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Full length article

First trimester serum biomarkers to predict gestational diabetes in a high-risk cohort: Striving for clinically useful thresholds

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ABSTRACT

Objectives: Screening and diagnosis of gestational diabetes (GDM) has been a source of controversy. The prevalence has increased in line with an obesity epidemic and a trend towards delayed child-bearing. Treatment of even modest glycaemic impairment in pregnancy has been shown to be beneficial in preventing its clinical sequalae. However the cumbersome nature and timing of the oral glucose tolerance test coupled with debate around universal versus risk factor based screening have been problematic. This group aimed to investigate a panel of biomarkers which have shown promise in the literature to predict GDM from the first trimester in a group of high risk women.
Methods: Serum samples were drawn on 248 women deemed at risk of GDM before 15 weeks' gestation to measure C-reactive protein, sex hormone binding globulin, adiponectin and 1,5 anhydroglucitol. Patients underwent an oral glucose tolerance test as per IADPSG criteria at 28 weeks' gestation. Multiple logistic regression was used to examine the link between incidence of GDM and early pregnancy serum biomarkers.
Results: Adiponectin levels in the first trimester are independently linked to the risk of GDM. Serum adiponectin <8.9 μg/ml gives an odds ratio of 3.3 for GDM.Mean 1,5 AG levels are significantly lower in those that go on to develop GDM. SHBG levels measured in the first trimester were linked to the risk of GDM. However, this was no longer statistically significant once BMI, ethnicity and family history were taken into consideration. First trimester measurement of CRP is not a useful indicator of GDM risk.
Conclusions: First trimester measurement of Adiponectin and 1,5 Anhydroglucitol are potential early biomarkers for the later onset of GDM. Risk stratification using these biomarkers may facilitate early diagnosis and management of GDM to mitigate against its complications.

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Introduction

Screening and diagnosis of GDM have presented a challenge for the last four decades or more. Research in this area is marred by controversy as different studies have used varying diagnostic criteria, rendering comparison of methodology and results problematic. GDM has come sharply in to the clinician's focus in recent years, owing to the obesity epidemic, delayed childbearing and an increasingly ethnically diverse pregnant population [1–4]. The clinical sequelae [5–7], high prevalence of glucose intolerance in the population and evidence of improved outcomes with even modest prenatal intervention, may make the case for universal screening clear [5,8,9]. However, universal screening may equally result in an increased healthcare burden and over-medicalisation of pregnancy.

In most cases of GDM, lifestyle interventions are effective at achieving normo-glycaemia throughout pregnancy [10,12]. A small subgroup will require hypoglycaemic agents to achieve this goal and reduce the risk of adverse outcome. Early intervention is key to optimising pregnancy outcome for mother and baby. Traditionally, screening for GDM involves selecting a sub-group of the population deemed to be at high risk of developing the condition. Risk factors include a family history of diabetes, those with a BMI >30, a history of polycystic ovarian syndrome or non-Caucasian ethnicity. Women with history-based or demographic risk factors

undergo a formal oral glucose tolerance test (OGTT) at 28 weeks' gestation. The National Institute for Clinical Excellence (NICE) in the UK quote a 60% detection rate for a 40% false positive rate using this risk-factor based screening approach.

Early identification of women that will likely go on to develop GDM would allow the introduction of targeted dietary and lifestyle interventions in a more timely and effective manner, leading to potentially improved outcomes. There have been many biomarkers which have shown promise in the field of GDM [13–16]. Aiming to build on evidence already available in this field, our team elected to investigate a panel of promising biomarkers measured in the first trimester in a group of women deemed to be at high risk of GDM. We aimed to investigate the link between 1st trimester serum C-Reactive protein (CRP), Sex hormone binding globulin (SHBG), adiponectin and 1,5 Anhydroglucitol(1,5AG) and subsequent onset of GDM in a high risk cohort.

