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Published in:
Placenta

DOI (link to publication from Publisher):
[10.1016/j.placenta.2018.06.309](https://doi.org/10.1016/j.placenta.2018.06.309)

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Publication date:
2018

Document Version
Accepted author manuscript, peer reviewed version

[Link to publication from Aalborg University](#)

Citation for published version (APA):

Thunbo, M. Ø., Sinding, M., Bogaard, P., Korsager, A. S., Frøkjær, J. B., Østergaard, L. R., Petersen, A., & Sørensen, A. (2018). Postpartum placental CT angiography in normal pregnancies and in those complicated by diabetes mellitus. *Placenta*, 69, 20-25. <https://doi.org/10.1016/j.placenta.2018.06.309>

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Accepted Manuscript

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

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PII: S0143-4004(18)30183-8

DOI: [10.1016/j.placenta.2018.06.309](https://doi.org/10.1016/j.placenta.2018.06.309)

Reference: YPLAC 3844

To appear in: *Placenta*

Received Date: 24 April 2018

Revised Date: 11 June 2018

Accepted Date: 28 June 2018

Please cite this article as: Thunbo MetteØ, Sinding M, Bogaard P, Korsager AS, Frøkjær JensBrø, Østergaard LR, Petersen A, Sørensen A, Postpartum placental CT angiography in normal pregnancies and in those complicated by diabetes mellitus, *Placenta* (2018), doi: 10.1016/j.placenta.2018.06.309.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

1 Postpartum placental CT angiography in normal
2 pregnancies and in those complicated by
3 diabetes mellitus

4 **Running headline:** Placental CT angiography in diabetic pregnancies

5
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25
26 **Word count, abstract: 250**

27 **Word count, main text: 2498**

28

29 **Declarations of interest:** None

30

31 Abstract**32 Introduction**

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

38 Methods

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

44 Results

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

50 Discussion

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

55 Keywords

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

58 Abbreviations

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

63 Introduction

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

72 It is known that DM pregnancies are associated with increased placental weight and birth weight and
73 an increased birth weight/placental weight-ratio[6]. Current knowledge on the fetoplacental vasculature in
74 DM pregnancies is based on macroscopic examinations[7], histomorphometry[3,8–16], stereology[4,17–
75 20], x-ray angiograms[21], and measurements of the placental residual blood volume after birth[22]. In
76 T1DM pregnancies conflicting results are demonstrated as some studies describe an increased
77 fetoplacental vascular volume, surface area, and capillary length compared to normal[3,4,8,9,17–19,22],
78 while others describe decreased vessel diameter and number of vessels[7,10–15,21]. Also in GDM
79 pregnancies, existing knowledge on the fetoplacental vasculature demonstrates conflicting results with
80 studies reporting increased vascular volume[15], surface area[15], and number of vessels[12,23] as well as
81 decreased number of vessels[20,24]. The inconsistent findings in the literature may be explained by
82 differences in glycemic control, treatment regime, and lack of methods to demonstrate vascular
83 pathology[25].

84 Imaging technologies such as placental computed tomography angiography (CTA) and magnetic
85 resonance angiography (MRA) have a great potential to investigate the fetoplacental vasculature in three-
86 dimensions (3D). By using these methods the fetoplacental vasculature has been investigated in normal
87 pregnancies[26–29], however to the best of our knowledge CTA has never been performed in pregnancies
88 complicated by different types of DM.

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

93 Methods

94 Twenty-five placentas (35-41 weeks' gestation) from singleton pregnancies complicated by DM (8 T1DM
95 placentas, 8 GDMd placentas, and 9 GDMi placentas) were included in the study[30,31]. 32 placentas (30-
96 42 weeks' gestation) from normal singleton pregnancies constituted the control group. We excluded
97 stillbirths, abnormal fetal karyotype or congenital malformations, and pregnancies with clinical signs of
98 placental insufficiency (umbilical artery Doppler flow Pulsatility index (PI) Z-score ≥ 2 [32], cerebroplacental
99 Doppler ratio Z-score ≤ -2 [33] and birth weight $\leq -22\%$ [34]. All placentas were collected at Aalborg
100 University Hospital, Denmark, between July 1st, 2015 and December 1st, 2016. The Danish National Ethics
101 Committee (N-20150018) and the Danish Data Protection Agency (2008-58-0028) approved the study, and
102 all participants gave oral and written informed consent. Maternal and pregnancy characteristics are

103 presented in Table 1. Data were collected from medical records and the electronic ultrasound database
104 Astraia version 1.24.7 (Astraia Software GmbH, Munich, Germany).

