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Confined placental mosaicism: placental size and function evaluated on magnetic resonance imaging

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KEYWORDS: confined placental mosaicism; magnetic resonance imaging; MRI; placental function; placental volume; transverse relaxation time; ultrasound

CONTRIBUTION

What are the novel findings of this work?

Pregnancies with confined placental mosaicism (CPM) are characterized by an enlarged and dysfunctional placenta when evaluated on magnetic resonance imaging. Placental function in such pregnancies is related to the chromosomal subtype of CPM.

What are the clinical implications of this work?

Determining the relationship between the specific chromosome involved and the degree of placental dysfunction in CPM pregnancies is important to facilitate accurate parental counseling and appropriate fetal monitoring.

ABSTRACT

Objectives Evidence regarding placental function in pregnancies complicated by confined placental mosaicism (CPM) is conflicting. We aimed to compare placental function between CPM and non-CPM pregnancies prenatally and at birth. A secondary objective was to evaluate the relationship between placental function and chromosomal subtype of CPM.

Methods This was a retrospective study of pregnancies with CPM and control pregnancies delivered at a tertiary hospital in Denmark between 2014 and 2017. Placental volume and placental transverse relaxation time (T2*) were estimated on magnetic resonance imaging (MRI), fetal weight and uterine artery pulsatility index (UtA-PI) were estimated on ultrasound and fetoplacental ratio was assessed on MRI and at birth. These estimates of placental function were adjusted for gestational age and

compared between groups using the Wilcoxon rank-sum test. Within the group of CPM pregnancies, measures of placental function were compared between those at high risk (chromosome numbers 2, 3, 7, 13 and 16) and those at low risk (chromosome numbers 5, 18 and 45X).

Results A total of 90 pregnancies were included, of which 12 had CPM and 78 were controls. MRI and ultrasound examinations were performed at a median gestational age of 32.6 weeks (interquartile range, 24.7–35.3 weeks). On MRI assessment, CPM placentae were characterized by a lower placental T2* Z-score ($P = 0.004$), a lower fetoplacental ratio ($P = 0.03$) and a higher UtA-PI Z-score ($P = 0.03$), compared with non-CPM placentae. At birth, the fetoplacental ratio was significantly lower ($P = 0.02$) and placental weight Z-score was higher ($P = 0.01$) in CPM pregnancies compared with non-CPM pregnancies. High-risk CPM pregnancies showed a reduced placental T2* Z-score ($P = 0.003$), lower birth-weight Z-score ($P = 0.041$), earlier gestational age at delivery ($P = 0.019$) and higher UtA-PI Z-score ($P = 0.028$) compared with low-risk CPM pregnancies. Low-risk CPM pregnancies did not differ in any of these parameters from non-CPM pregnancies.

Conclusions CPM pregnancies are characterized by an enlarged and dysfunctional placenta. Placental function was highly related to the chromosomal type of CPM; placental dysfunction was seen predominantly in high-risk CPM pregnancies in which chromosomes 2, 3, 7, 13 or 16 were involved. © 2023 The Authors. Ultrasound in Obstetrics & Gynecology published by John Wiley & Sons Ltd on behalf of International Society of Ultrasound in Obstetrics and Gynecology.

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INTRODUCTION

Mosaicism is defined as the presence of two or more distinct cell lines in the same individual or conceptus^{1–6}. In confined placental mosaicism (CPM), the abnormal chromosomal cell lines are restricted to the placenta^{1–6}. CPM is often detected incidentally on analysis of a chorionic villus sample (CVS) at combined first-trimester screening (cFTS)^{1,5–8}. CPM is detected in approximately 2% of all CVS analyses performed¹.

Evidence regarding the effect of CPM on placental function and pregnancy outcome is conflicting. Some studies have found that CPM pregnancies are associated with an increased risk of low birth weight and preterm delivery^{1–6,8,9}, whereas others have not demonstrated such associations^{7,10,11}. This inconsistency may be due to variation in placental function, depending on the chromosomal subtype of CPM; it has been suggested that CPM involving chromosome numbers 2, 3, 7, 13, 15, 16 or 22 has an increased risk of adverse pregnancy outcome².

Placental function can be estimated indirectly using fetal weight, placental size, ratio of estimated fetal weight to placental volume (fetoplacental ratio (FPR)) and uterine artery pulsatility index (UtA-PI), as no direct measurement of placental function is available^{12–14}. Previous literature suggests a positive correlation between placental size and placental function^{12–16}. However, in the context of CPM, placental size has only been addressed briefly; one study found the placenta to be small and FPR to fall within the normal range in CPM pregnancies¹⁵.

