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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

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Conflicts of interest

None declared

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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

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

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

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

To the best of our knowledge, this is the first study to investigate placental T2* in dichorionic twin pregnancies. This study aimed to investigate intertwin placental T2* difference as a predictor of intertwin BW difference, and to compare placental T2* to ultrasound estimates of fetal weight in the prediction of intertwin BW differences in dichorionic twin pairs.

Methods

Subjects

This prospective study was carried out in the period from July 2014 to July 2015 at Aalborg University Hospital, Denmark. We included 25 dichorionic twin pregnancies at 19 – 38 week's gestation attending for routine or specialized antenatal care of which ultrasound EFW is part of the clinical practice. Transabdominal ultrasound examination was performed by experienced specialized sonographers or specialists in fetal medicine, and the EFW was calculated using the Hadlock formula, based on the head circumference, the abdominal circumference, and the femur length [25]. MRI scan was performed on the same day, and the twin fetuses and their placentas were assigned 1 or 2 based on their location to either the left or the right side of the uterus, respectively. In addition, the presenting fetus was assigned A and the second fetus B. This labeling followed the Danish obstetric guidelines [26]. The MRI findings were carefully correlated to the ultrasound findings and the medical records from the delivery. BW and EFW were converted into Z-scores and the corresponding percentages based on the reference by Marsal *et al.* [27]. The procedures were approved by the Regional Committees on Biomedical Research Ethics (Journal number M-20090006 and N-20090052), and reported to the Danish Data Protection Agency (2008-58-0028). Oral and written consent were obtained from all participating women.

MRI Procedure

Placental T2* measurements were acquired with a GE Discovery MR450 1.5 Tesla MRI system (GE Healthcare, Milwaukee, USA) using a cardiac-receiver coil placed over the abdomen, covering the entire uterus. In the bore, the participants were positioned in a left lateral position to avoid compression of the inferior vena cava.

Initially, a T2 weighted localizing scan was performed to obtain the anatomic orientation of the two fetuses and their placentas. This was followed by a placental T2* scan, using a multi-echo gradient-recalled sequence with the following parameters: TR 70.9ms; 16 echoes ranging from 3.0 to 67.5ms in steps of 4.3ms; flip-angle 30°, field of view 350×350 mm; and matrix 256×128. This matrix resulted in an in-plane resolution of 1.37×2.73 mm. In each placenta, two separate 8-mm slices were acquired in a plane perpendicular to the placentas. Each slice was obtained within a single breath-hold of 12 seconds.

MRI Analysis

An in-house developed software; RoiTool 3.8 written in MATLAB (MathWorks Inc, Natick, MA, USA) was used to process the MRI data. All images were carefully checked for placental susceptibility artifacts. For each placenta, regions of interest (ROIs) were drawn on two separate slices covering the entire placenta (Figure 1). In each placental slice the size and the location of the ROI was adjusted to correct for artifacts including uterine contractions and both fetal and maternal movements during the 12 second T2* acquisition time. A single examiner [MS], who was blinded to pregnancy outcomes, performed the ROI drawings. Placental T2* values were calculated by fitting the average signal within each ROI as a function of echo time using a mono-exponentially decaying function with the equilibrium magnetization (M_0) and T2* as free parameters [28]. The mean placental T2* value of each placenta was calculated as an average of the two separate placental slices. Placental T2* values were converted into Z-scores based on a previously published dataset of normal singleton pregnancies [21].

Statistical analysis

Each intertwin difference was calculated as twin 1 minus twin 2. The correlations between intertwin placental T2* difference, intertwin EFW difference and intertwin BW difference were examined separately using simple linear regression analysis. Models to predict intertwin BW difference including the combination of both intertwin EFW difference and intertwin placental T2* difference, and also the intertwin EFW difference alone, were examined using multiple linear regression. The performances of the models were compared by the likelihood ratio test. Statistics were performed with the software IBM SPSS Statistics version 24.0. Statistical significance was assumed at the 5 % level.

Results

Of the 25 dichorionic twin pairs included in the study, three (12.0 %) were diagnosed with intertwin BW difference ≥ 20 %. The median time interval between MRI and birth was 12.4 gestational weeks (interquartile range, 5.6 ; 14.3). Maternal and pregnancy characteristics for the participating women are shown in Table 1.

