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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.

Keywords

Diabetes mellitus, placenta, CT angiography, vasculature, fetoplacental vascular volume, gestational diabetes

Abbreviations

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

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/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[26–29], 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)).

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[30,31]. 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[32], cerebroplacental Doppler ratio Z-score ≤ -2[33] and birth weight ≤ - 22%[34]. 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 5cm from the umbilical cord insertion using 3 venous cannulas size 1.3x32mm (BD Venflon Pro, Helsingborg, Sweden). The placenta was flushed with a saline 9mg 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 0.05g/ml (Urtegaarden Djursland, Allingåbro, Denmark), barium sulphate 0.17g/ml (E-Z Em Inc, Westbury, NY, USA), and saline 9mg 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 (Figure 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: 0.6mm slice thickness, 0.4mm increment, 1° pitch, 140kV, effective 200mAs, 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 volume of all voxels above 550HU (Figure 1 (B, D, and E)). 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[35] 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[36], delayed villous maturation[35], and the umbilical cord[37].

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. 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).

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 Figure 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 (Figure 1E).

The smallest vessels of the fetoplacental vascular tree (capillaries) were not included as a part of the computed fetoplacental vascular volume.

In normal pregnancies at term (GA 40+0) the fetoplacental vascular volume was 172.2ml (95% CI: 154.2-189.9 ml/kg), 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) (Figure 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: 44.5-56.7ml/kg). In all DM groups the FVV/BW-ratio was lower, however this difference was only significant in the insulin dependent DM groups; T1DM (-16.2ml/kg, p=0.003), GDMi (-12.1ml/kg, p=0.009), and GDMd (-7.8ml/kg, p=0.198).

In normal pregnancies at term (GA 40+0) the FVV/PW-ratio was 33.9ml/kg (95% CI: 32.9-37.9ml/kg), and this ratio was reduced in all DM groups, but the difference was only significant for pregnancies complicated by GDMi (-81.5ml/kg, p=0.012) and with a strong trend in T1DM (-66.0ml/kg, p=0.068) (Table 2).

The placental histopathological examination is presented in Table 3. Characteristic diabetic abnormalities are seen predominantly in the insulin treated diabetic pregnancies, as two or more diabetic findings are seen in 12.5% of pregnancies complicated by T1DM and in 44.4% of pregnancies complicated by GDMi.

Discussion

This study demonstrated that in normal pregnancies the fetoplacental vascular volume increased with GA, placental weight, and birth weight. In pregnancies complicated by T1DM and GDMi, the placental weight and birth weight was higher than normal. However, in these pregnancies the relative fetoplacental vascular volume was reduced, as demonstrated by a lower FVV/PW-ratio and FVV/BW-ratio. These findings indicate, that the large placenta in pregnancies complicated by insulin dependent diabetes has relatively fewer fetoplacental vessels, and therefore a relatively smaller fetoplacental volume supplies the macrosomic diabetic fetus. This finding might explain one of the underlying mechanisms why fetuses from insulin dependent diabetic pregnancies are more vulnerable to asphyxia during pregnancy and labor.

This study had some methodological limitations. Proper placental preparation is crucial to obtain reliable fetoplacental vascular assessments. To ensure sufficient contrast filling of the entire fetoplacental vasculature without presence of intravascular blood clots, the placentas in this study were frozen postpartum, which is known to reduce clotting without adverse effects on the fetoplacental vasculature[38–40]. Furthermore, the thawed placentas were flushed with heparinized saline to remove vascular clots prior to contrast injection. The fetoplacental vascular volume may have varied according to the degree of vascular contrast filling injected by a hand syringe. However in this study, one person (MØT) performed the contrast injection, and in each placenta contrast injection was performed uniformly until a specific resistance was felt. To avoid contrast drainage we added gelatin to the contrast solution, and the contrast-perfused placenta was cooled on ice packs to set the contrast solution.

Strength of our study was the ability to demonstrate the entire fetoplacental vasculature except for the smallest vessels (capillaries). The majority of previous studies is based on placental biopsies[3,9,14,15], which might not reflect the placental pathology of the entire placenta. It is well known that the normal placenta has a heterogeneous vessel maturation[41], and also the diabetic placenta is known to have focal

pathology such as dysmature villous structures[25]. Another strength of the present method was the demonstration of the fetoplacental vasculature in 3D. 3D reconstruction provides information of spatial vessel architecture such as the fetoplacental vascular volume, which is not available by 2D imaging[42] which is the basis of the majority of previous studies[3,7,9,14,15,20,21]. Lastly, angiography allows for histopathological placental examination to be performed following the vascular investigation, which is not available with comparable methods such as corrosion casting.

