Pregnancy outcome of confined placental mosaicism: meta-analysis of cohort studies

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OBJECTIVE: This study aimed to assess the rate of adverse obstetrical and neonatal outcomes in pregnancies diagnosed with confined placental mosaicism relative to that of unaffected controls.

DATA SOURCES: Web-based databases were searched using relevant key words, and articles published from 1980 to February 2022 were retrieved.

STUDY ELIGIBILITY CRITERIA: Observational studies in English language including ≥10 cases of singleton pregnancies with diagnosis of confined placental mosaicism were included. The diagnosis was established after detection of any chromosomal abnormality at chorionic villus sampling for any indication, followed by normal karyotype from amniotic fluid or neonatal leukocyte culture.

METHODS: Two authors independently screened the references for eligibility, data extraction, and assessment of methodological quality using the Newcastle–Ottawa scale. All available obstetrical and neonatal outcomes were recorded. Random-effect meta-analysis was performed to estimate pooled odds ratios and 95% confidence intervals of available outcomes in pregnancies with and without confined placental mosaicism. Statistical heterogeneity was evaluated with I^2 statistics (International Prospective Register of Systematic Reviews registration number: CRD42021260319).

RESULTS: Of the 80 articles reviewed, 8 retrospective matched-cohort studies (708 cases of confined placental mosaicism and 11,599 unaffected controls) compared cases with and without confined placental mosaicism and were included in the meta-analysis.

The risk of delivering small-for-gestational-age neonates was significantly increased in confined placental mosaicism pregnancies according to crude analysis (odds ratio, 2.45; 95% confidence interval, 1.23–4.89; I^2=72%) and to sensitivity analysis of high-quality studies (odds ratio, 3.65; 95% confidence interval, 2.43–5.57; I^2=0%). Similarly, confined placental mosaicism resulted in an increased risk of birthweight below the third centile (odds ratio, 5.33; 95% confidence interval, 1.19–24.19; I^2= 83%). Subgroup analysis revealed that the risk of delivering small-for-gestational-age neonates was 3-fold higher for confined placental mosaicism excluding trisomy 16, and 11-fold higher for cases including trisomy 16 only vs unaffected controls, respectively. No difference was found in the risk of low birthweight and preterm birth (at <37 weeks' gestation). Other outcomes were insufficiently reported, therefore they were not analyzed.

CONCLUSION: Pregnant women prenatally diagnosed with confined placental mosaicism have an increased risk of impaired fetal growth, suggesting the need for intensified antenatal surveillance.

Key words: chorionic villus sampling, confined placental mosaicism, fetal growth restriction, genetics, placenta, pregnancy outcome, prenatal diagnosis, small for gestational age

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Approval by the local ethics committee was not deemed necessary for this study based on data collection available in the published literature.

This study was presented at the 31st World Congress of the International Society of Ultrasound in Obstetrics and Gynecology (VP36.03), held virtually, October 15–17, 2021, and the 19th World Congress of the Fetal Medicine Foundation, Crete, Greece, June 26–30, 2022.

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AJOG at a Glance

Why was this study conducted?

Confined placental mosaicism showed the theoretical potential for being an etiologic precursor of placental dysfunction.

There was no available conclusive answer regarding the risk of reduced fetal growth and abnormal obstetrical outcomes of pregnancies with prenatal diagnosis of confined placental mosaicism.

Key findings

In pregnancies with prenatal diagnosis of confined placental mosaicism, there are higher rates of reduced birthweight (both <3rd and 10th centiles), with a 3-fold or 11-fold risk increase for birthweight <10th centile when excluding or including trisomy 16.

There is insufficient reporting of other obstetrical and neonatal outcomes of pregnancies with confined placental mosaicism.

What does this add to what is known?

Robust evidence suggests increased risk of impaired fetal growth irrespective of prematurity in pregnancies with confined placental mosaicism, suggesting the need for closer antenatal surveillance.

Further studies are needed to evaluate the association between confined placental mosaicism and other adverse obstetrical and neonatal outcomes.

