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Association of Low Placental Growth Factor Gene Expression with Maternal and Neonatal Outcomes in Type 1 Diabetes: A Single Center, Cross-Sectional Study

ABSTRACT

Objective: The placental growth factor (PlGF) plays a crucial role in early and late pregnancy placental development. Pregestational type 1 diabetes (T1D) is a pregnancy complication that may lead to serious fetomaternal complications. Our study analyzed the association between placental PlGF mRNA expression and metabolic control, fetal weight and development in women with T1D.

Materials and methods: A cross-sectional study on 65 pregnant women with T1D in singleton pregnancies admitted to the tertiary-level perinatal care unit. The study examined associations between the placental mRNA-PlGF gene expression measured with quantitative real-time PC and markers of maternal metabolism in the third trimester. The expression was also compared across maternal subgroups stratified according to the birth weight (small- vs. appropriate- vs. large-for-gestational age; SGA, AGA, LGA, respectively) and the following neonatal outcomes: mode of delivery, Apgar score and pH in the umbilical vessels.

Results: Placental PlGF mRNA expression was significantly lower in SGA than in AGA and LGA patients (0.60 ± 0.34 vs. 0.63 ± 0.54 vs. 1.02 ± 0.15, respectively, $p < 0.05$). In the SGA group, the expression of the PlGF-mRNA correlated positively with maternal 3rd trimester BMI ($r = 0.49$, $p = 0.04$), pH and BE cord blood values, and maternal 3rd trimester mean BP. There was no correlation between 3rd-trimester glycated hemoglobin and mean blood glucose levels (MBG) and PlGF expression.

Conclusions: Our data suggest that lower PlGF mRNA expression may predict neonatal outcomes in women with T1D giving birth to SGA newborns. (Clin Diabetol 2023; 12; 1: 38–44)

Keywords: diabetes, pregnancy, glycemia, placenta, growth factor, fetal weight

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Introduction

Pregnancy complicated by type 1 diabetes (T1D) is still associated with an increased risk of severe maternal

and fetal complications. Maternal glycemic control in the mother deeply impacts the proper fetal development. Various maternal blood-released substances related to metabolic processes can be used to indicate fetal and newborn status.

The placental growth factor (PlGF) is a molecule encoded in humans by the PlGF gene [1]. The PlGF gene is located on chromosome 14q14 and encodes four isoforms of PlGF [1, 2]. The placental growth factor belongs to the family of vascular endothelial growth factors (VEGF). This protein plays a key role in angiogenesis, particularly in vasculogenesis which is vital during human embryogenesis [3]. The main source of PlGF in humans is a placental trophoblast. The expression of PlGF under physiological conditions has been demonstrated at a low level in many other tissues such as the thyroid gland, heart, prostate, lung or skeletal muscles [1, 4].

Mechanisms by which PlGF expression is regulated are still investigated, but it has been proved that PlGF plays a significant role in trophoblast growth and differentiation. These processes are essential in proper embryonic development [2]. The PlGF and its soluble receptor sFlt-1 (soluble fms-like tyrosine kinase-1) are circulating angiogenic factors released into the maternal circulation during pregnancy from the placenta [5]. Many authors reported that serum levels of PlGF and sFlt-1 are altered in women with preeclampsia. Placental expression of sFlt-1 was significantly increased, but PlGF decreased in preeclamptic women compared to subjects with uncomplicated pregnancies [5]. These data support the hypothesis that placental concentrations of these proteins mirror the maternal serum changes and confirm that the placenta is the main source of sFlt-1 and PlGF during pregnancy.

Some findings support the role of PlGF in the pathogenesis of atherosclerotic disease and neovascularisation [6, 7]. Most studies suggest that PlGF is a potential biomarker of preeclampsia and intrauterine growth restriction (IGR) [2, 8]. Patients with a medical history of hypertensive disorders and low PlGF levels in the early second trimester have an increased risk for preeclampsia [9]. It was demonstrated that in patients with low levels of PlGF, trophoblastic villi invasion into the maternal arcuate arteries might be impaired, resulting in inappropriate vascular differentiation. This contributes to the abnormal placental vascular structure resulting in vessel narrowing, causing a high blood pressure — the main symptom of preeclampsia.