Recently, it has been shown that placental transverse relaxation time (T2*), obtained by magnetic resonance imaging (MRI), is related to placental oxygenation and, therefore, placental function^{17–21}. Studies have demonstrated that pregnancies complicated by intrauterine growth restriction (IUGR) are associated with reduced placental T2* values^{17–19,21}. However, placental function in CPM pregnancies remains to be evaluated by T2*-weighted placental MRI.

We aimed to investigate placental function in CPM pregnancies using placental T2* and placental volume, estimated on MRI, and UtA-PI and fetal size, estimated on ultrasound. In addition, we stratified our analysis of CPM pregnancies into high and low risk, based on chromosomal subtype of mosaicism. Delineating the relationship between the specific chromosome involved and the degree of placental dysfunction in CPM pregnancies is important to facilitate accurate parental counseling and appropriate fetal monitoring.

METHODS

This was a retrospective study of pregnancies with CPM and control pregnancies without CPM that were delivered at Aalborg University Hospital, Aalborg, Denmark, between 2014 and 2017. The due date was estimated based on the crown–rump length at first-trimester ultrasound²² and cFTS was performed routinely²³. The diagnosis of CPM was verified by array comparative

genomic hybridization, in which the placental genome was compared to a normal reference genome²⁴. This study was approved by the Regional Committees on Biomedical Research Ethics (Journal number N-20090052 and N-20170052). Oral and written informed consent was obtained from all participating women.

Ultrasound examination

A detailed ultrasound examination was performed on the same day as MRI. Fetal weight was estimated using fetal biometry and the Hadlock formula²⁵, and fetal-weight deviation was estimated using reference growth charts of Marsal *et al.*²⁶. UtA-PI was measured on Doppler ultrasound, using the values reported by Kaminopetros *et al.*²⁷ as a reference.

Magnetic resonance imaging

MRI was performed using a 1.5-Tesla GE Discovery MR450 System (GE Healthcare, Zipf, Austria). An eight-channel cardiac coil was placed over the abdomen, covering the uterus, with the woman in the left lateral position. Placental T2* scanning was performed with use of a gradient-recalled echo sequence and the following parameters: repetition time, 70.9 ms; 16 echoes ranging from 3.0 to 67.5 ms in steps of 4.3 ms; field of view, 350 × 350 mm; and matrix, 256 × 128 mm. The in-plane resolution of the matrix was 1.37 × 2.73 mm. Three placental slices of 8 mm thickness with a gap of 2 cm were obtained from the central part of the placenta. Each slice was obtained during a 12-s breath-hold. A balanced gradient echo sequence (Fast Imaging Employing Steady-state Acquisition (FIESTA); GE Healthcare) was performed using the following parameters: field of view, 380 × 380 mm; slice thickness, 10 mm; flip angle, 50°; and no slice spacing. The entire MRI session lasted for 30 min.

Image analysis was performed using software developed in-house and written in MATLAB (MathWorks Inc., Natick, MA, USA). Regions of interest (ROI) were drawn manually by two independent investigators (M.S. and D.N.H.). The ROI included the entire placenta in the transverse orientation, and ROI placement was corrected manually in each image slice (Figure 1). T2* values were calculated in each ROI by fitting the averaged signal as a function of the echo time. The placental T2* value was calculated as the average of the three placental slices. As described previously, there is a negative correlation between placental T2* and gestational age¹⁹. To adjust for any difference in gestational age between the groups, placental T2* Z-scores (i.e. the number of standard deviations by which they differ from the expected mean for gestational age) were calculated using the normal values published previously by our group¹⁹.

Placental volume was calculated as the total number of pixels within the placental ROI multiplied by the voxel volume. The level of mosaicism was determined by the percentage of mosaic cells in the CVS obtained at first-trimester screening.

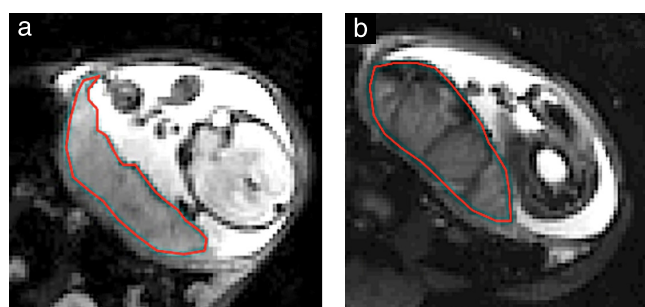


Figure 1 Placental T2*-weighted magnetic resonance images at 28 weeks' gestation, showing region of interest (red outline) in: (a) non-mosaic placenta (transverse relaxation time (T2*), 117 ms) and (b) mosaic placenta (T2*, 52 ms). Placentae are visually different, with that in (b) appearing larger and darker than that in (a).

