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Placental transverse relaxation time (T2) estimated by MRI: Normal values and the correlation with birthweight

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Conflicts of interest

None

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ABSTRACT

Introduction: Placental transverse relaxation time (T2) assessed by magnetic resonance imaging (MRI) may have the potential to improve the antenatal identification of small for gestational age. The aims of this study were to provide normal values of placental T2 in relation to gestational age at the time of MRI and to explore the correlation between placental T2 and birthweight.

Material and methods: A mixed cohort of 112 singleton pregnancies was retrieved from our placental MRI research database. MRI was performed at 23.6-41.3 weeks' gestation in a 1.5T system (TE (8): 50 - 440 ms, TR: 4000 ms). Normal pregnancies were defined by uncomplicated pregnancies with normal obstetric outcome and birthweight deviation within ±1 SD of the expected for gestational age. The correlation between placental T2 and birthweight was investigated using the following outcomes; small for gestational age (birthweight ≤-2SD of the expected for gestational age) and birthweight deviation (birthweight Z-scores).

Results: In normal pregnancies (n=27), placenta T2 showed a significant negative linear correlation with gestational age (r=-0.91, p=0.0001) being 184 ms ±15.94 (mean ± SD) at 20 week's gestation and 89 ms ±15.94 at 40 week's gestation. Placental T2 was significantly reduced among small for gestational age pregnancies (mean Z-score -1.95, p<0.001). Moreover, we found a significant positive correlation between placenta T2 deviation (Z-score) and birthweight deviation (Z-score) (R2=0.26, p=0.0001).

Conclusions: This study provides normal values of placental T2 to be used in future studies on placental MRI. Placental T2 is closely related to birthweight and may improve the antenatal identification of small for gestational age pregnancies.

Keywords

Fetal monitoring, placental transverse relaxation time, high-risk pregnancy, placenta, pregnancy, prenatal diagnosis

Abbreviations

SGA, small for gestational age;

BW, birthweight;

T2, transverse relaxation time;

MRI, magnetic resonance imaging;

ROI, regions of interest;

GA, gestational age;

Key Message

The placental T2 value decreases as pregnancy advances and placental T2 is significantly reduced among small for gestational age pregnancies. Thereby placental T2 may improve the antenatal identification of small for gestational age pregnancies.

INTRODUCTION

Small for gestational age (SGA) caused by placental dysfunction complicates 5-10% of pregnancies depending on population and definition (1). The association between insufficient fetal growth and adverse pregnancy outcomes is well described (2–5). Currently, there is no effective treatment of placental dysfunction, and therefore the only way to improve pregnancy outcome in these high-risk pregnancies is to improve the antenatal identification. Antenatal identification of SGA pregnancies allows for adequate fetal monitoring and timely delivery, which is known to improve the neonatal outcome by four-fold (6).

The current antenatal identification of SGA is based on ultrasound estimates of fetal weight. However, even in a routine setting, when performed in late third trimester, ultrasound estimated fetal weight is limited by low sensitivity and high false positive rates in identifying SGA pregnancies (7–10). This is a major challenge in modern obstetrics as false suspicion of fetal growth restriction leads to unnecessary obstetric interventions (11) and the lack of antenatal identification of SGA leads to delayed delivery (6). New methods to improve the antenatal identification of SGA pregnancies may improve the neonatal outcome considerably.

Placental transverse relaxation time (T2) assessed by magnetic resonance imaging (MRI) is a tissue constant that depends on interactions between protons and their surrounding environment, thereby reflecting tissue morphology (12). In addition to that, T2 is influenced by different magnetic properties of oxygenated and deoxygenated hemoglobin (13,14) and by that registers tissue oxygenation (12,13,15,16). Because of these associations, placental T2 may be directly related to placental function.

Previous studies on placental T2 suggests that a low placental T2 value is associated with placental related complications of pregnancy such as SGA (17–19) and preeclampsia (18,19). However, these studies are limited by small sample size with a total of 11 to 35 included pregnancies, and the lack of normal reference values.

The main aim of this study was to provide normal values for placental T2 in relation to gestational age at MRI. In addition, we aimed to explore the correlation between placental T2 and birthweight (BW) using two outcomes; SGA (BW≤-2SD of the expected for gestational age (GA)) and BW deviation (BW Z-score).