However, it remains unclear whether this biomarker could be useful for predicting the newborn's condition [10].

To our knowledge, there are no studies on the role of PlGF expression in women with T1D investigating any relationship between this biomarker and newborn weight and condition. Since the PlGF as vascular factor has the potential role in vessels' development and the T1D with/without vascular complications may have a role in fetal growth and condition — we decided to study the role of this placental molecule in the specified group of pregnant women. We aimed to determine the expression of PlGF in the placentas of women with T1D and assess its relation to metabolic control during pregnancy, fetal development and neonatal condition. Moreover, we attempted to verify the hypothesis of whether the PlGF gene expression is or is not correlated with maternal metabolic control in the course of pregnancy in women with T1D.

Materials and methods

The study protocol was described in detail elsewhere [11]. The study included 65 pregnant women with T1D and singleton pregnancy, hospitalized in a tertiary level perinatal care unit in the Department of Obstetrics and Women's Diseases of the Poznań University of Medical Sciences in Poznań, Poland. The study group was offered a routine follow-up, including at least three visits to the Department (11–14 weeks, 18–24 weeks, 28–32 weeks and close to delivery) and regular checkups in our outpatient clinic, according to Polish recommendations [12]. During every visit, all pregnant women participated in training about intensive insulin therapy, optimal diet, and blood glucose self-control. We collected data from general, obstetrical, and T1D history, including age at onset, duration of diabetes and the presence of the vascular complications before pregnancy. Glycemic/lipid profile, as well as blood pressure and HbA1c concentration, was retrieved from patient records. All the subjects had a retinal examination and renal function checked once a trimester. All participants were treated with insulin analogs following a basal-bolus protocol. All the doses were adjusted to meet the target glucose values set for the pregnant population at 3.88–5.0 mmol/L for fasting glycemia and less than 6.67 mmol/L for 2 hours postprandial glucose level, according to the local recommendations [12]. All biochemical parameters were analyzed in the Central Laboratory of the University Hospital, holding ISO 9000 quality certificate.

We examined placentas from 65 normotensive Caucasian subjects with T1D. Placental tissue was obtained immediately after placenta delivery, cleaned from amniotic membranes and maternal deciduae, rinsed in saline, snap-frozen in liquid nitrogen, and stored at –80°C until assayed. To examine the PlGF gene expres-

sion, the study group was divided into three subgroups according to neonatal birth weight (NBW): 1 subgroup — neonatal birth weight < 10 percentile (SGA — Small for Gestational Age), two subgroups — neonatal birth weight between 10–90 percentile (AGA — Appropriate for Gestational Age), three subgroup — neonatal birth weight exceeding 90 percentile (LGA — Large for Gestational Age, macrosomic). All participants gave informed consent, and the study protocol obtained approval from the Ethics Committee of Poznań University of Medical Sciences. We also affirm that the Declaration of Helsinki has carried out original studies.

RNA extraction and cDNA synthesis

Total cellular RNA was isolated from the placenta tissue using TriPure Isolation Reagent (Roche, Germany) according to the manufacturer's protocol. The concentrations and the purity of RNA were determined using a NanoDrop spectrophotometer (Thermo Fisher Scientific Inc., USA). RNA samples were stored at –80°C. Complementary DNA was synthesized from 2 μg of total RNA in a total volume of 20 μL using the Transcriptor First Strand cDNA Synthesis Kit (Roche, Germany). The transcripts were stored at –20°C or used directly for the real-time quantitative PCR (RT-PCR).