A limitation of the study design was the relatively small study population. GDM pregnancies were grouped according to the White Classification of Diabetes in Pregnancy[43], but because of the small number of T1DM pregnancies in this study, this group was not further subdivided.

Strength of the study was the placental histopathological examination that confirmed, that placental pathology is predominantly seen in pregnancies complicated by insulin dependent diabetes. Another strength was the adjustment for GA in the analysis when comparing the fetoplacental vasculature between groups. This is of major importance, as the fetoplacental vascular volume is known to increase dramatically as pregnancy advances[44,45], which is also in accordance with the findings of our study.

In normal pregnancies, this study demonstrated that the normal fetoplacental vascular volume at term is 172.2ml (95% CI: 154.2-189.9 ml/kg). As demonstrated by images of the 3D segmentation, the vascular volume includes the chorionic vessels, the stem villi vessels, and the intermediate villi vessels. This finding is very much in line with the previous published literature, where the normal fetoplacental vascular volume is estimated to be 5-159ml based on residual placental blood-volume[22,46] or 12-124ml based on MR-angiography[27],. The normal fetoplacental vascular volume in this study is reassuring, as it indicates that under-segmentation was not a major limitation of this study. Furthermore, a positive linear association was found between the fetoplacental vascular volume and GA. This finding is in accordance with a previous study based on stereological analysis of placental biopsies demonstrating a linear increase of stem and intermediate villi vessel volume throughout pregnancy[47]. Furthermore, our study demonstrated a linear correlation between the fetoplacental vascular volume and placental weight and birth weight. This finding is in accordance with a previous study on placental MRA in normal pregnancies at term by Rasmussen et al[27]. In contrast to our study, Rasmussen et al. were not able to demonstrate an association between placental vascular volume and placental weight. However, this discrepancy may be explained by a different range of GA included in the two studies, as our study included placentas at a wide range of GA (30-42 weeks' gestation) as compared to Rasmussen et al. who included term placentas.

We found an increased placental weight and birth weight in pregnancies complicated by insulin dependent DM, which is in line with previous literature[6]. However there is evidence to support that this pathology should also be found among diet dependent diabetes[48]. In this study, the GDMd group had a lower HbA_{1c} suggesting a good glycemic control, which may explain why this group did not demonstrate such pathology in our study.

Furthermore, we found that in all three DM groups the fetoplacental vascular volume did not differ from that in normal pregnancies. In previous studies, the fetoplacental vascular volume has been investigated by different methods, which could explain the rather conflicting results. By estimating the placental residual blood volume, Klebe et al[22] found an increased fetoplacental vascular volume in DM pregnancies when compared to normal pregnancies. However, another study by Singer et al[14] found no difference in the vascular volume and surface areas of the chorionic vessels and stem villi vessels when estimated by placental histological examination.

In this study, intrauterine and intrapartum asphyxia, defined as umbilical blood pH < 7 and Apgar score < 7 after 5 minutes, was not present. This might be due to a very small number of patients included in the study, appropriate antenatal monitoring, and adequate obstetric intervention of the included diabetic pregnancies. In Table 1, it should be noted, that there is a trend towards a higher proportion of elective and acute cesarean section among the DM pregnancies.

The disparities in FVV/BW-ratio among insulin dependent and insulin independent DM pregnancies in this study might be caused by differences in the placental pathophysiology. As fetoplacental vascular abnormalities are hypothesized to result from hypoxia caused by fetal and maternal hyperglycemia[1], the observed differences might indicate differences in time of onset and severity of hyperglycemia between the different DM types and differences in preexisting maternal factors[49]. It is known that when DM is well controlled during pregnancy, the fetoplacental vasculature is normally developed and the neonatal outcome improved[25]. The measured HbA_{1C} values in this study is highest in T1DM both pre-gestational and during pregnancy (Table 1), but time for onset of hyperglycemia in the GDM pregnancies cannot be withdrawn. Future research is recommended to consider this.

