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Placental T2* estimated by magnetic resonance imaging and fetal weight estimated by ultrasound in the prediction of birthweight differences in dichorionic twin pairs

Sofie Sondrup Poulsen, Marianne Sinding, Ditte Nymark Hansen, David A. Peters, Jens B. Frøkjær, Anne Sørensen

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1 **Placental T2* estimated by magnetic resonance imaging and fetal weight**
2 **estimated by ultrasound in the prediction of birthweight differences in**
3 **dichorionic twin pairs**
4

5 Authors
6 Sofie Sondrup Poulsen, MD[1], Marianne Sinding, MD, PhD[2], Ditte Nymark Hansen, MD[1,3], David
7 A. Peters, MSc, PhD[4], Jens B. Frøkjær, MD, PhD, prof[3,5], Anne Sørensen, MD, PhD[1,3]
8

9 [1] Department of Obstetrics and Gynecology, Aalborg University Hospital, Aalborg,

10 Reberbansgade 15, 9000 Aalborg, Denmark

11 [2] Department of Obstetrics and Gynecology, Viborg Regional Hospital

12 Heibergs Alle 4, 8800 Viborg, Denmark

13 [3] Department of Clinical Medicine, Aalborg University Hospital,

14 Sdr. Skovvej 15, 9000 Aalborg, Denmark

15 [4] Department of Clinical Engineering, Central Denmark Region, Aarhus,

16 Olof Palmes Alle 13, 8200 Aarhus N, Denmark

17 [5] Department of Radiology, Aalborg University Hospital, Aalborg,

18 Hobrovej 18-22, 9000 Aalborg, Denmark

19

20 Corresponding author
21 Dr. Marianne Sinding
22 Department of Obstetrics and Gynecology
23 Aalborg University Hospital
24 Reberbansgade 15
25 9000 Aalborg
26 Denmark
27 Mobile: +45 29437505
28 E-mail: masore78@hotmail.
29
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31 Conflicts of interest
32 None declared
33

37
38 **Introduction**

Intertwin birthweight (BW) difference is associated with an increased risk of adverse outcome. Ultrasound estimated fetal weight (EFW) is the current method to predict intertwin BW difference, however, the sensitivity is poor. Therefore, new methods are needed. Placental T2* estimated by magnetic resonance imaging (MRI) reflects placental oxygen environment and thus placental function. This study aimed to investigate placental T2* difference as a new predictor of BW difference, and to compare it to the EFW.

Methods

We included 25 dichorionic twin pairs at 19-38 weeks' gestation. Placental T2* was obtained by MRI and EFW by ultrasound. Correlations between each predictor and BW difference were examined by simple linear regression, and the combined model was analyzed by multiple linear regression and likelihood ratio test.

Results

Strong positive correlations were demonstrated between intertwin differences in placental T2* and BW (r=0.80, p<0.005), and EFW and BW (r=0.64, p<0.005). Placental T2* difference was a strong independent predictor of BW difference (p<0.001), and the combined model performed better than each predictor alone (p<0.0001).

Discussion

This pilot study demonstrates that placental T2* difference may be a predictor of intertwin BW difference irrespectively of fetal size. The clinical potential of this method deserves further investigation in a larger clinical study

Introduction

The twinning rate (twin deliveries per 1,000 deliveries) has increased remarkable in many

76 developed countries over the last four decades. In Denmark, the rate has more than doubled
77 from 10 to 21 per. 1000 deliveries [1]. This is due to increased maternal age and the extensive
78 use of assisted reproductive technologies. When compared to singletons, twin pregnancies are
79 at higher risk of adverse neonatal outcomes, including fetal growth restriction, late
80 miscarriage, and preterm delivery [1]. In addition, the risk is further increased in twin
81 pregnancies with birthweight (BW) discordance [2-4]. Intertwin BW discordance has various
82 definitions, but most commonly it is expressed as an intertwin BW difference ≥ 20 % relative
83 to the larger twin [2,4-8], and it occurs in approximately 16 % of all twin pregnancies [4].