Methods

This study was conducted at a single centre in the Rotunda Hospital Dublin between January 2014 and October 2015. The Rotunda is a large tertiary and stand-alone maternity unit delivering more than 8500 births annually. Institutional Review Board approval was sought and granted. Patients were considered eligible if they were less than 15 weeks' gestation at enrolment and had one or more of the following risk factors for gestational diabetes identified at the registration visit;

- BMI ≥ 30 kg/m2 (as objectively measured by midwife; not self-reported)
- Maternal age >40 years
- Ethnicity – Indian, Pakistani, South East Asian, Middle eastern, Afro-Caribbean
- History of Polycystic Ovarian Syndrome (PCOS)
- Family history of first degree relative with type 2 diabetes
- Previous macrosomic baby (>4 kg birthweight)
- Previous unexplained stillbirth

Exclusion criteria

- Persistent fasting glycosuria (as this merits first trimester screening for GDM and implies a risk of pre-existing type II diabetes)

- Gestational diabetes in a prior pregnancy (as the recurrence risk for gestational diabetes approximately 65%)
- Twin Pregnancy. (due to potential difficulty in interpreting serum biomarkers)

Study participants underwent non-fasting serum testing of CRP, SHBG, Adiponectin and 1,5 AG taken alongside first pre-natal visit blood tests. All patients were scheduled for a 75 g OGTT at 28 weeks gestation. Using International Association of Diabetes and Pregnancy Study Group (IADPSG) criteria, the patient was considered to have GDM if the fasting serum glucose was greater than or equal to 5.1 mmol/L, the 1-h serum glucose was greater than or equal to 10.0 mmol/L or if the 2-h post prandial serum glucose was greater than or equal to 8.5 mmol/L. One or more of the readings above-threshold was sufficient for a diagnosis of GDM. Body mass index (BMI) was objectively measured. Clinicians and patients were blinded to biomarker results. Data was analysed using a univariate and multivariate logistic regression to determine the odds ratio of a positive OGTT for a given biomarker result. ROC curves were generated for those biomarkers with significant results in an attempt to define clinically useful thresholds. SPSS was used to perform statistical analyses and $p < 0.05$ was considered significant.

With regard to a power calculation we estimated that approximately 20% of our high risk cohort would screen positive for GDM. This study was largely exploratory (most especially with regard to 1,5 AG) which makes a detailed and exact power calculation difficult. We had no pilot study upon which to base our calculations and because the literature is variant and contradictory in some aspects regarding each biomarker, supposing the effect size was challenging. Using a background population incidence of 12% GDM (based on ATLANTIC DIP results) and taking the probability of a type 1 error (α) to be 0.05, while taking the power at 90% we determined we would need a sample size of 206 to show a statistically significant difference between screen positive and screen negative groups. We chose to extend our recruitment significantly beyond this due to the factors discussed above (Figs. 1–3 Tables 1 and 2).