In conclusion, we have demonstrated that the placental weight and birth weight is increased in insulin dependent diabetic pregnancies, however the fetoplacental vasculature is not correspondingly increased. This study highlights that insulin dependent pregnancies are subject to relative placental insufficiency, as in these pregnancies the macrosomic fetus is supplied by a relatively smaller fetoplacental vascular volume. This finding might explain one of the underlying mechanisms, why fetuses from insulin dependent diabetic pregnancies are more vulnerable to asphyxia during pregnancy and labor.

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Author's contribution: MØT, MS, and AS planned the research project. MØT collected all placentas and prepared it for scanning. JBF took part of planning the CT angiography. ASK, LRØ, and JBF participated in cooperation with MØT, MS, and AS in extracting the fetoplacental vascular volume based on the scannings. PB and AP performed all the placental pathological examinations and assessed the pathological data. MØT, MS, and AS performed the statistical analysis and data assessment and wrote the manuscript. All authors read and approved the final manuscript.

References

[1] K. Kc, S. Shakya, H. Zhang, Gestational diabetes mellitus and macrosomia: A literature review, Ann. Nutr. Metab. 66 (2015) 14–20.

[2] H. Madsen, Fetal oxygenation in diabetic pregnancy. With special reference to maternal blood oxygen affinity and its effectors, Dan. Med. Bull. 33 (1986) 64–74. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed3&NEWS=N&AN=167

06861.
[3] F. Teasdale, Histomorphometry of the human placenta in Class B diabetes mellitus., Placenta. 4 (1983) 1–12.
[4] T.M. Mayhew, F.B. Sørensen, J.G. Klebe, M.R. Jackson, The effects of mode of delivery and sex of newborn on placental morphology in control and diabetic pregnancies., J. Anat. 183 (1993) 545–52.
[5] C.M. Scifres, W.T. Parks, M. Feghali, S.N. Caritis, J.M. Catov, Placental maternal vascular malperfusion and adverse pregnancy outcomes in gestational diabetes mellitus, Placenta. 49 (2017) 10–15.
[6] F. Gloria-Bottini, A. Neri, L. Coppeta, A. Magrini, E. Bottini, Correlation between birth weight and placental weight in healthy and diabetic puerperae, Taiwan. J. Obstet. Gynecol. 55 (2016) 697–699.
[7] M.H. Rahman, S.Z. Sultana, S. Mannan, S. Sultana, M.A. Hossain, Vascular change in the placenta of diabetic mothers and hypertensive diabetic mothers., Mymensingh Med. J. 15 (2006) 176–9.
[8] I. Asmussen, Ultrastructure of the villi and fetal capillaries of the placentas delivered by non-smoking diabetic women (White group D)., Acta Pathol. Microbiol. Immunol. Scand. A. 90 (1982) 95–101.
[9] F. Teasdale, Histomorphometry of the human placenta in Class C diabetes mellitus., Placenta. 6 (1985) 69–81.
[10] F. Stoz, R.A. Schuhmann, A. Schmid, Morphometric investigations of terminal villi of diabetic placentas in relation to the White classification of diabetes mellitus., J. Perinat. Med. 15 (1987) 193–8.
[11] A. Maly, G. Goshen, J. Sela, A. Pinelis, M. Stark, B. Maly, Histomorphometric study of placental villi vascular volume in toxemia and diabetes., Hum. Pathol. 36 (2005) 1074–9.
[12] I.M.P. Calderon, D.C. Damasceno, R.L. Amorin, R.A.A. Costa, M.A.M. Brasil, M.V.C. Rudge, Morphometric study of placental villi and vessels in women with mild hyperglycemia or gestational or overt diabetes., Diabetes Res. Clin. Pract. 78 (2007) 65–71.
[13] M. Jirkovská, T. Kučera, V. Dvořáková, M. Jadrníček, M. Moravcová, Z. Žižka, V. Krejčí, Impact of maternal diabetes type 1 on proliferative potential, differentiation and apoptotic activity in villous capillaries of term placenta, Placenta. 40 (2016) 1–7.
[14] D.B. Singer, C.T. Liu, J.A. Widness, R.A. Ellis, Placental morphometric studies in diabetic pregnancies., Placenta. Suppl. 3 (1981) 193–202.
[15] F. Teasdale, Histomorphometry of the placenta of the diabetic women: class A diabetes mellitus., Placenta. 2 (1981) 241–51.
[16] F. Stoz, R.A. Schuhmann, R. Schultz, Morphohistometric investigations of placentas of diabetic patients in correlation to the metabolic adjustment of the disease., J. Perinat. Med. 16 (1988) 211–6.
[17] T.M. Mayhew, F.B. Sørensen, J.G. Klebe, M.R. Jackson, Growth and maturation of villi in placentae from well-controlled diabetic women., Placenta. 15 (1994) 57–65.
[18] T.M. Mayhew, Enhanced fetoplacental angiogenesis in pre-gestational diabetes mellitus: The extra growth is exclusively longitudinal and not accompanied by microvascular remodelling, Diabetologia. 45 (2002) 1434–1439.
[19] M. Higgins, P. Felle, E.E. Mooney, J. Bannigan, F.M. McAuliffe, Stereology of the placenta in type 1 and type 2 diabetes, Placenta. 32 (2011) 564–569.