Statistical analysis

Estimates of placental function were converted into standardized Z-scores to enable comparison between CPM and control pregnancies, which was performed using the Wilcoxon rank-sum test. A subgroup analysis was performed in which CPM pregnancies were stratified by chromosomal subtype, according to the classification scheme of Eggenhuizen *et al.*². CPM pregnancies were classified as high risk (chromosome number 2, 3, 7, 13 or 16) or low risk (chromosome number 5, 18 or 45X) and analyzed using the Wilcoxon rank-sum test. Lastly, the correlation between the level of mosaicism and placental function was investigated using Pearson's correlation coefficient. Statistical analysis was performed using Stata®/MP 17 (StataCorp. LP, College Station, TX, USA) and the significance level was set at $P < 0.05$.

RESULTS

A total of 90 pregnancies were included, of which 12 had CPM and 78 were controls. In 11/12 CPM pregnancies, CVS was performed owing to an increased risk of fetal trisomy (risk of trisomy 21, $> 1:300$; risk of trisomy 18 and 13, $> 1:150$) on cFTS. In one CPM pregnancy, CVS was performed because a previous pregnancy was complicated by trisomy 18. In 11/12 CPM pregnancies, a normal fetal karyotype was confirmed by amniocentesis. In the remaining CPM pregnancy, the neonatal phenotype was normal and no further testing was performed. The control group included presumed non-CPM pregnancies, of which five were considered to have an increased risk of fetal trisomy on cFTS. In two of these five pregnancies, a normal placental karyotype was revealed by CVS. The remaining three pregnancies underwent non-invasive prenatal testing in the first trimester. As these pregnancies were uneventful and the neonatal phenotypes were normal, no further genetic testing was performed. Thus, 73/78 pregnancies in the control group did not undergo any genetic testing during pregnancy or postpartum.

Characteristics of the study population are presented in Tables 1 and S1. CPM pregnancies were characterized

by significantly higher maternal age, lower level of pregnancy-associated plasma protein-A and increased risk of fetal trisomy on cFTS. No difference was found between groups regarding smoking status or the rate of hypertensive disorders of pregnancy, but the incidence of gestational diabetes mellitus (GDM) was significantly higher in the CPM group. All pregnancies underwent placental MRI and detailed ultrasound examination at a median gestational age of 32.6 weeks (interquartile range, 24.7–35.3 weeks).

On MRI, placental T2* Z-score ($P = 0.004$) and FPR ($P = 0.03$) were reduced significantly (Figure 2, Table 2), and UtA-PI Z-score ($P = 0.03$) was increased significantly (Table 2), in CPM pregnancies compared with control pregnancies. However, no difference was found in estimated fetal weight Z-score ($P = 0.89$) or placental volume Z-score ($P = 0.18$) between pregnancies with and without CPM.

At birth, placental weight Z-score was significantly higher ($P = 0.01$), and FPR significantly lower ($P = 0.02$), in CPM pregnancies compared with control pregnancies (Figure 3, Table 2). However, no difference was demonstrated regarding birth-weight Z-score ($P = 0.56$).

In high-risk CPM pregnancies (7/12), placental T2* Z-score was significantly reduced ($P = 0.003$) and UtA-PI Z-score was significantly increased ($P = 0.028$) when compared with low-risk CPM pregnancies (5/12) (Figure 4). Furthermore, high-risk CPM pregnancies were delivered earlier in gestation ($P = 0.019$) and with a significantly reduced birth-weight Z-score ($P = 0.041$) compared with low-risk CPM pregnancies. No difference was demonstrated when comparing the same parameters

Table 1 Demographic and clinical characteristics of 12 pregnancies with confined placental mosaicism (CPM) and 78 control pregnancies

