

## Short Research Report

### **Placental volume relative to fetal weight estimated by sonography in diabetic pregnancies**

**Running headline:** Feto-placental growth in mid-pregnancy complicated by diabetes mellitus

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## **Abstract**

Our purpose was to analyze the placental volume and fetal weight ratio in diabetic pregnancies during mid-pregnancy. Fifty-four diabetic pregnancies (27 gestational diabetes mellitus (GDM) and 27 diabetes mellitus (DM) type I with good glycemic control) and three-hundred and sixteen healthy cases were analyzed by three-dimensional sonographic volumetry of the placenta, while fetal weight was estimated by two-dimensional technique. The gestational age-specific estimated fetal weight and placental volume-to-fetal weight ratio was significantly higher in GDM pregnancies, whereas placental volume in GDM was similar compared to control data. DM with good glycemic control did not predispose to any changes in sonographic volumetric differences compared to control values. The disproportional placental growth correlated to fetal growth takes place in the second trimester in GDM, whereas DM with good glycemic control does not pose a significant risk of unequal feto-placental development in mid-pregnancy.

*Keywords: gestational diabetes mellitus, pregnancy; estimated fetal weight, placental volume, three-dimensional ultrasound*

*Abbreviations:* DM type I: diabetes mellitus type I; EFW: estimated fetal weight; GA: gestational age; GDM: gestational diabetes mellitus; PV: placental volume; s: second; 2 or 3-D: two or three dimensional

## **Introduction**

The placenta has a limited lifespan which significantly determines the fetal growth, since placental weight is strongly associated with the fetal and neonatal weight (1-3). Placental volumetry is the most common way to characterize placental growth and it is a summary of many dimensions of placental growth. Diabetic state has a profound effect on the microvasculature of developing placenta leading to increased volume of terminal villi and to non-branching angiogenesis in type I diabetes (DM type I) (4-5) or to degenerative lesions induced by chronic hypoxia in gestational diabetes mellitus (GDM) (6) irrespective of the adequacy of glycemic control (5).

The prevalence of GDM and DM type I has increased over the past decade. DM affects 0.5% of singleton pregnancies, whilst the prevalence of GDM is 1% (1) - 8.7% (7). It is well established that a higher risk of large for gestational age infants and heavier placentas are associated with maternal diabetes (1,8), but in a recent study was published that placental weight-to-birth weight ratio is also higher among them (1). However, large placentas related to birth weight is associated with more adverse perinatal outcome (1,2), however it is unclear when this disproportional ratio appears during pregnancy complicated by diabetes.

Therefore we aimed to describe the changes of placental growth and its relation to fetal growth by gestational age (GA) in gestational diabetes, DM type I and in healthy pregnant women. We studied both types of diabetes combined, and we also made separate analyses for DM and GDM pregnancies in relation to gestational age.

The control group consisted of 316 women and besides 54 pregnant women with diabetes (27 had DM type I and 27 had GDM) were enrolled in the study and the studied factors were as follows: estimated fetal weight (EFW), placental volume (PV) and placental ratio (PR) as defined by EFW/PV (1). Inclusion and exclusion (e.g. preeclampsia, assisted reproductive technology) criteria, diagnostic requirements for diabetes, determination of gestational age, fetal biometry and Doppler artery flowmetry in uterine and umbilical arteries were described in our previous article (9). After standard 2-D measurements were taken, a 3-D sweep was performed through the placenta by a Voluson 730 ultrasound machine (Voluson 730 system, RAB 2-5 MHz probe, and 4D View version 10.4 program; GE Healthcare, Kretztechnik, Zipf, Austria) during a period of maternal apnoea and fetal rest. The entire view of the placenta was identified by two-dimensional ultrasound, and the volume box was adjusted to involve the entire placenta. The angle of volume acquisition varied between 45° and 70° according to placental size. The volume acquisition was obtained at 'maximum' speed and its duration was below 10 seconds keeping the probe perpendicular to the placental plate. A multiplanar technique was applied and after the entire volume was scanned, the 3-D volumetric data were stored on a removable hard disk. The longest view of the placenta on plane 'A' was chosen as reference image. The same pre-established instrument settings were used in all the cases (power 96%; frequency low; quality normal, density 6, ensemble 16; balance 150; filter 2; smooth 3/5; pulse repetition frequency 0.9 kHz). Each image was recovered from the disk in succession for processing. The stored volumes were further analyzed using the virtual organ computer-aided analysis (VOCAL) program pertaining to the computer software 4D VIEW (GE Medical Systems, Austria, version 10.4) , which consists of

outlining the contour of the placenta repeatedly after rotating its image 6 times by 30°, with careful attention to exclude decidua and maternal blood vessels. After the complete rotation was finished, the placental volume was automatically calculated by the software. For each patient, placental volumes were measured 3 times by a specifically trained sonographer (A.S.) to eliminate inter-observer error.

Statistical Package for the Social Sciences was utilized for Mann-Whitney U-probes and adjustments were made by multiple logistic regressions. The associations between PV, EFW and PR and 2-D color Doppler indices (pulsatility (PI) and resistance indices (RI) of umbilical and uterine arteries) were determined by Spearman's rank correlations. The local medical ethics committee of University of Szeged approved the study.