Discussion

Gestational Diabetes (GDM) is an increasingly common complication of pregnancy [2]. It confers a risk of adverse outcome upon both the mother (increased rate of obstetric intervention, operative
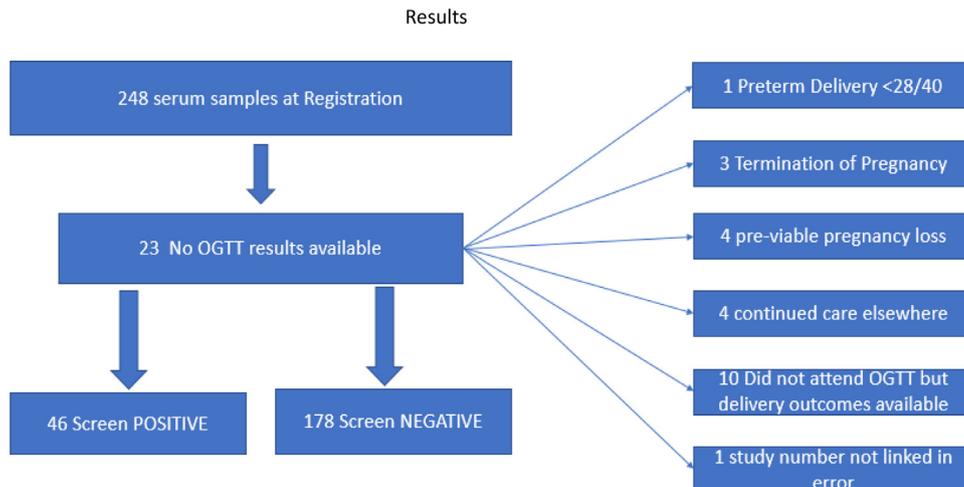
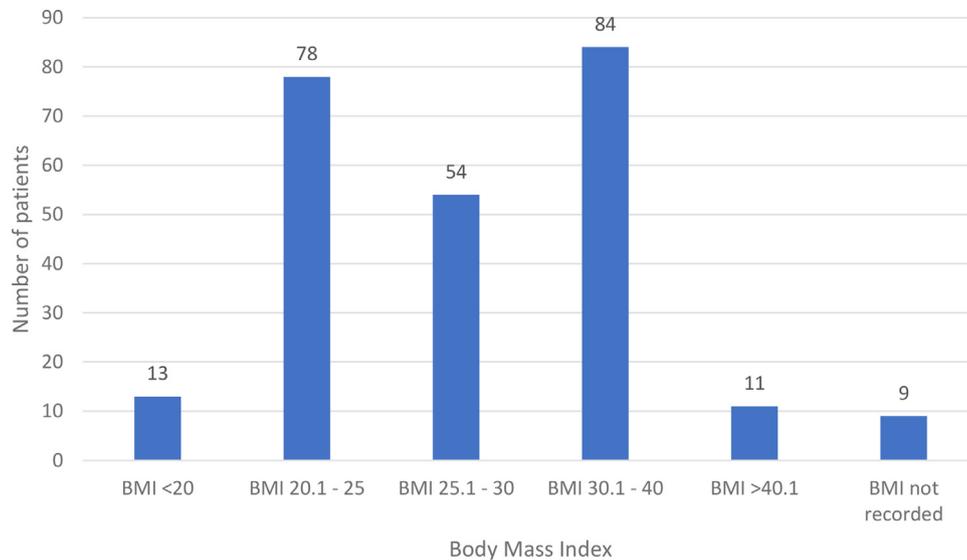Results

Fig 1. Study Population.
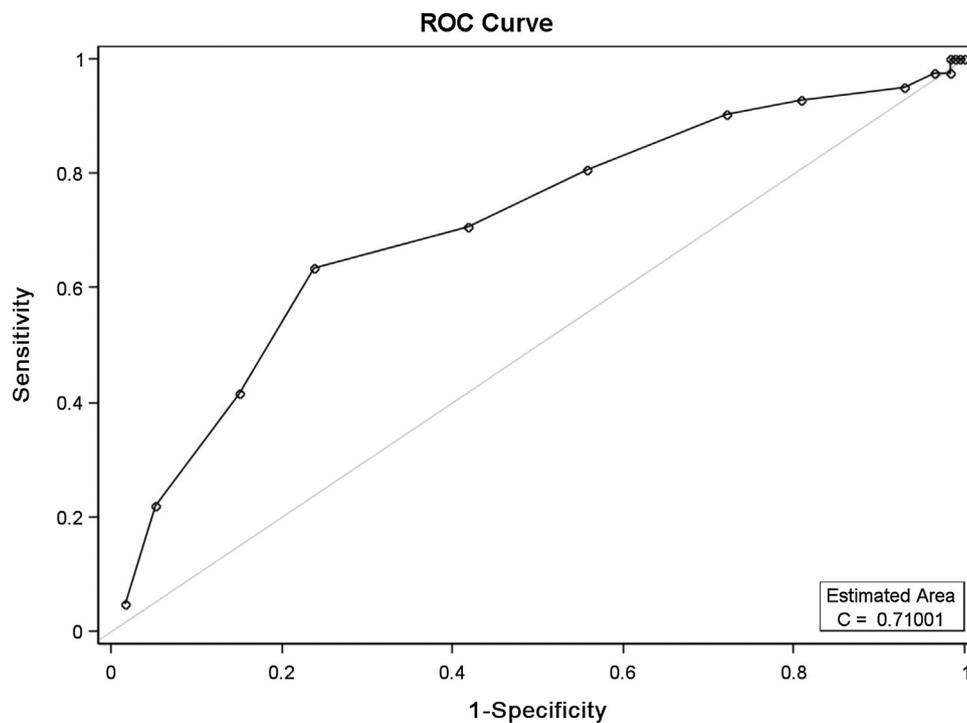
Fig 2. Body Mass Indices of the cohort.