MATERIAL AND METHODS

Study population

A mixed cohort of 112 singleton pregnancies, consisting of both pregnancies with normal and low birthweight, was retrieved from our placenta-MRI research database. MRI was performed at 23.6-41.3 weeks' gestation. All subjects were volunteers and MRI was performed for research only. From this mixed cohort, we selected 27 normal pregnancies defined by BW within normal range (BW±1SD) (20), delivery at ≥37 weeks' gestation, and no evidence of diabetes, preeclampsia, prescription of acetylsalicylic acid or maternal smoking. SGA was defined as BW≤-2SD of expected for GA. Characteristics of the total mixed population and the normal population are presented in Table 1.

Magnetic Resonance Imaging

The MRI was conducted in a 1.5 Tesla MRI system (Optima™ GE450w, GE Healthcare, Milwaukee, WI, USA). During the MRI scan, the pregnant women were placed in a left lateral tilt position to avoid aorto-caval compression. An eight-channel receiver coil was placed over the abdomen, covering the entire uterus. Initially, a T2-weighted localizer scan was performed to determine the anatomic orientation of the placenta. The orientation of image slices was perpendicular to the placenta (Figure 1). An echo-planar imaging spin-echo sequence; FOV: 40 x 40 cm, TE(8): 50- 440 ms, TR: 4000 ms, slice spacing: 20 mm, slice thickness: 8 mm. A total of 5 slices was obtained, and three slices covering the most central part of placenta were selected for further analysis. The total MRI examination time was approximately 30 minutes, as it was part of a multi-sequence placental MRI research protocol. An in-house developed software (RoiTool) written in MATLAB (The MathWorks Inc., Natick, MA, USA) was used to process the MR-images. Regions of interest (ROI) were drawn covering the entire placenta in three cross-sectional placental slices (Figure 1). In each image, the ROI position was adjusted according to maternal and fetal movements. For each placenta, the T2 value was estimated as the mean of the three slices. The T2 value for each slice was fitted as a single exponential with M0 and T2 as free parameters using a non-linear least-square fitting algorithm (Figure 2).

Statistical analyses

Simple linear regression analysis and Pearson's correlation was used to investigate the correlation between placental T2 and GA in normal pregnancies. In order to adjust for gestational age, T2 values were converted into standardized variables (Z-scores) in which the difference between the estimated and the expected T2 value was divided by the standard deviation at the specific gestational age. The correlation between placental T2 Z-scores and BW Z-scores was also investigated using linear regression and Pearson's correlation analyses (Figure 5). The difference between mean T2 Z-score in the group of SGA pregnancies (BW≤-2SD) and normal BW pregnancies (BW>-2SD) was tested using student t-test. The statistical software package Stata®15.1 (StataCorp LP, College Station, TX, USA) was used, and the statistical level was set at p-value <0.05.

Ethical approval

This study was approved by the Regional Committee on Biomedical Research Ethics of North Denmark Region (Journal number N-20170052) on 30 August 2017). Data handling was reported as a regional notification to the Danish Data Protection Agency, journal number 2017-148.

RESULTS

In normal pregnancies, placenta T2 and GA showed a significant negative linear correlated (r=-0.91, p=0.0001). Placental T2 was reduced by 4.78 ms per gestational week. At 20 weeks' gestation, placental T2 was 184 ±15.94 ms (mean ±SD) and at 40 weeks' gestation placental T2 was 89 ±15.94 ms (Figure 3). The correlation between placental T2 deviation (Z-score) and BW deviation (Z-score) showed a significant positive correlation (r=0.51, p=0.0001), see Figure 5. In SGA pregnancies, placental T2 was significantly reduced (mean T2 Z-score=-1.95) when compared to pregnancies with BW>-2SD (mean T2 Z-score=-0.61); p<0.001, see Figure 4.

DISCUSSION

This cohort study provides normal values of placental T2 at 23.6 to 41.3 week's gestation in 1.5 MRI system. The placental T2 value was significantly reduced among SGA pregnancies, when compared to normal BW pregnancies and a positive association was demonstrated between placental T2 Z-score and BW deviation. These findings suggest that placental T2 may have the potential to improve the antenatal identification of SGA pregnancies.

The strength of this study is the clinical well-defined pregnancies and the broad range of GA at MRI. Both provide a solid base to estimate normal placental T2 values and to investigate the correlation between placental T2 and BW deviation. The normal material is based on very strict inclusion criteria, which improves the validity of the values in spite of the rather small number of pregnancies included in the normal material. The study includes 27 normal pregnancies, which to our knowledge, is the largest and most well defined normal material published until this date. In addition, placental T2 values are given as a mean of three placental slices, which leads to higher precision of the T2 estimates, as placental tissue has a high level of heterogeneity (21). The ROI drawing was blinded to all clinical data.

