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First-Trimester Placental Growth Factor in Screening for Gestational Diabetes

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Key Words
Placental growth factor · First trimester · Maternal serum screening · Gestational diabetes · Glycosylated hemoglobin

Abstract
Objective: The aim of this study was first to assess whether first-trimester serum concentrations of placental growth factor (PlGF) differ between patients with and without gestational diabetes (GDM) and second to test whether there is a correlation between glycosylated hemoglobin (HbA1c), a factor recently shown to be useful in predicting GDM, and PlGF. ***Methods:*** PlGF was measured at 8–14 weeks with the Kryptor Immunoassay Analyzer (Brahms, Berlin, Germany). Absolute values were converted to multiples of the median using the software provided by the Fetal Medicine Foundation London. GDM was diagnosed using internationally accepted criteria. HbA1c levels were quantified using the TOSOH G7 automated hemoglobin analyzer. ***Results:*** From January to December 2014, 328 women were included in the study, 51 (15.5%) of whom developed GDM. First-trimester PlGF quantification does not discriminate between women at risk to develop GDM and controls, while HbA1c is able to do so. No correlation was found between PlGF and HbA1c. ***Conclusion:*** Our findings do not lend support to the hypothesis that early PlGF values are different in women who later develop GDM.

Introduction

Overweight, obesity and associated metabolic disorders such as diabetes and cardiovascular disorders are increasing worldwide in a pandemic manner and affect also the fertile population, increasing the prevalence of complications such as gestational diabetes (GDM) and hypertensive disorders of pregnancy in particular [1]. GDM is defined as glucose intolerance with first onset or recognition during pregnancy. As glycemic changes become overt in the second half of pregnancy, the International Association of the Diabetes and Pregnancy Study Groups (IADPSG) has recommended a general screening for GDM using a 75-g oral glucose tolerance test (oGTT) at 24–28 weeks of gestation [2], based on the findings of the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study [3]. However this metabolic disorder may already be present preconceptionally as impaired fasting glucose, impaired glucose tolerance or unrecognized pre-existing diabetes mellitus type 2 [4]. Therefore, international and national societies have recommended screening for these pre-existing metabolic disorders at the first antenatal visit by a fasting glucose measurement, 75-g oGTT, or by assessment of glycosylated hemoglobin (HbA1c) [2, 5, 6]. Recently an association been first-trimester HbA1c and GDM was reported [7, 8].

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Placental growth factor (PlGF) belongs to the vascular endothelial growth factor (VEGF) family and is an angiogenic factor that stimulates endothelial cells via fms-like tyrosine kinase-1. PlGF is expressed in trophoblastic cells and is suggested to play a vital role in the development of the placental vasculature [9]. Hypoxia and inflammation alter angiogenic and anti-angiogenic factors in the placenta [10], and maternal serum levels of PlGF are reduced in the first trimester of pregnancies that will develop preeclampsia (PE) or small for gestational age infants [11, 12]. While earlier studies reported increased PlGF levels in pre-gestational diabetes (PGDM) and GDM [13], a recent publication demonstrated that in PGDM first-trimester maternal serum levels of PlGF are reduced [14], while yet another study showed again increased PlGF levels in pregnancies that developed GDM [15].

As there are still only limited and somehow also conflicting data available about first-trimester PlGF in GDM, the purpose of this study was to add data by comparing first-trimester PlGF in the general low-risk setting of our outpatient women who later developed GDM to those who did not, and to test whether a correlation exists between HbA1c and PlGF in the first trimester, as HbA1c is known to be increased in women who later develop GDM.

Subjects and Methods

In this prospective study we included consecutive pregnant women attending for their first routine antenatal visit at 8–14 weeks gestation who accepted to have a blood test for PlGF and HbA1c and a 75-g oGTT at 24–28 weeks gestation to diagnose GDM. As part of routine PE screening most women had a second PlGF measured at 11–14 weeks if the first one had been taken before 11 weeks gestation, as there are too limited existing data on the performance of PlGF drawn before 11 weeks for PE screening. Patients were recruited between January and December 2014 at the outpatient clinics of the Department of Obstetrics and Gynecology of the University Hospital Bern. Written informed consent was obtained from the women agreeing to participate in the study, which was approved by the Ethics Committee of the Canton of Bern. Exclusion criteria were pre-existing diabetes type 1 or 2 and also women with a first-trimester HbA1c value of ≥6.5%.

Maternal serum samples for PlGF were assayed with the Kryptor Immunoassay Analyzer (Brahms, Berlin, Germany) and results were expressed as absolute values and as multiples of the median (MoM) at 11–14 weeks only using The Fetal Medicine Foundation software (www.fetalmedicine.org). The lower detection limit was 3.6 pg/ml.

HbA1c levels were quantified using the TOSOH G7 automated hemoglobin analyzer. The method principle is based on high-performance liquid chromatography and is fully traceable IFCC standard in accordance with the European Union directive 98/79/EC on in vitro diagnostic medical devices. The HbA1c level is given in percent and SI units (mmol/mol) [16].