Characteristic	CPM (n = 12)	Controls (n = 78)	P*
Maternal age (years)	36 (33–40)	28 (26–32)	0.0003
Caucasian ethnicity	12 (100)	78 (100)	—
Current smoker	0 (0)	13 (16.7)	0.126
BMI (kg/m ²)	26.8 (22.8–31.2)	22.0 (20.5–23.5)	0.003
Parous	9 (75.0)	37 (47.4)	0.121
β-hCG MoM	0.8 (0.3–1.8)	1.0 (0.7–1.6)	0.055
PAPP-A MoM	0.4 (0.2–0.7)	1.1 (0.7–1.7)	< 0.0001
High risk of trisomy 21†	9 (75.0)	5 (6.4)	< 0.0001
High risk of trisomy 18‡	5 (41.7)	0 (0)	< 0.0001
High risk of trisomy 13‡	2 (16.7)	0 (0)	< 0.0001
Hypertensive disorder of pregnancy	1 (8.3)	4 (5.1)	0.652
Gestational diabetes mellitus	2 (16.7)	1 (1.3)	0.006

Data are given as median (interquartile range) or n (%). *Calculated using Wilcoxon rank-sum test or χ -square test. †Defined as risk $> 1:300$. ‡Defined as risk $> 1:150$. β-hCG, beta-human chorionic gonadotropin; BMI, body mass index; MoM, multiples of the median; PAPP-A, pregnancy-associated plasma protein-A.

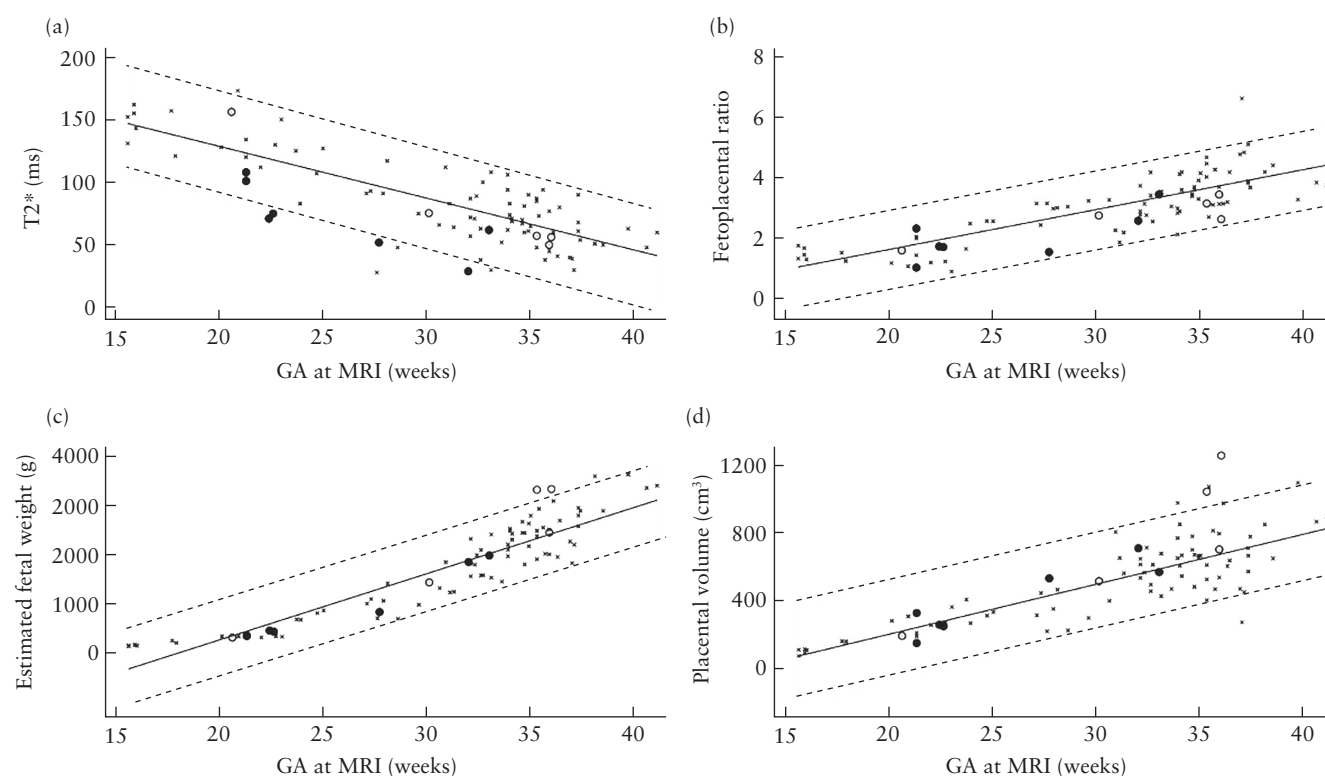


Figure 2 Scatterplots illustrating transverse relaxation time ($T2^*$) (a), fetoplacental ratio (b), estimated fetal weight (c) and placental volume (d) as a function of gestational age (GA) on magnetic resonance imaging (MRI) in low-risk confined placental mosaicism (CPM) pregnancies (○), high-risk CPM pregnancies (●) and control pregnancies (×). Ordinary least-squares fit (—) and 95% prediction intervals (---) for control pregnancies are presented.

