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The role of confined placental mosaicism in fetal growth restriction: A retrospective cohort study

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Abstract

Objective: To evaluate which cytogenetic characteristics of confined placental mosaicism (CPM) detected in the first trimester chorionic villi and/or placentas in terms of chromosome aberration, cell lineage involved and trisomy origin will lead to fetal growth restriction and low birthweight.

Methods: Cohort study using routinely collected perinatal data and cytogenetic data of non-invasive prenatal testing, the first trimester chorionic villi sampling and postnatal placentas.

Results: 215 CPM cases were found. Fetal growth restriction (FGR) and low birthweight below the 10th percentile (BW < p10) were seen in 34.0% and 23.1%, respectively. Excluding cases of trisomy 16, 29.1% showed FGR and 17.9% had a BW < p10. The highest rate of FGR and BW < p10 was found in CPM type 3, but differences with type 1 and 2 were not significant. FGR and BW < p10 were significantly more often observed in cases with meiotic trisomies.

Conclusion: There is an association between CPM and FGR and BW < p10. This association is not restricted to trisomy 16, neither to CPM type 3, nor to CPM involving a meiotic trisomy. Pregnancies with all CPM types and origins should be considered to be at increased risk of FGR and low BW < p10. A close prenatal fetal monitoring is indicated in all cases of CPM.

Key points

What's already known about this topic?

- CPM may have an impact on fetal growth and birthweight.
- CPM type 3 often involving a meiotic trisomy is associated with an adverse pregnancy outcome.

What does this study add?

- Although fetal growth problems were more often seen in CPM type 3 and those involving a meiotic trisomy, both CPM type 1 and CPM involving a mitotic trisomy were also associated with an increased risk of impaired fetal growth and low birthweight.

- Irrespective of CPM type, trisomy origin, or involved chromosome aberration, we advocate to closely monitor all pregnancies where CPM is suspected, except for CPM type 2.

1 | INTRODUCTION

Confined placental mosaicism (CPM) is a type of chromosomal mosaicism with one or more chromosomally abnormal cell line(s) restricted to the placenta, while the chromosomal constitution of the fetus is normal.[1] Many pregnancies with CPM are uneventful. However, CPM may be associated with fetal growth restriction (FGR), premature birth, structural fetal anomalies and pregnancy complications such as preeclampsia.[2] Several studies investigated the association of CPM with adverse pregnancy outcomes with conflicting conclusions.[3–10] Recent studies based on non- invasive prenatal testing (NIPT) also confirmed an association between a rare autosomal trisomy (RAT), which is most probably confined to the placenta and low birthweight.[11,12] CPM has historically been a rare finding accounting for 1%–2% of CVS in a genetic high-risk population. For most genetic laboratories, this meant a few cases per year. With the introduction of NIPT, which analyses cfDNA fragments in maternal plasma of which the fetal component originates from the placenta, the CPM numbers increased, making CPM a potential important clinical problem.[13] Apart from some older studies on CPM detected in chorionic villi, little is known about the cytogenetic characteristics that determine whether a CPM will have a clinical impact or not.[2]

CPM can be categorized into three different subtypes (type 1, 2 and 3) depending on the affected cell lineage.[14,15] If the chromosome aberration is only present in the cytotrophoblast (CTB), this is called CPM type 1. When the chromosomal abnormality is restricted to the mesenchymal core (MC) of the chorionic villi, it is categorized as type 2. Type 3 is defined as the presence of the abnormality in both cell-layers, MC and CTB. Only types 1 and 3 can be detected with NIPT. Moreover, if CPM involves a trisomy, this chromosome aberration may have a meiotic or mitotic origin. Some suggest that there is only an association between adverse pregnancy outcomes and CPM trisomy 16.[16] Others showed that CPM type 3 may be associated with FGR and pregnancy complications, whereas type 1 and type 2 are probably benign.[2,6,16]

In this study, we investigated fetal growth and birthweight in pregnancies affected with CPM that were cytogenetically characterized in CV and/or placental biopsies. We investigated whether fetal growth problems only occur in specific types of CPM in terms of chromosome aberration involved, cell lineage involved and trisomy origin.