84   Currently the prediction of BW discordance in twin pairs is performed by
85 ultrasound estimates of fetal weight (EFW) using fetal biometrics. These methods have been
86 extensively studied throughout the last decades. The majority of publications have reached
87 the conclusion of poor sensitivity in predicting intertwin BW discordance [5,6,9-13], however
88 the performance is better when performed near delivery [7,8,13-15]. Recently, Hehir *et al.*
89 [13] investigated the performance of ultrasound EFW in predicting intertwin BW discordance
90 at different gestational ages. Overall they found low sensitivity in predicting intertwin BW
91 discordance, however, the sensitivity did increase throughout gestation (24-28 weeks'
92 gestation: sensitivity 40 %, specificity 87 %, 32-36 weeks' gestation: sensitivity 65 %,
93 specificity 72 %).

94   Thus, new methods to improve the prediction of BW discordance in twin
95 pregnancies are highly needed, in order to improve the antenatal management and thereby
96 the neonatal outcome in these high-risk pregnancies. New methods in this field may focus on
97 placental function rather than fetal size, in order to detect placental dysfunction rather than
98 abnormal fetal growth. It has been demonstrated, that placental dysfunction is associated
99 with placental hypoxia [16]. Placental oxygenation can be investigated non-invasively by the
100 use of T2* weighted magnetic resonance imaging (MRI) as demonstrated previously in human
101 singleton studies [17-22]. The transverse relaxation time constant (T2*) is based on the
102 magnetic properties of deoxyhemoglobin, as it causes local magnetic field inhomogenties, and
103 thereby reduces the tissue T2* relaxation time [23]. Previous studies indicate that placental
104 T2* may have the potential to detect placental dysfunction in singleton pregnancies, as
105 reduced placental T2* is closely correlated to low BW and abnormal placental histopathology
106 in singleton pregnancies [21,22,24].

107   To the best of our knowledge, this is the first study to investigate placental T2* in

108 dichorionic twin pregnancies. This study aimed to investigate intertwin placental T2*

109 difference as a predictor of intertwin BW difference, and to compare placental T2* to

110 ultrasound estimates of fetal weight in the prediction of intertwin BW differences in

111 dichorionic twin pairs.

112

113 Methods

114

115 **Subjects**

116 This prospective study was carried out in the period from July 2014 to July 2015 at Aalborg

117 University Hospital, Denmark. We included 25 dichorionic twin pregnancies at 19 – 38 week's

118 gestation attending for routine or specialized antenatal care of which ultrasound EFW is part

119 of the clinical practice. Transabdominal ultrasound examination was performed by

120 experienced specialized sonographers or specialists in fetal medicine, and the EFW was

121 calculated using the Hadlock formula, based on the head circumference, the abdominal

122 circumference, and the femur length [25]. MRI scan was performed on the same day, and the

123 twin fetuses and their placentas were assigned 1 or 2 based on their location to either the left

124 or the right side of the uterus, respectively. In addition, the presenting fetus was assigned A

125 and the second fetus B. This labeling followed the Danish obstetric guidelines [26]. The MRI

126 findings were carefully correlated to the ultrasound findings and the medical records from the

127 delivery. BW and EFW were converted into Z-scores and the corresponding percentages

128 based on the reference by Marsal *et al.* [27]. The procedures were approved by the Regional

129 Committees on Biomedical Research Ethics (Journal number M-20090006 and N-20090052),

130 and reported to the Danish Data Protection Agency (2008-58-0028). Oral and written consent

131 were obtained from all participating women.

132

133 **MRI Procedure**

134 Placental T2* measurements were acquired with a GE Discovery MR450 1.5 Tesla MRI system

135 (GE Healthcare, Milwaukee, USA) using a cardiac-receiver coil placed over the abdomen,

136 covering the entire uterus. In the bore, the participants were positioned in a left lateral

137 position to avoid compression of the inferior vena cava.