We demonstrated significant positive correlations between the intertwin BW difference and both variables: Intertwin placental T2* difference ($r=0.80$, $p<0.005$, Figure 2) and intertwin EFW difference ($r=0.64$, $p<0.005$, Figure 3). Using multiple linear regression analysis we found that the intertwin placental T2* difference remained a significant predictor ($p<0.001$) of intertwin BW difference even after adjusting for intertwin EFW difference. This explains why the combined model including both of the variables intertwin EFW difference and intertwin placental T2* difference performed significantly better (adjusted $R^2 = 0.72$) than the model based on intertwin EFW difference alone (adjusted $R^2=0.39$), $p<0.0001$ (Table 2).

Discussion

In this study we investigated intertwin placental T2* and EFW differences as predictors of intertwin BW difference in 25 dichorionic twin pairs. We demonstrated a strong positive correlation between intertwin placental T2* difference and intertwin BW difference. Furthermore, we demonstrated a significant positive correlation between intertwin EFW difference and intertwin BW difference, however this correlation was not as strong as the correlation between intertwin placental T2* difference and intertwin BW difference. A combined model to predict intertwin BW difference including a combination of intertwin placental T2* difference and intertwin EFW difference performed significantly better than a model based on intertwin EFW difference alone. These findings indicate that intertwin placental T2* difference is a significant predictor of intertwin BW difference even after adjusting for intertwin EFW difference.

Strength of this study was that the ultrasound EFW was performed at the time of the MRI scan (Table 1) thereby allowing a direct comparison of placental T2* and EFW.

Another strength of this study was the thorough processing of placental T2* data. A single observer who was blinded to pregnancy outcome drew all placental ROIs, and the ROIs of each frame were corrected according to fetal and maternal movements. Furthermore, T2* of each placenta was based on an average of two different placental cross-sections. This is

in accordance with a previous publication by our group, demonstrating that calculating placental $T2^*$ as an average of several slices improves the reproducibility of the method considerably when compared to placental $T2^*$ based on a single slice [21]. This is most likely due to the heterogeneity of the placental tissue, which contains both fetal and maternal compartments with different morphology and oxygenation. These compartments may not be equally represented in each placental cross-sections.

There are some limitations to this study. The placental MRIs and the ultrasound examinations were performed at a wide range of gestational ages between individuals. As the time interval between examination and birth may have an influence on the correlation between the measurements and intertwin BW difference, it might have biased our results. Previous studies on ultrasound EFW suggests that EFW is a better predictor of low birth weight when performed close to delivery [7,8,13-15]. This may however not apply to placental $T2^*$. As previously demonstrated by our group, the performance of placental $T2^*$ in predicting low BW may not be negatively affected by the long time interval between MRI and delivery [22]. This finding demonstrates, that placental abnormalities are likely to occur prior to fetal growth abnormalities, and therefore placental $T2^*$ may have the potential to be an early marker of placental dysfunction before abnormal fetal growth has become clinically apparent.

The relatively complex interpretation of the placental $T2^*$ signal is also a limitation of this study. According to *Wright et al.* [29] normal physiological maturation of placental tissue morphology may reduce the transverse relaxation time as pregnancy advances. Thus, the placental $T2^*$ value does not only reflect the placental oxygen environment, it may also be influenced by other factors such as tissue morphology. Unfortunately, this cannot be elucidated further by this study, as placental histological examination was not included.

In addition, we have used the normal material of singletons [21] in order to calculate placental $T2^*$ Z-scores as a normal material in dichorionic twins are currently not available. We thereby assume that the $T2^*$ value of dichorionic twin placentas are similar to those of singleton placentas. This is in accordance with current clinical practice in regards to calculation of BW and EFW Z-scores, which are also based on the normal material of singletons.

Furthermore, the small population size of this study only involved a total of 25 dichorionic twin pairs, and only three of these were diagnosed with intertwin BW discordance as defined by an intertwin BW difference $\geq 20\%$. However, even in this small pilot study we found intertwin placental T2* difference to be a strong independent predictor of intertwin BW difference. This finding supports the great clinical potential of the method, and this study is supposed to precede larger twin studies including a larger number of discordant twin pairs.