[20] R. McCarthy, N.M. Orsi, D. Treanor, O. Moran, M. Vernooij, D.R. Magee, N. Roberts, J. Stahlschmidt, N.A.B. Simpson, Three-dimensional digital reconstruction of human placental villus architecture in normal and complicated pregnancies., Eur. J. Obstet. Gynecol. Reprod. Biol. 197 (2016) 130–5.
[21] O. Björk, The fetal arterial vasculature in placentas of insulin-dependent diabetic mothers., Acta Pathol. Microbiol. Immunol. Scand. A. 90 (1982) 289–94.
[22] J.G. Klebe, C.J. Ingomar, Placental transfusion in infants of diabetic mothers elucidated by placental residual blood volume., Acta Paediatr. Scand. 63 (1974) 59–64. http://www.ncbi.nlm.nih.gov/pubmed/4830412 (accessed August 28, 2017).
[23] M. Jirkovská, L. Kubínová, J. Janácek, M. Moravcová, V. Krejcí, P. Karen, Topological properties and spatial organization of villous capillaries in normal and diabetic placentas, J. Vasc. Res. 39 (2002) 268–278.
[24] F. Stoz, R.A. Schuhmann, B. Haas, Morphohistometric investigations in placentas of gestational diabetes., J. Perinat. Med. 16 (1988) 205–9.
[25] K. Benirschke, G.J. Burton, R.N. Baergen, Maternal Diseases Complicating Pregnancy: Diabetes, Tumors, Preeclampsia, Lupus Anticoagulant, in: Pathol. Hum. Placenta, 6th ed., Springer-Verlag Berlin Heidelberg, 2012.
[26] A.S. Rasmussen, H. Lauridsen, C. Laustsen, B.G. Jensen, S.F. Pedersen, L. Uhrenholt, L.W.T. Boel, N. Uldbjerg, T. Wang, M. Pedersen, High-resolution ex vivo magnetic resonance angiography: a feasibility study on biological and medical tissues., BMC Physiol. 10 (2010) 3.
[27] A.S. Rasmussen, E. Stæhr-Hansen, H. Lauridsen, N. Uldbjerg, M. Pedersen, MR angiography demonstrates a positive correlation between placental blood vessel volume and fetal size., Arch. Gynecol. Obstet. 290 (2014) 1127–31.
[28] Z.J. Wang, X.W. Zhu, Q.T. Huang, Z.Q. Yun, Y.W. Cao, Y.Y. Chen, M. Zhong, Three-dimensional reconstruction of human placental vascular network using in-vitro MRI data, Ultrasound Obstet. Gynecol. 47 (2016) 790–792.
[29] R. Pratt, C. Hutchinson, A. Melbourne, M. Zuluaga, A. Virasami, T. Vercauteren, S. Ourselin, N. Sebire, O. Arthurs, A. David, Imaging the human placental microcirculation with micro-focus computed tomography: Optimisation of tissue preparation and image acquisition, Placenta. 60 (2017) 36–39.
[30] Dansk Endokrinologisk Selskab, Type 1 Diabetes Mellitus, (2016). http://www.endocrinology.dk/index.php/nbvhovedmenu/1-diabetes-mellitus/3-type-1-diabetes-mellitus (accessed December 4, 2017).
[31] Dansk Selskab for Obstetrik og Gynækologi (DSOG), Gestationel diabetes mellitus (GDM). Screening og diagnose., Sandbjergmødet. (2014).
[32] M. Parra-Cordero, C. Lees, H. Missfelder-Lobos, P. Seed, C. Harris, Fetal arterial and venous Doppler pulsatility index and time averaged velocity ranges., Prenat. Diagn. 27 (2007) 1251–7.
[33] A.A. Baschat, U. Gembruch, The cerebroplacental Doppler ratio revisited., Ultrasound Obstet. Gynecol. 21 (2003) 124–7.
[34] K. Marsál, P.H. Persson, T. Larsen, H. Lilja, A. Selbing, B. Sultan, Intrauterine growth curves based on ultrasonically estimated foetal weights., Acta Paediatr. 85 (1996) 843–8.
[35] T.Y. Khong, E.E. Mooney, I. Ariel, N.C.M. Balmus, T.K. Boyd, M.-A. Brundler, H. Derricott, M.J. Evans, O.M. Faye-Petersen, J.E. Gillan, A.E.P. Heazell, D.S. Heller, S.M. Jacques, S. Keating, P. Kelehan, A. Maes, E.M. McKay, T.K. Morgan, P.G.J. Nikkels, W.T. Parks, R.W.