When the two diabetic groups were analyzed combined, the case and the control group were satisfactorily comparable in relation to maternal (range: 20-39 years) and gestational age (range: 10<sup>+0</sup>-28<sup>+2</sup> weeks) ~~as well as, whereas~~ pregestational BMI (Table 1). ~~Although all the studied sonographic parameters (EFW, PV and PR) were similar higher in the diabetes group, they and~~ were not significantly different ~~in the diabetes and in the from the~~ control group (p=0.904662, p=0.07681 and p=0.645154, respectively). If the comparison of these modalities were adjusted for gestational age and BMI, it resulted in an unchanged pattern (p=0.89902, p=0.73421, p=0.88930; respectively). Diabetes subgroups analyzed separately exhibited the following results concerning GDM vs. control group: EFW: 40013±28966 vs. 28872±18593 grams, p=0.274006; PV: 253300±319 vs. 1889±1198cm<sup>3</sup>, p=0.046001 and PR: 0.6396±0.2285 vs. 0.7586±0.4463 cm<sup>3</sup>/gram, p=0.29167) and regarding DM type I vs. control group: (EFW:

27223±2174 vs. 288±185272±193 grams, p=0.01211; PV: 18755±99466 vs. 188±119cm<sup>3</sup>189±118 cm<sup>3</sup>, p=0.667222 and PR: 0.856±0.2976 vs. 0.75±0.440.86±0.63 cm<sup>3</sup>/gram, p=0.034791). After adjustment for gestational age and BMI in the analyses, a different pattern could be observed in ~~GDM-DM type I~~ vs. control group (EFW: p=0.805017; PV: p=0.48475 and PR: p=0.39901) and in ~~GDM-DM type I~~ vs. control group (EFW: p=0.825502; PV: p=0.798970 and PR: p=0.441701).

PVs and EFWs were plotted against gestational age, which showed exponential trend lines (Figure 1), which are acceptable according to our previous study (10). The rise of placental volume and fetal weight curves was the highest in DM type I, whereas trend lines of GDM and control groups were below that of DM type I.

PR was significantly correlated only to the resistance index of the uterine artery (p=0.007, r: 0.479) among 2-D color Doppler indices of the uteroplacental arteries.

## Discussion

In this sonographic study of singleton pregnancies, the estimated placental volumes and fetal weights are higher in pregnancies with diabetes, but not significantly different from the values of healthy control cases during mid-gestation. Thus a minimally higher placental ratio is characteristic for diabetes between 10<sup>+0</sup>-28<sup>+2</sup> weeks of gestation. Since the placental and fetal weight is increasing exponentially by length of gestation based on our present results, our data were adjusted for gestational age, and there was no significant difference between the tendency of the growth of placenta and fetus in maternal diabetes compared to the control cases during mid-pregnancy.

Our data may be consistent with the report stating that diabetic mothers have larger placenta at birth, their offsprings' weight and placental ratio are increased (1,6). We suggest that the disproportional fetal growth correlated to placental development in diabetes might occur generally in late pregnancy.

Interestingly, when associations were checked in the diabetic subgroups, the infants in DM type I pregnancies were found to be larger and the corresponding placental weight was just minimally-higher than those in the control group, whereas the GDM trend lines are similar to those of the control group. These results are also in line with the results of *Stor-Røum et al.* (1), who claimed that the DM type I pregnancies have the largest placentas at birth, followed by pregnancies in GDM and normal population. These facts advocate that the excessive placental growth is already measurable in the mid-pregnancies of expectant mothers with diabetes type I, whereas the disproportionate growth of the fetus and placenta might appear only in the late pregnancy in case of GDM. This is indicated by the fact that the diabetic trend lines are increasing more precipitously in the end of the studied period than trend lines of the control group. This is also in accordance with the conclusions of our former study (10), that placental growth is more significant in the latest phase of the gestation. In addition, our present study is also in conformity with the only one study so far representing evidence on minimally increased placental volumes *in utero* in DM type I compared to pregnancies in the control group (8), but this latter study was restricted to a gestational age between 11<sup>+0</sup> and 13<sup>+6</sup> weeks. The placental volume does not correspond notably to uteroplacental flow, which is also demonstrated earlier in normal pregnancies (11) and even in diabetic pregnancies (9). It is noteworthy, that our sample is collected based on the new principles of criteria of

diabetes, whereas there has not been reported any reports on placenta ratio according to the new guidelines.

Although a relative small number of participants were investigated in the present study, the prevalence of diabetes is low in the pregnant population (particularly diabetes type I) and this may allow to draw definitive conclusions. Our results demonstrate that it would be useful to improve our understanding on the pathophysiological constraints in diabetes in early and mid-pregnancy. Patient with diabetes type I were involved in our study, because in this case the sensitivity and specificity is high (the validity of diabetes type II may be uncertain which can cause possible misclassification) (1). A well-known technical limitation of placental volumetry is that a minority of placentas can be visualised entirely at late gestation, so we could not estimate placental volumes in the third trimester (10).

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## **Conflict of interest**

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

Table 1. Demographic and ultrasound characteristics of the study groups. Data are presented as

	mean±standard deviation.		
	Diabetic group (N=54)	Control group (N=31924)	p value
Maternal age (years)	31.2744±3.951	31.3593±63.9187	0.514891
Maternal pregestational BMI (kg/m <sup>2</sup> )	278.439±6.782.40	217.7591±1.842.32	<0.0010.761
Gestational age at the time of ultrasound examination (weeks)	19.38±4.31	18.43±3.813	0.375099
Estimated fetal weight (grams)*	35018.2845±26882.6319	2871.6976±18593.0846	0.904662
Placental volume (cm <sup>3</sup> )**	227.38±152.03	188.2266±118.5430	0.07681
Placental ratio (cm <sup>3</sup> /g)***	0.79183±0.272534	0.753857±0.444627	0.645154

\* Estimated fetal weight based on Hadlock 'B' formula (Hadlock)

\*\* measured with the help of 4D View program (VOCAL technique)

\*\*\* Placental ratio: placental volume relative to the estimated fetal weight

Figure 1. Sonographic characteristics in the study groups