Introduction

Confined placental mosaicism (CPM) is defined as the presence of a chromosomal abnormality restricted to the placenta with normal fetal karyotype.[1,2] This condition needs to be distinguished from true fetal mosaicism (TFM) that implies the presence of the same abnormality in amniotic fluid and fetal tissues.[3]

CPM is usually identified after first-trimester invasive diagnosis with chorionic villus sampling (CVS): when mosaicism is detected, amniocentesis is generally recommended to determine if the abnormal cell line is also present in fetal tissues. Amniotic fluid (AF) karyotype is reported to be normal in most cases—from 72% to 87%—when mosaicism is identified on placental samples from CVS.[4,5] Moreover, CPM could be also found in cytogenetic analysis of term placentae of euploid fetuses,[6–8] and it is recognized as a relevant source of false-positive results in noninvasive prenatal testing (NIPT).[9,10]

The prevalence of mosaicism after CVS is approximately 2% (0.9%–3%, depending on the sampled population),[11–14] with recent publications suggesting a higher prevalence of CPM after CVS when using chromosomal microarray on uncultured cells because of a higher diagnostic yield, the elimination of cultural artifacts (pseudomosaicism), and the possibility to identify additional defects such as copy number variations (CNVs).[15]

According to specific placental cell lineages presenting chromosomal abnormalities, CPM can be differentiated into: type I CPM when limited to the cytotrophoblast (direct preparation of CVS), type II CPM when limited to the mesenchymal core of the chorionic villi (long-term culture of CVS), and type III CPM when involving both cytotrophoblast and mesenchymal core of the chorionic villi (both direct and long-term culture of CVS).[16]

Underlying mechanisms leading to CPM can be generally explained by either a mitotic chromosome nondisjunction error occurring in an initially normal diploid conceptus ("mitotic origin") or meiotic error resulting in trisomy with subsequent postzygotic loss of the supernumerary chromosome (meiotic origin and "trisomy rescue").[17] Fetal uniparental disomy (UPD) analysis—defined as the inheritance of both homologous chromosomes from only 1 parent—is also suggested in chromosomal abnormalities involving imprinted chromosomes, occurring particularly after trisomy rescue, to exclude distinct syndromes.[18] CPM may present with various aneuploidies: autosomal trisomies or monosomies, sexual chromosome abnormalities, or ploidy abnormalities such as triploidy or tetraploidy. The genetic defect may be a submicroscopic rearrangement such as microdeletions or microduplications identified by chromosomal microarray (CMA) or as a supernumerary marker noted by karyotype analysis.[19,20]

Rationale

The outcome of CPM pregnancies is still debated and prenatal counseling is therefore challenging. Some authors described substantial association of CPM with adverse pregnancy and postnatal outcomes, mainly fetal growth restriction (FGR), small for gestational age (SGA) neonates, fetal loss, and preterm delivery,[8,21–28] whereas others confuted this finding.[29–33] Certainly, the outcome of pregnancies with confirmed CPM presents significant heterogeneity. Although there is robust evidence that mosaic trisomy of chromosome 16 (T16 CPM) detected by CVS is associated with fetal abnormalities, FGR, and preterm delivery with postnatal complications,[34,35] the risk of adverse pregnancy outcomes associated with CPM for other specific chromosomes is not well established,[36,37] and the prognosis seems favorable in most cases when the fetus appears normal at ultrasound (US) assessment, such as for CPM trisomy 8 and trisomy 2.[38,39]

The potential presence of UPD and related syndromes,[18] the percentage of mosaic cells,[3] and the hypothesis of a higher risk of FGR and TFM for type III CPM[25] further contribute to heterogeneity of CPM reports.

Objectives

This study aimed to evaluate the rates of all available adverse obstetrical and neonatal outcomes in pregnancies with diagnosis of CPM compared with unaffected matched pregnancies, with

particular interest in the rate of SGA neonates (birthweight <10th or 3rd centiles) for expected reference ranges.

Methods

Eligibility criteria, information sources, search strategy

This review was performed according to an a priori designed protocol recommended for systematic reviews and meta-analyses, and the study was registered with the International Prospective Register of Systematic Reviews (PROSPERO) database (ID CRD42021260319; https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021260319). The MEDLINE and Embase databases were searched from 1980 to February 2022 using the following key words alone or in different combinations: "confined placental mosaicism," "mosaicism confined to the placenta," and "prenatal," "fetal," "ultrasound," "fetus," "outcome," "small for gestationale age" (search strategy described in the Appendix). The references of relevant articles and reviews were hand-searched for additional reports.

The current study is presented in agreement with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines.[40,41]

Study selection

Only published articles in English language restricted to human species were considered eligible.