2 | METHODS

2.1 | Study design and population

From January 2008 to December 2019, all cases of (potential) CPM diagnosed in the Erasmus MC (Rotterdam, the Netherlands) and LUMC (Leiden, the Netherlands) were collected. In the beginning of this time frame, CPM was exclusively identified through CVS. After the introduction of NIPT in the Netherlands in 2014, CPM could also be identified by NIPT. Exclusion criteria for this study were twin pregnancies and proven fetal genetic disorders.

According to the level of investigation, all CPM cases were subdivided in three groups: proven, suspected and assumed CPM. We defined cases of proven CPM as all cases with a chromosome aberration present in chorionic villi or postnatal placenta but absent in amniotic fluid (AF)/cord blood/fetal tissue. A separate second group that was included involved the cases of suspected CPM. These are cases in which chromosome anomalies were detected with NIPT that are typically involved in CPM, mostly rare autosomal trisomies (RAT), with normal results in AF/cord blood/fetal tissue and maternal blood, but with none or insufficient placental tissue available for cytogenetic confirmation. The last and smallest groups are cases of assumed CPM. These involve cases of RAT that were detected with NIPT and in 2 cases in CVS (both cytotrophoblast (CTB) and mesenchymal core (MC)) without follow-up investigations in fetus, but in which a healthy child was born.

2.2 | Cytogenetic analysis during pregnancy

In the majority of the CVS cases, both cell layers, CTB and MC, were analyzed separately. Amniotic Fluid was cytogenetically investigated with an SNP array on uncultured amniotic cells (Illumina HumanCytoSNP-12 array, Illumina Infinium-CytoSNP-850K genotyping array or Illumina Infinum GSA + MD-24 v1.0 BeadChip[17,18]) and with karyotyping or FISH of AF cell cultures (in situ method), in order to exclude mosaicism in uncultured as well as cultured cells. Uniparental disomy (UPD) studies and studies on the mitotic or meiotic origin of a trisomy were performed using an SNP array.[19] For this purpose, parental blood was also collected.

Genome-wide NIPT was performed as part of the Dutch Trident studies using a whole-genome shallow massively parallel shotgun sequencing with WISECONDOR for analysis of all chromosomes, except for the sex-chromosomes.[20] Therefore, cases of CPM detected with NIPT only involved autosomal chromosome aberrations. From 2014 to 2017, NIPT was only carried out if there was an increased risk of one of the common aneuploidies, mainly based on abnormal combined test results (Trident 1).[19,21] From 2017 onwards, NIPT was offered to all pregnant women as a first-tier screening test (Trident 2).[22] A part of this cohort (only Trident 2 of 2017–2019) is also published elsewhere in Prooyen-Schuurman et al,[11] but without investigation of the cytogenetic characteristics of the CPM such as trisomy origin and CPM type.

2.3 | Cytogenetic analysis after pregnancy

Placental biopsies of about 1 cm^3 from the four different quadrants were requested and in most cases cord blood or other fetal tissues were received as well. The collection of placental biopsies started in 2014 after the introduction of NIPT, in order to confirm the placental origin of the chromosome aberration detected with NIPT. Therefore, no placental biopsies were available before 2014. One to four placental chorionic villus biopsies were cytogenetically investigated with an SNP array on both CTB and MC separately.[13] Cord blood or other fetal tissue was investigated using the same technique.

2.4 | Clinical follow-up

Birthweight, fetal growth ultrasound measurements and pregnancy outcomes were collected at both university medical centers, midwife practices and referral hospitals. Written informed consent was obtained from all participating women. FGR was defined as (1) estimated fetal weight (EFW) <10th percentile, (2) fetal AC <10th percentile, or (3) declining fetal growth (decline of minimal 20 percentiles of AC and/or EFW). Ultrasound measurements were collected from the first trimester until the third trimester, including an (expert) ultrasound screening for congenital anomalies between 18 and 24 weeks. Estimated fetal weight was calculated with the use of Hadlock 3.[23] All birthweight percentiles were calculated with the use of the Hoftiezer curve and were categorized below the 10th percentile (BW < p10), below the 5th and 3rd.[24]

2.5 | Statistical analysis

IBM SPSS statistics 26 were used for computing statistical analysis. The significance level was set at p-value of <0.05. The following tests were used: One way ANOVA, Kruskal–Wallis test, Chi2 test and independent sample T test.

