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# Postpartum placental CT angiography in normal pregnancies and in those complicated by diabetes mellitus

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ABSTRACT

*Introduction:* Pregnancy complicated by diabetes mellitus (DM) is a central obstetric problem often complicated by fetal macrosomia and increased risk of intrapartum asphyxia. This risk might be explained by fetoplacental vascular abnormalities. This study aimed to investigate the fetoplacental vascular volume by placental CT angiography in normal pregnancies and in pregnancies complicated by type 1 DM (T1DM), diet controlled gestational DM (GDMd), and insulin treated gestational DM (GDMi).

*Methods:* Postpartum, barium contrast enhanced placental CT angiography was performed in 27 normal pregnancies and 25 DM pregnancies (8 T1DM, 8 GDMd, and 9 GDMi). The fetoplacental vascular volume/placenta weight (FVV/PW)-ratio and fetoplacental vascular volume/birth weight (FVV/BW)-ratio of each diabetic group were compared to the normal group with multiple regression analysis adjusted for GA. In all pregnancies a standardized histopathological placental examination was performed postpartum.

*Results:* In normal pregnancies, the fetoplacental vascular volume increased with GA ($p < 0.001$), placental weight ($p < 0.001$), and birth weight ($p < 0.001$). In T1DM and GDMi pregnancies, the gestational age adjusted placental weight and the birth weight were increased when compared to normal pregnancies ($p < 0.05$). The FVV/BW-ratio was significantly reduced in both T1DM and GDMi pregnancies when compared to normal pregnancies ($p = 0.003$ and $p = 0.009$, respectively).

*Discussion:* This study demonstrates, that in insulin treated DM pregnancies the fetus as well as the placenta is larger than normal. However, despite a large placenta, a relatively smaller fetoplacental vascular volume supplies the macrosomic fetus. This finding might explain why fetuses from insulin treated DM pregnancies have high vulnerability to intrauterine and intrapartum asphyxia.

## 1. Introduction

Pregnancies complicated by diabetes mellitus (DM), both type 1 DM (T1DM) and gestational DM (GDM), are a central obstetric challenge, as the fetal and maternal morbidity and perinatal mortality is high [1]. It is well described that DM pregnancies are associated with neonatal complications such as fetal macrosomia, perinatal asphyxia, and metabolic syndrome in later life [1]. The increased risk of intrauterine and intrapartum asphyxia in pregnancies complicated by DM may partly relay on the increased metabolic demand of the macrosomic diabetic fetus and a decreased transplacental oxygen transfer capacity due to altered oxygen binding capacity of hemoglobin [2]. However fetoplacental vascular abnormalities related to DM may also contribute to the increased risk [3–5].

It is known that DM pregnancies are associated with increased placental weight and birth weight and an increased birth weight/

*Abbreviations:* CTA, Computed tomography angiography; DM, diabetes mellitus; GDMd, diet controlled gestational diabetes mellitus; FVV/BW-ratio, fetoplacental vascular volume/birth weight-ratio; FVV/PW-ratio, fetoplacental vascular volume/placenta weight-ratio; GA, gestational age; GDMi, insulin treated gestational diabetes mellitus; MRA, magnetic resonance angiography; T1DM, type 1 diabetes mellitus

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placental weight-ratio [6]. Current knowledge on the fetoplacental vasculature in DM pregnancies is based on macroscopic examinations [7], histomorphometry [3,8–16], stereology [4,17–20], x-ray angiograms [21], and measurements of the placental residual blood volume after birth [22]. In T1DM pregnancies conflicting results are demonstrated as some studies describe an increased fetoplacental vascular volume, surface area, and capillary length compared to normal [3,4,8,9,17–19,22], while others describe decreased vessel diameter and number of vessels [7,10–15,21]. Also in GDM pregnancies, existing knowledge on the fetoplacental vasculature demonstrates conflicting results with studies reporting increased vascular volume [15], surface area [15], and number of vessels [12,23] as well as decreased number of vessels [20,24]. The inconsistent findings in the literature may be explained by differences in glycemic control, treatment regime, and lack of methods to demonstrate vascular pathology [25].

Imaging technologies such as placental computed tomography angiography (CTA) and magnetic resonance angiography (MRA) have a great potential to investigate the fetoplacental vasculature in three-dimensions (3D). By using these methods the fetoplacental vasculature has been investigated in normal pregnancies [26–30], however to the best of our knowledge CTA has never been performed in pregnancies complicated by different types of DM.

To improve our understanding of the perinatal risk of asphyxia associated with DM, a better knowledge of the fetoplacental vasculature is essential. Therefore this study aimed to investigate the fetoplacental vascular volume by using postpartum 3D placental CTA in normal pregnancies in comparison to pregnancies complicated by DM (T1DM, diet controlled GDM (GDMd), and insulin treated GDM (GDMi)).

## 2. Methods

Twenty-five placentas (35–41 weeks' gestation) from singleton pregnancies complicated by DM (8 T1DM placentas, 8 GDMd placentas, and 9 GDMi placentas) were included in the study [31,32]. 32 placentas (30–42 weeks' gestation) from normal singleton pregnancies constituted the control group. We excluded stillbirths, abnormal fetal karyotype or congenital malformations, and pregnancies with clinical signs of placental insufficiency (umbilical artery Doppler flow Pulsatility index (PI)) Z-score ≥ 2 [33], cerebroplacental Doppler ratio Z-score ≤ −2 [34] and birth weight ≤ −22% [35]. All placentas were collected at Aalborg University Hospital, Denmark, between July 1st, 2015 and December 1st, 2016. The Danish National Ethics Committee (N-20150018) and the Danish Data Protection Agency (2008-58-0028) approved the study, and all participants gave oral and written informed consent. Maternal and pregnancy characteristics are presented in Table 1. Data were collected from medical records and the electronic ultrasound database Astraia version 1.24.7 (Astraia Software Gmbh, Munich, Germany).