Observational studies including singleton pregnancies with confirmed diagnosis of CPM (≥10 cases) and unaffected controls with normal karyotype were considered eligible. Case reports, reviews, and congress abstracts were excluded. Diagnosis of CPM was established in the presence of the following: (1) any chromosomal abnormality detected after CVS for any indication; (2) normal karyotype on the corresponding AF or leukocyte culture of the neonate. Euploid fetuses from CVS that were reported in the same cohort were considered as controls. Criteria for matching controls were addressed and are presented in Table 1. Cases presenting any chromosomal abnormality either in AF or in neonatal leukocyte culture were excluded because they were classified as cases of TFM.[3] All types of CPM (CPM I, II, III) were included.

To ensure all cases had CPM, positive or high-risk NIPT cases followed by euploid amniotic cells were excluded because a different methodology might have affected our analysis. Studies including only a specific type of chromosomal mosaicism were not included because this could have resulted in selection bias and overall greater effect owing to the prevalence of a subgroup. We only included studies with specified diagnostic work-up, performing direct and long culture of CVS specimen at least with standard cytogenetic methods. No submicroscopic CNV abnormality resulting from CMA was included because data regarding mosaicism for submicroscopic CNVs are scarce.

Data extraction

The literature was searched and selected by 2 reviewers (S.L.S. and M.P.). Full-text articles were identified on the basis of the titles and abstracts, and then carefully evaluated by each reviewer independently. Reference lists of relevant articles and reviews were hand-searched for additional reports. Data extracted from all articles were tabulated, including study design, number of CPM cases, and unaffected euploid controls and corresponding outcomes observed (Table 1). Missing data were addressed and clearly defined. No automated tools were used for data extraction. Entries were compared for accuracy, and disagreements were resolved by reaching consensus about relevance and inconsistencies or by discussion with a third senior author (P.I.C.). In cases of duplicate publications or multiple reports for the same cohort, data extraction was optimized by using the best information available for all items from the same study to avoid overlapping populations. Additional search was rerun just before the final analyses to identify any further studies retrieved for inclusion.

Data items

Outcome measures were the occurrence of: neonatal SGA with birthweight (BW) <10th centile and neonatal SGA with BW <3rd centile as primary outcomes; low BW (LBW) <2500 g; hypertensive disorders (HDs) including either preeclampsia or gestational hypertension; preterm birth (PTB) at <37 weeks of gestation; any major fetal defects as defined by the Centers for Disease Control and Prevention[42]; neonatal intensive care unit (NICU) admission; intrauterine fetal demise (IUFD) defined as fetal demise at <24 weeks of gestation; stillbirth defined as fetal death at >24 weeks of gestation[43]; and termination of pregnancy (TOP). We looked for all other abnormal pregnancy outcomes, including PTB (at <34, <32, or <28 weeks), preterm prelabor rupture of membranes, obstetrical cholestasis, gestational diabetes mellitus, amniotic infection, antepartum or intrapartum fetal distress, operative delivery, cesarean delivery, and neonatal morbidity or mortality.

Study quality and risk of heterogeneity or bias

The Newcastle−Ottawa scale (NOS) was used to assess the study quality of cohort or case−control studies to improve the interpretation of meta-analytical results.[44] The scale ranges from 0 to 9, with 0 being the lowest possible quality. NOS evaluation focuses on the following 3 major areas: the selection of the study groups (0−4 points), the comparability of the groups (0−2 points), and the ascertainment of the outcome of interest (0−3 points).

Potential sources of bias were assessed: limited sample size (small study effect), characteristics of the population (obstetrical history and maternal age at sampling), criteria for matching euploid controls, indication for invasive prenatal diagnosis, CPM-subtype prevalence, collection of data, and clinical protocols used for pregnancy follow-up (Table 1).

Study quality and sources of bias underwent independent quality assessment by 2 reviewers (S.L.S. and M.P.). Discrepancies were resolved via discussions with a third assessor (P.I.C.).