3 | RESULTS

1. Clinical outcome in total cohort

A total of 215 pregnancies with CPM were prenatally detected between January 2008 and December 2019, as shown in the flowchart (Figure S1). According to the level of investigation, all CPM cases were subdivided in three groups: proven (n = 139 (64.7%)), suspected (n = 70 (32.6%)) and assumed CPM (n = 6 (2.8%)). Since most of CPM were detected with NIPT that does not investigate the sex-chromosomes in the Netherlands, and because of the criteria used to define cases of CPM, most CPM involved single autosomal trisomies (n = 168, 78.1%) and 10 (4.7%) involved multiple trisomies. Especially in the group of CPM detected with CVS, cases of structural chromosome aberrations, X-chromosomal aberrations and polyploidy were also found (n = 37, 17.2%).

3.1 | Pregnancy outcome

Pregnancy outcome could be retrieved in 208/215 (96.7%) CPM cases as shown in Figure S1. In 5/208 (2.4%) cases, the parents opted for termination of pregnancy (TOP): in two of these, the pregnancies were complicated with structural fetal anomalies (renal agenesis and the other bilateral palate cleft combined with complex cardiac defect and FGR), two others were complicated with immature rupture of membranes (in both cases the rupture of membranes could not be linked to the invasive procedure) and the last pregnancy was unplanned and unwanted. In 3/208 (1.4%) cases, pregnancies ended in intra uterine fetal demise (IUFD) before 20 weeks of gestation and one of them showed FGR. In 199/208 (95.7%) pregnancies, a live neonate was born and in 1/199 (0.5%) neonatal death was encountered: this fetus had a hypoplastic left heart syndrome and died 6 days after birth. In 1/208 perinatal death occurred; the neonate was born dysmature with a birthweight on the 5th percentile at 40 + 6 weeks without structural fetal anomaly (during the third trimester no fetal growth assessment was performed). In 18/208 (8.7%) cases, congenital fetal anomalies were detected: 13 cases showed isolated anomalies and in five cases there were multiple anomalies.

3.2 | Fetal growth

In 197/215 pregnancies (91.6%), growth data could be collected. In 67 cases (34.0%), the pregnancy was complicated with FGR and in the trisomy 16 groups this occurred in 16/22 (72.7%). When all cases with trisomy 16 were excluded, the prevalence of FGR was 29.1% (51/175). In Figure 1, the occurrence of FGR is given per chromosome aberration.

3.3 | Birthweight

In 199/215 (92.6%) cases birth weight (BW) data could be retrieved. 46/199 (23.1%) had a BW < p10, compared to 70.0% (14/20) in the trisomy 16 groups. Excluding the trisomy 16 cases, 32/179 (17.9%) had a BW < p10. The distribution per chromosome aberration is shown in Figure 2. Four chromosome aberrations had significantly more cases with a birth weight below the 10th percentile than expected based on the percentiles (shown with an asterix in Figure 2).

2. Clinical outcome in relation to cytogenetic characteristics of CPM

In 139/215 (64.7%) cases, CPM characteristics such as CPM type and trisomy origin could be studied since the chromosome aberration