According to current guidelines [2, 3] the diagnosis of GDM was made when any of the following criteria were met on the 75-g oGTT: fasting plasma glucose ≥5.1 mmol/l, or glucose ≥10 mmol/l at 1 h, or glucose ≥8.5 mmol/l 2 h. Blood was also drawn from the antecubital vein. Plasma glucose was estimated using the Roche Modular Analytics Chemistry Systems. The principle of the method is enzymatic utilizing hexokinase, which catalyzes the phosphorylation of glucose to glucose-6-phosphate [17].

Statistical analyses were performed with GraphPad Prism version 5.0 for Windows (GraphPad Software, San Diego, Calif., USA). Correlations were explored using the nonparametric Spearman rank test, while proportions were analyzed using Fisher exact or χ^2 test where appropriate. Mann-Whitney U test was used to compare continuous variables. Statistical significance was considered achieved when p was <0.05.

Results

From January to December 2014 we included 328 women in our study. Of those 51 (15.5%) fulfilled the criteria for GDM and 277 served as controls. The demographic characteristics of the study population are depicted in table 1. As expected, women with GDM were older and had a significantly higher body mass index (BMI) than those in the control group.

310 women had PlGF assessed at 11–14 weeks (50 with GDM), 131 had an additional PlGF measurement at 8+0 to 10+6 weeks gestation and 18 women had only a PlGF at 8–11 weeks, adding up to 149 patients with a PlGF measurement before 11 weeks gestation (28 with GDM).

HbA1c, always measured at the same time as the first drawn PlGF between 8+0 and 14 weeks gestation, was analyzed in 262 out of the 328 women.

In table 2 the results of first-trimester HbA1c and PlGF and PlGF MoM, dichotomized between women who did and those who did not develop GDM, are presented. PlGF was converted to MoM at 11–14 weeks only as there is too limited information on PlGF MoM before that gestational age. There was no difference in gestational age or crown-rump length between the groups. No difference was found comparing first-trimester PlGF between the groups (fig. 1), while HbA1c significantly discriminated between women who developed GDM and those who did not. There is no significant correlation between the absolute values of PlGF and HbA1c ($r = 0.09$, $p = 0.145$) or between PlGF MoM and HbA1c ($r = 0.08$, $p = 0.172$). Similarly, no correlation was found between HbA1c and PlGF in the GDM group only ($r = 0.20$, $p = 0.20$) or in the control group only ($r = 0.09$, $p = 0.55$).

Table 1. Maternal demographic characteristics in comparison between the GDM and the control group

	GDM (n = 51)	Control (n = 277)	p value
Maternal age, years	32.22±4.81	30.65±5.52	0.034*
Maternal BMI	27.02±6.32	23.1±4.34	<0.0001*
Nulliparity	17 (33.3%)	145 (52.3%)	0.015*
Maternal ethnicity			
White	33 (64.7%)	196 (70.6%)	0.409
Black	9 (17.6%)	43 (15.5%)	0.680
South Asian	6 (11.8%)	15 (5.4%)	0.114
East Asian	2 (3.9%)	18 (6.5%)	0.750
Mixed	1 (2.0%)	5 (1.8%)	1.000
Smoking	2	28	0.195
Chronic hypertension	1	4	0.573
Conception by ART	4	20	0.776
Outcomes			
GA at delivery, weeks gestation	38.56±1.90	39.54±1.52	0.0007*
Birthweight, kg	3.130±0.57	3.290±0.50	0.194
LGA (>90th percentile)	6.9%	4.5%	0.634

Comparisons between each outcome group with controls: all values are given as absolutes and percent or mean ± SD. χ^2 test and Fisher exact test for categorical variables and Mann-Whitney U test.

ART = Assisted reproductive technology; GA = gestational age; LGA = large for gestational age. * $p < 0.05$.

Table 2. Distributions of biochemical parameters in the GDM and in the control group

	GDM (n = 51)	Control (n = 277)	p value
Crown-rump length at 11–14 weeks, mm	64.49±8.33	65.17±8.23	0.602
GA at study inclusion, weeks gestation	10.8±1.46	11.21±1.53	0.094
PlGF, pg/ml			
At 8+0 to 14 weeks	34.30±18.65	36.10±24.47	0.818
At 11 to 14 weeks	44.13±21.23	44.95±24.75	0.729
At 8+0 to 10+6 weeks	23.44±8.41	24.13±9.90	0.926
PlGF MoM at 11 to 14 weeks	1.05±0.38	1.03±0.48	0.454
HbA1c, %	5.39±0.37	5.18±0.28	0.0007*

Comparisons between each outcome group with controls by Mann-Whitney U test: all values are given as mean ± SD.

GA = Gestational age. * $p < 0.05$.