Table 2 Findings at prenatal magnetic resonance imaging (MRI) and at birth in 12 pregnancies with confined placental mosaicism (CPM) and 78 control pregnancies

Characteristic	CPM (n = 12)	Controls (n = 78)	P*
On MRI			
GA (weeks)	28.9 (21.9 to 34.2)	33.1 (27.1 to 35.4)	0.17
$T2^*$ (ms)	66.5 (54.1 to 88.2)	78.5 (60.0 to 107.0)	—
Z-score†	−1.35 (−3.22 to −0.94)	−0.45 (−1.37 to 0.33)	0.004
Estimated fetal weight (g)	1126 (391 to 2201)	1864 (805 to 2464)	—
Z-score‡	−0.73 (−1.20 to −0.39)	−0.56 (−1.38 to 0.18)	0.89
Placental volume (cm ³)	525.2 (255.3 to 708.3)	536.8 (312.5 to 669.2)	—
Z-score	0.15 (−0.16 to 0.87)	0.06 (−0.59 to 0.49)	0.18
FPR	2.45 (1.66 to 2.96)	3.14 (2.27 to 3.76)	0.03
UtA-PI Z-score¶	0.34 (−0.65 to 1.13)	−0.49 (−1.12 to 0.02)	0.03
At birth			
GA (weeks)	39.0 (35.3 to 40.0)	40.0 (38.3 to 40.9)	0.03
Birth weight (g)	3005 (2115 to 3435)	3360 (2680 to 3810)	—
Z-score‡	−0.72 (−1.38 to −0.25)	−0.36 (−1.43 to 0.26)	0.56
Placental weight (g)	608 (529 to 753)	600 (498 to 710)	—
Z-score	0.86 (0.20 to 1.53)	−0.09 (−0.63 to 0.52)	0.01
FPR	4.73 (3.50 to 5.40)	5.40 (4.85 to 5.92)	0.02

Data are given as median (interquartile range). *Calculated using Wilcoxon rank-sum test. †Using reference of Sinding *et al.*²¹. ‡Using reference of Hadlock *et al.*²⁵. ¶Using reference of Kaminopetros *et al.*²⁷. FPR, fetoplacental ratio; GA, gestational age; $T2^*$, transverse relaxation time; UtA-PI, uterine artery pulsatility index.

between low-risk CPM pregnancies and control pregnancies.

No correlation was observed between placental function, estimated by placental $T2^*$ Z-score, and the level of mosaicism in the placenta ($r = 0.007$; $P = 0.982$) (Figure 5).

DISCUSSION

This study demonstrates that CPM pregnancies are characterized by an enlarged and dysfunctional placenta when evaluated by $T2^*$ -weighted placental MRI, which serves as a non-invasive measure of tissue oxygenation.