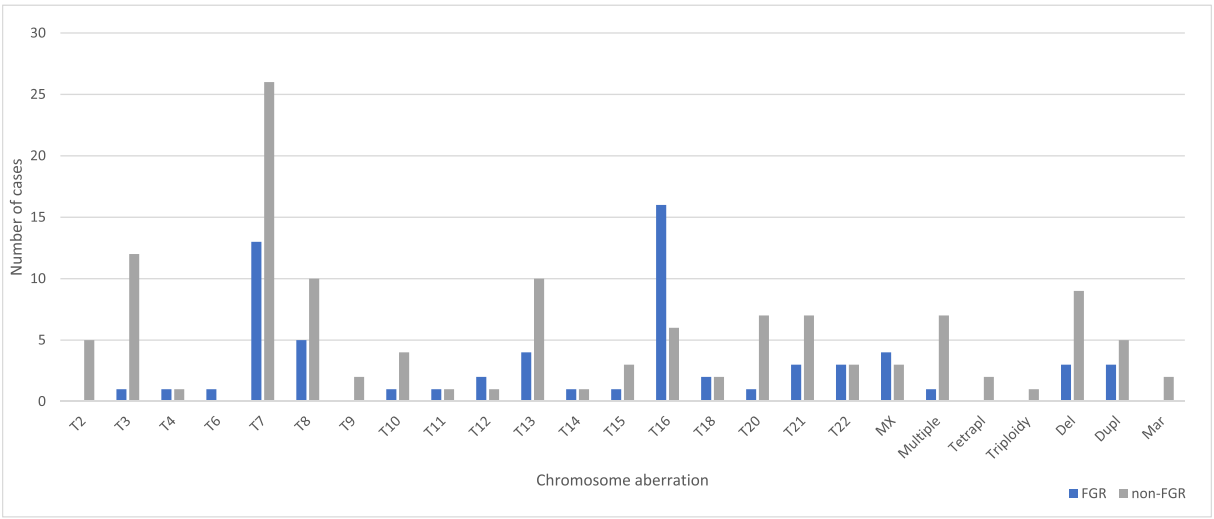

FIGURE 1 Analysis of fetal growth restriction. Different chromosomal aberrations on *X*-axis and number of cases on *Y*-axis. (Del, Deletion; Dupl, Duplication; Mar, marker chromosome; Multiple, multiple trisomies; MX, monosomy X; Tetrapl, Tetraploidy; *T*, trisomy).

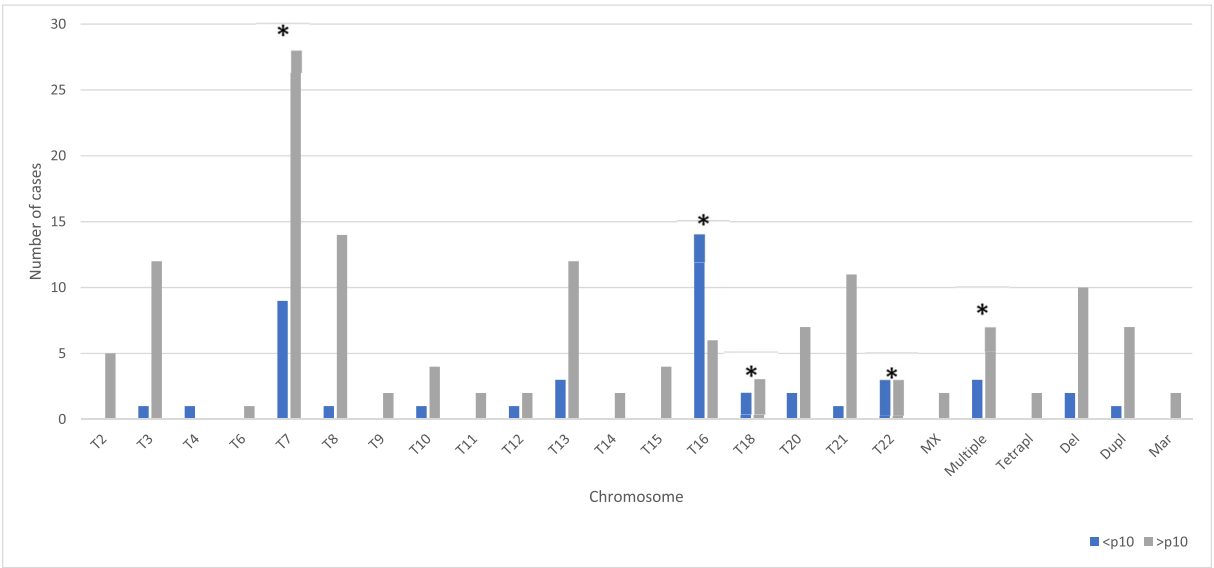

FIGURE 2 Analysis of low birthweight below the 10th percentile (<p10). Different chromosomal aberrations on *X*-axis and number of cases on *Y*-axis. (Del, Deletion; Dupl, Duplication; Mar, marker chromosome; Multiple, multiple trisomies; MX, monosomy X; Tetrapl, Tetraploidy; *T*, trisomy) * = significantly more cases with low birthweight than expected (*p* value below 0.05).

was present in the first trimester CV and/or at least in one of the placental biopsies. This allowed us to investigate whether the clinical outcome is dependent on specific cytogenetic features of the CPM. Therefore, only the proven cases are described in this section of the paper. Table S1 shows the cytogenetic results in cytotrophoblast (CTB) and mesenchymal core (MC) of first trimester CV and/or term placental CV per case, including pregnancy outcome for all proven cases. In most cases, multiple placental biopsies were investigated and the result in CTB and MC reflects the presence of the chromosome aberration (in red) in at least one of the biopsies or absence (in green) in all biopsies.