Redline, I. Scheimberg, M.H. Schoots, N.J. Sebire, A. Timmer, G. Turowski, J.P. van der Voorn, I. van Lijnschoten, S.J. Gordijn, Sampling and Definitions of Placental Lesions: Amsterdam Placental Workshop Group Consensus Statement, Arch. Pathol. Lab. Med. 140 (2016) arpa.2015-0225-CC.

[36] H. Pinar, C.J. Sung, C.E. Oyer, D.B. Singer, Reference values for singleton and twin placental weights., Pediatr. Pathol. Lab. Med. 16 (1996) 901–7.

[37] R. Naeye, Umbilical cord length: Clinical significance, J. Pediatr. 107 (1985) 278–281.

[38] I.S. Cooper, K. Samra, K. Wisniewska, Effects of Freezing on Major Arteries, Stroke. 2 (1971) 471–482.

[39] M. Nordenvall, U. Ullberg, J. Laurin, G. Lingman, B. Sandstedt, U. Ulmsten, Placental morphology in relation to umbilical artery blood velocity waveforms., Eur. J. Obstet. Gynecol. Reprod. Biol. 40 (1991) 179–90.

[40] U. Ullberg, G. Lingman, G. Ekman-Ordeberg, B. Sandstedt, Hyrtl's anastomosis is normally developed in placentas from small for gestational age infants., Acta Obstet. Gynecol. Scand. 82 (2003) 716–21.

[41] J. Stanek, Hypoxic Patterns of Placental Injury: A Review, Arch. Pathol. Lab. Med. 137 (2013) 706–720.

[42] T.M. Mayhew, Stereology and the placenta: where's the point? - a review., Placenta. 27 Suppl A (2006) 17–25.

[43] S.G. Gabbe, J.R. Niebyl, J.L. Simpson, Obstetrics: Normal and Problem Pregnancies, 4th ed., Churchill Livingstone, New York, 2002.

[44] K. Benirschke, G.J. Burton, R.N. Baergen, Architecture of Normal Villous Trees, in: Pathol. Hum. Placenta, 6th ed., Springer-Verlag Berlin Heidelberg, 2012.

[45] N. Gude, C. Roberts, B. Kalionis, R. King, Growth and function of the normal human placenta., Thromb Res. 114 (2004) 397–407.

[46] J. Kjeldsen, J. Pedersen, Relation of residual placental blood-volume to onset of respiration and the respiratory-distress syndrome in infants of diabetic and non-diabetic mothers, Lancet. 289 (1967) 180–184.

[47] M.R. Jackson, T.M. Mayhew, P.A. Boyd, Quantitative description of the elaboration and maturation of villi from 10 weeks of gestation to term., Placenta. 13 (1992) 357–70.

[48] A. Vambergue, I. Fajardy, Consequences of gestational and pregestational diabetes on placental function and birth weight., World J. Diabetes. 2 (2011) 196–203.

[49] S. Cvitic, G. Desoye, U. Hiden, Glucose, Insulin, and Oxygen Interplay in Placental Hypervascularisation in Diabetes Mellitus, Biomed Res. Int. 2014 (2014) 145846.

Figure legends

Figure 1: Images of a placenta from a normal pregnancy GA 37+4 (A and B) and a placenta from a pregnancy complicated by type 1 diabetes mellitus, GA 37+1 (C and D). Macroscopic photography (A and C) and a 3D reconstruction of the fetoplacental blood vessels (B and D).