In normal pregnancies, we found a negative linear correlation between placental T2 and GA at the time of MRI. This finding is in accordance with the majority of previous human studies (12,18,22–24) and murine models (22,23). The negative correlation between placental T2 and gestational age at MRI may be explained by normal morphological changes evolving during gestation such as increasing villous density and fibrin deposition (12) as well as decreasing placental oxygenation (25). This finding is highly important, as it underlines that any comparison of placental T2 between groups needs to be adjusted for differences in gestational age at MRI.

In the normal placenta, we found that placental T2 was 184 ms at 20 weeks' gestation and 89 ms at 40 weeks' gestation in a 1.5T system. It corresponds largely with previous smaller studies made in a 1.5T system (12,17,24). Kameyama et al. (24) found the placental T2 value to be 100ms at 35 weeks' gestation, and Derwig et al. (17) found placental T2 to be 149ms at 27 weeks' gestation. However, the T2 values of our current study are slightly lower than the values reported by Wright et al., as they found placental T2 to be 195 ms at 29 weeks' gestation (12). This difference may be related to different definition of normal pregnancies, as we have defined normal pregnancies by BW within +/-1SD, when compared to BW > 5^{th} centile by Wright et al. (12).

According to our data, pregnancies complicated by low BW (SGA) have a low placental T2 value when compared to pregnancies with normal BW. This correlation is underlined by a strong positive linear correlation between BW deviation and placental T2 Z-score. This correlation is in accordance with previous smaller studies (17–19). However, the correlation between placental T2 and low BW is not completely understood. According to a single study, the low T2 value may be related to altered placental morphology such as placental fibrin deposition (12).

However, other studies failed to demonstrate such correlation with other specific tissue characteristics for instance placental villous density and total vascular volume (12,26,27).

Low placental T2 values may also be related to placental hypoxia. It is well established, that both quantity of hemoglobin and changes in the saturation of the hemoglobin molecule, that causes changes in the spin of iron atoms, can be depicted as changes in the transverse relaxation time (13,15). In addition, the negative association between placental T2 and tissue hypoxia have also been demonstrated in several in vitro studies of human blood (15,28), and in invasive animal studies (29) (16).

Our findings on placental T2 in relation to gestational age and BW are in line with previous findings on placental T2* (21,30–32). The two relaxation times are closely related, as they are both sensitive to changes in tissue morphology and tissue oxygenation However, T2* is a combination of T2 relaxation and relaxation caused by magnetic field inhomogeneities, which may be induced by the presence of deoxyhemoglobin. Therefore T2* may be particularly sensitive to changes in tissue oxygenation (33).

CONCLUSION

This large study provides important information regarding normal values of placental T2 at a wide range of gestational ages and is proposal for normal reference values, but normal T2 values of this study need to be further investigated in a multicenter setting comparing different MRI systems to confirm the final normal reference values. Placental T2 is closely related to BW, and thereby, this method provides direct non-invasive information of placental function, with the potential to improve the antenatal identification of SGA pregnancies. Thus, in a clinical setting placental T2 may be used as a supplement to conventional fetal examination by ultrasound and Doppler flow measurements. Future studies should include placental MRI at early gestation to explore the early predictive value of this method and histopathological placental examination should be included to improve the understanding of the direct correlation between specific placental morphology and the placental T2 value.

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Legends of Figures

Figure 1. Image processing. Schematic illustration of five placental slices and screenshots from RoiTool with regions of interest marked at three slices of the most central part of placenta (marked with colored lines) covering the entire cross section of the placenta.

Figure 2. Fitting algorithm. The mean signal within the regions of interest as a function of echo time for a single slice (dots). Nonlinear least squares fit of the monoexponential T2 decay (line). Abbreviation: a.u = arbitrary units.

Figure 3. Placental T2-relaxation times and gestational age in normal pregnancies. The correlation between T2-relaxation times (T2) in milliseconds and gestational age in weeks at the time of MRI in normal pregnancies (BW±1SD) (n=27, r= -0.91, p<0.001). Trendlines indicating predicted mean and 95% prediction interval.

Figure 4. Placental T2-relaxation times and gestational age. The correlation between T2-relaxation times (T2) in milliseconds and gestational age in weeks at the time of MRI in the pregnancies with birthweight ≤ -2SD (n=17, open circle) and in pregnancies with birth weight > -2SD (n=95, closed circle) (r= -0.44, p<0.001). The trendline describes normal material from Figure 3.

