the International Association of Diabetes in Pregnancy Study Groups (IADPSG), i.e. any one abnormal value was diagnostic of GDM – fasting glucose ≥5.1mmol/l, one-hour glucose ≥10mmol/l, or two-hour glucose ≥8.5mmol/l [4].

For the analysis of biomarkers we conducted a nested case-control study. HIV negative patients with GDM were selected. Twice the number of HIV negative patients without GDM were selected as the control group. The groups were matched for age, parity and gestational age. HIV positive women were excluded as HIV may be a confounder. HIV has an effect on insulin resistance, chronic inflammation, and is associated with lipodystrophy thus affecting the adipokines [16].

At the time of analysis the frozen serum specimens were thawed and diluted. Insulin, C-reactive protein (CRP), and adiponectin were measured in the serum sample. The Homeostasis Model Assessment (HOMA) was calculated from the fasting insulin and fasting glucose values using the equation: fasting insulin (microU/L) x fasting glucose (mmol/L) / 22.5 [17]. The Quantitative Insulin Sensitivity Check Index (QUICKI) was calculated by the following equation: $1 / [\log (I_0) + \log (G_0)]$ [17].

Data was analysed using STATA 13 software. The women were stratified into two groups based on the presence or absence of GDM. Means or proportions were calculated for the two groups and the Students t-test and x^2 were used to assess univariate differences between the groups for continuous and categorical variables respectively. Statistical significance was set at 0.05. The groups were further stratified according to obesity. Obesity was defined as a body mass index (BMI) ≥30kg/m^2. Analysis of variance (ANOVA) tests were used to test for differences between the groups. Logistic regression was performed to assess the independent association of the BMI, fasting glucose, fasting insulin, adiponectin, and CRP with GDM. We calculated the odds ratio for fasting glucose, fasting insulin, HOMA, QUICKI, adiponectin, and CRP to assess its usefulness in predicting GDM. We added the biomarkers to clinical variables that we previously identified in being significant in being able to detect GDM , viz. BMI, random venous glucose, and a history of delivery of a baby >4000g, to assess whether this would improve the predictive ability of the model.

Results:

One thousand (1000) pregnant women were recruited. Eighty two (8.2%) women had fetal losses and did not continue with the study, 163 (16.3%) women moved away from the area and were thus lost to follow up, 194 (19.4%) women were unreachable and 7 (0.7%) women withdrew consent for the study. Thus 554 (55.4%) women had complete data available for analysis. Four hundred and eleven (74.2%) women had a normal OGTT and 143 (25.8%) women were diagnosed with GDM.

One hundred and sixty (28.9%) women were HIV positive, and five (2.6%) had an unknown HIV status and were thus excluded. Three hundred and eighty-nine women (70.2%) were included in this nested case-control study. One hundred and twenty seven women were excluded as there was no serum sample available for analysis or the specimen was haemolysed and unsuitable for analysis.

Thus, two hundred and sixty two women were included in this study. In this cohort one hundred and seventy nine (68.3%) women had a normal OGTT and eighty three (31.7%) were diagnosed with GDM. Figure 1 describes the demographic data of the study population.

Figure 1: Demographic description of GDM vs non GDM women

	GDM[a] (n=83)	**No GDM[a] (n=179)**	**P**
Age (years) (mean, range)	27.5 (26.10 – 28.90)	26.3 (25.40 – 27.20)	0.15
Gestational age (weeks) (mean, range)	24.1 (23.13 – 25.13)	24.4 (23.70 – 25.16)	0.64
Parity (mean, range)	1 (0.89-1.17)	1.02 (0.80 – 1.20)	0.82
Body mass index at 1st visit (kg/m^2) (mean, range)	27.6 (26.34-29.01)	26.05 (25.20-26.9)	0.04
Haemoglobin (g/dl) (mean, range)	12.7 (12.44 – 13.11)	12.4 (12.14 – 12.75)	0.19
HbA1c[b] (%, mmol/mol) (mean, range)	5.3 (34) (5.21 – 5.39) (33 – 35)	5.1 (32) (5.07-5.18) (32-33)	0.0009
Random glucose (mmol/l) (mean, range)	4.7 (4.55 – 4.79)	4.4 (4.27 – 4.50)	0.004
≥1 Risk factors[c] present (n, %)	47 (56.60%)	70 (39.10%)	0.008

GDM[a] gestational diabetes

HbA1c[b] glycated haemoglobin

Risk factors[c] advanced maternal age (age ≥35 years), obesity (BMI ≥30kg/m2), family history of diabetes mellitus, history of delivery of a baby >4000g, glucosuria, previous recurrent pregnancy loss, stillbirth, or birth of a baby with congenital abnormalities

Women with GDM had a higher BMI than the control group at their first antenatal clinic visit. The HbA1c and random glucose were also significantly higher compared with women who did not have GDM. Women with GDM were more likely to have at least one of the traditional risk factors for GDM, i.e. advanced maternal age (age ≥35 years), obesity (BMI ≥30kg/m^2), family history of diabetes mellitus, delivery of a previous baby more

than four kilograms, glucosuria, previous recurrent pregnancy loss, stillbirth, or birth of a baby with congenital abnormalities.