Fig 3. ROC curve of Adiponectin values in the first trimester as a predictor of GDM status.

Table 1
Risk factors for GDM in screen positive and screen negative groups.

	GDM Screen Positive N = 46	GDM Screen Negative N = 178	p-value
Average Age (years)	33.4	32.7	p = 0.65
Average BMI (kg/m^2)	31.7	27.8	p = 0.043
Average number of Risk Factors for GDM	1.65	1.25	p = 0.61

delivery and anal sphincter injury) and the fetus (macrosomia, shoulder dystocia, birth injuries and long term risks of childhood obesity and diabetes) [5–7]. There is a trend towards identifying pregnancies at risk of complications earlier in many fields of obstetric practice [13]. Examples include first trimester screening for aneuploidy, risk-factor and sonographic screening for intrauterine growth restriction and many biomarkers have been investigated in the prediction of pre-eclampsia. This approach allows us to identify and focus on a subgroup of high risk pregnancies whilst allowing the majority to proceed with minimal intervention and cost.

Table 2
Basic statistical parameters of the biomarkers.

	SHBG (nmol/L)	CRP (mg/L)	Adiponectin (μg/mL)	1,5 AG (μg/mL)
Number of samples analysed	219	222	213	213
Mean Value (st dev)	281 (88.8)	5.6 (5.8)	8.9 (2.9)	15.9 (6.3)
Median Value	281	3.9	9	15.9
Mode Value	282	1	8	10.9
Range	67–644	1–62	4–31	2–35.3

Table 3
Logistic Regression Analysis of first trimester biomarker values and likelihood of a screen positive OGTT. Odds ratios correspond to 1 standard deviation increase in a biomarker level. Adjusted analysis* is multiple logistic regression adjusting for BMI, ethnicity and family history of diabetes.

Biomarker	Unadjusted Analysis		Adjusted Analysis*	
	OR (95% CI)	P-value	OR (95% CI)	P-value
SHBG	0.64 (0.44–0.94)	0.021	0.78 (0.52–1.17)	0.231
CRP	1.34 (0.98–1.82)	0.063	1.01 (0.69–1.47)	0.952
Adiponectin	0.47 (0.31–0.69)	<0.001	0.64 (0.41–0.99)	0.047
1,5 AG	0.71 (0.50–1.02)	0.063	0.57 (0.37–0.90)	0.016

In this study, we identified four biomarkers which have demonstrated early promise in the literature as biomarkers for GDM [17]. We investigated their utility in predicting GDM in a high risk first trimester cohort.

