

1 **Title: Remodeling of the Cardiovascular Circulation in Fetuses of Diabetic**
2 **Mothers: A Fetal Computational Model Analysis**

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19 **Abstract**

20 **Aims:** Myocardial structural and functional abnormalities are known to occur in
21 fetuses of maternal diabetes mellitus (FMDM) and in their offspring. The main
22 aim of this investigation was to explore the cardiovascular circulatory patterns in
23 FMDM using a validated lumped computational model of the cardiovascular
24 system.

25 **Methods:** This was a multi-institutional study involving FMDM compared to
26 fetuses of maternal controls (FC). Fetal echocardiographic Doppler data from left
27 and right ventricular outflow tracts, aortic isthmus, middle cerebral and umbilical
28 arteries were fitted into a validated fetal circulation computational model to
29 estimate patient-specific placental and vascular properties. Non-parametric
30 comparisons were made between resistances, compliances and flows in the
31 brain and placenta in FMDM and FC.

32 **Results:** Data from 23 FMDM and 31 FC were fitted into the model. In FMDM,
33 compared to FC, placental relative resistance was lower (0.59 ± 0.50 versus
34 0.91 ± 0.41 ; $p < 0.05$) with higher brain relative resistance (2.36 ± 1.65 versus
35 1.60 ± 0.85 ; $p < 0.05$). Middle cerebral artery flow was lower in FMDM than FC
36 (0.12 ± 0.14 vs. 0.27 ± 0.21 ml/min; $p = 0.04$) with a lower cerebral-placental flow
37 ratio. Combined stroke volume was lower in FMDM (3.65 ± 2.05 ml) than FC
38 (4.97 ± 2.45 ml) ($p = 0.04$).

39 **Conclusions:** Blood flow is redistributed in FMDM to the placenta, away from the
40 brain. This alteration may play a role in the postnatal health of these fetuses.

41 **Key words:** Fetus; Maternal Diabetes Mellitus; Computational model;
42 Resistance; Compliance
43 **Abbreviations:** MDM – Maternal diabetes mellitus; FMDM – Fetuses of mothers
44 with diabetes mellitus; FC – Fetuses of control mothers; EFW – Estimated fetal
45 weight; UA – Umbilical artery; MCA – Middle cerebral artery; LVOT – Left
46 ventricular outflow tract; RVOT – Right ventricular outflow tract; CCO- Combined
47 cardiac output; VTI – Velocity time integral; vol – Volume; SV – stroke volume

48 **Introduction**

49 Significant short and long-term morbidities have been known to occur in the
50 offspring of mothers with diabetes mellitus. There is a five-fold increase in the risk
51 of congenital heart disease in fetuses of mothers with diabetes mellitus (FMDM);
52 they also have a higher incidence of a reversible hypertrophic cardiomyopathy
53 and subclinical myocardial dysfunction.[1-3] Maternal diabetes mellitus (MDM)
54 has been linked to fetal macrosomia, fetal growth restriction (FGR), and fetal and
55 neonatal demise.[4] There also may be other lasting effects in these offspring
56 including a propensity for neurological deficits, obesity, diabetes, hypertension
57 and cardiovascular events later in life.[4-6]

58 Current knowledge of the underlying mechanism of disease in FMDM suggests a
59 combination of chemical, molecular and epigenetic influences on the fetus and
60 placenta.[4, 7-9] Animal studies have shown that fetuses of hyperglycemic dams
61 have reduced pancreatic β cell mass and reduced expression of insulin like
62 growth factor.[10] Increased villous stromal capillarization and concentration of
63 endogenous nucleoside adenosine (a potent vasodilator and anti-inflammatory
64 agent) are seen in the placentae of FMDM.[11, 12] Rodent experiments have
65 noted lower number of nephrons in the neonatal kidneys of MDM.[4] It is likely
66 that these alterations in the fetal organ systems are associated with circulatory
67 adaptations in FMDM. Computational modeling of the fetal circulation allows
68 assessment of the relevant parameters non-invasively and in their natural
69 environment in human fetuses.