Real-time PCR

The level of mRNA expression was analyzed using the RT-PCR method. The primer sequences used for the analysis of PlGF and GAPDH genes were as follows: PlGF Forward: GTT CAG CCC ATC CTG TGT CT, PGF Reverse: CTT CAT CTT CTC CCG CAG AG, GAPDG Forward: GAA GGT GAA GGT CGG AGT C, GAPDH Reverse: GAA GAT GGT GAT GGG ATT TC. The primers for PGF and GAPDH were synthesized by TIB Molbiol (Poznań, Poland). Amplicon size and reaction specificity were confirmed by agarose gel electrophoresis and melting curve analysis. RT-PCR was carried out using a LightCycler®480 Instrument (Roche, Germany) and a LightCycler® 480 SYBR Green I Master (Roche, Germany) according to the manufacturer's protocol. GAPDH was used as a housekeeping gene for normalization (endogenous internal standard). The PCR program was initiated with activation at 95°C for 10 min. Each PCR cycle comprised a denaturation step at 95°C, an annealing step at a specific temperature and an extension step at 72°C. The quantitative PCR was monitored by measuring the increase in fluorescence by binding SYBR Green I dye to the generated double-stranded cDNA. All samples were run in duplicate using the LightCycler®480 Instrument, and the melting curves were analyzed using the LightCycler®480 Basic Software.

Table 1. Characteristics of the Study Group

Characteristics (total n = 65)	
Maternal	
Age [years]	28.7 ± 5.1
Duration of diabetes [years]	14.1 ± 10.9
Nulliparity, N (%)	48 (73.8)
Mode of delivery, N (%)	
Vaginal	11 (17.0%)
Cesarean section	53 (81.5%)
Other	1 (1.5%)
Newborn	
Birth weight [g]	3382.6 ± 783.1
Placental weight [g]	633.6 ± 168.2
Apgar score at 1 min. [median, min–max]	9 [4–10]
Apgar score at 5 min. [median, min–max]	10 [6–10]
Percentiles for birth weight by gestational age	
SGA — below the 10th percentile for the age and sex	19 (29.2%)
AGA — between 10th and 90th percentile for the age and sex	30 (46.2%)
LGA — above the 90th percentile for the age and sex	16 (24.6%)

Values are means ± SD or N (%)
AGA — appropriate for gestational age, LGA — large for gestational age; SD — standard deviation; SGA — small for gestational age

Statistical analysis

We performed a statistical analysis using Statistica 12.0 for Windows. All data are presented as mean ± standard deviation (SD). The normality of data distribution was checked with the Kolmogorov-Smirnoff test. As the distribution of variables met the criteria for normal distribution, we compared the PlGF gene expression using analysis of variance (ANOVA) for more than two groups and a post-hoc test (Fisher LSD — Least Significant Difference) to specify the groups in which the differences are significant. Statistical significance was established at $p < 0.05$ for all comparisons.

Results

Table 1 shows the descriptive characteristics of 65 studied women-newborns pairs. The mean age was 28.7 ± 5.1 years with a 73.8% rate of nulliparity. The average duration of diabetes was 14.1 ± 10.8. Table 2 presents maternal metabolic parameters, placental PlGF mRNA expression, birth weight, and percentiles in studied groups at delivery time.

The patients who delivered LGA neonates had the poorest 3rd-trimester metabolic control.

Table 2. Maternal Metabolic Parameters, Placental PlGF Expression and Neonatal Birthweight in the Cohort at Delivery