Figure 2: Association between fetoplacental vascular volume (ml) and A) gestational age at birth (weeks), B) placental weight (g), and C) birth weight (g). The solid lines indicate ordinary least squares fit. The dashed lines indicate 95% confidence interval for the normal placentas. Normal placentas (open circle), type 1 diabetes mellitus (T1DM) (squares), diet controlled gestational diabetes mellitus (GDMd) (triangles), insulin treated gestational diabetes mellitus (GDMi) (pentagons).

406 **Table 1: Maternal, placental, and neonatal characteristics of included patients.**

Characteristics	Normal (N=27)	T1DM (N=8)		GDMd (N=8)		GDMi (N=9)	
			p-value		p-value		p-value
Maternal age at birth, yr	29.0 (27.0 – 34.0)	27.5 (26.5 – 31.0)	0.433	29.0 (27.0 - 34.8)	0.884	31.0 (27.0 – 36.5)	0.443
Pre-gestational maternal BMI, kg/m^2	24.1 (20.7 – 30.1)	29.1 (26.8 – 33.5)	0.027	26.6 (20.4-31.9)	0.550	28.2 (25.9 – 34.6)	0.086
Nulliparity	48.1 (13/29)	37.5 (3/8)	0.700	50.0 (4/8)	1.000	33.3 (3/9)	0.700
Maternal smoking	14.8 (4/29)	0.0 (0/8)	0.553	37.5 (3/8)	0.312	22.2 (2/9)	0.627
Umbilical artery Doppler, Z-score[32]	0.3 (-0.6 – 0.9) (N=22)	0.2 (-0.3 – 1.6)	0.185	-0.1 (-0.6 – 0.4)	0.530	0.4 (-0.3 – 0.9)	0.362
Cerebroplacental-ratio, Z-score[33]	-0.5 (-0.7 – 0.2) (N=7)	-1.3 (-3.7 - -0.7) (N=4)	0.065	-1.1 (-1.3 - .) (N=2)	0.283	0.0 (-1.5 - .) (N=3)	0.922
Gestational age, weeks	38.9 (34.3 – 40.6)	36.9 (35.9 – 37.1)	0.192	40.6 (39.4 – 41.1)	0.104	37.6 (36.7 - 38.2)	0.295
Birth weight, Z-score[34]	-0.4 (-0.7 – 0.5)	2.2 (1.5– 3.2)	**<0.001**	0.0 (-0.1 – 2.2)	0.286	1.1 (0.2 – 3.2)	**0.003**
Placental weight, Z-score	-0.1 (-0.4 – 0.4)	0.5 (0.0 – 1.9)	**0.026**	-0.2 (-0.9 – 0.8)	0.784	1.5 (0.4 – 2.3)	**0.002**
Umbilical venous vessel pH < 7.00	0.0 (0/27)	0.0 (0/8)	-	0.0 (0/8)	-	0.0 (0/9)	-
Apgar score < 7 after 5 min	0.0 (0/27)	0.0 (0/8)	-	0.0 (0/8)	-	0.0 (0/9)	-
Delivery mode							
• Vaginal birth	• 70.4 (19/27)	• 37.5 (3/8)	0.116	• 75.0 (6/8)	1.000	• 33.3 (3/9)	0.111
• Elective cesarean section	• 7.4 (2/27)	• 25.0 (2/8)	0.218	• 12.5 (1/8)	0.553	• 33.3 (3/9)	0.088
• Acute cesarean section	• 22.2 (6/27)	• 37.5 (3/8)	0.396	• 12.5 (1/8)	1.000	• 33.3 (3/9)	0.660
Shoulder dystocia	0.0 (0/27)	0.0 (0/8)	-	0.0 (0/8)	-	0.0 (0/9)	-
Vacuum delivery	11.1 (3/27)	0.0 (0/8)	1.000	0.0 (0/8)	1.000	0.0 (0/9)	0.558
Postpartum bleeding >500ml	14.8 (4/27)	0.0 (0/8)	0.559	12.5% (1/8)	1.000	0.0 (1/9)	0.553
Maternal age at DM debut, yr	-	12.5 (3.0 – 17.8)	-	29.0 (27.0 - 34.8)	-	31.0 (27.0 – 36.5)	-
Gestational age at debut, weeks	-	-	-	30.9 (28.8 – 33.2)	-	28.6 (21.0 – 30.6)	-
HbA_{1c}, mmol/mol	-		-		-		-