70 A lumped model of the fetal circulation was created, validated and explored in
71 FGR fetuses (implemented in Simulink, MATLAB 2013b, The MathWorks Inc.,
72 Natick, MA).[13, 14] This model provides a good non-invasive approximation of
73 the fetal circulation to study hemodynamic changes induced by abnormal growth
74 conditions. Alterations in fetal hemodynamics (predominantly flows) can be
75 assessed non-invasively in clinical practice by localized Doppler measurements.
76 However, computational models have the advantage of providing a more global
77 view on hemodynamics as well as allowing the quantification of circulatory
78 parameters that are currently not measurable non-invasively, such as pressures
79 and vascular or organ properties like resistance and compliance. We applied this
80 model to FMDM and compared them to normal fetal controls to understand if
81 there were circulatory remodeling patterns in FMDM. This is a pilot study with an
82 exploratory hypothesis that the circulatory systems hemodynamics/blood flow
83 circulation in FMDM and FC may be different.

84 **Methods**

85 **Study Population**

86 This was a cross-sectional multi-institutional case control study of 54 fetuses, 23
87 FMDM) and 31 fetuses of control mothers (FC). The cases were enrolled from
88 2013 to 2016; these were compared to normal fetal controls (FC) recruited from
89 2012 to 2016. Of the 23 FMDM, 18 were recruited at Bronx Lebanon
90 Hospital Center, Bronx, New York (Center 1), the remaining 5 were enrolled at
91 Barcelona Center for Fetal and Neonatal Medicine (Center 2). Of the 31 FC, 9
92 were enrolled at Center 1 and the remaining at Center 2. All mothers were

93 referred for standard of care clinical indications.[15] Fetuses with arrhythmias,
94 congenital heart disease, known genetic and chromosomal abnormalities, and
95 multiple gestations were excluded. Singleton fetuses of mothers with DM and
96 with structurally normal hearts without hypertrophy were included as cases, if the
97 mothers agreed to participate and signed an informed consent. Cardiac
98 hypertrophy was assessed based on gestational age and previously published
99 nomograms.[16] Singleton fetuses of mothers without DM, with structurally and
100 functionally normal hearts, and with the following additional inclusion criteria were
101 included as FC:

102 a) Estimated fetal weight within the 10th and 90th percentiles.

103 b) No history of medical, surgical or obstetric complications.

104 Gestational age was based on the beginning of the last menstrual period and
105 verified by sonographic measurement of the crown-rump length in early
106 pregnancy. The Institutional Review Boards at both institutions approved the
107 study protocols.

108 Estimated fetal weight (EFW) was calculated from the biparietal diameter, head
109 and abdominal circumference, and femur length using the Hadlock formula.[17]

110 Umbilical artery (UA) Doppler was evaluated in a free loop of the umbilical cord.
111 Middle cerebral artery (MCA) Doppler was measured in a transverse view of the
112 fetal skull at the level of its origin from the circle of Willis.[18] Aortic isthmus (Aoi)
113 flow velocity was recorded either in a sagittal view of the fetal thorax with a clear
114 visualization of the aortic arch or in a cross section of the fetal thorax at the level
115 of the 3-vessel and trachea view. Pulse wave Doppler velocity waveforms of the

116 left ventricular outflow tract (LVOT) were obtained in the 5-chamber view and of
117 the right ventricular outflow tract (RVOT) were obtained from the short axis of the
118 fetal heart in sagittal section. Doppler tracings were recorded with the sample
119 volume positioned just proximal to the valve in the center of the vessel. The angle
120 of insonation between the vessel and the Doppler beam was kept as close as
121 possible to 0° and always below 30° . Diameters of the aortic and pulmonary
122 artery valves were measured in frozen real-time magnified images during systole
123 by the leading edge-to-edge method.[19]