Funnel plots for publication bias assessment were performed when appropriate.[45]

TABLE 1
Characteristics of included studies

Study (y)	Country andduration	CPM	Controls (non-CPM)	Outcomes observed	Matching controls	Type I	Type II	Type III	Type not classified	Stillbirths -IUFD <24 -TOP	Mosaic T16/ total of CPM	Maternal age CPM (mean±SD)	Maternal age controls (mean±SD)	Indications for invasive procedure
Grati et al,[31] 2020	Italy 2000–2018	124	468	SGA, BW below the third percentile, HD, PTB, congenital abnormality, stillbirth, IUFD, NICU	Maternal age, GA at procedure, and indication for prenatal diagnosis	55	49	20	0	Stillbirth: 1 CPM and 1 control IUFD <24: 0 CPM and 3 controls TOP: 2 CPM and 4 controls	12/124	NA	NA	Most common indications for CVS in the entire data set were maternal anxiety/elective decision (women <35 y) or advanced maternal age
Baffero et al,[30] 2012	Italy 2005–2009	102	222	SGA, BW below the third percentile, HD, PTB, LBW, congenital abnormality, stillbirth, IUFD, NICU, neonatal death	Random selection of CVS in the same day	52	50	13	0	Stillbirth: 0 CPM and 0 controls IUFD <24: 3 CPM and 1 control No TOP mentioned	NA	37.3±4.2	37.2±3.0	No differences in indication to CVS in cases and controls (P=.39)
Wolstenholme et al,[27] 1994	United Kingdom 1985–1992	73	74	SGA, stillbirth, IUFD	Consecutive patients from the same referral category (obstetrical and familiar history and maternal age at sampling) where outcome data on the pregnancy were available	32	18	9	14	Stillbirth: 1 CPM and 0 controls IUFD <24: 2 CPM and 1 control TOP: 5 CPM and 1 control	1/73	37.12	37.61	Referral category: -maternal age between 35 and 39 y -maternal age of ≥40 y - history of de novo numeric chromosome abnormality -family history of de novo numeric chromosome abnormality
Toutain et al,[25] 2018	France 2009–2015	36	93	SGA, BW below the third percentile, PTB	Same referral center and study period	0	13	23	0	NA	8/36	34±6	34±6	No differences were observed in the reason for CVS between the controland CPM group

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(continued)

TABLE 1
Characteristics of included studies *(continued)*

Study (y)	Country andduration	CPM	Controls (non-CPM)	Outcomes observed	Matching controls	Type I	Type II	Type III	Type not classified	Stillbirths -IUFD <24 -TOP	Mosaic T16/ total of CPM	Maternal age CPM (mean±SD)	Maternal age controls (mean±SD)	Indications for invasive procedure
Toutain et al,[26] 2010	France 1997–2009	57	198	SGA, BW below the third percentile, PTB	Indications in prenatal diagnosis	0	37	20	0	NA	8/57	36.1±4.90	36.3±5.44	The frequency of the various indications for prenatal diagnosis was identical in patients presenting with CPM and the control population
Amor et al,[29] 2006	Australia 1986–1997	36	195	LBW, PTB, congenital abnormality	Child's birth year, sex, and consent to be obtained by treating doctor	NA	NA	NA	NA	NA	0/36	42.9±4.7	45.0±3.4	The indication for CVS was not an abnormality detected on ultrasound
Wapner et al,[24] 1992	Unite Kingdom NA	254	10,297	SGA, LBW, PTB	Same center and study period	NA	NA	NA	NA	NA	NA	>35 y: 80%	>35 y: 79.5%	Maternal age Parental or previous chromosome abnormality
Roland et al,[22] 1994	United States 1984–1991	26	52	SGA, stillbirth, IUFD	Corresponding age (±2 y) and parity who had CVS performed on the same or closest date	NA	NA	NA	NA	No stillbirth reported IUFD <24: 1 CPM and 1 control TOP excluded	2/26	37.1	37.1	Most patients in both groups (24/26 cases, 46/52 controls) were referred for advanced maternal age

BW, birthweight; *CPM*, confined placental mosaicism; *CVS*, chorionic villus sampling; *GA*, gestational age; *HD*, hypertensive disorder; *IUFD*, intrauterine fetal demise at <24 weeks; *LBW*, low birthweight <2500 g; *NA*, not available; *NICU*, neonatal intensive care unit admission at birth; *PTB*, preterm birth; *SD*, standard deviation; *SGA*, small for gestational age; *TOP*, termination of pregnancy.

