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First-trimester biochemical markers of placentation in screening for gestational diabetes mellitus

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ARTICLE INFO

Article history:
Received 14 May 2015
Accepted 15 July 2015

Keywords:
First trimester screening
Placental growth factor
Pregnancy-associated plasma protein A
Gestational diabetes mellitus

ABSTRACT

Objective. To investigate whether first-trimester biochemical markers of placentation, including pregnancy-associated plasma protein-A (PAPP-A) and placental growth factor (PLGF), are altered in women that subsequently develop gestational diabetes mellitus (GDM) and to examine their potential value in improving the performance of screening for GDM by maternal characteristics and medical history.

Methods. The study population of 31,225 singleton pregnancies, including 787 cases that developed GDM, was drawn from women undergoing routine prospective screening for pregnancy complications at 11–13 weeks' gestation. Maternal serum PAPP-A and PLGF were measured and the levels were expressed as multiples of the median (MoM) after adjustment for maternal characteristics and medical history. The performance of screening for GDM by maternal factors and MoM values of PAPP-A and PLGF was evaluated by receiver operating characteristic (ROC) curves.

Results. In the GDM group, compared to the unaffected group, the median PAPP-A was reduced (0.949, 95% CI 0.913–0.987 MoM) ($p = 0.0009$) and median PLGF was increased (1.053, 95% CI 1.023–1.083 MoM) ($p = 0.004$). The performance of screening for GDM by maternal factors was not improved by the addition of PAPP-A and/or PLGF.

Conclusions. First trimester maternal serum PAPP-A and PLGF are not useful in screening for GDM.

1. Introduction

Maternal serum pregnancy associated plasma protein-A (PAPP-A) and placental growth factor (PLGF) at 11–13 weeks' gestation are reduced in pregnancies with fetal trisomies 21, 18 and 13 and in those that subsequently develop preeclampsia and in those that deliver small for gestational age (SGA) neonates [1–4]. The measurements of serum PAPP-A and PLGF are affected by several maternal and pregnancy characteristics, including gestational age at sampling, maternal racial origin, weight, smoking status, method of conception and diabetes mellitus type 1 or 2, and these are taken into account in the calculation of multiple of the median (MoM) values [5,6]. In pregnant women with diabetes mellitus type 2 treated

Abbreviations: PAPP-A, pregnancy associated plasma protein-A; PLGF, placental growth factor; MoM, multiple of the median; GDM, gestational diabetes mellitus; SGA, small for gestational age; OGTT, oral glucose tolerance test; ROC, receiver operating characteristic; DR, detection rate; FPR, false positive rate; IQR, interquartile range; SD, standard deviation; AUROC, area under receiver operating characteristic curve; CI, confidence interval.

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http://dx.doi.org/10.1016/j.metabol.2015.07.015
0026-0495/

with insulin, serum PAPP-A is decreased by about 20% and PLGF by 13%; in those treated with diet or metformin PAPP-A is reduced by about 10%, but PLGF is not significantly different from unaffected pregnancies [5,6].

Gestational diabetes mellitus (GDM) and type 2 diabetes mellitus are mainly caused by insulin resistance and insulin deficiency and they are both associated with obesity, advanced age and non-white racial origin [7]. Some studies that examined first-trimester serum PAPP-A in women who subsequently developed GDM reported that the levels were reduced, but other studies reported that the levels were not significantly altered [8–15]. In contrast, two case–control studies that examined first-trimester serum PLGF reported that in women who developed GDM the levels were increased [15,16].

The aim of this prospective screening study is to investigate whether first-trimester maternal serum PAPP-A and PLGF are altered in women who subsequently develop GDM and to examine their potential value in improving the performance of screening for GDM by maternal characteristics and medical history [17].