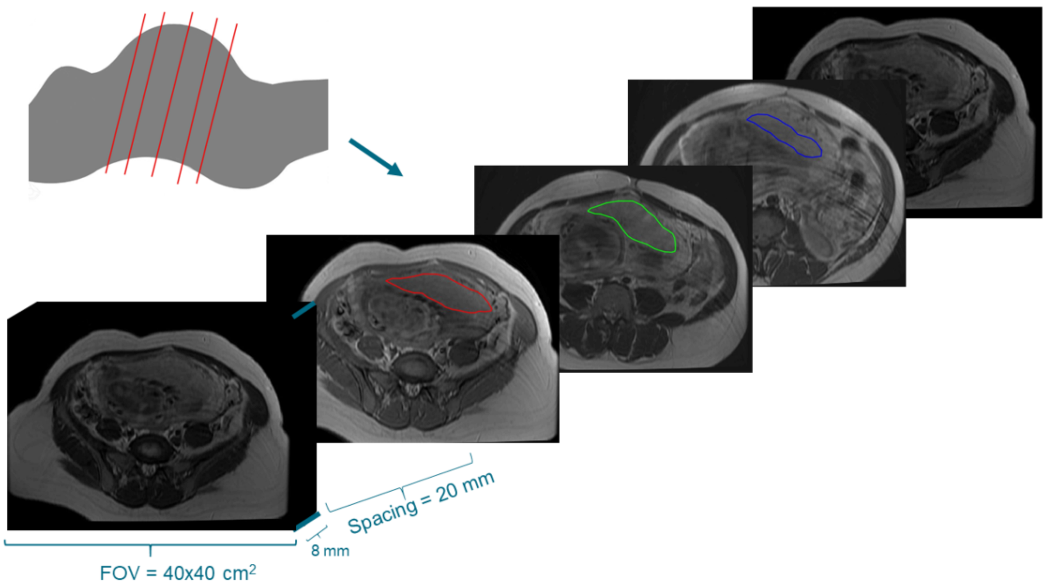
Figure 5. Placental T2-relaxation times and birthweight deviation. The correlation between placental T2-relaxation times Z-scores (T2 Z-score) and birthweight deviation Z-scores (BW Z-score) in the total study cohort (n=112, r= 0.51, p<0.001).

Table 1. Characteristics of the study population

Characteristics	Normal pregnancies (n=27)	Total (n=112)
Maternal age (years)	28 (26 - 30)	29 (27 - 34)
Maternal Body mass Index (kg/m^2)	27.3 (24.7 - 31.9)	27.3 (24.2 - 30.8)
Nulliparous	17 (63.0)	54 (48.2)
Cigarette smoker	0 (0)	15 (13.4)
Gestational age at MRI (weeks)	34.6 (30.6 - 40.6)	34.5 (31.1 - 37.5)
Time interval MRI and birth (weeks)	4.4 (0.9 - 9.7)	3.45 (1.3 - 7.1)
Gestational age at birth (weeks)	41.1 (40 - 41.6)	39.6 (38.1 - 40.9)
Birthweight (gram)	3490 (3350 - 3720)	2905 (2535 - 3390)
Birthweight Z-score	-0.36 (-0.8 to 0.3)	-1.35 (-1.4 to -0.7)
Diabetes (all types [a])	0 (0)	9 (8.0)
Preterm birth <37 weeks	0 (0)	14 (12.5)
Preeclampsia	0 (0)	23 (20.5)
Treatment with acetylsalicylic acid	0 (0)	7 (6.25)

Data are presented as median (25th, 75th quartiles) and n (%).

[a] Women with type I diabetes, type II diabetes or gestational diabetes mellitus.