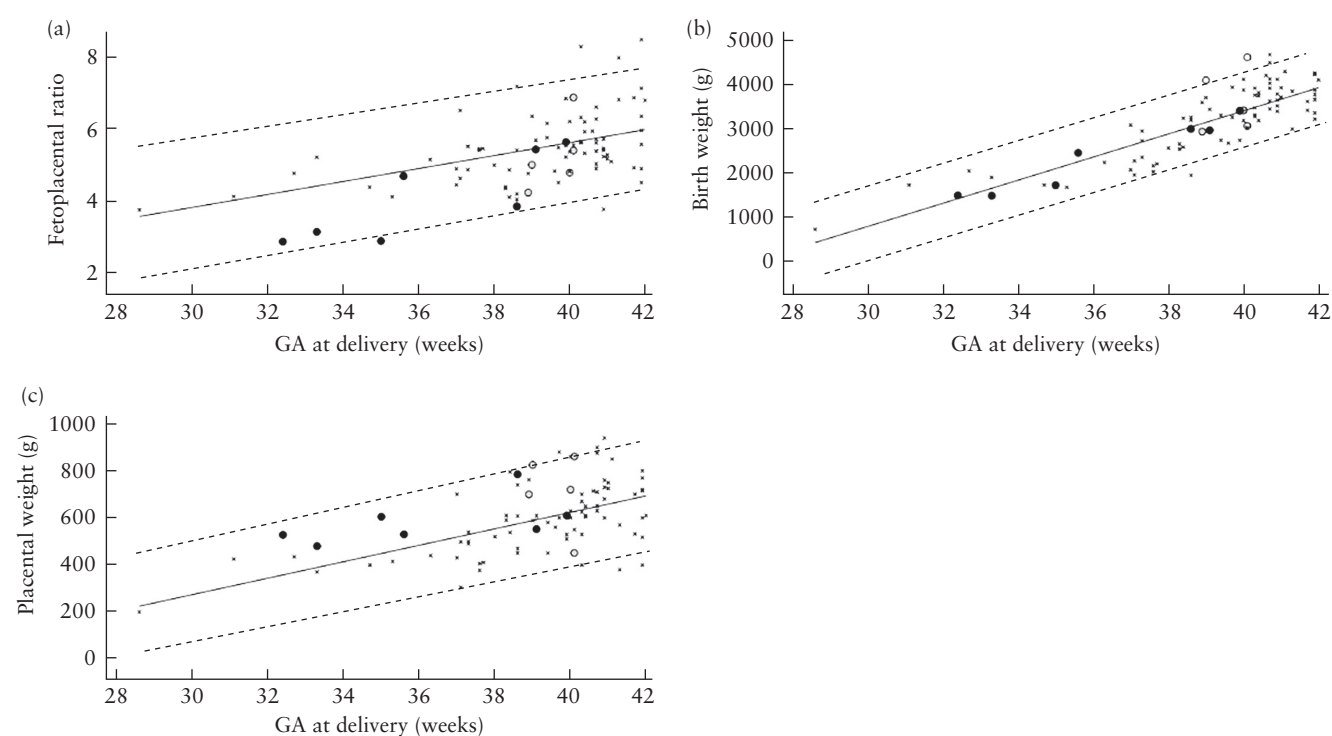


Figure 3 Scatterplots illustrating fetoplacental ratio (a), birth weight (b) and placental weight (c) as a function of gestational age (GA) at delivery in low-risk confined placental mosaicism (CPM) pregnancies (○), high-risk CPM pregnancies (●) and control pregnancies (×). Ordinary least-squares fit (—) and 95% prediction intervals (---) for control pregnancies are presented.