138 Initially, a T2 weighted localizing scan was performed to obtain the anatomic orientation of

139 the two fetuses and their placentas. This was followed by a placental T2* scan, using a multi-

140 echo gradient-recalled sequence with the following parameters: TR 70.9ms; 16 echoes

141 ranging from 3.0 to 67.5ms in steps of 4.3ms; flip-angel 30°, field of view 350×350 mm; and

142 matrix 256×128. This matrix resulted in an in-plane resolution of 1.37×2.73 mm. In each

143 placenta, two separate 8-mm slices were acquired in a plane perpendicular to the placentas.

144 Each slice was obtained within a single breath-hold of 12 seconds.

145

146 **MRI Analysis**

147 An in-house developed software; RoiTool 3.8 written in MATLAB (MathWorks Inc, Natick, MA,

148 USA) was used to process the MRI data. All images were carefully checked for placental

149 susceptibility artifacts. For each placenta, regions of interest (ROIs) were drawn on two

150 separate slices covering the entire placenta (Figure 1). In each placental slice the size and the

151 location of the ROI was adjusted to correct for artifacts including uterine contractions and

152 both fetal and maternal movements during the 12 second T2* acquisition time. A single

153 examiner [MS], who was blinded to pregnancy outcomes, performed the ROI drawings.

154 Placental T2* values were calculated by fitting the average signal within each ROI as a

155 function of echo time using a mono-exponentially decaying function with the equilibrium

156 magnetization (M_0) and T2* as free parameters [28]. The mean placental T2* value of each

157 placenta was calculated as an average of the two separate placental slices. Placental T2*

158 values were converted into Z-scores based on a previously published dataset of normal

159 singleton pregnancies [21].

160

161 **Statistical analysis**

162 Each intertwin difference was calculated as twin 1 minus twin 2. The correlations between

163 intertwin placental T2* difference, intertwin EFW difference and intertwin BW difference

164 were examined separately using simple linear regression analysis. Models to predict intertwin

165 BW difference including the combination of both intertwin EFW difference and intertwin

166 placental T2* difference, and also the intertwin EFW difference alone, were examined using

167 multiple linear regression. The performances of the models were compared by the likelihood

168 ratio test. Statistics were performed with the software IBM SPSS Statistics version 24.0.

169 Statistical significance was assumed at the 5 % level.

170 Results
171 Of the 25 dichorionic twin pairs included in the study, three (12.0 %) were diagnosed with

172 intertwin BW difference ≥ 20 %. The median time interval between MRI and birth was 12.4

173 gestational weeks (interquartile range, 5.6 ; 14.3). Maternal and pregnancy characteristics for

174 the participating women are shown in Table 1.

175   We demonstrated significant positive correlations between the intertwin BW

176 difference and both variables: Intertwin placental T2* difference (r=0.80, p<0.005, Figure 2)

177 and intertwin EFW difference (r=0.64, p<0.005, Figure 3). Using multiple linear regression

178 analysis we found that the intertwin placental T2* difference remained a significant predictor

179 (p<0.001) of intertwin BW difference even after adjusting for intertwin EFW difference. This

180 explains why the combined model including both of the variables intertwin EFW difference

181 and intertwin placental T2* difference performed significantly better (adjusted R^2 = 0.72)

182 than the model based on intertwin EFW difference alone (adjusted R^2=0.39), p<0.0001 (Table

183 2).

184 Discussion
185 In this study we investigated intertwin placental T2* and EFW differences as predictors of

186 intertwin BW difference in 25 dichorionic twin pairs. We demonstrated a strong positive

187 correlation between intertwin placental T2* difference and intertwin BW difference.