In this study, we demonstrated a significant positive correlation between intertwin placental T2* difference and intertwin BW difference, at a median time interval between MRI and birth of 12.4 weeks. The placenta of the smaller twin had lower T2* value, when compared to the larger twin. This finding is in accordance with a previous publication on placental T2* in singletons, in which a low placental T2* value is associated with a low BW²¹. We also demonstrated a positive linear correlation between intertwin EFW difference and intertwin BW difference. However, in our study all three cases of intertwin BW discordance were underestimated by EFW. This finding is in accordance with previous literature indicating that ultrasound tends to underestimate larger intertwin BW differences, thus ultrasound EFW has limitations as a predictor of intertwin BW discordance [10,13].

In conclusion, this study demonstrates that intertwin placental T2* difference assessed by MRI is a strong independent predictor of intertwin BW difference. According to our data, the intertwin placental T2* difference adds significant value to the current predictive model of intertwin BW difference based on intertwin EFW difference alone. This interesting finding highlights the clinical potential of placental T2* as a marker of abnormal fetal growth. We suggest that this small pilot study should be followed by larger twin studies investigating the clinical potential of placental T2* among dichorionic twins.

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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)

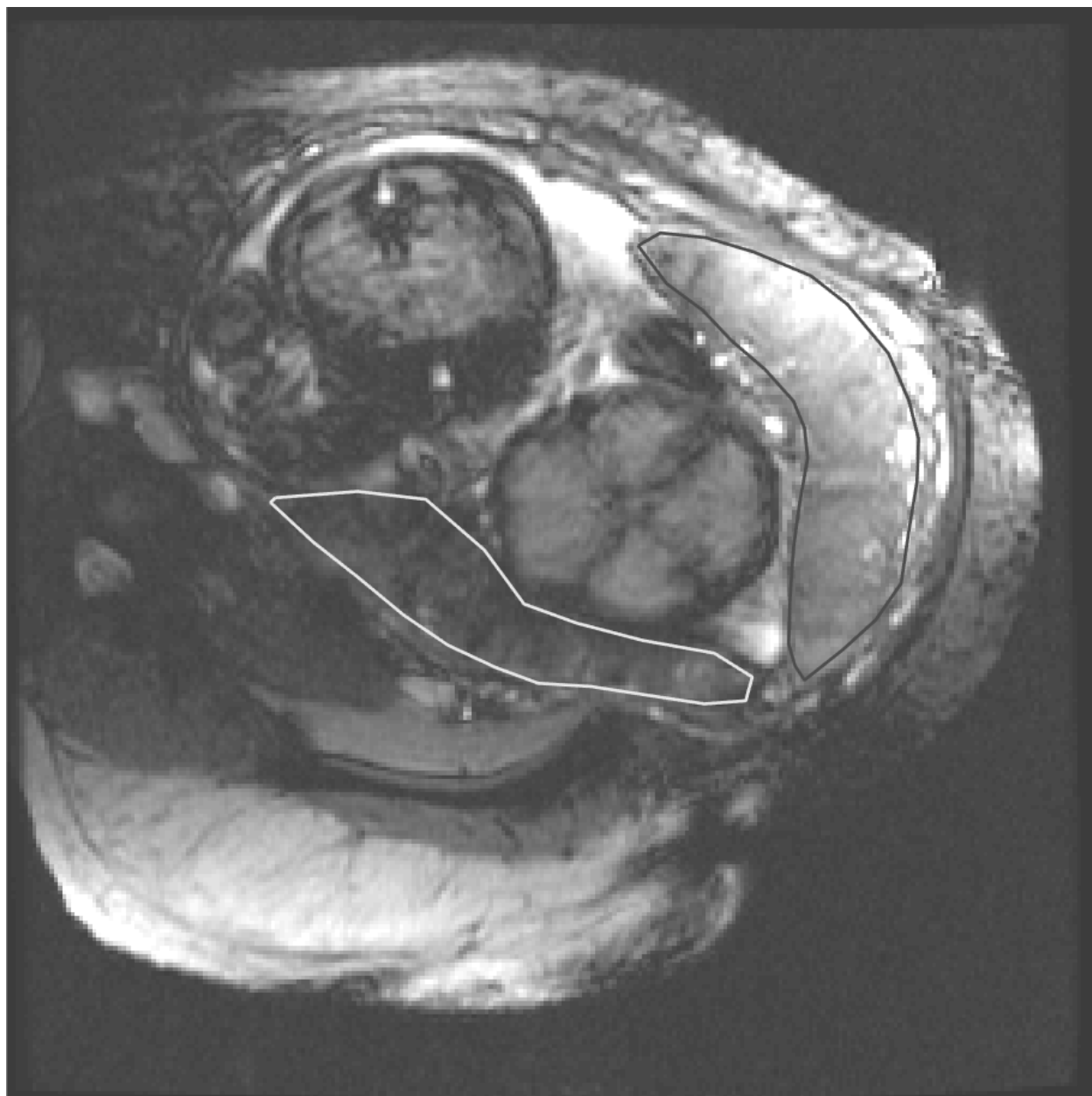
[‡]Relative to estimated fetal weight in singleton pregnancies¹