105 Just after delivery, the placentas were stored at -5°C , and on the day of CTA the placenta was thawed
106 in a warm water bath (37°C). The umbilical cord vessels were cannulated 5cm from the umbilical cord
107 insertion using 3 venous cannulas size 1.3x32mm (BD Venflon Pro, Helsingborg, Sweden). The placenta was
108 flushed with a saline 9mg NaCl/ml and Heparin 4.5IE/ml (Leo Pharma A/S, Ballerup, Denmark) solution until
109 the venous efflux was clear. Hereafter a heated ($<40^{\circ}\text{C}$) contrast mixture of gelatin 0.05g/ml (Urtegaarden
110 Djursland, Allingåbro, Denmark), barium sulphate 0.17g/ml (E-Z Em Inc, Westbury, NY, USA), and saline
111 9mg NaCl/ml was injected with a hand syringe. When the contrast mixture appeared in the venous efflux,
112 the vein was plugged, and injection was continued until resistance was felt. Hereafter the placenta was
113 cooled on ice to set the gelatin solution (Figure 1 (A and C)).

114 CTA was performed on a 128-slice Siemens SOMATOM Definition Flash scanner (Siemens Healthcare
115 GmbH, Erlangen, Germany) with software version VA48A and the flowing parameters: 0.6mm slice
116 thickness, 0.4mm increment, 1° pitch, 140kV, effective 200mAs, and 1sec rotation time. Post processing
117 analysis was performed using the commercial software AW Server version 3.0 (GE Healthcare, Little
118 Chalfont, Great Britain) to calculate the fetoplacental vascular volume by computing the volume of all
119 voxels above 550HU (Figure 1 (B, D, and E)). All 3D reconstructions of the fetoplacental vasculature were
120 visually inspected. Five placentas were excluded from the normal group due to insufficient contrast filling
121 of the fetoplacental vessels. No placentas were excluded from the DM group.

122 After the CTA, a standardized postnatal histopathological examination according to the Amsterdam
123 consensus guideline[35] was performed by experienced placental pathologists (PB and AP), who were
124 blinded to the CTA vascular outcome, but not the clinical information. Selected diabetic histopathological
125 findings are reported in Table 3 using the following references for placental weight[36], delayed villous
126 maturation[35], and the umbilical cord[37].

127 In normal pregnancies, the association between the fetoplacental vascular volume and the following
128 variables; gestational age at birth (GA), placental weight, and birth weight, was investigated by linear
129 regression analysis. In each of the diabetic groups, the fetoplacental vascular volume, the fetoplacental
130 vascular volume/placental weight (FVV/PW)-ratio and the fetoplacental vascular volume/birth weight
131 (FVV/BW)-ratio was compared to the normal group by multiple linear regression adjusting for GA. $p<0.05$
132 was considered significant. All analyses were performed in SPSS Statistics version 25.0 (IBM, North Castle,
133 New York, USA).

134 Results

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

142 As illustrated in Figure 1, the 3D reconstruction of the segmented fetoplacental vascular volume
143 included both the chorionic vessels on the placental surface and the stem villi vessels that bend
144 perpendicularly to the placental surface, which further branches into intermediate villi vessels (Figure 1E).

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

147 In normal pregnancies at term (GA 40+0) the fetoplacental vascular volume was 172.2ml (95% CI:
148 154.2-189.9 ml/kg), and we demonstrated a positive linear association between the fetoplacental vascular
149 volume and GA ($r^2=0.585$, $p<0.001$), placental weight ($r^2=0.405$, $p<0.001$), and birth weight ($r^2=0.499$,
150 $p<0.001$) (Figure 2). In the DM groups, the fetoplacental vascular volume did not differ from that in normal
151 pregnancies at equivalent GA.