124 **Lumped Model of Fetal Circulation**

125 Details of the fetal lumped computational model and its validation have been
126 published previously.[13, 14] A brief description is provided here. The electrical
127 equivalent model of the different compartments of the fetal circulation was
128 constructed using two main building blocks of the arterial segments and
129 peripheral vascular beds. The arterial segments were configured to include the
130 local resistance of blood due to blood viscosity that was modeled with a resistor,
131 the arterial compliance was modeled with a capacitor and the blood inertia was
132 modeled with an inductor. The peripheral vascular bed was constructed based on
133 a three-element Windkessel model. The simplified fetal circulation was modeled
134 as a set of 19 arterial segments and 12 vascular beds as described
135 previously.[13] The amount of blood flow that was distributed towards different
136 fetal areas, including the brain, the placenta and the coronary arteries, was
137 calculated as the percentage of combined cardiac output (CCO). For the
138 purposes of this study, both FMDM and FC Doppler data were fitted to the

139 validated model. Physical dimensions of all arterial segments were calculated
140 relative to the expected value from gestational age of the fetus using previously
141 published equations.[13, 14] Changes in length and diameter of the fetal arterial
142 segments, vascular bed resistances and compliances were scaled as a function
143 of the EFW too, as described in previous publications from this group and
144 reference data.[14, 20] The patient-specific model fitting was done by means of
145 an optimization algorithm in which a set of 13 parameters were estimated
146 automatically by minimizing the difference of model-based and measured flow
147 waveforms in the study cohort. Statistical comparisons were made from the
148 simulation outputs between FMDM and FC to assess differences.

149 **Statistical Analysis**

150 Descriptive data were expressed as mean \pm standard deviation. Kolmogorov-
151 Smirnov test were conducted in all variables to test for normality. Two-tailed t-test
152 comparisons were made for normally distributed data and Mann-Whitney U test
153 was used for non-parametric data comparisons. All tests of statistical significance
154 were two-sided and a p value \leq 0.05 was considered significant. Linear
155 regression analysis was performed in FMDM and FC groups for some key
156 parameters to determine the effects of gestation age on the variables (Table 4).
157 Also, liner regression including all the data (FMDM and FC) and an interaction
158 term between GA and case group was performed to evaluate the relationship
159 between gestational age and some key model parameters. All statistical analyses
160 were performed using SPSS version 9.4.

161

162 **Results**

163 Data from 23 FMDM and 31 FC were used to create a personalized fetal
164 circulation computational model. The baseline characteristics in the two groups
165 are detailed in table 1. The median gestational age (weeks) was similar in FMDM
166 and FC. Overall, in the FMDM, 17 mothers were controlled on insulin (10 mothers
167 had type 2 DM, 4 had type 1 DM, 3 had gestational DM), 4 on oral medications
168 (all mothers had gestational diabetes) and 2 were controlled on diet alone (2 had
169 gestational DM). Mean maternal BMI in FMDM group was significantly higher
170 than the FC group. Two mothers in the FMDM group had additional co-
171 morbidities of chronic hypertension, three mothers had pre-pregnancy
172 hypothyroidism and one mother had genetic prothrombin deficiency. None of the
173 mothers in the FC group had additional co-morbidities. The estimated fetal
174 weights (grams) were similar between the two groups. All fetuses were born full
175 term (>37 weeks gestation), except for one born premature at 31 weeks
176 gestation in the FMDM group and one in the FC group at 30 weeks 6 days. Birth
177 weights were also similar in both groups.