Discussion

The incidence of GDM in our collective is in accordance with the described incidence of 17.5% (9.3–25.5%) in the IADPSG collaborating centers [18]. Our findings do not show any difference of first-trimester PlGF concentrations or their MoM between pregnant women who later developed GDM and controls, contradicting a recently published study that presented significantly higher first-trimester PlGF values in the GDM group [15]. The

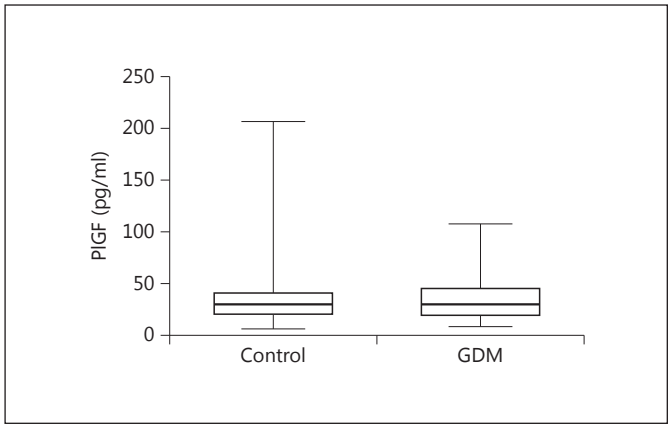

Fig. 1. Comparison of first-trimester PlGF concentrations in women with later GDM and in controls.

diagnosis of GDM in that study was also based on the HAPO criteria. However, no information was provided on how cases and controls were recruited.

Ong et al. [13] examined serum PlGF at 11–14 weeks gestation in 82 women with diabetic pregnancies consisting of 32 women with PGDM and 50 high-risk women with GDM diagnosed with a 75-g oGTT and by applying the World Health Organization criteria. They also found increased serum PlGF in PGDM, at least in the non-insulin-dependent subgroup. Newer data however found that serum PlGF was decreased in women with diabetes mellitus type 1 and in those with type 2 disease requiring treatment with insulin [14].

Eleftheriades et al. [15] explained their finding of higher first-trimester serum PlGF in pregnancies that later developed GDM by a hyperglycemia-induced alteration in placental angiogenesis. They based this assumption on a correlation they found between fasting oGTT glucose values and first-trimester PlGF concentration. It is well established that hyperglycemia affects angiogenesis [19]. In diabetic retinopathy VEGF is upregulated, while decreased VEGF levels contribute to impaired wound healing in diabetes [19]. Vasculogenesis and angiogenesis are essential for placental development and the VEGF family has been shown to play a key role [20]. Moreover, a recent meta-analysis of studies investigating postpartum placental histology derived from pregnancies complicated by PGDM or GDM demonstrates that there is increased placental volume, higher incidence of villous immaturity and increased angiogenesis [21]. Particularly the fetoplacental vasculature and endothelium were shown to be susceptible to hyperglycemia [22]. Fetal hyperinsulinism as a result of maternal hyperglycemia stimulates placental angiogenesis [23]. Therefore, an increase in angiogenic markers such as PlGF might be a consequence of these alterations. However, PlGF is not altered in umbilical cord blood serum of neonates born to diabetic mothers [24]. Moreover, Tsiakkas et al. [14] found that first-trimester maternal PlGF serum concentration was decreased in pregnancies complicated by diabetes mellitus type 1, and also in type 2 when treatment with insulin was required. Using three-dimensional sonography and power Doppler, it could be shown that first-trimester placental vascularization in pregnancies with PGDM is reduced, explaining in part the increased incidence of pregnancy-associated hypertensive disorders in diabetic pregnancies [25] and the lower first-trimester maternal serum PlGF found in both PE [26] and PGDM [14]. However, these findings also remain contradictory, as Cohen et al. [27], examining women with PGDM, could not demonstrate a difference in PlGF in early pregnancy in women who developed PE compared to women who remained normotensive or even compared to pregnant controls without diabetes, while later in pregnancy there was a significant change among the different groups.

A possible explanation for these divergent results in the literature and our findings might be that we excluded most of the possible cases with PGDM by screening for them using first-trimester HbA1c and excluding women with an HbA1c of ≥6.5% according to the recommendation of the American Diabetes Association [5] and the International Expert Committee on Diabetes [28]. However, even after excluding PGDM, there remain some first-trimester metabolic changes in pregnancies that will develop GDM, as HbA1c was elevated in our and other studies [7, 8]. The fact that we found no correlation between HbA1c and PlGF in the first trimester further lends support to the conclusion that PlGF in the first trimester is not a good marker for GDM.

In the time of turning the pyramid of obstetric care [29], early screening for GDM with timely intervention is desirable. Besides HbA1c, several first-trimester markers for GDM such as adiponectin, SHBG, TNRF1 and PAI2 have been described [30]. While first-trimester maternal serum PlGF is an excellent marker for PE [26], our results could not confirm any use of first-trimester PlGF in screening for GDM.

In conclusion, contradictory to previously published data, our results do not lend support to the theory that maternal serum PlGF is altered in the first trimester in pregnancies that will develop GDM. We also could not find any correlation between first-trimester HbA1c, in our study an early marker for GDM, and PlGF.

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Disclosure Statement

Analysis of PlGF was performed by L. Risch's laboratory.

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