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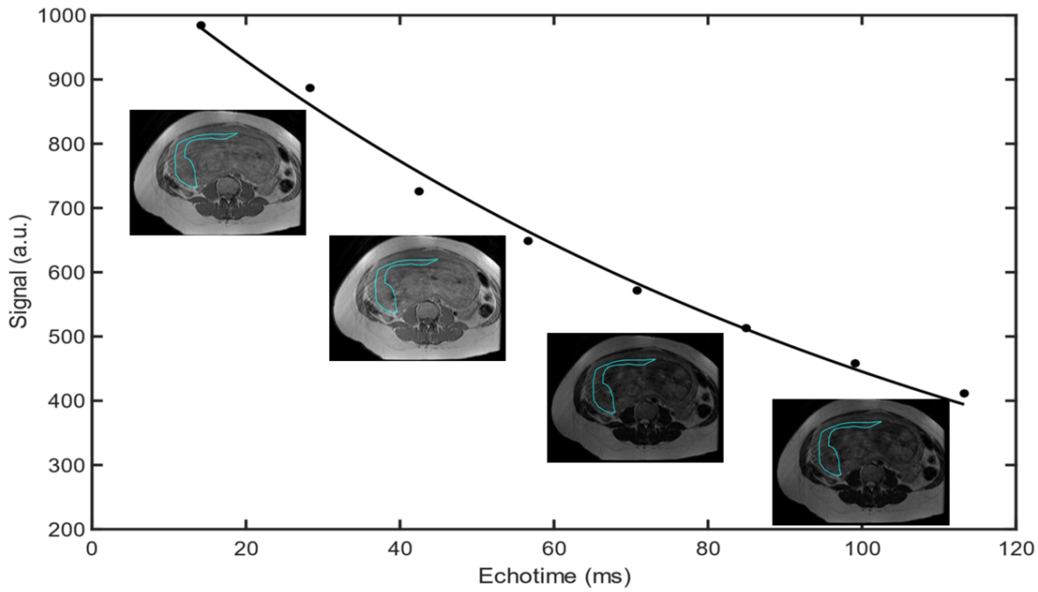

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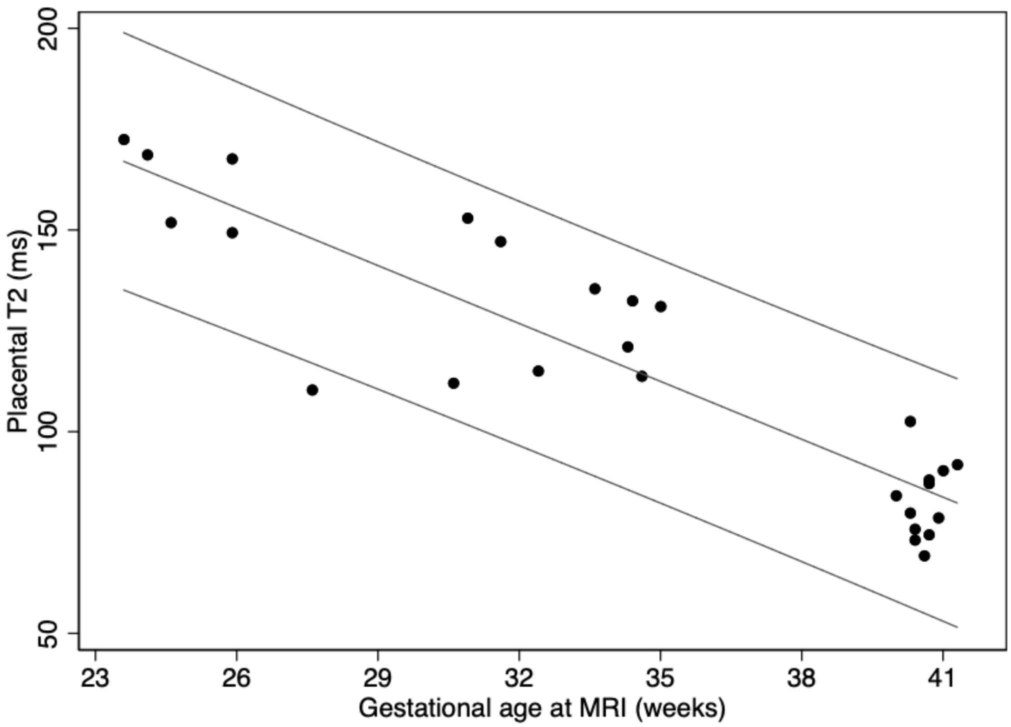