178 Table 2 shows the results of the hemodynamic parameters that were measured
179 and modeled from the echocardiographic data. There were significant differences
180 in the baseline parameters for the velocity time integrals (VTI) of the left and right
181 ventricular outflow tracts (LV_VTI: VTI of left ventricular outflow tract Doppler,
182 RV_VTI: VTI of right ventricular outflow tract Doppler) measured from the
183 recorded fetal Doppler echocardiograms between the two groups. Right
184 ventricular stroke volume (RVSV) and total stroke volume were lower in FMDM;

185 the differences in left ventricular stroke volume (LVSV), RVSV and SV between
186 FMDM and FC became more apparent beyond 22 weeks (Figure 1A, 1B and
187 1C).

188 The results of the fitted organ and vessel parameters from the fetal
189 cardiovascular lumped model have been presented in Table 3. There was
190 redistribution of blood flow away from the brain toward the placenta in FMDM.
191 There was an increase in model-based brain resistance ($R_{\text{brain}}/R_{\text{brain0}}$) (FMDM
192 2.36 ± 1.66 , FC 1.60 ± 0.85 , $p = 0.03$) (Table 3) with associated lower MCA blood
193 volume (MCA_vol/SV) (Figure 2A, Table 2) in FMDM compared to FC. Aortic
194 isthmus blood volume (AoI_vol/SV) (Figure 2B) was higher in FMDM (Table 2).
195 Model-based placental resistance ($R_{\text{plac}}/R_{\text{plac0}}$) was significantly lower in
196 FMDM compared to FC (0.59 ± 0.5 vs. 0.91 ± 0.41 ; $p < 0.05$) (Table 3) with
197 associated increased UA blood volume (UA_vol/SV) (Table 2). Thus, compositely
198 there the cerebral placental blood volume ratio (MCA_vol/UA_vol) was lower in
199 FMDM group (Table 2) (0.23 ± 0.20 vs. 0.46 ± 0.34 ; $p = 0.05$).

200 Model-based diameters of the cerebral arteries were significantly smaller
201 compared to controls whereas aortic diameters were higher and umbilical arteries
202 remained unchanged (Table 3, figure 3). No vessels or organ compliances were
203 significantly altered. Pressures estimates by the model were not different at any
204 location. No significant differences in the variables were noted when data was
205 reevaluated after exclusion of FDM with maternal DM control on diet alone or
206 after excluding FDM with maternal hypertension. No significant correlation was
207 found between $R_{\text{plac}}/R_{\text{plac0}}$ ($R^2 = 1.3$, $p = 0.95$) or $R_{\text{brain}}/R_{\text{brain0}}$ ($R^2 = 0.0234$,

208 p= 0.49) to HgbA1c levels. When evaluating the relationship between GA and
209 some of the model parameters, Rplac/Rplac0 was noted to slightly increase with
210 increasing GA as is seen in all pregnancies ($R^2 = 0.221$, $p = 0.006$) and no
211 significant change was noted in Rbrain/Rbrain0 with GA ($R^2 = 0.125$, $p = 0.08$).
212 However, when considering the non-normalized values of both placenta and
213 brain resistances (Rplac, Rbrain) the same results were observed (see
214 supplementary figure). Moreover, when performing the linear regression analysis
215 in their normal values (Rplac0, Rbrain0), no differences between control and
216 FDMD groups were found (see supplementary figure), which suggest that
217 differences in model-based parameters were not due to differences in GA
218 between groups.

Commented [PGC1]: I think you should add the statistical analysis also in the methods parts.

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221 Discussion

222 The present investigation assessed circulatory remodeling in FMDM as
223 compared to FC using a validated lumped model of the fetal circulation. Our key
224 findings from the model are that placental resistance decreases in FMDM, (while
225 compliance remains similar), and that cerebral resistance increases
226 concomitantly. Consequently, there is a redistribution of blood flow predominantly
227 towards the placenta, and diminished blood flow to the brain with concurrently
228 with decreased SV.