•Pre-gestational (T1DM) or pre-treatment (GDM) •1st trimester •2nd trimester •3rd trimester		• 58.0 (51.25 – 90.0) • 55.0 (46.8 – 67.0) • 50.0 (42.5 – 60.3) • 52.0 (49.5 – 57.8)		• 31.5 (28.8-35.8) • - • 37.0 (N=1) • 32.0 (29.5 – 38.5)		• 39.0 (36.0 – 45.5) • - • 37.0 (33.8 – 38.0) (N=4) • 41.0 (34.0 – 46.5)	
White classification[43], class	-	C: 50.0 (4/8) D: 25.0 (2/8) R: 25.0 (2/8)	-	A1: 8/8	-	A2: 9/9	-

Data are given as median (IQR) or % (n/N). All p-values indicate comparison to normal pregnancy. The continuous data are analyzed with independent samples Student t-test or Mann-Whitney U-test based on the appearance of normal distribution, and categorical data are analyzed with Fishers exact test. GDMd = diet controlled gestational diabetes mellitus, GDMi = insulin treated gestational diabetes mellitus, T1DM = type 1 diabetes mellitus.

Table 2: Summary of multiple regression analysis. The normal pregnancies are the reference.

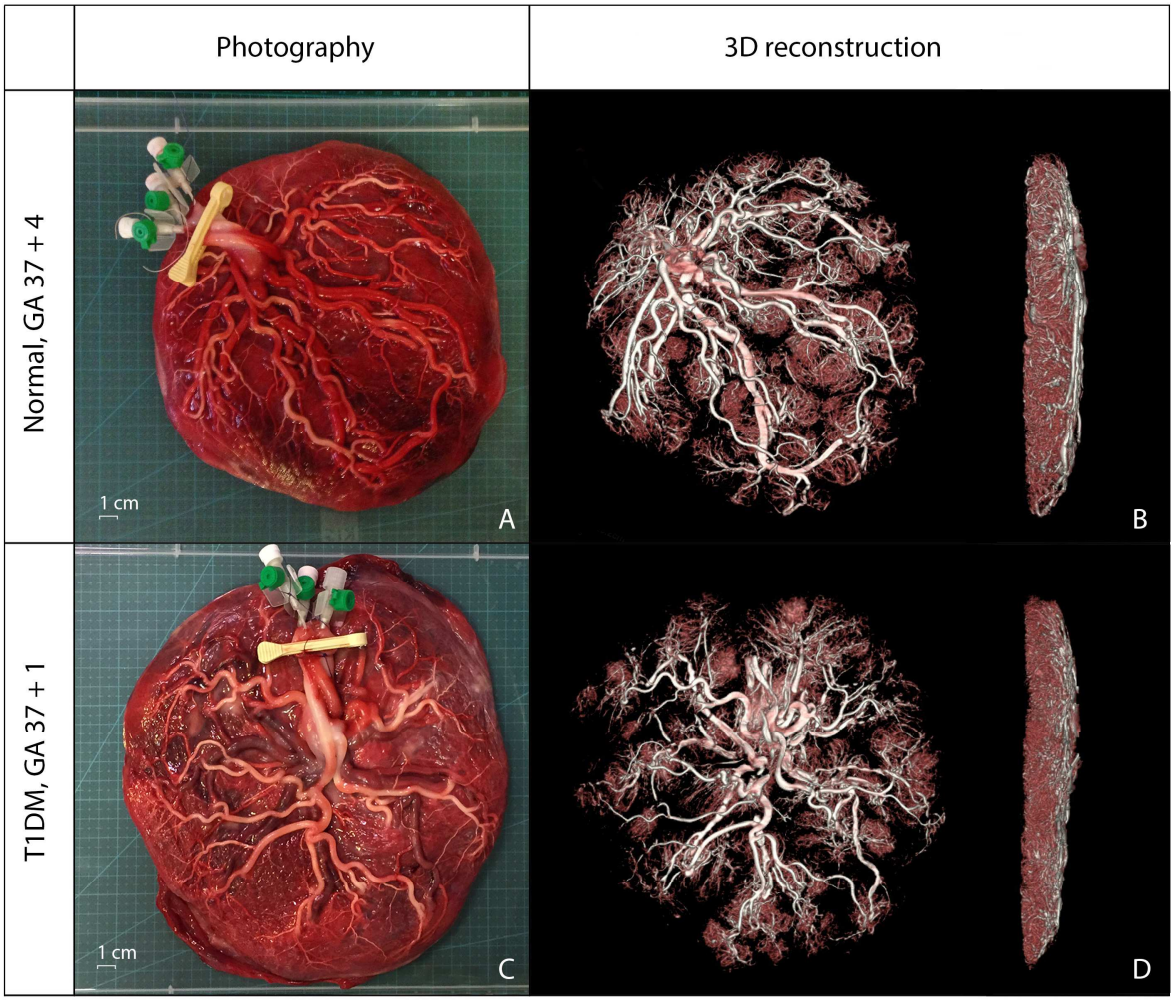
	Unstandardized coefficients		*p*-value	95% confidence interval for B	
	B	Std. Error		Lower bound	Upper bound
Fetoplacental vascular volume (ml)					
T1DM	-14.3	15.2	0.356	-45.3	16.8
GDMd	-18.6	19.9	0.357	-59.3	22.0
GDMi	-10.9	13.9	0.440	-39.2	17.4
Fetoplacental vascular volume / placental weight ratio (ml/kg)					
T1DM	-66.0	34.9	0.068	-137.2	5.2
GDMd	-48.8	40.0	0.231	-130.2	32.6
GDMi	-81.5	30.6	**0.012**	-143.7	-19.3
Fetoplacental vascular volume / birth weight ratio (ml/kg)					
T1DM	-16.2	49.5	**0.003**	-26.3	-6.1
GDMd	-7.8	5.9	0.198	-19.8	4.3
GDMi	-12.1	4.4	**0.009**	-21.0	-3.3