188 Furthermore, we demonstrated a significant positive correlation between intertwin EFW

189 difference and intertwin BW difference, however this correlation was not as strong as the

190 correlation between intertwin placental T2* difference and intertwin BW difference. A

191 combined model to predict intertwin BW difference including a combination of intertwin

192 placental T2* difference and intertwin EFW difference performed significantly better than a

193 model based on intertwin EFW difference alone. These findings indicate that intertwin

194 placental T2* difference is a significant predictor of intertwin BW difference even after

195 adjusting for intertwin EFW difference.

196   Strength of this study was that the ultrasound EFW was performed at the time of

197 the MRI scan (Table 1) thereby allowing a direct comparison of placental T2* and EFW.

198   Another strength of this study was the thorough processing of placental T2* data.

199 A single observer who was blinded to pregnancy outcome drew all placental ROIs, and the

200 ROIs of each frame were corrected according to fetal and maternal movements. Furthermore,

201 T2* of each placenta was based on an average of two different placental cross-sections. This is

202 in accordance with a previous publication by our group, demonstrating that calculating

203 placental T2* as an average of several slices improves the reproducibility of the method

204 considerably when compared to placental T2* based on a single slice [21]. This is most likely

205 due to the heterogeneity of the placental tissue, which contains both fetal and maternal

206 compartments with different morphology and oxygenation. These compartments may not be

207 equally represented in each placental cross-sections.

208 There are some limitations to this study. The placental MRIs and the ultrasound

209 examinations were performed at a wide range of gestational ages between individuals. As the

210 time interval between examination and birth may have an influence on the correlation

211 between the measurements and intertwin BW difference, it might have biased our results.

212 Previous studies on ultrasound EFW suggests that EFW is a better predictor of low birth

213 weight when performed close to delivery [7,8,13-15]. This may however not apply to

214 placental T2*. As previously demonstrated by our group, the performance of placental T2* in

215 predicting low BW may not be negatively affected by the long time interval between MRI and

216 delivery [22]. This finding demonstrates, that placental abnormalities are likely to occur prior

217 to fetal growth abnormalities, and therefore placental T2* may have the potential to be an

218 early marker of placental dysfunction before abnormal fetal growth has become clinically

219 apparent.

220 The relatively complex interpretation of the placental T2* signal is also a

221 limitation of this study. According to *Wright et al.* [29] normal physiological maturation of

222 placental tissue morphology may reduce the transverse relaxation time as pregnancy

223 advances. Thus, the placental T2* value does not only reflect the placental oxygen

224 environment, it may also be influenced by other factors such as tissue morphology.

225 Unfortunately, this cannot be elucidated further by this study, as placental histological

226 examination was not included.

227 In addition, we have used the normal material of singletons [21] in order to

228 calculate placental T2* Z-scores as a normal material in dichorionic twins are currently not

229 available. We thereby assume that the T2* value of dichorionic twin placentas are similar to

230 those of singleton placentas. This is in accordance with current clinical practice in regards to

231 calculation of BW and EFW Z-scores, which are also based on the normal material of

232 singletons.

233   Furthermore, the small population size of this study only involved a total of 25

234   dichorionic twin pairs, and only three of these were diagnosed with intertwin BW discordance

235   as defined by an intertwin BW difference ≥ 20 %. However, even in this small pilot study we

236   found intertwin placental T2* difference to be a strong independent predictor of intertwin

237   BW difference. This finding supports the great clinical potential of the method, and this study

238   is supposed to precede larger twin studies including a larger number of discordant twin pairs.

239   In this study, we demonstrated a significant positive correlation between

240   intertwin placental T2* difference and intertwin BW difference, at a median time interval

241   between MRI and birth of 12.4 weeks. The placenta of the smaller twin had lower T2* value,

242   when compared to the larger twin. This finding is in accordance with a previous publication

243   on placental T2* in singletons, in which a low placental T2* value is associated with a low

244   BW[21]. We also demonstrated a positive linear correlation between intertwin EFW difference

245   and intertwin BW difference. However, in our study all three cases of intertwin BW

246   discordance were underestimated by EFW. This finding is in accordance with previous

247   literature indicating that ultrasound tends to underestimate larger intertwin BW differences,

248   thus ultrasound EFW has limitations as a predictor of intertwin BW discordance [10,13].