152 In normal pregnancies at term (GA 40+0) the FVV/BW-ratio was 48.9 ml/kg (95% CI: 44.5-56.7ml/kg).
153 In all DM groups the FVV/BW-ratio was lower, however this difference was only significant in the insulin
154 dependent DM groups; T1DM (-16.2ml/kg, $p=0.003$), GDMi (-12.1ml/kg, $p=0.009$), and GDMd (-7.8ml/kg,
155 $p=0.198$).

156 In normal pregnancies at term (GA 40+0) the FVV/PW-ratio was 33.9ml/kg (95% CI: 32.9-37.9ml/kg),
157 and this ratio was reduced in all DM groups, but the difference was only significant for pregnancies
158 complicated by GDMi (-81.5ml/kg, $p=0.012$) and with a strong trend in T1DM (-66.0ml/kg, $p=0.068$) (Table
159 2).

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

164 Discussion

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

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

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

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

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

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

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

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

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

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

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

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

249
250 **Acknowledgements:** The authors are grateful to Pernille Veiss-Pedersen, radiologist, for competent
251 assistance in performing the CTA. The author thanks Anne Staub Rasmussen, MD, for fruitful discussions
252 regarding the placental preparation and the angiography method.

253
254 **Funding:** This work was supported by The Faculty of Medicine at Aalborg University and by Aalborg
255 University Hospital at The North Denmark Region.

256
257 **Conflicts of interest:** The authors declare no conflict of interest.

258
259 **Author's contribution:** MØT, MS, and AS planned the research project. MØT collected all placentas and
260 prepared it for scanning. JBF took part of planning the CT angiography. ASK, LRØ, and JBF participated in
261 cooperation with MØT, MS, and AS in extracting the fetoplacental vascular volume based on the scanings.
262 PB and AP performed all the placental pathological examinations and assessed the pathological data. MØT,
263 MS, and AS performed the statistical analysis and data assessment and wrote the manuscript. All authors
264 read and approved the final manuscript.

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396 **Figure legends**

397

398 **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
399 diabetes mellitus, GA 37+1 (C and D). Macroscopic photography (A and C) and a 3D reconstruction of the fetoplacental blood
400 vessels (B and D).

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

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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	
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	-	-	-	-	-	-	-

<ul style="list-style-type: none"> •Pre-gestational (T1DM) or pre-treatment (GDM) •1st trimester •2nd trimester •3rd trimester 		<ul style="list-style-type: none"> • 58.0 (51.25 – 90.0) • 55.0 (46.8 – 67.0) • 50.0 (42.5 – 60.3) • 52.0 (49.5 – 57.8) 		<ul style="list-style-type: none"> • 31.5 (28.8-35.8) • - • 37.0 (N=1) • 32.0 (29.5 – 38.5) 		<ul style="list-style-type: none"> • 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.

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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