Parameter	T1D SGA N = 19[A]	T1D AGA N = 30[B]	T1D LGA N = 16[C]	P-value*
Mean diurnal glycemia at delivery [mmol/L]	5.34 ± 0.99	4.81 ± 1.25	5.52 ± 0.91	< 0.05[1]
HbA1c at delivery [%]	5.7 ± 0.9	6.2 ± 1.7	7.1 ± 1.5	< 0.05[2]
BMI at delivery [kg/m^2]	29.1 ± 8.1	28.1 ± 6.3	24.9 ± 5.6	NS
Total cholesterol at delivery [mmol/L]	5.26 ± 1.12	5.11 ± 0.33	5.62 ± 0.87	NS
Total triglycerides at delivery [mmol/L]	1.89 ± 1.65	1.91 ± 0.55	1.92 ± 0.76	NS
HDL at delivery [mmol/L]	1.95 ± 0.56	2.71 ± 0.62	2.18 ± 0.82	NS
LDL at delivery [mmol/L]	3.18 ± 0.91	3.03 ± 0.87	3.92 ± 0.53	< 0.05[3]
GFR at delivery [mL/min]	90.11 ± 51.20	92.71 ± 38.24	116.21 ± 45.26	NS
Neonatal birth weight [g]	2450 ± 340	3430 ± 260	4420 ± 230	< 0.05[4]
Gestational age at delivery [weeks]	37 ± 2	37 ± 1	38 ± 1	NS
pH umbilical artery	7.29 ± 0.10	7.21 ± 0.18	7.21 ± 0.14	NS
pH umbilical vein	7.25 ± 0.10	7.28 ± 0.12	7.28 ± 0.15	NS
Placental PlGF	0.60 ± 0.34	0.63 ± 0.54	1.02 ± 0.15	< 0.05[5]
Placental mass	510 ± 130	648 ± 130	790 ± 130	< 0.05[6]

*ANOVA, post-hoc LSD; [1]C vs. B; [2]A vs. C; [3]B vs. C; [4]Significant in all groups; [5]C vs. A, B; [6]Significant in all groups
AGA — appropriate for gestational age; BMI — body mass index; GFR — glomerular filtration rate; HbA1c — glycated hemoglobin; HDL — high density lipoprotein; LDL — low density lipoprotein; LGA — large for gestational age; PlGF — placental growth factor; SD — standard deviation; SGA — small for gestational age; T1D — type 1 diabetes

Table 3. Correlations between Placental Growth Factor Expression and Selected Feto-Maternal Parameters in the Type 1 Diabetes Women

Variables	Spearman Rank			
	N	R Spearman	t(N-2)	p
3rd-trimester HbA1C vs. PlGF (whole group)	65	-0.051	-0.38	0.705
3rd-trimester MBG vs. PlGF (whole group)	65	-0.06	-0.42	0.674
pH_vein vs. PlGF (SGA group)	19	0.38	3.14	**0.003**
BE_vein vs. PlGF (SGA group)	19	-0.04	-0.31	0.045
pH_artery vs. PlGF (SGA group)	19	0.31	2.40	**0.020**
BE_artery vs. PlGF (SGA group)	19	0.18	1.39	0.171
3rd-trimester BP_Sys vs. PlGF (SGA group)	19	-0.25	-2.01	**0.049**
3rd-trimester BP_Dia vs. PlGF (SGA group)	19	-0.17	-1.31	0.195
3rd trimester BMI vs. PlGF (SGA group)	19	-0.24	-1.90	**0.042**
3rd-trimester weight vs. PlGF (SGA group)	19	-0.24	-1.94	0.060

BE — base excess; BP — blood pressure; HbA1c — glycated hemoglobin; MBG — mean blood glucose; PlGF — placental growth factor; SGA — small for gestational age

We also analyzed maternal factors that may affect the placental mRNA PlGF in the whole study group and separately in the AGA, LGA, and SGA subgroups). For this analysis, we used the third-trimester biochemical parameters and blood pressure values as explanatory variables and newborn status after delivery as the outcome. Results are presented in Table 3, Figures 1 and 2. We noted that T1D women, who delivered SGA neonates, had the lowest placental mRNA PlGF expression and placental mass. In contrast, participants who gave birth to the LGA babies had the highest placental PlGF expression.

All calculations were performed for the whole T1D group and separately for each subgroup defined for the birthweight as mentioned above. Neither in the whole study group nor the subgroups defined according to the birth weight there was a significant relationship between placental mRNA PlGF expression and 3rd--trimester metabolic parameters of maternal metabolic status and glycemic control (3rd-trimester MBG, HbA1c, $p = 0.674063$ and $p = 0.705239$, table data).