Just after delivery, the placentas were stored at −5 °C, and on the day of CTA the placenta was thawed in a warm water bath (37 °C). The umbilical cord vessels were cannulated 5 cm from the umbilical cord insertion using 3 venous cannulas size 1.3 × 32 mm (BD Venflon Pro, Helsingborg, Sweden). The placenta was flushed with a saline 9 mg NaCl/ml and Heparin 4.5IE/ml (Leo Pharma A/S, Ballerup, Denmark) solution until the venous efflux was clear. Hereafter a heated (< 40 °C) contrast mixture of gelatin 0.05 g/ml (Urtegaarden Djursland, Allingåbro, Denmark), barium sulphate 0.17 g/ml (E-Z Em Inc, Westbury, NY, USA), and saline 9 mg NaCl/ml was injected with a hand syringe. When the contrast mixture appeared in the venous efflux, the vein was plugged, and injection was continued until resistance was felt. Hereafter the placenta was cooled on ice to set the gelatin solution (Fig. 1 (A and C)).

CTA was performed on a 128-slice Siemens SOMATOM Definition Flash scanner (Siemens Healthcare GmbH, Erlangen, Germany) with software version VA48A and the flowing parameters: 0.6 mm slice thickness, 0.4 mm increment, 300 mm Field of View, 512 × 512 matrix, 1° pitch, 140 kV, effective 200 mAs, and 1sec rotation time. Post processing analysis was performed using the commercial software AW Server version 3.0 (GE Healthcare, Little Chalfont, Great Britain) to calculate the fetoplacental vascular volume by computing the sum of voxel volumes with signal intensity above 550HU (Fig. 1 (B and D)) after manually cutting the residual of the umbilical cord as close to the placental disc as possible. All 3D reconstructions of the fetoplacental vasculature were visually inspected. Five placentas were excluded from the normal group due to insufficient contrast filling of the fetoplacental vessels. No placentas were excluded from the DM group.

After the CTA, a standardized postnatal histopathological examination according to the Amsterdam consensus guideline [36] was performed by experienced placental pathologists (PB and AP), who were blinded to the CTA vascular outcome, but not the clinical information. Selected diabetic histopathological findings are reported in Table 3 using the following references for placental weight [37], delayed villous maturation [36], and the umbilical cord [38].

In normal pregnancies, the association between the fetoplacental vascular volume and the following variables; gestational age at birth (GA), placental weight, and birth weight, was investigated by linear regression analysis. When comparing the demographic data between the normal group and in each of the diabetic groups the continuous data are analyzed by Student t-test for normally distributed data and Mann-Whitney *U* test for non-normally distributed data, and categorical data are analyzed by Fishers exact test. In each of the diabetic groups, the fetoplacental vascular volume, the fetoplacental vascular volume/placental weight (FVV/PW)-ratio and the fetoplacental vascular volume/birth weight (FVV/BW)-ratio was compared to the normal group by multiple linear regression adjusting for GA. $p < 0.05$ was considered significant. All analyses were performed in SPSS Statistics version 25.0 (IBM, North Castle, New York, USA).

## 3. Results

As demonstrated in Table 1, the placental weight and birth weight (given as Z-scores and hence corrected for GA) were increased in pregnancies complicated by T1DM ($p = 0.026$ and $p < 0.001$, respectively) and in GDMi ($p = 0.002$ and $p = 0.003$, respectively) pregnancies. In addition, the T1DM and GDMi groups had a higher $HbA_{1c}$ when compared to GDMd pregnancies, indicating poorer glycemic control in these diabetic groups. Given the small number of patients in this study, the rare event of umbilical cord pH < 7 and Apgar score < 7 five minutes postpartum was not apparent. However, there was a trend towards more caesarian sections (elective and acute) among the patients with insulin dependent diabetes.

As illustrated in Fig. 1, the 3D reconstruction of the segmented fetoplacental vascular volume included both the chorionic vessels on the placental surface and the stem villi vessels that bend perpendicularly to the placental surface, which further branches into intermediate villi vessels. The smallest vessels of the fetoplacental vascular tree (capillaries) could not be identified in the CT angiography as the CT scan was limited by the resolution (Field of View of 300 mm, matrix of 512 × 512, and slice thickness of 0.6 mm giving a voxel size of 0.58 mm × 0.58 mm x 0.6 mm).

In normal pregnancies at term (GA 40 + 0) the fetoplacental vascular volume was 172.2 ml (95% CI: 154.2–189.9 ml), and we demonstrated a positive linear association between the fetoplacental vascular volume and GA ($r^2 = 0.585$, $p < 0.001$), placental weight ($r^2 = 0.405$, $p < 0.001$), and birth weight ($r^2 = 0.499$, $p < 0.001$) (Fig. 2). In the DM groups, the fetoplacental vascular volume did not differ from that in normal pregnancies at equivalent GA.

In normal pregnancies at term (GA 40 + 0) the FVV/BW-ratio was 48.9 ml/kg (95% CI: 44.5–56.7 ml/kg). In all DM groups the FVV/BW-ratio was lower, however this difference was only significant in the insulin dependent DM groups; T1DM (−16.2 ml/kg, $p = 0.003$), GDMi (−12.1 ml/kg, $p = 0.009$), and GDMd (−7.8 ml/kg, $p = 0.198$).