Figure 2 illustrates the comparison of biomarkers between women with and without GDM. The fasting insulin, HOMA, QUICKI, and adiponectin were significantly different between the groups.

Figure 2: Markers of insulin resistance, chronic inflammation, and adipokines

	GDM[a] (n=83)	**No GDM[a] (n=179)**	**P**
Fasting glucose (mmol/l) (mean, range)	5.9 (5.64 – 6.13)	4.4 (4.34 – 4.51)	<0.00001
Fasting insulin (uU/ml) (mean, range)	9.68 (7.46 – 11.90)	6.36 (5.74 – 6.98)	0.0003
Fasting insulin >10.4uU/ml (n, %)	20 (24.10%)	11 (6.10%)	<0.00001
Fasting glucose/ fasting insulin (mean, range)	0.94 (0.82 – 1.07)	0.91 (0.82 – 0.99)	0.65
QUICKI[b] (mean, range)	0.636 (0.61 – 0.66)	0.746 (0.72 – 0.77)	<0.00001
HOMA[c] (mean, range)	2.67 (1.95 – 3.40)	1.26 (1.13 – 1.40)	<0.00001
CRP[d] (mg/dl) (mean, range)	7.7 (5.84 – 9.66)	7.3 (6.05 – 8.58)	0.70
CRP[d]>5 mg/dl (n, %)	49 (59.00%)	85 (47.50%)	0.14
Adiponectin (mmol/l) (mean, range)	9.29 (7.83 – 10.75)	11.89 (10.24 – 13.54)	0.046

GDM[a] gestational diabetes

QUICKI[b] Quantitative Insulin Sensitivity Check

HOMA[c] Homeostasis Model Assessment

CRP[d] C-reactive protein

We stratified women with GDM by their BMI. Forty five women were categorised as non-obese, i.e. BMI <30 kg/m^2, and twenty three women were obese, i.e. BMI ≥30 kg/m^2. We did not have information on the height for fifteen women who were excluded from this analysis. We compared the concentrations of biomarkers between these two groups, as illustrated in Figure 3. The concentration of adiponectin was significantly lower in the obese group with GDM.

Figure 3: Concentrations of biomarkers in women with GDM stratified by weight

	Non-obese[d] (n=45)	Obese[e] (n=23)	P
Age (years) (mean, range)	26.9 (24.88 – 28.49)	29.1 (26.31 – 31.95)	0.1283
Gestational age (weeks) (mean, range)	18.7 (16.91 – 20.42)	20.3 (18.21 – 22.31)	0.2622
Parity (mean, range)	0.9 (0.67 – 1.20)	1.3 (0.93 – 1.68)	0.1066
Body mass index (kg/m^2) (mean, range)	24.6 (23.66 – 25.59)	33.6 (31.91 – 35.38)	<0.00001
Fasting glucose (mmol/l) (mean, range)	6.1 (5.72 – 6.48)	5.8 (5.43 – 6.07)	0.2326
Fasting insulin (uU/ml) (mean, range)	10.05 (6.90 – 13.19)	11.47 (6.29 – 16.64)	0.6205
Fasting glucose/ fasting insulin (mean, range)	0.98 (0.79 – 1.16)	0.75 (0.53 – 0.96)	0.1397
QUICKI[a] (mean, range)	0.64 (0.60 – 0.68)	0.60 (0.55 – 0.65)	0.2290
HOMA[b] (mean, range)	2.82 (1.82 – 3.82)	3.13 (1.36 – 4.90)	0.7378
CRP[c] (mg/dl) (mean, range)	7.31 (6.05 – 8.58)	7.83 (5.62 – 10.04)	0.3013
Adiponectin (mmol/l) (mean, range)	10.57 (8.32 – 12.82)	6.28 (4.64 – 7.92)	0.0128

QUICKI[a] Quantitative Insulin Sensitivity Check

HOMA[b] Homeostasis Model Assessment

CRP[c] C-reactive protein

Non-obese[d] BMI <30kg/m^2

Obese[e] BMI ≥30kg/m^2

We evaluated the usefulness of the biomarkers as a screening tool for GDM. (Figure 4). The addition of biomarkers to clinical factors available at the first antenatal visit, viz. BMI, history of delivery of baby >4000g, and random venous glucose greatly improved the predictive ability of the model to identify women at risk of developing GDM. The AUROC of the predictive model incorporating only the clinical factors was 0.69. The addition of biomarkers to the clinical factor-based model improved the predictive ability of this tool, especially the addition of either the HOMA or QUICKI.