249   In conclusion, this study demonstrates that intertwin placental T2* difference

250   assessed by MRI is a strong independent predictor of intertwin BW difference. According to

251   our data, the intertwin placental T2* difference adds significant value to the current

252   predictive model of intertwin BW difference based on intertwin EFW difference alone. This

253   interesting finding highlights the clinical potential of placental T2* as a marker of abnormal

254   fetal growth. We suggest that this small pilot study should be followed by larger twin studies

255   investigating the clinical potential of placental T2* among dichorionic twins.

256

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358

359 Figure legends

360 **Figure 1:** T2* weighted magnetic resonance image of the uterus in a twin pregnancy (34+1

361 weeks gestation) complicated by birthweight discordance. Regions of interest (ROIs) mark

362 the normal placenta to the right (black ROI) and the darker dysfunctional placenta to the left

363 (white ROI).

364

365 **Figure 2:** Correlation between intertwin placental T2* difference and intertwin birthweight

366 (BW) difference (n=25), with best-fitted linear regression line and 95 % confidence interval,

367 r=0.80, p<0.005.

368

369 **Figure 3:** Correlation between intertwin ultrasound estimated fetal weight (EFW) difference

370 and intertwin birthweight (BW) difference (n=25), with best-fitted linear regression line and

371 95 % confidence interval, r=0.64, p<0.005.

Table 1: Maternal and pregnancy characteristics.

Characteristics	Study population (n=25)
Maternal age at nuchal scan (years)	31 (28 ; 35)
Maternal Body Mass Index (kg/m^2)	23.0 (20.7 ; 25.5)
Nulliparous	12 (48.0 %)
Cigarette smoker	1 (4.0 %)
Diabetes	0 (0.0 %)
Caesarean section	12 (48.0 %)
Preeclampsia	0
Abnormal Umbilical Artery Doppler	0
Gestational age† at MRI (weeks)	24.6 (21.6 ; 26.8)
Gestational age† at birth (weeks)	37.3 (36.0 ; 37.9)
Time between MRI and birth (weeks)	12.4 (5.6 ; 14.3)
BW (Z-score)‡	-0.8 (-1.4 ; -0.4)
Intertwin BW difference (%)§	8.0 (4.5 ; 12.7)
Twin pairs with intertwin BW difference ≥ 20 %	3 (12.0 %)

Data are given as median (interquartile range) or n (%). MRI: magnetic resonance imaging, BW: birthweight.
†Gestational age in weeks and days (converted into continuous data by dividing number of days beyond full weeks with 7)
‡Relative to estimated fetal weight in singleton pregnancies[1]
§Intertwin BW difference = $(BW_{Larger\ twin} - BW_{Smaller\ twin}) / BW_{Larger\ twin}$ x 100 %

Table 2: Multiple linear regression analysis. For each predictor is given the β-coefficient and the 95 % confidence interval. The two models are compared by the likelihood ratio test*.