CRP is a protein found in plasma which rises in response to inflammation and as part of the acute phase response. It is synthesised in the liver and has a half-life of 48 h which is constant. CRP levels vary depending on the rate of production and so correlate to the severity of the precipitating cause. CRP has also been independently investigated as a biomarker capable of predicting the onset of gestational diabetes. Wolf et al. [18] found that in a prospective nested case-control study where 43 women subsequently developed GDM; higher levels of CRP in the first trimester positively correlated with the onset of disease and the difference between the two groups was statistically significant. However, once the results were adjusted for obesity the association was attenuated leading the authors to recommend that further larger studies should evaluate this in more detail. CRP is a biomarker that can change in great magnitude from day to day and a single measurement at a point in time may not truly reflect the background inflammatory metabolic milieu of the subject. Our CRP data was not normally distributed, with a small number of very high results skewing the data. This may have affected our results. Based on our study and the conflicting findings of the current body of available research on CRP use as a biomarker for GDM, we feel it is unlikely to prove a useful tool to this end. A serious draw back to employing CRP as a screening tool is its non-specific nature and the plethora of unnecessary investigations which may ensue following a high result. Routinely measuring CRP in otherwise healthy asymptomatic women would likely lead to unnecessary diagnostics, unfounded patient anxiety and increased healthcare costs.

1,5 Anhydroglucitol is a monosaccharide which is present in almost all foods. 1,5 AG is in a steady state normally and almost completely reabsorbed within the renal tubules. Serum levels decrease during periods of hyperglycaemia due to increased urinary excretion. In the absence of hyperglycaemia the levels

return to normal within 14 days. It may be used therefore to detect short term excursions in glycaemia which may not be represented by the traditional methods such as measurement of HbA1c and fructosamine. It has been shown to more accurately detect hyperglycaemic episodes than other markers when compared to continuous glucose monitoring packs (CGM) [19]. Initially this marker was not investigated in pregnancy as it was felt that physiological changes in kidney function and haemodynamic parameters may invalidate the results but Dworacka et al. recently demonstrated it to be a reliable indicator of short term hyperglycaemic episodes in pregnancy in a group of 55 women (both with gestational and pregestational diabetes) and suggests its use as an adjunct to HbA1c [20]. Recently a study of 85 patients with a mixture of T1DM, T2DM and gestational diabetes were investigated by Delaney et al. They found an inverse relationship between the 1,5 AG levels measured at 28 weeks gestation and the birthweight of the infants. The group conclude that this marker "may be useful in the assessment of glycaemic control in pregnancy in addition to A1c" [21]. Nowak et al. also published on the inverse relationship between mid-trimester 1,5 AG levels and birthweight in women with T1DM. They found 1,5 AG to be a stronger predictor of macrosomia than HbA1C [22]. There is only one study we identified that attempts to determine the normal 1,5 AG values in diabetic, non-diabetic pregnancies and non-pregnant women. Tetsuo et al. showed the level of 1,5 AG in the non-pregnant woman was 18.6 ± 5.2 mg/L (mean $\pm$ SD). While the group noted that levels began to decrease in parallel with gestation from about 9 weeks they do not present reference ranges for pregnancy [23].

Table 3 shows that each one standard deviation increase in 1,5 AG measured in the 1 st trimester is associated with a lowered risk of developing GDM in later pregnancy. In our unadjusted analysis, this association is not quite statistically significant, however once we adjust for BMI, ethnicity and family history we see the biomarker emerge as a more powerful independent predictor of GDM status (OR of 0.57 for GDM, p = 0.016). Table 5 demonstrates a significantly lower mean 1,5 AG in those that went on to develop GDM. Fig. 4 is a receiver operating characteristic curve for 1,5 AG levels in the 1 st trimester in a high-risk cohort as a predictor of a screen positive OGTT. Disappointingly here we see no distinct threshold at which 1st trimester 1,5 AG functions with acceptable sensitivity or specificity as a predictor of GDM status (Table 4).

Sex hormone-binding globulin (SHBG) or sex steroid-binding globulin (SSBG) is a glycoprotein that binds to the sex hormones, androgen and estrogen. Levels of SHBG have been shown to decrease with high levels of insulin. Smirnakis at al described the use of SHBG measurement in the first trimester as a predictor of later onset of gestational diabetes [14]. The study evaluated SHBG taken in the first trimester or early in the second trimester in 35

Table 4
OR of a screen positive OGTT at selected thresholds.