229 Morphological changes such as vascular anomalies, increased placental
230 thickness and weight have commonly been seen in placentae of women with

231 DM.[7, 21] A higher release of cytokines, such Tumor Necrosis Factor- α , an
232 upregulation of inflammation related genes, increased concentration of
233 vasodilator endogenous nucleoside adenosine and increased vascular
234 endothelial growth factor involvement have been noted in these placentae.[7, 11,
235 12] Increased size, vascularization and vasodilatation in FMDM placentae
236 support the decrease in placental resistance noted in our study and the resulting
237 alterations in uterine artery flow. Interestingly, no change in placental compliance
238 was found suggesting the absence of fibrosis of tissue damage altering vessel
239 and tissue elasticity.

240 In this study, we have shown that blood flow to the brain in FMDM is altered with
241 higher brain resistance, lower MCA flow and lower relative cerebral placental
242 blood volume. It is likely that these changes contribute to the functional and
243 developmental neurological abnormalities in FMDM that are seen in postnatal
244 life. Electroencephalograms performed on neonates of MDM have been
245 described to have features suggestive of abnormal development of brain function
246 that correlate to maternal diabetes control.[22] Abnormal visual evoked
247 potentials, lower cognitive scores and lower gross and fine motor achievements
248 as well as higher attention deficits are seen in children born to MDM.[6, 23]

249 We noted decreased SV in FMDM compared to FC. In a previous publication, we
250 have noted a subclinical decrease in myocardial deformation in FMDM that
251 further supports this finding.[3] There have been limited publications that evaluate
252 CO in MDM. Previous fetal MCA and UA Doppler studies have not been able to

253 demonstrate any changes in FMDM likely due to their limited and focused
254 evaluations.[24, 25]

255 The EFW in FMDM were comparable to FC. It is speculative if other circulatory
256 abnormalities may be seen in FMDM who are large for gestational age or have
257 evidence of intra-uterine growth retardation. The circulatory abnormalities in
258 IUGR have been well characterized. A fascinating observation in this report was
259 that, from 22 weeks GA, there seemed to a different trend in the change in
260 circulatory parameters with GA between FMDM and FC (Figures 2-4). It is
261 unknown if these alterations are a continuum of ongoing processes from the first
262 trimester or if this GA represents a critical tipping point when the changes
263 become irreversible.

264 The observed decrease in stroke volume (and to a lesser extent cardiac output)
265 is either related to myocardial dysfunction or to decreased demand from the
266 peripheral organs. Given that there is no evidence of pressure overload and that
267 the enlarged placenta, with increased flow, likely increases oxygenation and
268 nutrition, a decreased demand is most likely. Interestingly, this seems to go
269 together with a trend of a blunted decrease in organ resistances/diameters (in our
270 model, the brain and coronaries, from literature, possibly the kidneys as well),
271 ultimately resulting in the decreased organ flow as clearly illustrated in the brain
272 in FMDM and potentially predisposing them to post-natal problems when
273 oxygenation and nutrition normalizes.

274 The present fetal circulation model does not account for changes that may occur
275 because of other alterations in fetal milieu such as chemical and inflammatory

276 markers and genetic influences in FMDM. However, since we used patient
277 specific data to build the model and its boundary conditions (GA, EFW, heart
278 rate, Doppler velocities and valve radius) to estimate the specific hemodynamic
279 parameters variation for each individual fetus, we believe this provides a
280 reasonable estimate of the circulatory adaptations in FMDM. Limitations of the
281 model have been discussed in a previous publication.[14] The changes described
282 in this study may not be applicable to all trimesters of pregnancy in FMDM.
283 Additionally, most mothers in the FDM group were well controlled. It is likely that
284 some changes in the FDM were blunted because of the adequate glucose control
285 in the mothers; it is speculative that the results may vary in the setting of
286 inadequate maternal diabetes control. Despite these significant limitations, the
287 novel application of these emerging methods suggests the potential for future
288 applications in prospective studies.

289

290 This study provides a comprehensive evaluation of the circulatory remodeling in
291 FMDM using patient specific computational modeling. Increased cerebral
292 resistance and decreased placental resistance contribute to the reversal of CPR
293 that is unique to FMDM. The prognostic impact of these findings is unclear at the
294 present time, however, we believe this study is utilitarian to future investigations.