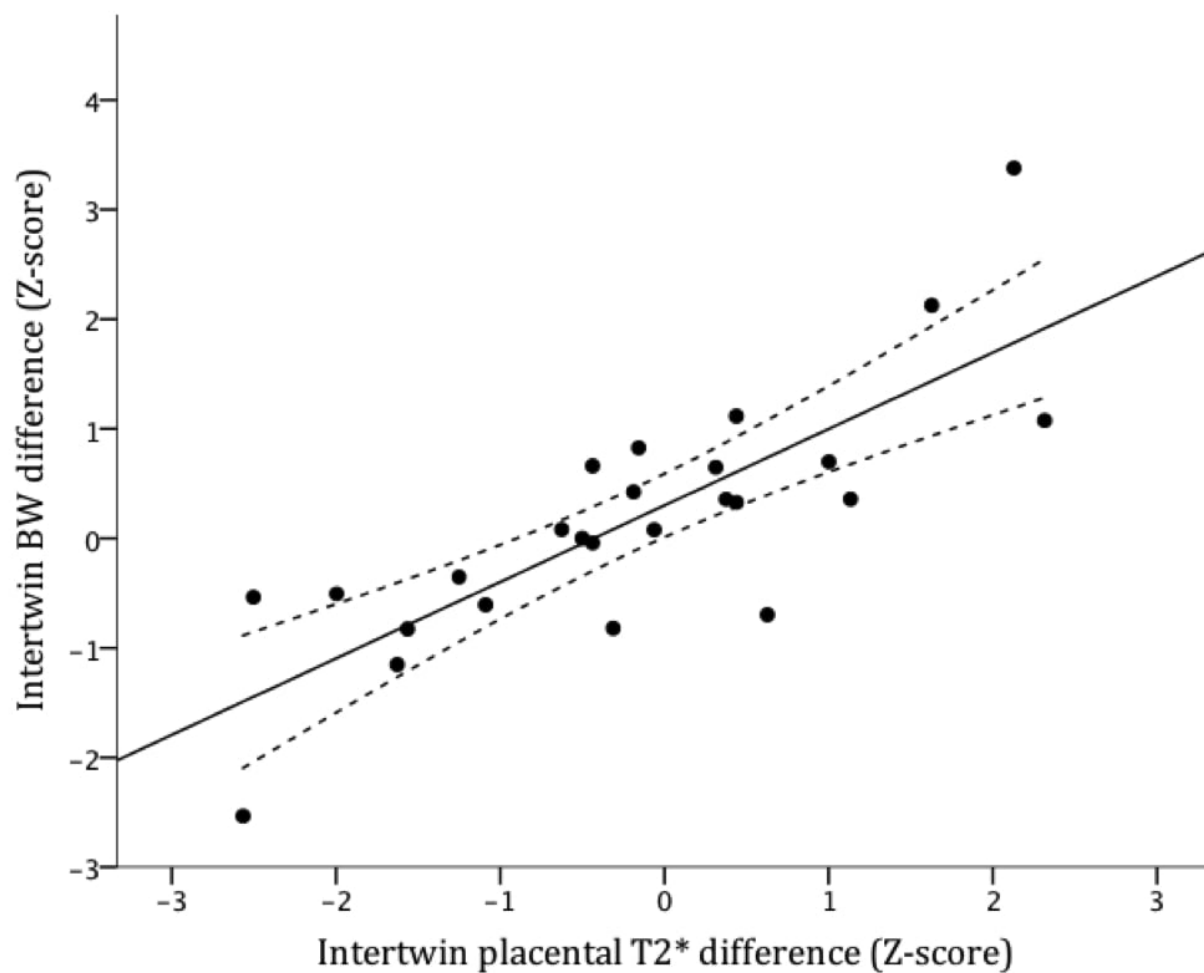
[§]Intertwin BW difference = $(BW_{\text{Larger twin}} - BW_{\text{Smaller twin}}) / BW_{\text{Larger twin}} \times 100 \%$