Biomarker	Odds-Ratio of Screen positive OGTT	95% CI	P-value
Adiponectin ≤8.9 μg/ml (mean value in our cohort)	3.3	1.6528–6.7	p = 0.0008
Adiponectin ≤12 μg/ml (mean value in healthy general pregnant population) [38]	1.2	0.3297–4.4402	p = 0.77

Table 5
Mean 1, 5 AG results in gdm and non-GDM patients compared using *t*-test.

|	Mean μg/mL	SD	p-value
Screen Neg (No GDM)	16.39	6.14	p = 0.041
Screen Pos (GDM)	14.23	6.9	

women with subsequent GDM versus 73 controls and 37 patients with an abnormal glucose challenge test. They note that among three different biomarkers examined in the first trimester, SHBG gave the best performance as a predictor of subsequent diagnosis of gestational diabetes. The authors also highlight how SHBG is a test which most hospital laboratories can do readily and at little cost. Maged at al [15] analysed 269 patients of which 27 developed GDM. They found that SHBG at a cut-off value of 211.5 nmol/L showed a sensitivity and a specificity of 85% and 37%, respectively. They also looked at high sensitivity C-reactive protein (CRP) and note that when the two biomarkers are combined GDM is predicted with a sensitivity and specificity of 74.07% and 75.62%, respectively with an overall accuracy of 75.46%. In our study we found that SHBG levels measured in the first trimester were indeed linked to the risk of GDM. However, this was no longer statistically significant once BMI, ethnicity and family history were taken into consideration. It appears that SHBG may not be an independent predictor of GDM status.

Adiponectin is a protein which modulates glucose metabolism by affecting insulin sensitivity. It is secreted both from adipose tissue and the placenta in pregnancy [24]. Adiponectin is anti-inflammatory and insulin sensitising. This is achieved by initiating glucose uptake in the skeletal muscle mass and by decreasing glucose production in the liver. Adiponectin levels inversely correlate with body fat percentage and so low levels are seen in obesity which is surprising given that it is produced in adipose tissue. Levels are seen to decline through pregnancy [25] and correlate negatively to BMI and adiposity [39,40]. Low levels of adiponectin have been repeatedly shown to be an independent risk factor for the development of type 2 diabetes [26–28] Low levels of adiponectin are strongly associated with the onset of GDM independently of maternal pre-pregnancy body mass index (BMI) and insulin sensitivity [29–33]. Lain et al. demonstrated in a nested case control study of 59 women (30 of whom developed gestational diabetes) that women with a first trimester adiponectin concentration which was below the 25th percentile were ten times more likely to be diagnosed with GDM when compared to women with higher adiponectin levels [34]. In 2014 Xu et al. published a systematic review and meta-analysis of 15 studies showing lowered adiponectin levels in GDM patients compared to controls even after adjusting for BMI [35]. To date the available information on adiponectin as a biomarker for GDM has come from small, retrospective case-control or cross-sectional studies. Different sampling sources (maternal, cord or placental) and different assay methods reported have added further complexity. Adiponectin is easily accessible in serum and routine phlebotomy occurs as part of standard antenatal care. Adiponectin has the added benefit of being reproducible despite the fasting or non-fasting state of the subject (up to 72 h) [36].

In our study we found that Adiponectin levels in the first trimester are independently linked the risk of GDM later in pregnancy. Higher first-trimester adiponectin levels are associated with a lower risk of subsequent development of GDM. This association appears to be a continuum. There is no clearly identifiable threshold below which GDM is predicated with good sensitivity and specificity.