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408 normal pregnancies: a Doppler velocimetry of middle cerebral and umbilical
409 arteries, *Acta Neurol Belg* 114(1) (2014) 15-23.

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411

412 **Figure legends:**

413 **Figure 1:** Regression plots illustrating left ventricular stroke volume (LVSV)(1A),
414 right ventricular stroke volume (RVSV) (1B) and total stroke volume (SV) (1C) as
415 a function of gestation age (GA)

416

417 **Figure 2:** Regression plots illustrating middle cerebral artery blood volume
418 (MCA_vol)(2A) and aortic isthmus blood volume (AoI_vol) (2B) as a function of
419 gestation age (GA)

420

421 **Figure 3:** Regression plots illustrating the modelled vessel diameters (relative to
422 the expected value for gestational age (GA) from literature) and their changes
423 with GA: A: aortic diameter (Ao_diam); B: cerebral artery diameter (cA_diam); C:
424 umbilical artery diameter (uA_diam)

425 **Table 1:** Baseline maternal, fetal and neonatal characteristics in diabetic and
 426 control groups

	Diabetic group (n=23)	Control group (n=31)	P value
Gestational age at time of fetal echocardiogram (weeks)	26.8±3.8	28.1±4.1	0.24
Hemoglobin A1c	6.06±0.8%	-	-
Maternal BMI	32.5±7.4	23.8±4.02	<0.001
Estimated fetal weights (grams)	1164±683	1371±688	0.58
Birth weights (grams)	3411±554	3240±556	0.27

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429 **Table 2:** Comparisons of (modeled and measured) flow related parameters
 430 between fetuses of mothers with diabetic mellitus (FMDM) and fetal controls (FC)

	Variable	FMDM (n=23)	FC (n=31)	p value
Heart	LV_VTI (cm)	1.57 ± 0.96	2.19 ± 1.23	0.058 [§]
	RV_VTI (cm)	2.08 ± 1.14	2.78 ± 1.35	0.069 [§]
	LV_SV (ml)	1.57 ± 0.96	2.19 ± 1.23	0.058 [§]
	RV_SV (ml)	2.08 ± 1.14	2.78 ± 1.35	0.05*
	SV (ml)	3.65 ± 2.05	4.97 ± 2.45	0.04*
	RCO (ml/min)	303 ± 165	391 ± 183	0.07
	LCO (ml/min)	228 ± 138	307 ± 160	0.076 [§]
	CCO (ml/min)	531 ± 295	698 ± 326	0.06
	HR	147 ± 9	142 ± 10	0.05*
	MCA_VTI (cm)	6.44 ± 2.04	7.09 ± 2.17	0.48
Brain	MCA_vol (ml)†	0.12 ± 0.14	0.27 ± 0.21	0.01* [§]
	MCA_vol/SV (%)†	5.79 ± 3.94	9.08 ± 5.06	0.01* [§]
	Aol_VTI (cm)	11.6 ± 2.07	11.29 ± 2.62	0.82
Aorta	Aol_vol (ml)†	0.81 ± 0.48	0.78 ± 0.44	0.82
	Aol_vol/SV (%)†	23.07 ± 8.93	16.8 ± 5.83	< 0.01* [§]
	UA_VTI (cm)	10.57 ± 2.53	11.38 ± 3.71	0.86
Placenta	UA_vol (ml)†	0.64 ± 0.56	0.56 ± 0.27	0.54
	UA_vol/SV (%)†	34.1 ± 15.94	25.32 ± 11.7	0.01* [§]
	MCA_vol/UA_vol†	0.23 ± 0.20	0.46 ± 0.34	0.01* [§]