3.4 | Type of CPM

In 58 cases, the chromosome aberrations were found in the CTB only (type 1), in 20 cases in the MC only (type 2) and in 45 cases in both CTB and MC (type 3). In 16 cases, only the MC of CV was investigated, and therefore, the type could not be identified conclusively (type 2 or 3). Based on the distribution of abnormal cells across CTB and MC, 8 cases should be considered to be CPM type 2 (abnormal cells only in MC). However, since these were detected with NIPT that essentially investigates the CTB, they were classified as CPM type 3 (highlighted with blue color in Table S1). In 11 cases, both first

trimester CV and postnatal placental biopsies were analyzed, highlighted with a light yellow color in Table S1. In only two cases (cases 87 and 168 in Table S1) the chromosome aberration was present in both first trimester CV after CVS and in CV of the postnatal placenta. In six cases, the trisomy that was detected with NIPT was not found in the first trimester CV but was seen in the postnatal placenta and in three cases vice versa (trisomy present in CV, but absent in term placenta). The distribution of the three CPM types per chromosomal aberration is shown in Figure S2.

The highest rate of FGR was found in CPM type 3 (45.2%, compared to 29.4% and 7.0% for type 1 and 2, respectively) (Table 1). The percentage of BW < p10 was higher in type 3 (33.3%) than in type 1 (21.8%) and type 2 (5.9%), although the difference was not significant (*p* value 0.110) as shown in Table 1.

3.5 | Origin of the trisomy

In 116/139 cases, a trisomy was involved and in 75/116 (64.7%) the trisomy was detected with SNP array, so the mitotic or meiotic origin could be determined. The trisomy was meiotic in 25/75 (33.3%) and mitotic in 50/75 (66.7%) of the cases. In Figure S3, the origin of the trisomy is shown per chromosome. We found a significant difference, with more FGR in the meiotic origin group as compared to the mitotic group (p0.001) (Table 2). Also, for low BW < p10, a significant difference was found between the meiotic group (54.2%), and the mitotic group (16.7%) (Table 2).

3.6 | Involved chromosome aberration

Due to the number of cases (>10 cases) of CPM trisomy 3, 7, 8, 13, 16 and 21, a subgroup analysis could be performed, which is shown in Table S2. This table shows the number of cases with FGR and BW < p10 per chromosome aberration, and also the numbers according to CPM type and origin of the trisomy. For instance, in case of trisomy 7, all having a mitotic origin, as far as investigated, and half of them were involved in CPM type 1 and the other half in type 3, there were more cases with FGR/low BW if trisomy 7 was involved in CPM type 1 than type 3. Moreover, only the meiotic trisomy 3 case showed normal fetal growth. Also, both CPM type 1 trisomy 16 cases showed FGR. This illustrates that at the individual level, CPM characteristics such as CPM type, involved chromosome aberration and origin of the trisomy, do not allow to differentiate between CPM affecting fetal growth and CPM without clinical consequences and therefore cannot be used for accurate individual prenatal growth prognosis assessment.

3.7 | High-risk genetic population versus general screening population

Based on the a priori genetic risk, the total cohort can be divided into a high genetic risk (CVS and Trident 1) and a general screening population (Trident 2). The cytogenetic characteristics and clinical outcome of CPM in both groups are shown in Table S3. Although we found a higher percentage of BW < p10 and FGR in the high-genetic risk group (29.1% and 36.1%, respectively) compared to the general risk population (19.1% and 32.8%, respectively), this difference was not significant (p0.103 and p0.637, respectively).

TABLE 2 Comparing the prevalence of fetal growth restriction and birthweight below the 10th, 5th and 3rd percentile according to the trisomy origin.

	Origin of trisomy		
	Mitotic *N* = 50	Meiotic *N* = 25	Sign (*p*)
FGR	12/47 (25.5%)	15/24 (62.5%)	**0.002**
Birthweight < p10	8/48 (16.7%)	13/24 (54.2%)	**0.001**
Birthweight < p5	5/48 (10.4%)	10/24 (41.7%)	**0.002**
Birthweight < p3	4/48 (8.3%)	10/24 (41.7%)	**0.001**

Note: Bold format indicates *p* values below 0.05, that is, significant difference was there between a meiotic and mitotic origin of the trisomy.

