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First trimester screening for gestational diabetes mellitus by maternal factors and markers of inflammation

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ARTICLE INFO

Article history:
Received 26 August 2015
Accepted 27 October 2015

Keywords:
First trimester screening
Tumor necrosis factor-α
C-reactive protein
Gestational diabetes mellitus

ABSTRACT

Objective. To examine the potential role of maternal serum levels of tumor necrosis factor-α (TNF-α) and high sensitivity C-reactive protein (Hs-CRP) in the first trimester of pregnancy in the prediction of gestational diabetes mellitus (GDM).

Methods. Maternal serum TNF-α and Hs-CRP concentrations were measured in a case–control study of singleton pregnancies at 11–13 weeks' gestation, which included 200 cases that subsequently developed GDM and 800 unaffected controls. Measured levels of TNF-α and Hs-CRP were expressed as multiples of the median (MoM) after adjustment for maternal characteristics and history. The performance of screening for GDM by maternal factors and MoM values of TNF-α and Hs-CRP was evaluated by the area under the receiver operating characteristic curves (AUROC).

Results. In the GDM group, compared to the normal group, the median TNF-α was significantly increased (1.303 MoM, interquartile range [IQR] 1.151–1.475 vs. 1.0 MoM, IQR 0.940–1.064; p = 0.031) and the median Hs-CRP was not significantly different (1.113 MoM, IQR 0.990–1.250 vs. 1.0 MoM, IQR 0.943–1.060; p = 0.084). In the prediction of GDM, the AUROC for maternal characteristics with TNF-α or Hs-CRP was not significantly different than the AUROC for maternal characteristics alone (p = 0.5055 and p = 0.2197, respectively).

Conclusions. In pregnancies that develop GDM there is no evidence of an inflammatory response at 11–13 weeks' gestation and the levels of serum TNF-α and Hs-CRP are not useful in first-trimester screening for GDM.

Abbreviations: TNF-α, tumor necrosis factor-α; Hs-CRP, high sensitivity C-reactive protein; MoM, multiple of the median; GDM, gestational diabetes mellitus; LGA, large 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.2015.10.029
0026-0495/

1. Introduction

The incidence of gestational diabetes mellitus (GDM) has been estimated to be around 5% [1], but nowadays may be as high as 26% depending on the population, method of screening and glucose threshold values [2]. GDM is associated with increased risk of adverse perinatal outcomes [3] and the development of type 2 diabetes mellitus later in life [4]. There is evidence that inflammation is associated with insulin resistance and is a central feature in the development of Type 2 diabetes mellitus [5,6]. Similarly, inflammation has been reported in GDM but the prognostic significance of this remains to be fully elucidated.

C-reactive protein (CRP), an inflammatory marker released by the liver under cytokine stimulation [7] and tumor necrosis factor-α (TNF-α) a pro-inflammatory cytokine synthesized and secreted by adipose tissue as well as placenta [8], have both been extensively examined in women with GDM [9]. Numerous case–control studies, involving 5–124 cases of GDM, provided contradictory evidence that in pregnancies with established GDM serum TNF-α and high sensitivity CRP (hs-CRP) are increased [10–41]. Similarly, there is some limited evidence that altered levels in these biomarkers may precede the clinical onset of the disease [42–45]. We have previously reported a first-trimester prediction model for GDM based on maternal characteristics and medical history, including maternal age, weight, height, racial origin, family history of diabetes mellitus, method of conception, previous history of GDM and previous delivery of macrosomic neonate [46]. Screening by this method can predict 55%, 68% and 84% of cases of GDM at respective false positive rates (FPRs) of 10%, 20% and 40%. The model allows the estimation of the patient-specific a priori risk for GDM which could be combined with potentially useful biomarkers for further improvement in the performance of screening.

The objectives of this study are first, to examine the application of Bayes theorem to combine the prior risk from maternal characteristics and history with serum levels of TNF-α and hs-CRP at 11–13 weeks' gestation in defining the patient-specific risk for GDM and second, to estimate the potential performance of such combined screening for early identification of affected pregnancies.

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. In this visit, which is held at 11^{+0} to 13^{+6} weeks' gestation, we record maternal characteristics and medical history and perform an ultrasound scan to firstly, confirm gestational age from the measurement of the fetal crown-rump length [47], secondly, diagnose any major fetal abnormalities [48] and thirdly, screen for chromosomal abnormalities based on fetal nuchal translucency thickness and maternal serum pregnancy associated plasma protein-A and free β-human chorionic gonadotropin [49,50]. Women attending for this visit were invited to participate in a study on the prediction of pregnancy complications and from those who provided informed written consent serum samples were stored at −80 °C for subsequent biochemical analysis. The study was approved by the National Research Ethics Committee.

Details of maternal characteristics and the findings of the 11–13 weeks assessment 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.

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, 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 the last pregnancy was complicated by GDM or resulted in the delivery of a large for gestational age (LGA) neonate, defined as birth weight above the 95th percentile [51].

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 [52].

2.3. Case–Control Study

In this study we measured maternal serum TNF-α and hs-CRP concentrations in 200 cases that developed GDM and 800 controls. The cases of GDM were selected at random from our database of stored samples and each case was matched to four controls that were sampled on the same or next day. The controls were normal pregnancies without GDM or other pregnancy complications resulting in live birth after 37 weeks' gestation of phenotypically normal neonates with birth weight between the 5th and 95th percentiles for gestational age [50].

Serum TNF-α was measured by a Quantikine TNF-α ELISA kit (distributed by R&D Systems Europe, Abingdon, UK); the lower limit of detection of the assay was 0.6 ng/L, the intra-assay coefficient of variation at a concentration of 45.6 to 50.6 ng/L was 5.2% and the inter-assay coefficient of variation at a concentration of 42.4 to 49.2 ng/L was 7.4%. Serum hs-CRP was measured by a Cormay hs-CRP assay (kit distributed by P.Z. Lublin, Poland); the lower limit of detection of the assay was 0.01 mg/dL, the intra-assay coefficient of variation at a concentration of 0.046 to 0.981 mg/dL was 2.0% and the inter-assay coefficient of variation at a concentration of 0.047 to 0.976 mg/dL was 3.3%. All samples