431 LV_VTI: Velocity time integral (VTI) of left ventricular outflow tract Doppler,
432 RV_VTI: VTI of right ventricular outflow tract Doppler, LV_SV: Left ventricular
433 stroke volume, RV_SV: Right ventricular stroke volume, SV: Stroke volume,
434 RCO: Right ventricular cardiac output, LCO: Left Ventricular cardiac output,
435 CCO: Combined left and right ventricular cardiac output, HR: Heart rate
436 MCA_VTI: VTI of middle cerebral artery Doppler, MCA_vol: Middle cerebral
437 artery blood volume/heartbeat, AoI_VTI: VTI of aortic isthmus Doppler, AoI_vol:
438 Aortic isthmus blood volume/heartbeat, UA_VTI: VTI of umbilical arterial Doppler,
439 UA_vol: Umbilical Artery blood volume/heartbeat , ‡ Modeled variables,
440 *Significant $p \leq 0.05$, § not-normally distributed.
441

442 **Table 3:** Comparisons of the modeled vessel diameters, organ resistances and
 443 compliances between fetuses of mothers with diabetic mellitus (FMDM) and fetal
 444 controls (FC)

Variable	FMDM (n=23)	FC (n=31)	p value
Rplac/Rplac0	0.59 ± 0.5	0.91 ± 0.41	<0.01* [§]
Cplac/Cplac0	1.54±0.78	2.12±1.35	0.07
Rbrain/Rbrain0	2.36 ± 1.66	1.60 ± 0.85	0.03*
Cbrain/Cbrain0	0.43±0.46	0.40±0.25	0.74
RcorA/RcorA0	1.64 ± 0.60	1.65 ± 1.10	0.09 [§]
D_Aorta/D_Aorta0	1.19 ± 0.25	1.07 ± 0.14	0.05* ^{2*§}
C_Aorta/C_Aorta0	2.49±0.90	2.69±1.12	0.48
D_cerA/D_cerA0	0.73 ± 0.25	1.00 ± 0.33	< 0.01* [§]
C_cerA/C_cerA0	1.04±1.26	0.75±0.67	0.28
D_UA/D_UA0	1.18 ± 0.32	1.10 ± 0.19	0.35
C_UA/CUA0	1.87±1.14	1.80±0.84	0.80

445 Rplac: Placental resistance, Cplac: Placental compliance, Rbrain: Brain
 446 resistance, Cbrain: Brain compliance, RcorA: Coronary arteries resistance,
 447 D_Aorta: Aorta diameter, C_Aorta: Aorta compliance, D_cerA: Cerebral arteries
 448 diameter, C_cerA: Cerebral arteries compliance, D_UA: Umbilical arteries
 449 diameter, C_UA: Umbilical arteries compliance, * Significant $p \leq 0.05$, [§] not-
 450 normally distributed.

451 **Table 4: Linear Regression Analysis of Fetuses of Mothers with Diabetes**
 452 **Mellitus (FMDM) and Fetal Controls (FC)**

Variable	R ² FMDM (n=23)	R ² FC (n=31)
Rplac/Rplac0	0.055	0.188
Rbrain/Rbrain0	0.024	0.095
RcorA/RcorA0	0.099	0.528
LV_SV	0.615	0.753
RV_SV	0.707	0.783
MCA_vol	0.395	0.596
Aol_vol	0.412	0.467
UA_vol	0.314	0.422
CCO	0.685	0.849

Commented [PGC2]: Why here is not included the p-value??? Before we have it...

453 Rplac: Placental resistance, Rbrain: Brain resistance, RcorA: Coronary arteries
 454 resistance, LV_SV: Left ventricular stroke volume cardiac output, RV_SV: Right
 455 ventricular stroke volume, MCA_vol: Middle cerebral artery blood
 456 volume/heartbeat, Aol_vol: Aortic isthmus blood volume/heartbeat, UA_vol:
 457 Uterine Artery blood volume/heartbeat, CCO: Combined left and right ventricular
 458 cardiac output.