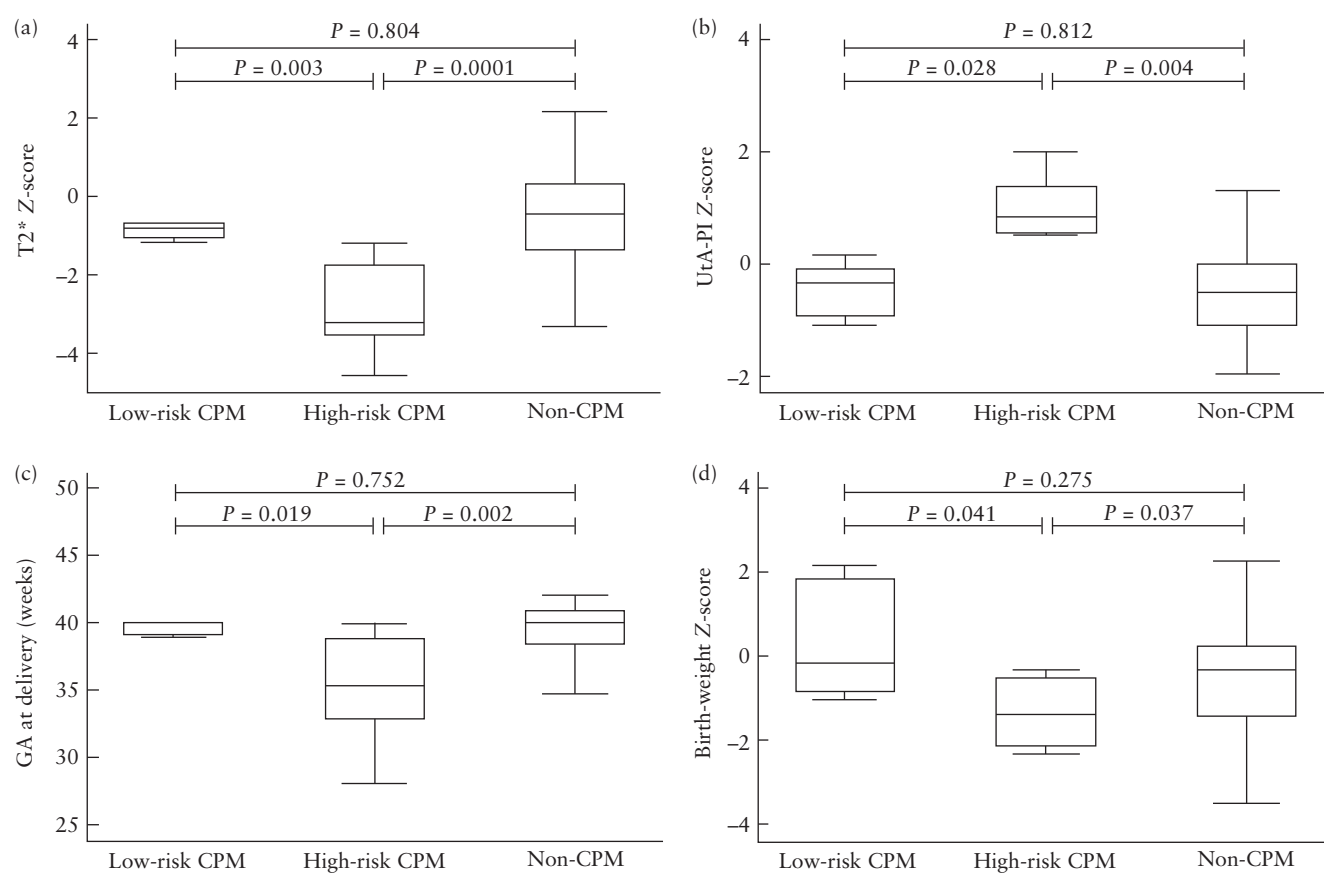


Figure 4 Boxplots illustrating transverse relaxation time (T2*) Z-score (a), uterine artery pulsatility index (UtA-PI) Z-score (b), gestational age (GA) at birth (c) and birth-weight Z-score (d) for low-risk confined placental mosaicism (CPM) pregnancies, high-risk CPM pregnancies and non-CPM pregnancies. Outliers are excluded from figures, but were included in analysis. Differences between groups were examined using Wilcoxon rank-sum test. Boxes show median and interquartile range and whiskers are range.

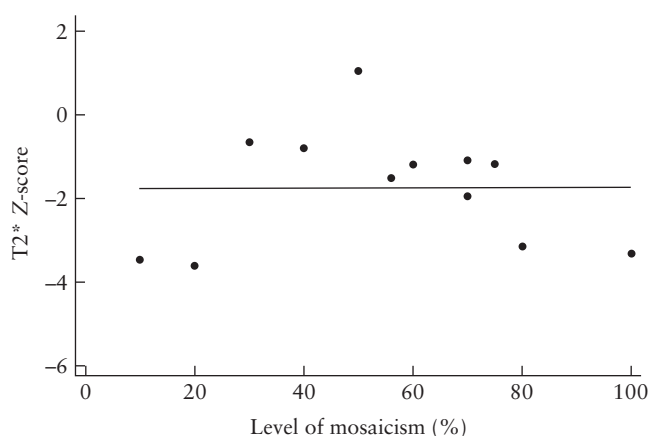


Figure 5 Scatterplot illustrating correlation between placental transverse relaxation time (T2*) Z-score and level of placental mosaicism, examined using Pearson's correlation coefficient.

This study also suggests that placental dysfunction is associated predominantly with specific high-risk chromosomal subtypes of CPM, involving chromosome numbers 2, 3, 7, 13 or 16.

A limitation of the study is the small sample size and large variation in chromosomal subtypes of CPM. A further limitation is that the control group could potentially include undiagnosed CPM cases, as most (73/78) women in this group did not undergo chromosomal testing. The incidence of CPM is approximately 2%, thus one or two undiagnosed CPM cases may have been present in the control group. However, the inadvertent inclusion of undiagnosed CPM pregnancies in the control group would tend to reduce the true difference between the two groups. Accordingly, this study may have underestimated the difference between the groups. Another limitation is that two of the CPM pregnancies were complicated by GDM, which is a significantly increased rate compared with that of the control group. It is well documented that GDM is characterized by increased placental size and reduced FPR²⁸. Thus, GDM could be a confounder in this study. However, in both GDM pregnancies, the FPR on MRI was high, at 4.99 and 4.68, respectively, and placental function was normal, indicated by T2* Z-scores within the normal range, at -0.66 and -1.19, respectively. Accordingly, it is reasonable to assume that the two GDM cases did not drive the conclusions of this study. A strength of this study is the use of the T2* value as a direct measure of placental function. To our knowledge, T2*-weighted placental MRI has not been used previously for the assessment of placental function in CPM pregnancies.