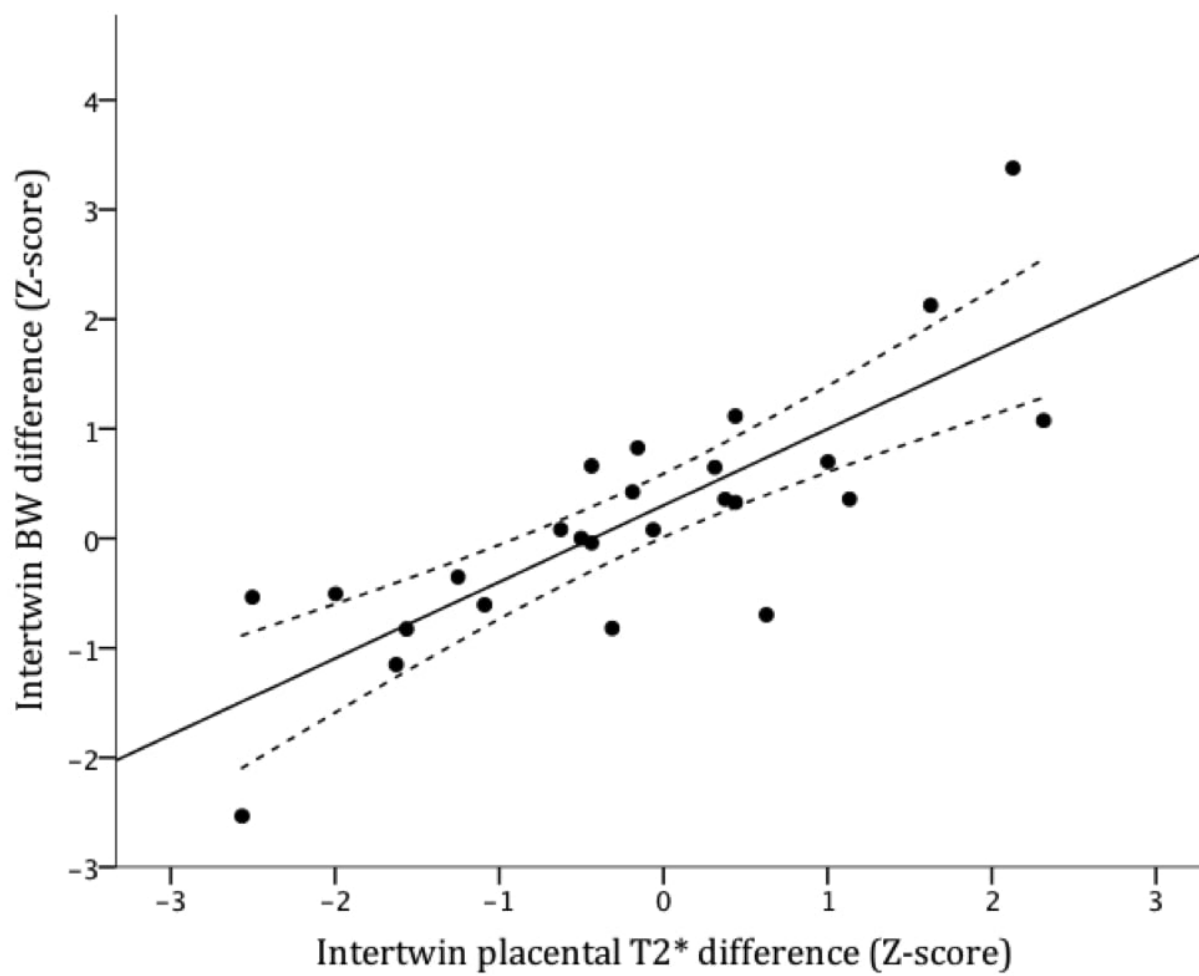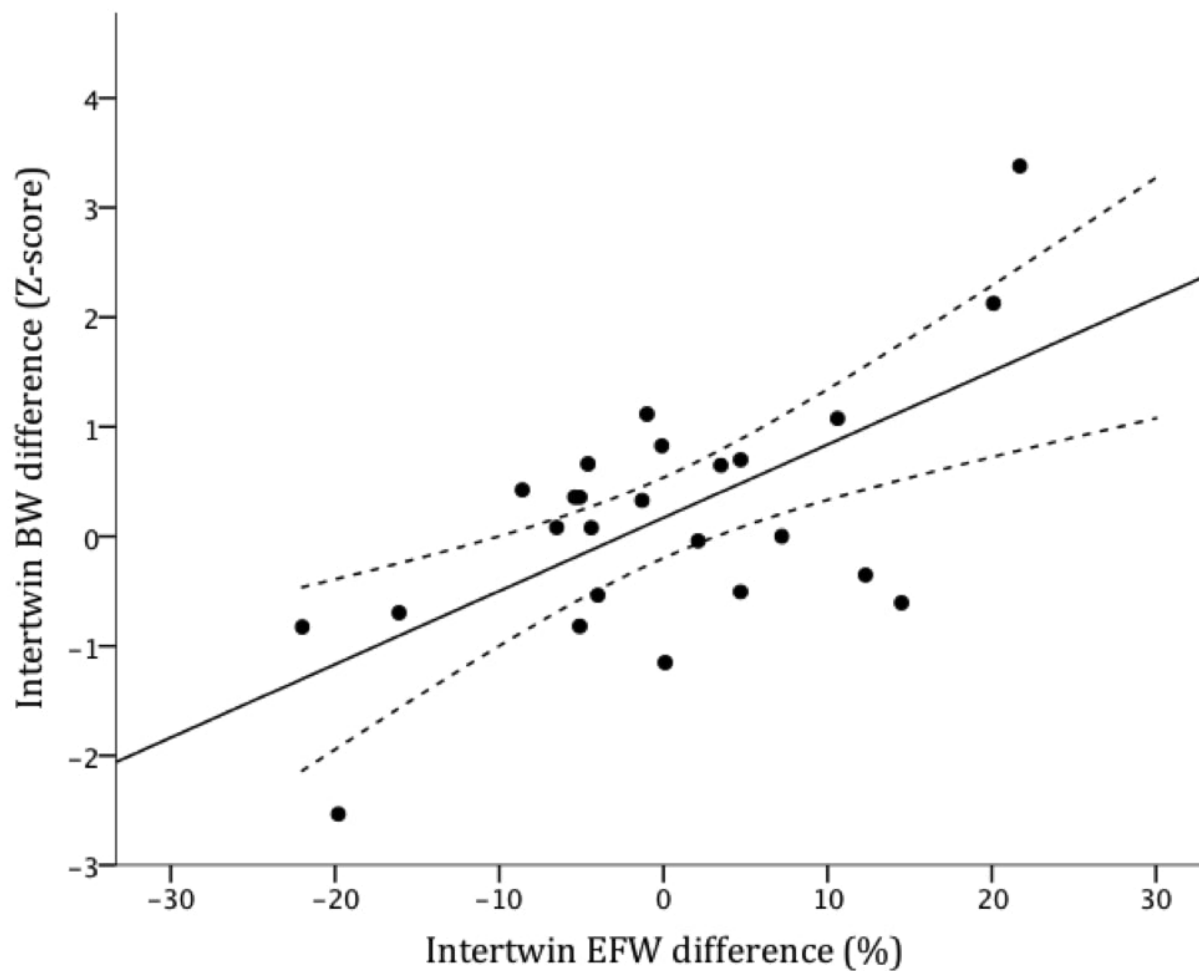|	EFW Model			T2* Model			Combined model (EFW and Placental T2*)		
Predictor	β-coeff.	95 % - CI	p-value	β-coeff.	95 % - CI	p-value	β-coeff.	95 % - CI	p-value
Intertwin EFW difference	0.067	(0.032 – 0.101)	0.001	-	-	-	0.038	(0.012 - 0.063)	0.006
Intertwin placental T2* difference	-	-	-	0.698	(0.473 – 0.923)	<0.0001	0.560	(0.345 – 0.775)	<0.001
R^2	0.39			0.63			0.72		<0.001