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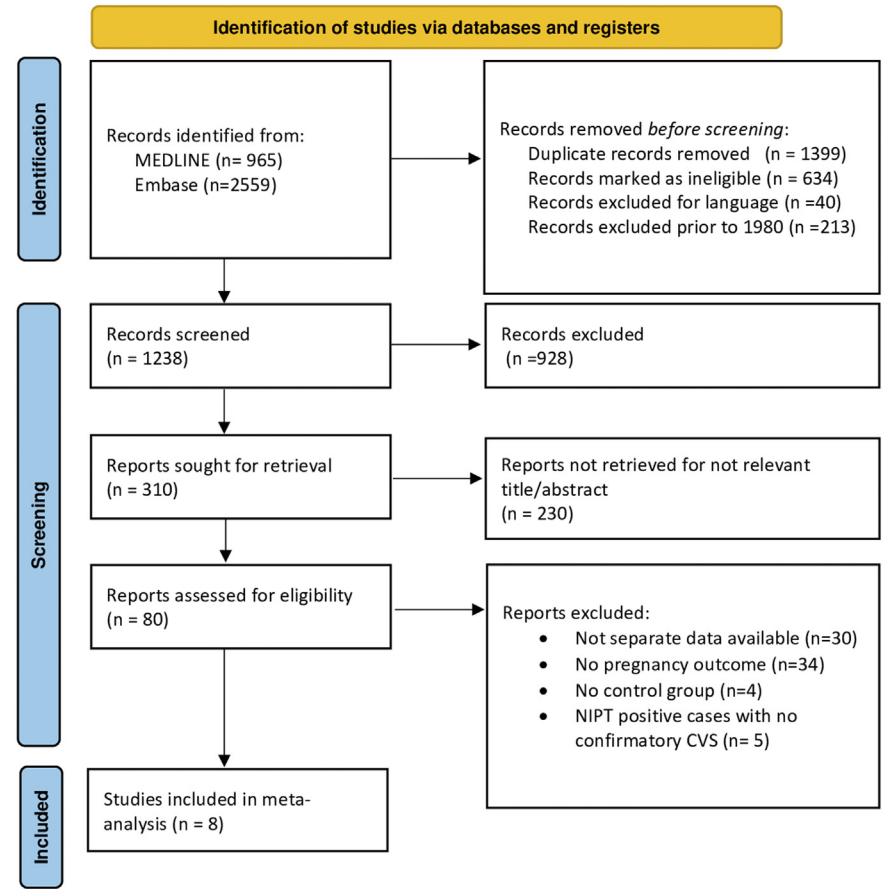
Data synthesis.
Raw data on the dichotomous study outcomes were used for creating the 2×2 contingency tables. Dichotomous outcomes were pooled using the Mantel–Haenszel random-effects model to measure pooled estimates. Results were reported as overall pooled odds ratios (ORs) and corresponding 95% confidence intervals (CIs). The significance of the pooled OR was determined by the *Z*-test and the *P* value. A *P* value of <.05 indicated statistical significance. The source of between-study heterogeneity was explored using the I^2 statistic, whereas I^2 values of 25%, 50%, and 75% correspond to low, moderate, and high heterogeneity, respectively.[46] Forest plots were used to display pooled ORs and 95% CIs for the analyzed outcomes. Outcome data available in ≥3 studies were meta-analyzed. Sensitivity analysis was performed for highest-quality studies with a NOS score of 8 or 9, whereas subgroup analyses were performed for cases with CPM limited to trisomy 16 vs controls and for all CPM with the exclusion of trisomy 16 vs controls. In case of moderate or high heterogeneity, subgroup analyses by specific subsets of CPM or comparison group, as defined a priori, were considered when appropriate if ≥3 studies existed for each group. The Cochrane Collaboration Review Manager software (RevMan, version 5.3; Nordic Cochrane Centre, Copenhagen, Denmark) was used for data analysis.

FIGURE 1
PRISMA 2020 flow diagram



CVS: chorionic villus sampling, NIPT: non-invasive prenatal testing
PRISMA, Preferred Reporting Items of Systematic Reviews and Meta-analysis.
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Results

Study selection and characteristics of studies included

Of the 310 manuscripts retrieved, 80 studies were assessed for eligibility. Twelve original studies reporting >10 cases of pregnant women with prenatally diagnosed CPM were selected; 4 retrospective observational studies were excluded because no control group was mentioned, and 1 retrospective matched cohort study was excluded because none of the prespecified outcomes were available.

Eight retrospective matched cohort studies (reporting on 708 cases of CPM and 11,599 euploid controls, published between 1994 and 2020, with CPM sample size of 26–254) investigating the prespecified obstetrical and neonatal outcomes in CPM compared with those of unaffected matched controls were included in the quantitative meta-analysis (Table 1).

The flowchart of study selection is shown in Figure 1.