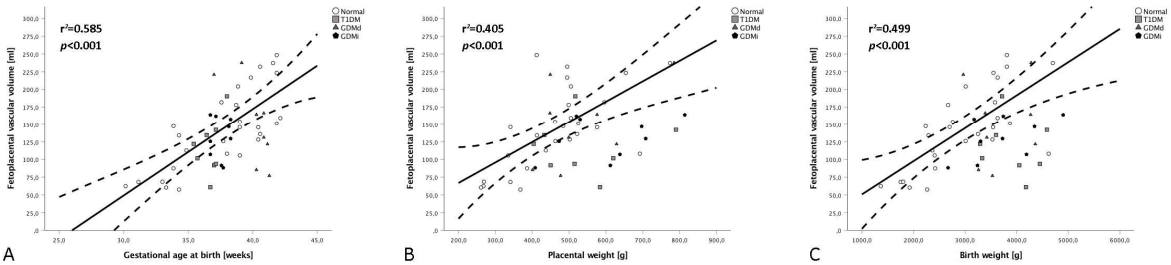
GDMd = diet controlled gestational diabetes mellitus, GDMi = insulin treated gestational diabetes mellitus, T1DM = type 1 diabetes mellitus.

Table 3: Diabetic placental histopathological findings.

Placenta pathology \ Group	Normal	T1DM	GDMd	GDMi
Large placental weight, p>90 [36]	14.8 (4/27)	37.5 (3/8)	12.5 (1/8)	55.6 (5/9)
Delayed villous maturation [35]	0.0 (0/27)	25.0 (2/8)	0.0 (0/8)	33.3 (3/9)
Long umbilical cord [37]	22.2 (6/27)	12.5 (1/8)	12.5 (1/8)	33.3 (3/9)
≥ 2 diabetic findings	7.4 (2/27)	12.5 (1/8)	0.0 (0/8)	44.4 (4/9)

Data are given as % (n/N). GDMd = diet controlled gestational diabetes mellitus, GDMi = insulin treated gestational diabetes mellitus, T1DM = type 1 diabetes mellitus.


Photography
3D reconstruction
Normal, GA 37 + 4
T1DM, GA 37 + 1
1 cm
A
B
1 cm
C
D



Highlights

- Pregnancies complicated by diabetes (DM) are at high risk of intrapartum asphyxia.
- This risk may be related to fetoplacental vascular abnormalities.
- This study examines the fetoplacental vascular volume by placental CT angiography.
- In insulin dependent DM the fetoplacental vascular volume/birthweight-ratio is low.
- This finding might partly explain the higher vulnerability to fetal asphyxia.