Regarding the neonatal status parameters, we found a significant correlation between placental

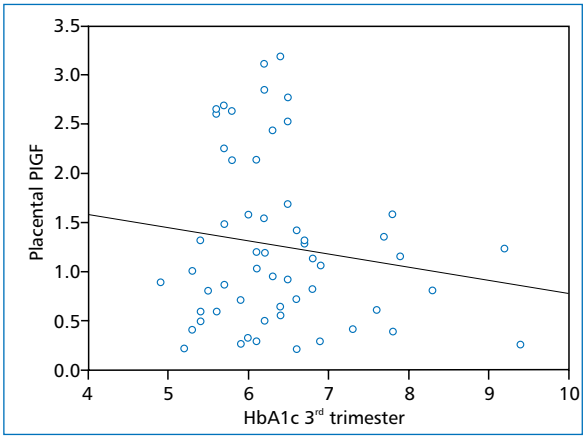

Figure 1. No Correlation between Maternal 3rd-Trimester HbA1c and Placental mRNA PlGF in the Whole T1D Group (R = –0.05, p = 0.705)
HbA1c — glycated hemoglobin; PlGF — placental growth factor; T1D — type 1 diabetes

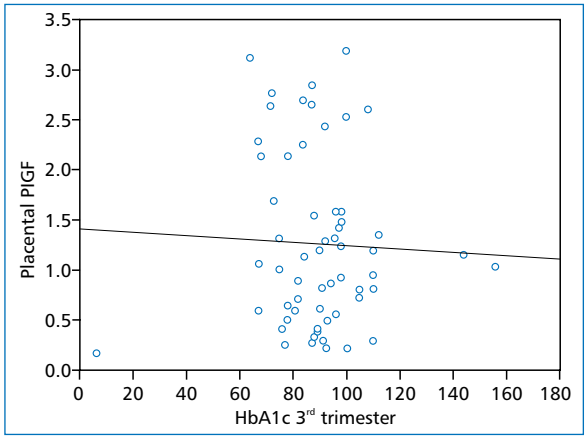

Figure 2. No Correlation between Maternal 3rd-Trimester MBG and Placental mRNA PlGF in the Whole T1D Group (R = –0.06, p = 0.674)
MBG — mean blood glucose; PlGF — placental growth factor; T1D — type 1 diabetes

mRNA and PlGF expression in the SGA T1D subgroup. In the SGA T1D subgroup, we discovered a negative correlation between low placental mRNA PlGF expression and the following parameters: venous pH, BE, and arterial pH. We also found that low placental mRNA PlGF expression was negatively related to maternal BMI (R = –0.24, p = 0.042). We also noted a trend for a negative relationship between the biomarker and the maternal 3rd-trimester body weight (R = –0.24, p = 0.06). There was also a significant negative correlation between maternal 3rd trimester systolic BP and placental mRNA PlGF in the same group of women (R = –0.25, p = 0.05). The analogical calculations conducted in the AGA and LGA T1D subgroups revealed no significant correlations.

Discussion

Every pregnancy affected by T1D should be perceived as high-risk and demands more attention than the pregnancy in a healthy woman. Type 1 diabetes in pregnant women increases the risk of adverse outcomes for mother and offspring [13].

Generally, a wide range of maternal factors regulates fetal growth throughout gestation. The most significant ones include glycemic control, pregnancy weight gain, energy intake, lipid profile, and other concomitant maternal diseases such as hypertension, preeclampsia, cardiovascular disease, or thyroid dysfunction. [14–17]. Earlier studies have demonstrated decreased maternal serum PlGF concentrations in preeclampsia in T1D pregnancy [18–22].

We have already conducted several studies on leptin and VEGF's possible role in fetal growth [11, 15]. Both substances play a significant role in proper pregnancy courses. Nevertheless, in this study case, we also aimed to assess placental growth factor (PlGF) expression and its impact on fetal development, which seems vital, especially regarding proper placenta development.