Figure 4: Performance of biomarkers in the prediction of gestational diabetes

Biomarker	AUROC[a]	OR[b]	SE[c]	p	95% CI[d]	AUROC[a] (Biomarker + clinical markers[e])
Fasting insulin (uU/ml)	0.62	1.10	0.03	0.003	1.03 – 1.16	0.77
Fasting glucose/ fasting insulin	0.52	1.12	0.28	0.65	0.68 – 1.84	0.72
QUICKI[f]	0.73	0.0006	0.0009	<0.00001	0.00 – 0.01	0.82
HOMA[g]	0.73	2.11	0.38	<0.00001	1.48 – 3.01	0.82
CRP[h] (mg/dl)	0.55	1.01	0.02	0.70	0.97 – 1.04	0.73
Adiponectin (mmol/l)	0.60	0.95	0.02	0.048	0.90 – 0.99	0.75

AUROC[a] area under receiver operating curve

OR[b] odds ratio

SE[c] standard error

CI[d] confidence interval

Clinical biomarkers[e] body mass index, random venous glucose, history of delivery of baby >4000g

QUICKI[f] Quantitative Insulin Sensitivity Check

HOMA[g] Homeostasis Model Assessment

CRP[h] C-reactive protein

Discussion:

Pregnancy is a physiologically hyperglycaemic state, due in part to several circulating maternal and placental diabetogenic hormones such as oestrogen, progesterone, human placental lactogen, placental ACTH, and placental growth hormone variant. This results in a compensatory pancreatic insulin production leading to hyperinsulinaemia, which is an essential event preceding the development of GDM. When the pancreas fails to mount this insulin response maternal hyperglycaemia results [9].

This pathogenic phenomenon was illustrated in our study by the statistically significant differences detected in the fasting insulin concentration, HOMA and QUICKI. Similar findings were found in other studies [4, 9]. We, like Endo et al, have illustrated that the insulin insensitivity was significantly different between the women with GDM and normogylycaemia. This difference was not attributed to obesity [18]. Insulin insensitivity is a hallmark

feature in the development of GDM and thus these tests show potential as a screening and diagnostic tool for GDM.

Currently the OGTT is the gold-standard for the diagnosis of GDM. An ideal screening test should be accessible, affordable, and acceptable. The OGTT is labour- and time-consuming, and unpleasant for the pregnant women who may already be experiencing nausea. Insulin sensitivity tests such as the HOMA and QUICKI offer an attractive alternative tool for identifying women at high risk of developing GDM.

We also demonstrated that adiponectin is significantly decreased in women with GDM suggesting that an adiponectin deficiency is necessary for the pathogenesis of GDM. Previous studies have identified adiponectin as having anti-diabetic activity [10, 19]. Adiponectin is strongly correlated with insulin sensitivity across a wide range of glucose tolerance [19]. However, adiponectin levels are negatively correlated with maternal BMI in addition to insulin sensitivity [8]. Several studies have shown that adiponectin is decreased independent of BMI or insulin sensitivity in pregnancies affected by GDM [20-22]. When we considered obese women (BMI $\geq$30kg/m^2) with GDM there was a significant difference in adiponectin concentrations, indicating that adiponectin levels were influenced by the presence of obesity in our study population.

Low grade inflammation is associated with T2DM and GDM [11]. This low-grade inflammation, as measured by the CRP, has also been associated with the presence of obesity in pregnancy [23]. Wolf et al demonstrated that CRP concentrations in the first trimester predicted the development of GDM [24]. Other studies found inconsistent results regarding the association between inflammatory markers and the incidence of GDM, and the interdependence of the degree of adiposity [23, 25]. We did not find any significant difference in CRP concentrations between women with or without GDM, nor did we find a difference in CRP levels when we considered obese women with GDM. Inconsistent results may be attributed to different populations, socio-economic groups, and the presence of underlying sub-clinical infections.

As we are working towards global consensus on the guidelines for the screening of GDM there has been increasing interest in the role of biomarkers. The strengths of our study were that we included a large South African population cohort, and we investigated the role of multiple biomarkers. The limitations of this study were that we only considered HIV negative women, and that we measured the biomarkers at a single point in gestation between 24 and 28 weeks.

The OGTT is a cumbersome test and this may lead to decreased compliance by healthcare workers and pregnant women in achieving universal screening for GDM. There is a need to find a simple, more efficient tool that identifies women at risk of GDM before GDM develops. There has been great interest in biomarkers as a tool for the prediction of GDM. The CRP and adiponectin were shown to have promise as biomarkers in other studies [10, 12, 24], but we did not find this useful in our population. The tests of insulin sensitivity (HOMA, QUICKI) were shown to be significantly different in women with GDM compared to normoglycaemic controls in our population. The addition of these tests further improved the predictive ability of clinical parameters alone in identifying women at risk of GDM. More research is needed to investigate the use if these indices, especially early in pregnancy, as a tool to identify pregnant women at high risk of developing GDM.

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Declaration of interest:

The authors have no conflict of interest to declare.

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