EFW: estimated fetal weight, β-coeff.: β-coefficient, 95 % - CI: 95 % confidence interval
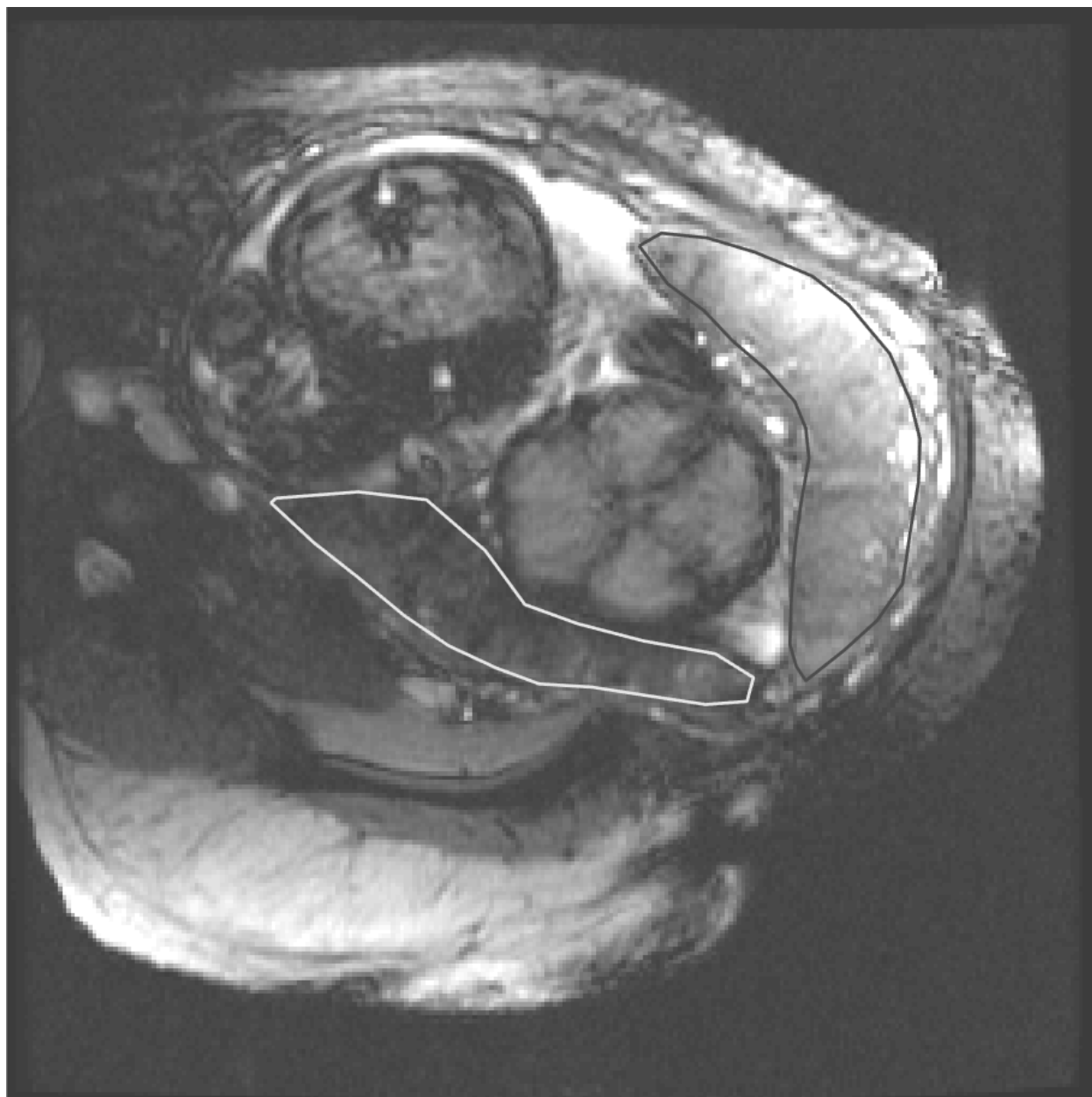
Highlights

- Intertwin birthweight difference is associated to a high risk of adverse outcome
- Placental T2* provides non-invasive information about the placental function.
- Intertwin placental T2* difference correlates to intertwin birthweight difference
- Placental T2* may be used in the prediction of intertwin birthweight difference