At birth, the CPM placenta was larger than the control placenta at an equivalent gestational age. This finding is supported by the non-significant trend towards increased placental volume on MRI assessment. This finding conflicts with that of a previous study on placental weight by Yong *et al.*¹⁵, which compared 69 CPM pregnancies with a reference population of 787 normal pregnancies. They found the CPM placenta to be smaller than the normal placenta at birth. However, the authors noted

that CPM pregnancies complicated by IUGR were more likely to be included in the study, which may explain why CPM placentae were smaller than the normal placentae. Accordingly, in their study, the FPR did not differ between CPM and normal pregnancies¹⁵.

On MRI, we found a lower T2* Z-score in CPM pregnancies compared with control pregnancies. Recently, the T2* value has been described as a marker of placental function^{17–21}. The T2* value is sensitive to local magnetic field inhomogeneities created by the presence of deoxyhemoglobin and to tissue morphology such as fibrotic tissue, infarction and altered villus density^{17–21}. Therefore, a low placental T2* value may be indicative of reduced oxygenation and, consequently, impaired placental function^{17–21}. We also found that placental weight was increased without a corresponding increase in birth weight, resulting in a reduced FPR. It is surprising that placental size is increased at the same time as placental function is impaired in CPM pregnancies, given that a low FPR is generally considered to be a sign of placental dysfunction²⁹. These findings contrast with the traditional understanding of a positive correlation between placental size and placental function^{12–16}. The etiology behind placental overgrowth in CPM pregnancies cannot be identified from the present study, but it could be a consequence of genetic changes leading to placental hyperplasia, with a negative effect on placental function. In pregnancies complicated by obesity and GDM, it has also been shown that the placenta is large and slightly inefficient, when evaluated by the FPR²⁸. Moreover, CPM pregnancies showed an increased UtA-PI Z-score, suggesting abnormal transformation of the spiral arteries, which is related to impaired placental function^{5,18,20,22,30}. This result is supported by a previous study of IUGR pregnancies by Miura *et al.*⁴, which found higher UtA-PI in pregnancies with CPM compared to those without⁴. This finding is also consistent with previous work showing an increased risk of placenta-related obstetric complications, such as hypertensive disorders of pregnancy, in CPM pregnancies³¹. However, such clinical manifestation was not found among CPM pregnancies in the small sample analyzed here.

The present study demonstrates that the chromosomal subtype of CPM is crucially related to placental function. According to Eggenhuizen *et al.*², involvement of specific chromosomes is associated with adverse pregnancy outcomes, such as impaired fetal growth, low birth weight and preterm delivery. This is supported by a recent meta-analysis³². Correspondingly, we found placental function to be impaired predominantly in high-risk CPM pregnancies, illustrated by a lower T2* Z-score, a higher UtA-PI Z-score, lower birth weight Z-score and earlier gestational age at delivery compared with low-risk CPM pregnancies. Furthermore, we found that low-risk CPM pregnancies did not differ from control pregnancies in these parameters, suggesting near-normal placental function in low-risk CPM cases.

In contrast to a previous review by Eggenhuizen *et al.*², we failed to demonstrate a correlation between the level

of mosaicism and placental function reflected by placental T2*. According to our study, the chromosomal subtype of CPM is the dominant determinant of placental function. However, large-scale studies on CPM pregnancies with different chromosomal subtypes and levels of mosaicism are needed to further delineate this association. It has been suggested that placental function and the development of adverse obstetric outcomes may be related to the specific location of mosaicism: in the cytotrophoblast (Type 1), mesenchymal core (Type 2) or the cytotrophoblast and the mesenchymal core (Type 3)^{1,2,4–6,8}. Such subdivision could contribute to further understanding of impaired placental function in CPM pregnancies, but it was not possible to carry out such a test in the present study.

New technologies, such as cell-based non-invasive prenatal testing, have the potential to identify CPM and determine the specific location of mosaicism non-invasively^{1,33}. In the light of future diagnostic opportunities, in-depth understanding of the association between genetic subtypes, placental function and obstetric outcomes in CPM pregnancies is highly important.

In conclusion, this study demonstrates that the CPM placenta was enlarged and dysfunctional. Placental function was highly related to the chromosomal subtype of CPM, as placental dysfunction was seen predominantly in high-risk CPM pregnancies involving chromosome numbers 2, 3, 7, 13 or 16. Further understanding of placental function in CPM is essential to facilitate evidence-based parental counseling and rational fetal monitoring in pregnancies complicated by CPM.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:



Table S1 Characteristics of 12 pregnancies with confined placental mosaicism