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Elevated placental growth factor concentrations at 11–14 weeks of gestation to predict gestational diabetes mellitus☆

Makarios Eleftheriades[a,b,c,*], Ioannis Papastefanou[d], Irene Lambrinoudaki[e], Dimitra Kappou[f], Demetrios Lavranos[g], Athanasios Akalestos[c], Athena P. Souka[d], Panagiota Pervanidou[c], Demetrios Hassiakos[e], George P. Chrousos[c]

[a] Embryocare, Fetal Medicine Unit, Athens, Greece
[b] Bioiatriki SA, Department of Ultrasound and Fetal Medicine, Athens, Greece
[c] First Department of Pediatrics, University of Athens Medical School, Athens, Aghia Sophia Children's Hospital, Athens, Greece
[d] Fetal Medicine Unit, 3rd Department of Obstetrics and Gynaecology, University of Athens Medical School, Attikon University Hospital, Athens, Greece
[e] 2nd Department of Obstetrics and Gynecology, University of Athens Medical School, Aretaieio Hospital, Athens, Greece
[f] 1st Department of Obstetrics and Gynecology, University of Athens Medical School, Alexandra Hospital, Athens, Greece
[g] Bioiatriki SA, Hormone Laboratory, Athens, Greece

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ABSTRACT

Objective. To examine maternal serum concentrations of placental growth factor (PlGF) at 11–14 gestational weeks in pregnancies that developed gestational diabetes mellitus (GDM) and to create first trimester prediction models for GDM.

Methods. Case control study including 40 GDM cases and 94 controls. PlGF, biophysical and biochemical markers and maternal–pregnancy characteristics were analyzed.

Results. Log_{10} transformed PlGF (log_{10} PlGF) was not related to maternal factors. Log_{10} PlGF was increased ($p = 0.008$) in the GDM group compared to the control group. Log_{10} PlGF was associated with fasting glucose levels ($p = 0.04$) in the oral glucose tolerance test. Log_{10} PlGF had a strong relation with birth weight adjusted for gestational age in the control but not in the GDM group. Maternal weight and maternal age were the only predictors of GDM among the maternal factors [area under the curve (AUC) = 0.73, $p < 0.001$]. Log_{10} PlGF alone was a significant predictor of GDM (AUC = 0.63, $p < 0.001$). Combination of maternal weight,

Abbreviations: GDM, gestational diabetes mellitus; OGTT, oral glucose tolerance test; PlGF, placental growth factor; CRL, fetal crown-rump length; FHR, fetal heart rate; NT, fetal nuchal translucency; free β-hCG, free β-human chorionic gonadotrophin; PAPP-A, pregnancy-associated plasma protein A; log_{10} PlGF, log_{10} transformed values of placental growth factor; ROC curve, receiver operator characteristic curve; d-NT, delta values for fetal nuchal translucency; d-FHR, delta values for fetal heart rate; z–BW, birth weight z scores; log_{10} MoM PAPP-A, log_{10} transformed multiples of the median of pregnancy associated plasma protein-a; log_{10} MoM free β-hCG, log_{10} transformed multiples of the median of free β-human chorionic gonadotrophin; AUC, area under the curve; OR, odds ratio; FPR, false positive rate; Glu_0, glucose concentrations at time 0 of the OGTT; Glu_{60}, glucose concentrations at 60 minutes of the OGTT; Glu_{120}, glucose concentrations at 120 minutes of the OGTT; SHBG, sex hormone-binding globulin; DR, detection rate.

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* *Corresponding author at:* Embryocare, Fetal Medicine Unit, Address: 194 Alexandras Avenue, 11522, Athens, Greece. Tel.: +30 210 6441100, +30 6944 223060; fax: +30 210 6441102.
E-mail addresses: makarios@hotmail.co.uk, makarioseleftheriades@gmail.com (M. Eleftheriades).

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maternal age and $\log_{10}$ PlGF resulted in an improved prediction (DR = 71.4%, for 25% FPR, AUC = 0.78, Model R^2 = 0.17, $p < 0.001$).

Conclusion. At 11–14 weeks in pregnancies that develop GDM, the maternal serum levels of PlGF are increased. Measurement of serum PlGF at 11–14 weeks improves the performance of early screening for GDM provided by maternal factors alone.