Abbreviation: FGR, fetal growth restriction.

TABLE 1 Comparing the prevalence of fetal growth restriction (FGR) and birthweight below the 10th, 5th and 3rd percentile according to the CPM type.

	CPM				
	Type 1	Type 2	Type 3	Type 2 or 3 (CTB not investigated)	Sign (*p*)
FGR	15/51 (29.4%)	3/15 (7.0%)	19/41 (44.2%)	5/15 (33.3%)	0.209
Birthweight < p10	12/55 (21.8%)	1/17 (5.9%)	14/42 (33.3%)	5/14 (35.7%)	0.110
Birthweight < p5	10/55 (18.2%)	1/17 (5.9%)	12/42 (28.6%)	1/14 (7.1%)	0.124
Birthweight < p3	8/55 (14.5%)	1/17 (5.9%)	11/42 (26.2%)	1/14 (7.1%)	0.150

Note: This shows that CPM type 3 has more FGR and low birthweight compared to type 1 and 2, but differences are not significant due to a low number of cases in type 2. Significant difference tested with Chi square.

Abbreviations: CTB, cytotrophoblast; FGR, fetal growth restriction.

4 | DISCUSSION

The aim of this study was to investigate whether CPM is associated with fetal growth restriction and low birthweight, since there is still controversy on this subject in the literature.[2,7,9,10,25] The present study includes the largest cohort of CPM that has been investigated on clinical outcome in terms of fetal growth and birthweight. Moreover, it involves a cytogenetically well-characterized CPM cohort, mostly based on placental studies in a large proportion of the cases.

Our data show that CPM is associated with FGR (34.0%) and low birthweight (23.1%) compared to 3%–10% FGR and 9.1% BW < p10 in the general obstetric population in the Netherlands (PERINED accessed March 2023) and this is higher as compared to other studies.[26,27] The definition of FGR in this study is aligned with the National Dutch Guideline on 'Fetal Growth Restriction 2017' (either AC and or EFW below the 10th percentile or a decline of minimal 20 percentiles of AC and/or EFW).[28] Consequently, decisions regarding pregnancies are grounded in adherence to this FGR definition. Since the international ISUOG guideline is more stringent and relies on the Delphi consensus (drops of more than two quartiles on the growth chart) to define FGR,[29,30] the used definition might have potentially caused an overestimation of the effect. This effect is expected to be minimal considering the size of our population and the consistent impact observed on birthweight, which correlates with FGR.

The highest rate of FGR and BW < p10 was found in CPM type 3 and if the CPM involved a meiotic trisomy. However, other CPM types (CPM type 1 or CPM involving a mitotic trisomy) were not without a risk of FGR and BW < p10.

CPM trisomy 16 has been held responsible for the majority of the adverse pregnancy outcomes in CPM pregnancies.[26,31] This study confirms the clinical impact of CPM trisomy 16. It also shows that when CPM trisomy 16 is excluded, one third of the pregnancies with CPM still are complicated with FGR and one fifth has a BW < p10, which is in line with a large meta-analysis.[32] In the recently published Dutch Trident study, analyzing the clinical impact of genome-wide NIPT in a general obstetric population, the risk of adverse pregnancy outcomes in cases of RAT that are mostly involved in CPM was also seen, even when trisomy 16 was excluded.[11]

Clinically, it is important to know if specific cytogenetic features can help to make a better risk estimation for FGR and improve prenatal counseling. We performed the current study to investigate if, for example, the chromosome involved or other CPM characteristics (cell lineage involved, trisomy origin) can discriminate between CPM with a low or high additional risk on FGR. It was previously shown that fetal growth restriction is mainly found in CPM type 3 often involving a trisomy of meiotic origin, whereas a mitotic origin would have less impact.[12,33,34] We confirmed significantly higher rates of FGR and BW < p10 in the meiotic versus mitotic cases (62.5% FGR and 54.2% BW < p10 in meiotic compared to 25.5% FGR and 16.7% BW < p10 in mitotic). However, not all meiotic trisomy cases were associated with growth restriction and not all mitotic cases were without. Therefore, at the individual level, the meiotic or mitotic origin cannot be used for the prediction of clinical outcome. Moreover, although it was previously shown that CPM type 1 and 2 are probably benign,[2,6,16] our study showed no statistical difference between the frequency of FGR and BW < p10 in type 3 and type 1 (44.2% FGR and 33.3% BW < p10 in type 3 compared to 29.4% FGR and 21.8% BW < p10 in CPM type 1). Only CPM type 2 did not show an association with FGR and BW < p10, confirming previous studies.[2,6]