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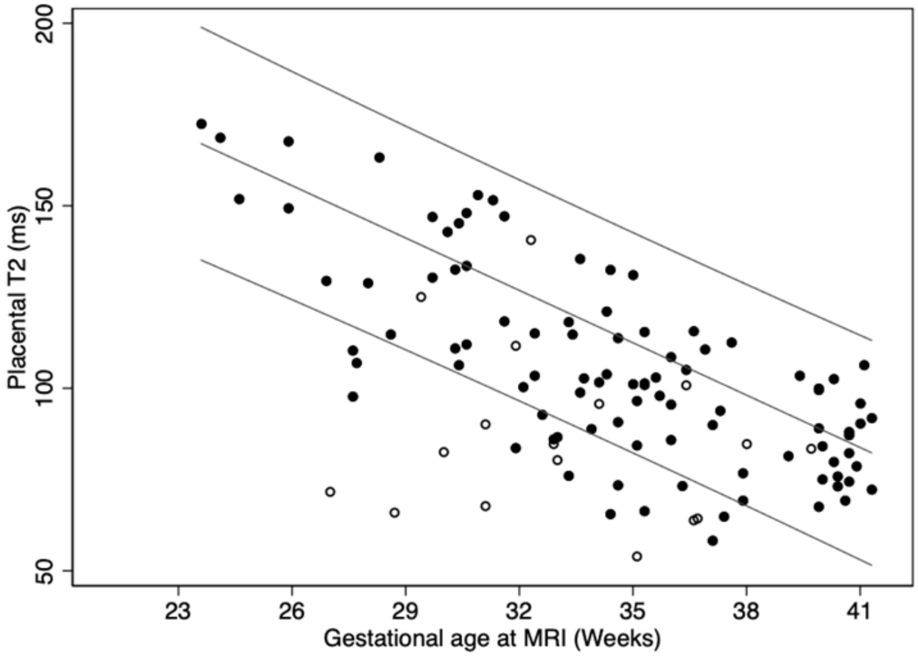

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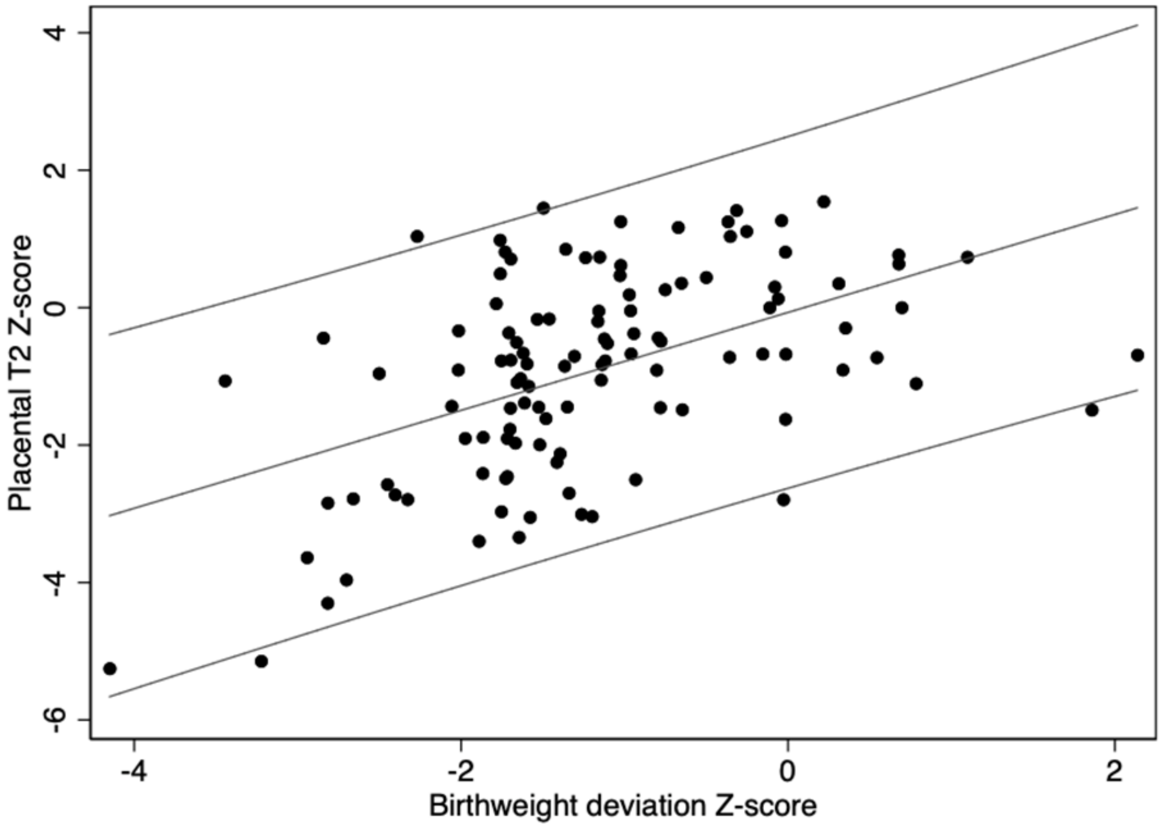

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