Study quality and risk of bias of included studies

According to the NOS scale, the study quality of included studies was generally high: 5 of the 8 studies included in the meta-analysis were scored 8 or 9 (Table 2).

Although the assessment of publication bias was not robust with <10 studies, we provided funnel plots for illustrative reasons, and at visual inspection there was no suspicion of publication bias (Supplemental Figure).

Criteria for matching controls, maternal age at CVS sampling, indication for invasive prenatal diagnosis, and type of CPM were assessed for potential bias, extracted from included studies, and summarized in Table 1.

Synthesis of results

SGA neonates occurred in 73 of 618 of CPM pregnancies (11.8%) and in 654 of 11,008 (5.9%) of unaffected matched controls among the 7 studies exploring this outcome (Figure 2). The pooled crude analysis showed a significant increase in SGA neonates in the CPM

TABLE 2
Study quality by Newcastle-Ottawa scale

Study name	Selection	Comparability	Outcome	NOS score
Grati et al,[31] 2020	★★★★	★★	★★★	9
Baffero et al,[30] 2012	★★★	★★	★★★	8
Wolstenholme et al,[27] 1994	★★★	★★	★★★	8
Toutain et al,[25] 2018	★★★	★★	★★★	8
Toutain et al,[26] 2010	★★★★	★★	★★★	9
Amor et al,[29] 2006	★★	★★	★★	6
Wapner et al,[24] 1992	★★	★	★★	5
Roland et al,[22] 1994	★★	★★	★★	6

NOS, Newcastle−Ottawa scale.

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compared with the unaffected matched control group, with moderate heterogeneity between studies (OR, 2.45; 95% CI, 1.23−4.89; P=.01; I^2=72%) (Figure 2).

The significant increase in the risk of SGA neonates in the CPM compared with the unaffected matched control group was confirmed by sensitivity analysis (OR, 3.65; 95% CI, 2.43−5.57; P<.00001; I^2=0%) including studies that scored 8 or 9 on the NOS (in total 5 of the 7 matched cohort studies of the pooled crude analysis) (Figure 3). The rate of SGA neonates was 73 of 618 (11.81%) in the CPM and 654 of 11,008 (5.94%) in the unaffected control group (P<.0001), and in the subgroup scoring 8 or 9 on the NOS it was 61 of 349 (17.47%) in the CPM and 63 of 971 (6.49%) in the unaffected control group (P<.0001).

Similarly, CPM was associated with an increased risk of BW below the third centile compared with unaffected matched control group (3 studies; OR, 5.33; 95% CI, 1.19−24.19; P=.03; I^2=83%) (Figure 4). The rate of BW below the third centile was 32 of 194 (16.49%) in the CPM and 24 of 674 (3.56%) in the unaffected control group (P<.0001).

There were no significant differences in LBW and PTB rates between the 2 groups (Figures 5 and 6).

In light of the potential remarkable association of HDs with reduced fetal growth, pooled crude analysis for HDs was explored, although only 2 studies reported on this specific outcome.

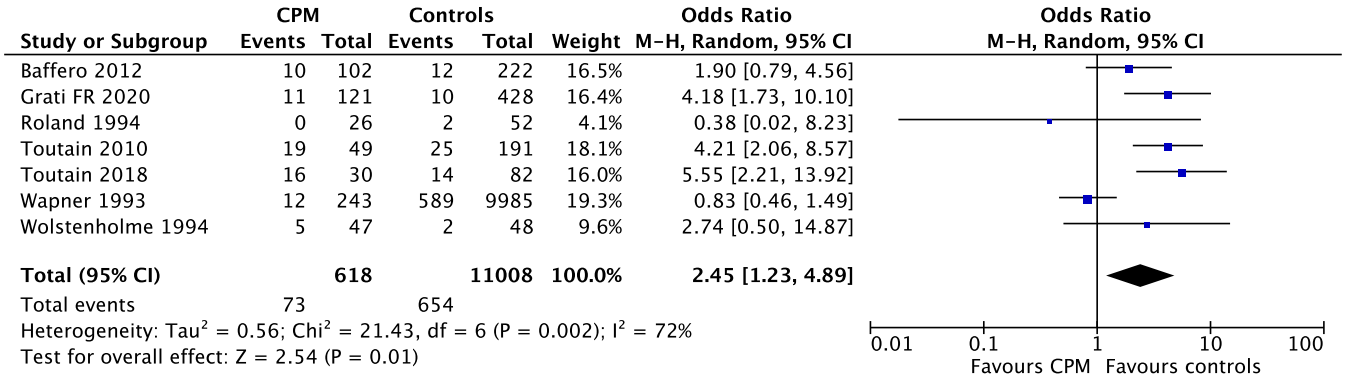
The risk of developing HDs may be doubled in the CPM compared with the unaffected control group (OR, 1.91; 95% CI, 1.05−3.48; P=.04; I^2=0%; only 2 studies).