The percentage of FGR and BW < p10 were indeed the most prevalent when CPM involved trisomy 16. However, based on our results, we consider the involved chromosome aberration not to be the main cause of the fetal growth problems, but we believe that it is the meiotic origin and the involvement in CPM type 3 in the majority of trisomy 16 cases that are the explanation for the higher prevalence of FGR and BW < p10 when trisomy 16 is involved.

Trisomy 7 was the most common RAT involved in CPM in our cohort as well as in genome-wide NIPT[12,22,27,35] and CVS studies.[6,7,33] All cases of trisomy 7 had a mitotic origin, which is concordant with other studies.[12,33,34] In contrast with previous studies where the majority of CPM trisomy 7 consisted of type 1 and 2,[14,15,27,33,36,37] half were involved in CPM type 1 and the other half in CPM type 3. This allowed us to investigate an association between clinical outcome and CPM type for this specific chromosome aberration. We found a slightly higher percentage of FGR and BW < p10 in the CPM type 1 group compared with CPM type 3, which is unexpectedly based on the literature. However, in most studies the CPM type was determined in a first trimester CV biopsy, whereas in the current study the type was mostly established in term placental biopsies and little is known about the representativity of a first trimester CV biopsy for the whole placenta in terms of CPM type. Perhaps, this may explain the different results. At the time of writing, there are no studies that have compared the cytogenetic constitution of CTB and MC of a single CV biopsy with that of placental biopsies. We found that only in two out of 11 (18%) cases, in which both first trimester CV and term placenta were investigated, cytogenetic results were comparable. The other 9 cases (82%) showed complete discordancy: CPM only in either CV or placenta, with the other showing normal results. When assessing these discordant cases, 6/9 had normal CV after abnormal NIPT with term placenta showing the chromosome aberration. This again demonstrates the higher sensitivity of NIPT as compared to CVS for detection of CPM.[38]

Since chromosomal mosaicism is a common feature of early human development,[39,40] the transfer of mosaic embryos is a growing practice in IVF.[41] Outcomes of such pregnancies may potentially provide further insight into the clinical impact of CPM, particularly concerning the specific risk of each type of chromosomal abnormality involved. Conversely, since mosaic embryo transfers may lead to CPM, we recommend close monitoring of fetal growth during these pregnancies.

In conclusion, fetal growth restriction and low birth weight occur more often in pregnancies affected by CPM and not only if trisomy 16 is involved. Both a meiotic and mitotic origin of the trisomy and both CPM type 1 and 3 can cause adverse pregnancy outcomes, but

the prevalence differs. Therefore, at the individual level in clinical practice, these CPM characteristics cannot be used for differentiating the clinically relevant from the clinically irrelevant CPM. Moreover, if (potential) CPM is detected with NIPT and amniocentesis is performed as a follow-up test, cytogenetic CPM characteristics cannot be assessed in the absence of CV investigations. Based on our results, irrespective of CPM type, trisomy origin, or involved chromosome aberration, we advocate to closely monitor all pregnancies where CPM is suspected. Such pregnancies should be classified as at increased risk of FGR and BW < p10. As such, we recommend closely tracking fetal growth starting at 26 weeks of gestation, with check-ups scheduled every 4 weeks. In cases where CPM pregnancies are complicated by FGR, it is crucial to adhere to the local growth restriction protocol.

Further research on the onset and patterns of FGR is needed to further optimize prenatal care in pregnancies complicated by CPM. Moreover, more research is needed to further explore prognostic variables that may aid in differentiating between clinically relevant and irrelevant CPM so that follow-up care can be limited to those that are at increased risk of FGR and low birthweight.

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CONFLICT OF INTEREST STATEMENT

The authors declare no competing interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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