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

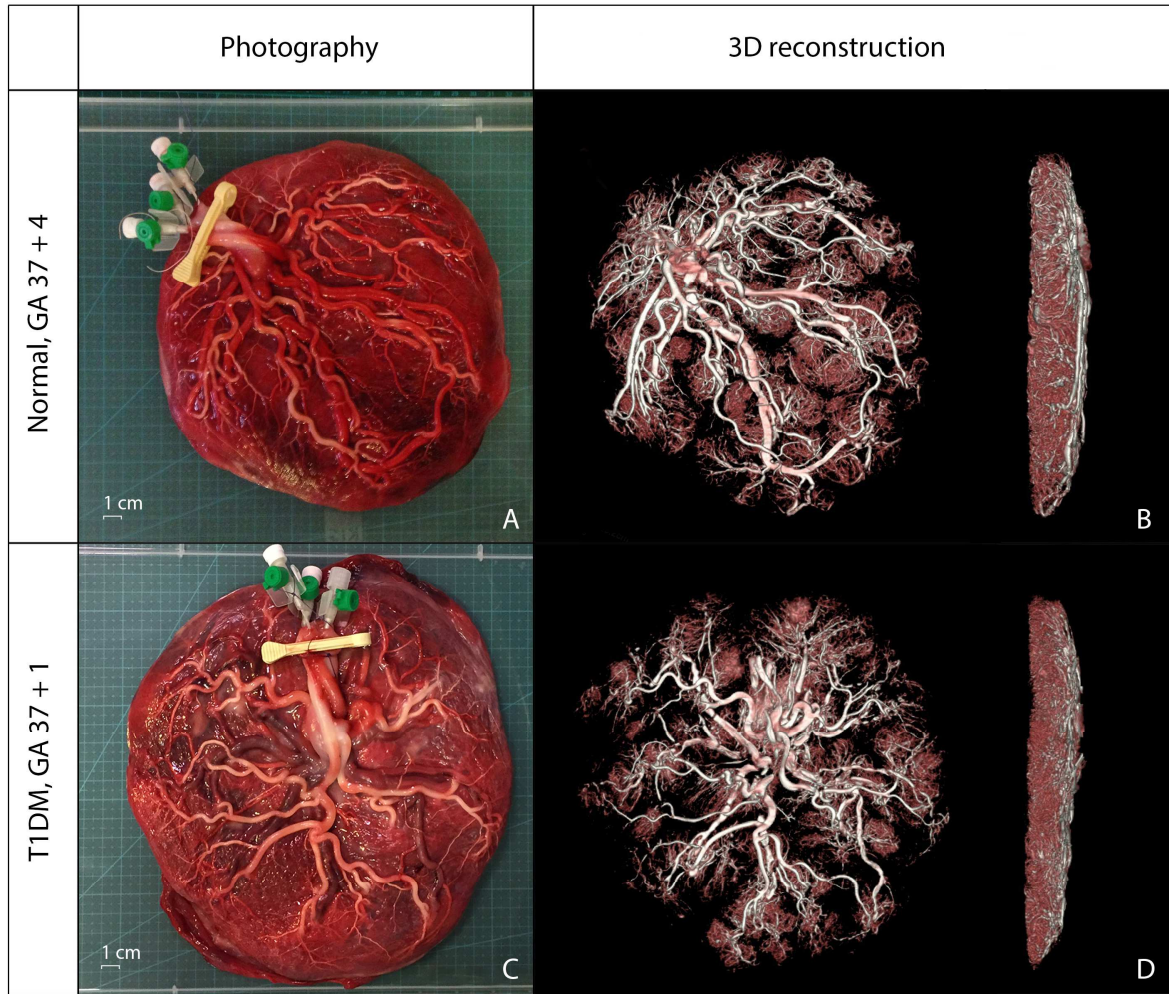
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Table 3: Diabetic placental histopathological findings.

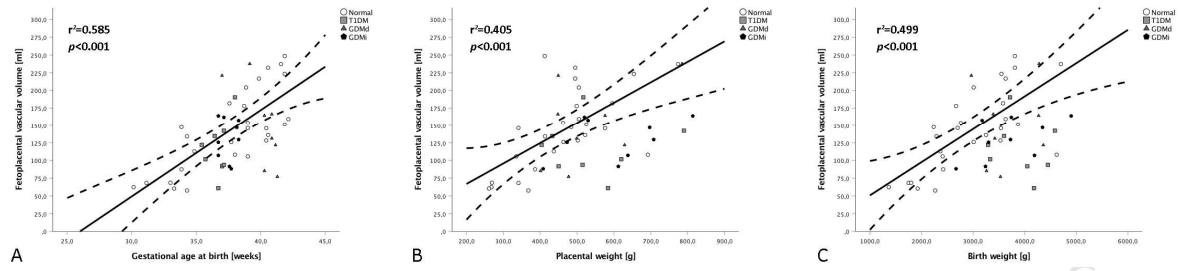
Placenta pathology \ Group	Normal	T1DM	GDMd	GDMi
Large placental weight, $p > 90$ [36]	14.8 (4/27)	37.5 (3/8)	12.5 (1/8)	55.6 (5/9)
Delayed villous maturation [35]	0.0 (0/27)	25.0 (2/8)	0.0 (0/8)	33.3 (3/9)
Long umbilical cord [37]	22.2 (6/27)	12.5 (1/8)	12.5 (1/8)	33.3 (3/9)
≥ 2 diabetic findings	7.4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

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

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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.