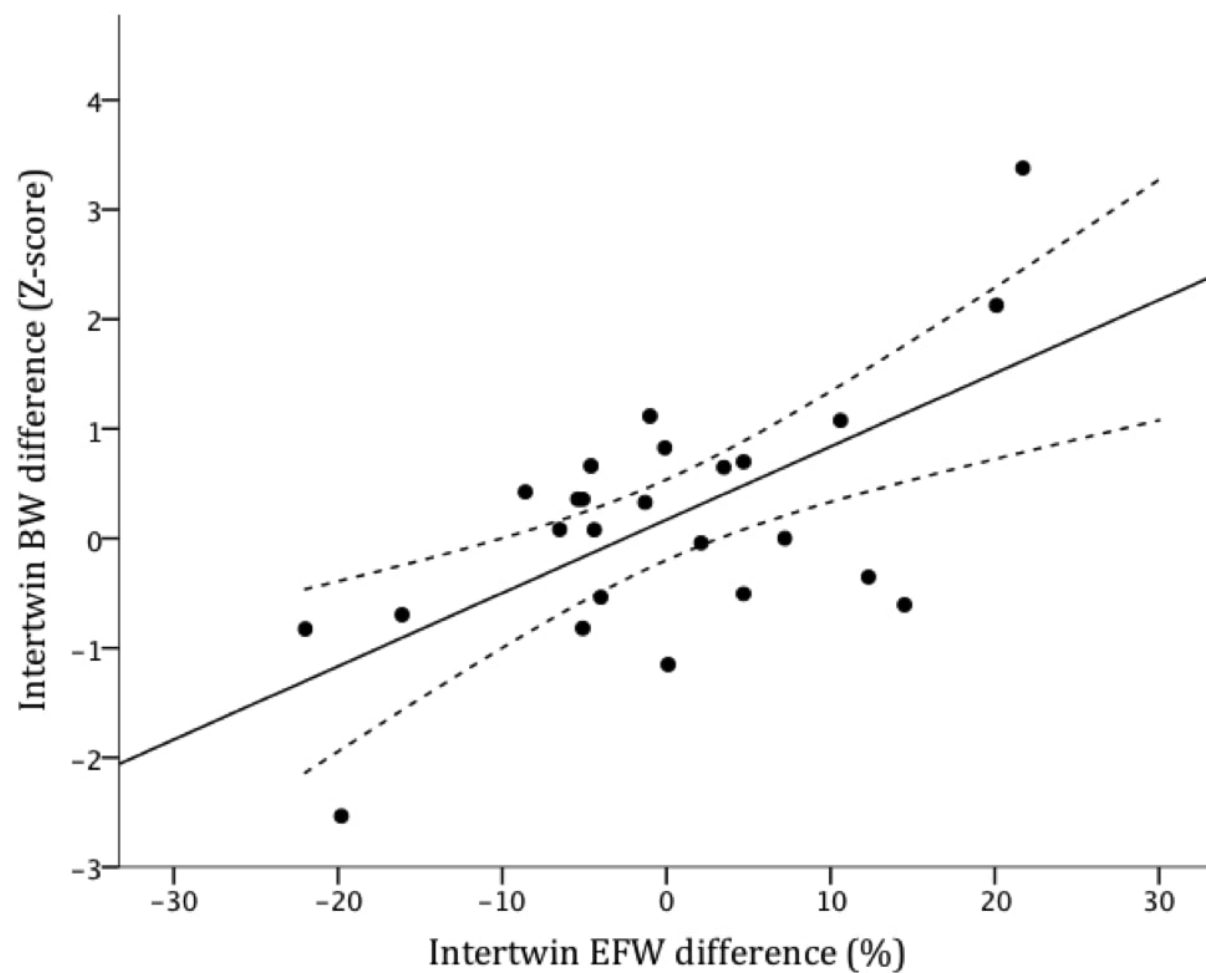
Table 2: Multiple linear regression analysis. For each predictor is given the β -coefficient and the 95 % confidence interval. The two models are compared by the likelihood ratio test*.

	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