European Journal of Obstetrics & Gynecology and Reproductive Biology 222 (2018) 7–12

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

Full length article

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

Siobhan M. Corcoran[a,*], Natalie Achamallah[a], John O' Loughlin[b], Philip Stafford[c], Pat Dicker[d], Fergal D. Malone[a], Fionnuala Breathnach[a]

[a] RCSI Department of Obstetrics and Gynaecology, Ireland
[b] Department of Laboratory Medicine, Rotunda Hospital, Ireland
[c] Department of Biochemistry, Dublin Institute of Technology, Ireland
[d] RCSI Department of Public Health and Epidemiology, Ireland

ARTICLE INFO

Article history:
Received 25 August 2017
Received in revised form 18 December 2017
Accepted 30 December 2017
Available online xxx

Keywords:
Gestational Diabetes
Screening
Biomarkers
First trimester

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.

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

* Corresponding author at: RCSI Department of Obstetrics and Gynaecology, Rotunda Hospital, Parnell Square Dublin 1, D01 K4H0, Ireland.
E-mail address: siobhancorcoran@rcsi.ie (S.M. Corcoran).

https://doi.org/10.1016/j.ejogrb.2017.12.051
0301-2115/

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 $\geq$ 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

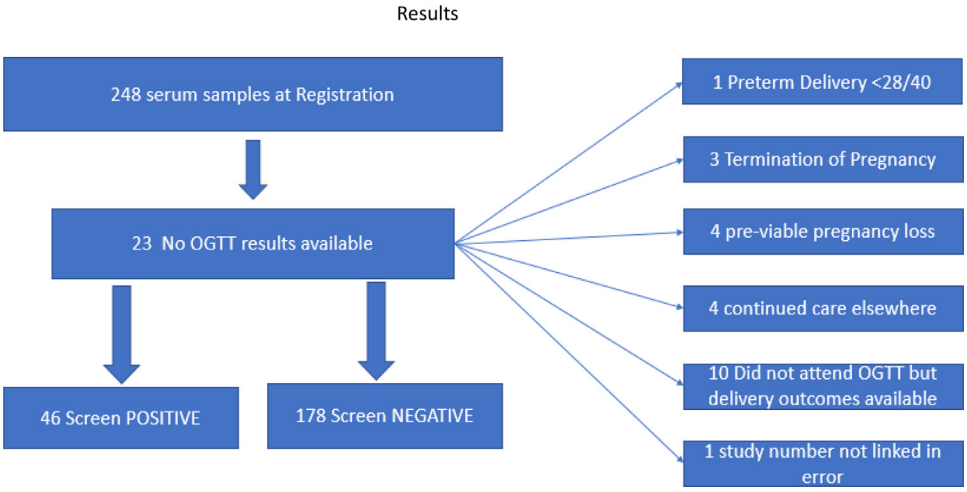

Fig 1. Study Population.