2. Methods

2.1. Study Population

This study was drawn from a large prospective observational study for early prediction of pregnancy complications in women attending for their routine first hospital visit in pregnancy at King's College Hospital, London, UK. This visit, which is held at 11^{+0} to 13^{+6} weeks' gestation, included recording of maternal characteristics and medical history, ultrasound examination to confirm gestational age from the measurement of the fetal crown–rump length [18] and diagnose any major fetal abnormalities [19] and measurement of maternal serum PAPP-A and PLGF. Maternal serum samples were analyzed by automated biochemical analyzers within 10 min of blood sampling using the DELFIA Xpress system (PerkinElmer Life and Analytical Sciences, Waltham, USA) or the Cobas e411 system (Roche Diagnostics, Penzberg, Germany). The women were screened between February 2010 and June 2013 and gave written informed consent to participate in the study, which was approved by the NHS Research Ethics Committee.

Details of maternal characteristics and the findings of the assessment at 11–13 weeks were recorded in our database. Data on pregnancy outcome were obtained from the maternity computerized records or the general medical practitioners of the women and were also recorded in our database.

The inclusion criteria for this study on screening for GDM were singleton pregnancy delivering a phenotypically normal neonate at ≥30 weeks' gestation. We excluded pregnancies with diabetes mellitus type 1 or 2, those ending in termination, miscarriage or delivery at <30 weeks because they may not have had screening and diagnosis of GDM.

2.2. Maternal History and Characteristics

Patients were asked to complete a questionnaire on maternal age, racial origin (Caucasian, African, South Asian, East Asian and mixed), cigarette smoking during pregnancy (yes or no), method of conception (spontaneous or assisted conception requiring the use of ovulation drugs), medical history including diabetes mellitus type 1 or 2, family history of diabetes mellitus (first, second or third degree relative with diabetes mellitus type 1 or 2) and obstetric history. The questionnaire was then reviewed by a doctor together with the patient. The maternal weight and height were measured. For the purpose of this study women were classified as parous or nulliparous with no previous pregnancies at or beyond 24 weeks and if parous we recorded whether any of the previous pregnancies were complicated by GDM or resulted in the delivery of a macrosomic neonate, defined as birthweight above the 95th percentile [20].

2.3. Outcome Measure

Screening for GDM in our hospital is based on a two-step approach. In all women random plasma glucose is measured at 24–28 weeks' gestation and if the concentration is ≥6.7 mmol/L, a 75 g oral glucose tolerance test (OGTT) is carried out within the subsequent 2 weeks. The diagnosis of GDM is made if the fasting plasma glucose level is ≥6 mmol/L or the plasma glucose level 2-h after the oral administration of 75 g glucose is ≥7.8 mmol/L [21].

2.4. Statistical Analysis

In each patient the measured serum PAPP-A and PLGF concentration was converted to MoM as previously described [5,6]. Mann Whitney-U test was used to compare the median MoM values of PAPP-A and PLGF between the GDM and unaffected groups. The *a priori* risk for GDM was estimated from an algorithm derived from multivariable logistic regression analysis of maternal characteristics and medical history in 75,161 singleton pregnancies including 1827 (2.4%) that developed GDM [17]. Bayes theorem was applied to combine the *a priori* risk of GDM with maternal serum PAPP-A and PLGF MoM values. To assess the performance of the markers in the prediction of GDM, detection rates (DRs) for various false positive rates (FPRs) were calculated, receiver operating characteristic (ROC) curves were produced and area under the curves (AUROC) calculated. The AUROCs were compared using DeLong's test.

The statistical software package R was used for all data analyses [22].

2.5. Literature Search

We searched MEDLINE and EMBASE in March 2015 without any time limits to identify English-language articles reporting on first-trimester maternal serum PAPP-A and/or PLGF in pregnancies complicated by GDM.

3. Results

3.1. Screening Population

During the period, the entry criteria were fulfilled by 31,225 singleton pregnancies, including 787 (2.5%) that developed GDM. In the GDM group, 280 cases were treated by dietary