The strengths of our study include that it is somewhat unique in looking at GDM in a high-risk cohort. We recruited larger numbers than many of the other studies cited above and the data was prospectively collected. One of the inherent limitations of any study of GDM is complicit in the diagnosis. Glucose tolerance is a spectrum and some women who skim below the diagnostic thresholds may still suffer the clinical consequences of uncontrolled hyperglycaemia. The concept of the "fetal glucose steal" phenomenon [37] could potentially affect the results of our study. It is long and well recognised that some patients clinically exhibit the signs of GDM – macrosomic fetus, polyhydramnios and
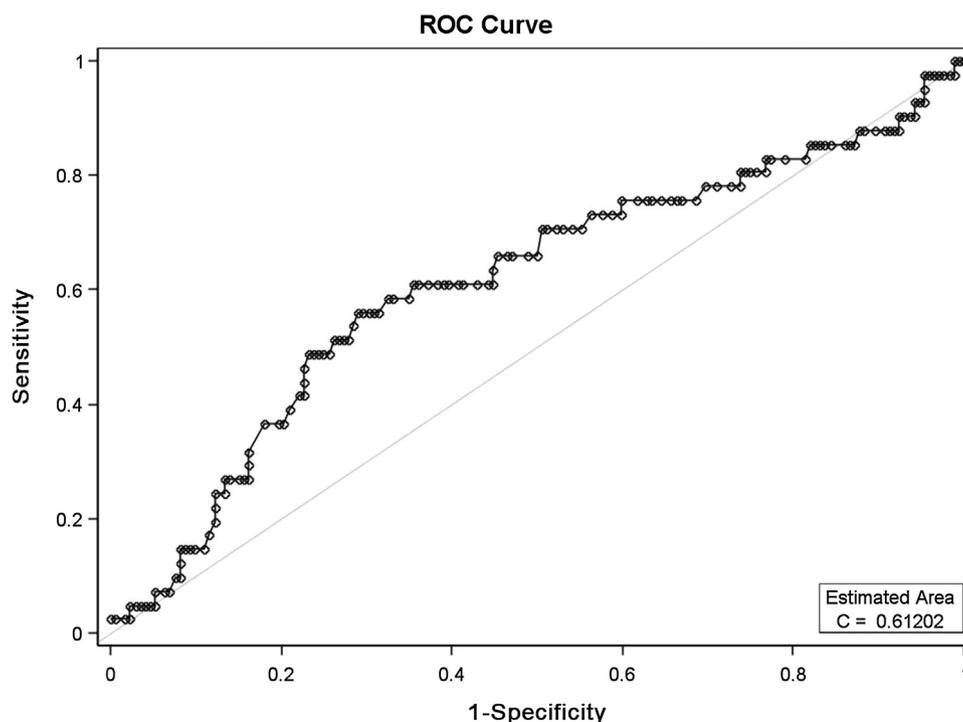
Fig 4. ROC Curve of 1 st trimester 1,5 AG as a predictor of a positive OGTT.

occasional glycosuria but yet they test negative for GDM when the OGTT is administered. It is postulated that early in gestation when glucose levels have been very high due to maternal insulin deficiency and or resistance, the fetus becomes hyperinsulinaemic. Then at the time of the OGTT, in the late second or early third trimester, since glucose readily and freely crosses the placenta, the fetus metabolises a proportion of it so that the serum glucose levels of the mother are somewhat attenuated and the OGTT is negative. In these cases, therefore, the clinical complications of uncontrolled hyperglycaemia develop in the pregnancy despite a "normal" serum fasting, 1-h and 2-h postprandial glucose level.

In summary Adiponectin levels in the first trimester are independently linked to the risk of GDM. Serum adiponectin <8.9 μg/ml gives an odds ratio of 3.3 for GDM. After correcting for maternal BMI, ethnicity and family history of diabetes 1,5 AG levels in the first trimester are linked to the likelihood of onset of GDM.

Further work should explore whether women with low adiponectin levels in early pregnancy may benefit from early institution of a diet and lifestyle programme to mitigate against the detrimental effects of GDM.

Acknowledgments

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