In normal pregnancy, levels of PlGF increase during gestation, with a peak at approximately 26–30 weeks [23]. On the contrary, decreased levels of PlGF have been found throughout gestation associated with preeclampsia [23–26]. Authors still consider if PlGF can be perceived as a first-trimester predictor of preeclampsia because its levels have been reported to be lowered in the group of women who subsequently developed preeclampsia [23]. Another study reported low PlGF concentrations as a negative predictor for intrauterine fetal death [26].

According to many previous studies, body mass index (BMI), caffeine intake, race or smoking may alter PlGF levels in pregnancy [27, 28].

The fact that the expression of PlGF has been confirmed in various human tissues suggests its diversified role in the human organism. There is a lack of studies on the relationships between placental growth factor expression and T1D pregnancy. In our study, we observed that expression of PlGF is strongly connected with maternal parameters in the 3rd trimester, like body mass index (BMI) and systolic and diastolic blood pressure.

A recent paper from the American Journal of Obstetrics & Gynecology suggests that, in women with suspected preeclampsia, low PlGF levels identify those at high risk for adverse perinatal outcomes, irrespective of a final diagnosis of preeclampsia [29].

Another study from Parchem et al. proved that abnormal PlGF levels were associated with a significant increase in the risk of adverse neonatal and maternal outcomes amongst women with suspected preeclampsia. It was found that abnormal plasma PlGF was significantly associated with the composite adverse neonatal and maternal outcomes, respiratory distress syndrome, SGA, and preterm or cesarean delivery [30]. Rouf et al. [31] documented that long-term hyperglycemia may significantly impair PLGF expression and arteriogenesis in T1D skeletal muscle.

In our study, we found that the lowest PlGF expression was present in women with the poorest blood pressure values in 3rd trimester of pregnancy. We conclude that it relates to the impaired process of placenta formation at the early pregnancy.

The studies on the placental PlGF expression in T1D pregnancy are inconsistent. In our paper, we conclude that in T1D pregnancy, placental growth factor expression is related to fetal weight, independently of maternal 3rd-trimester glycemic control. Interestingly, in the study of Gutaj et al. [32], in T1D pregnancies, decreased serum PlGF concentrations in SGA fetuses were found compared to non-SGA fetuses. On the other hand, in the Loukovaara et al. [33] cord serum paper, PlGF concentration was similar in normal pregnancies, in pregnancies complicated by T1D and in pregnancies complicated by insulin-treated — gestational, and cord serum PlGF did not correlate with relative birthweight. Another study proved that PlGF mRNA and protein levels are increased in FGR placentae [34].

Our study found that women with the highest 3rd trimester BMI similarly presented the lowest PlGF expression values. Moreover, we found a consistent correlation between PlGF expression and umbilical artery and venous pH and BE variables. As umbilical artery gas variables mainly reflect fetal oxygenation during labor, our results indicate that PlGF levels reflect the level of fetal hypoxia. Therefore, we assume that PlGF expression might be related to fetal well-being.

Interestingly, but similarly to our previous papers is that no other correlations were found between the 1st and 2nd-trimester maternal factors in the entire T1D group [32]. We suspect that the number of subjects should be increased and re-analyzed. Little is known about the role of PlGF expression amongst T1D subjects, and this topic should be further evaluated.

In conclusion, our study indicates that placental PlGF gene expression might be related to neonatal status but not maternal metabolic control in T1D pregnancy but there are several limitations of the study such as: single center study, cross-sectional study and therefore, it does not provide causal association, small sample size. There also was no priori hypothesis with sample size calculations and therefore, these findings must be interpreted with cautions. Also generalization may be limited due to single center and inclusion of only Polish women with type 1 diabetes. In the next step of the present study we will aim to compare our results with the subgroup of the healthy pregnant women.

Conflict of interest

None declared.

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