1. Introduction

Gestational diabetes mellitus [GDM] is a major cause of maternal and perinatal complications such as macrosomia, neonatal hypoglycemia, maternal hypertensive disorders and increased rates of primary cesarean section [1,2]. GDM is also related to long-term consequences both for the mother and her offspring, including the development of metabolic syndrome, type 2 diabetes and cardiovascular disease [3–5]. Current evidence suggests that early detection and management of GDM can rationalize the antenatal care and reduce the frequency of adverse pregnancy outcome [6–8]. However, there is no internationally accepted screening strategy for GDM and there is no consensus whether the oral glucose tolerance test (OGTT) test should be offered to all the pregnant women or upon presence of specific risk factors which vary significantly in selective screening guidelines [9–11]. According to the NICE guidelines the risk factors include body mass index (BMI) >30 kg/m^2, previous GDM, first-degree relative with diabetes, family origin with a high prevalence of diabetes, previous large-for-gestational-age infant [9]. The American Diabetes Association also recommends that hypertension, polycystic ovary syndrome, cardiovascular disease, or other conditions related to insulin resistance should be considered as risk factors as well [10]. NICE recommends that pregnant women should be offered second-trimester screening for GDM (24–28 weeks' gestation) according to a two-step risk factor screening procedure [9]. In particular, a 75-g load, 2-h OGTT is performed based on maternal risk factors or in those women with no risk factors if initial random plasma glucose is ≥6.7 mmol/l. New guidelines proposed by the International Association of Diabetes and Pregnancy Study Groups (IADPSG) recommend to screen high-risk women at the first encounter for pre-existing diabetes and to screen universally at 24–28 weeks' gestation with use of the 75-g oral glucose tolerance test interpreting abnormal fasting, 1-h, and 2-h plasma glucose concentrations as individually sufficient for the diagnosis of GDM [11].

Previous studies have investigated the first trimester maternal serum levels of biochemical factors associated to insulin resistance, inflammation and oxidative stress in pregnancies subsequently complicated with GDM [12–19]. However, only few recent studies present first trimester screening models for GDM that combine maternal and obstetric characteristics with biochemical indices [14–17]. Placental growth factor [PlGF] is a placenta-derived angiogenic protein involved in the regulation of placental vascular development [20]. PlGF has been extensively investigated as a first trimester biomarker for pregnancy complications related to impaired placentation such as preeclampsia and birth weight deviations [21–23]. Also, inclusion of serum PlGF improves the performance of first-trimester screening test for trisomy 21 [24]. There is only one study that examined first trimester maternal serum levels of PlGF in pregnancies that subsequently developed GDM [25]. To the best of our knowledge, there is no published first trimester screening model for GDM that incorporates PlGF among the predictors.

The aim of our study was to examine whether in the first trimester of pregnancy maternal serum levels of PlGF are altered in pregnancies that subsequently develop GDM and whether this biomarker can improve the performance of early screening for GDM achieved by a combination of maternal factors in a cohort of low-risk pregnant women.

2. Methods

2.1. Study population and data collection

The present study is a case–control study that is part of a large prospective observational study for the first trimester prediction of GDM. The study was undertaken in a private medical setting of antenatal care Embryocare, Fetal Medicine Unit, Athens, Greece, and was approved by the institution's review board and ethical committee. We recruited singleton pregnancies at 11–14 weeks of gestation, at the time of the combined screening for aneuploidies by ultrasound scan and maternal serum biochemistry. We recorded maternal–pregnancy characteristics (maternal age, ethnicity, smoking status, parity, mode of conception, medical history). Fetal crown-rump length (CRL), fetal heart rate (FRH), nuchal translucency (NT) thickness, fetal nasal bone, blood flow in the fetal ductus venosus, blood flow in the fetal tricuspid valve, maternal serum free β-human chorionic gonadotrophin (free β-hCG) and maternal serum pregnancy-associated plasma protein A (PAPP-A) were measured to evaluate the risk for aneuploidies. All the variables had been recorded in a dedicated computerized database (Astraia software; Astraia GmbH, Munich, Germany) and retrieved for the subsequent analysis. We stored serum and plasma samples at −80 °C for subsequent biochemical analysis, from women that had agreed to participate in this study.

Dating was based on the last menstrual period and confirmed by ultrasound scan. In cases when women were unsure of their dates and in the pregnancies where the difference between the menstrual dates and the ultrasound dates was 7 days or more, the ultrasound dating was chosen. We excluded pregnancies with hypertensive disorders of pregnancy, previous pregnancy complicated with GDM, pre-existing diabetes mellitus (type 1 and type 2), pregnancies with chromosomally abnormal fetuses and/or structural defects, pregnancies resulting in intra-uterine death or