All other abnormal pregnancy outcomes including congenital abnormalities, stillbirth, IUFD <24 weeks, TOP, NICU admission, PTB at <34, <32, or <28 weeks, preterm prelabor rupture of membranes, obstetrical cholestasis, gestational diabetes mellitus, amniotic infection, antepartum or intrapartum fetal distress, operative delivery, cesarean delivery, and neonatal morbidity or mortality were reported occasionally and insufficiently, and there was no opportunity for quantitative analysis.

Subgroup analysis: confined placental mosaicism including or excluding trisomy 16

Given the previously described association between T16 CPM and adverse pregnancy outcomes,[35,47,48] and the evidence of a moderate heterogeneity of the OR for SGA neonates, subgroup analysis by CPM limited to T16 and CPM with the inclusion of all aneuploidies except T16 vs controls was

FIGURE 2
Forest plot of SGA in CPM cases vs controls



Forest plot of studies collecting occurrence of birthweight <10th centile (SGA) in cases with prenatal diagnosis of confined placental mosaicisms and normal controls.

SGA, small for gestational age.

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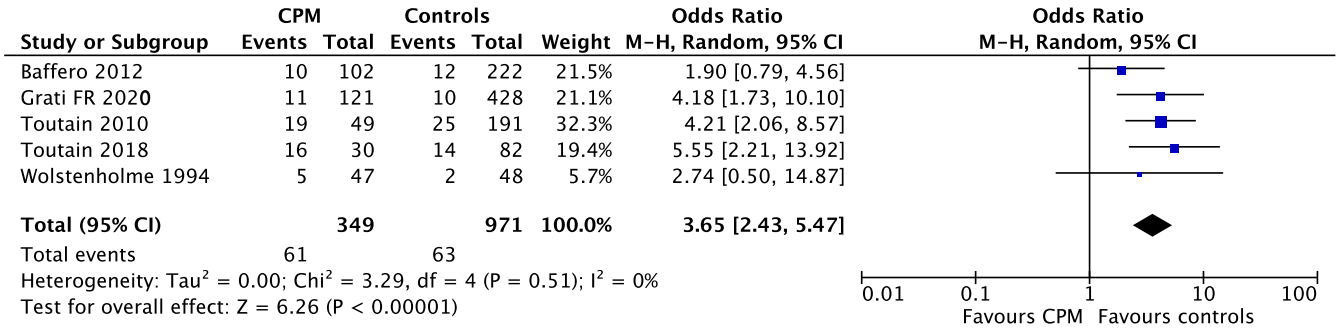
FIGURE 3
Sensitivity analysis - forest plot of SGA in CPM cases vs controls



Forest plot showing sensitivity analysis of studies with high quality on the Newcastle—Ottawa scale (scores 8 or 9) for occurrence of SGA neonates in cases with prenatal diagnosis of confined placental mosaicisms and normal controls.

SGA, small for gestational age.

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performed including studies with available data regarding the type of chromosome involved in CPM. Five studies reported on SGA neonates in CPM T16 only and in non-T16 CPM. Pooled ORs for SGA neonates were significantly increased for CPM excluding T16 compared with controls (OR, 3.09; 95% CI, 1.89—5.04; $P<.00001$; $I^2=0\%$) (Figure 7) and further increased in the CPM T16—only group compared with controls (OR, 11.64; 95% CI, 4.77—28.40; $P<.00001$; $I^2=0\%$) (Figure 8). None of the other investigated outcomes could be analyzed because of insufficient data in the original studies. Subgroup analysis for other potential confounding factors was not possible given the aggregate nature of the considered data.

Assessment of heterogeneity

Funnel plots for assessment of publication bias were not produced because of availability of <10 studies for each investigated outcome.[45]

A substantial variability in statistical heterogeneity was observed in the pooled data effect sizes of the outcomes, with I^2 ranging from 0% to 83%.

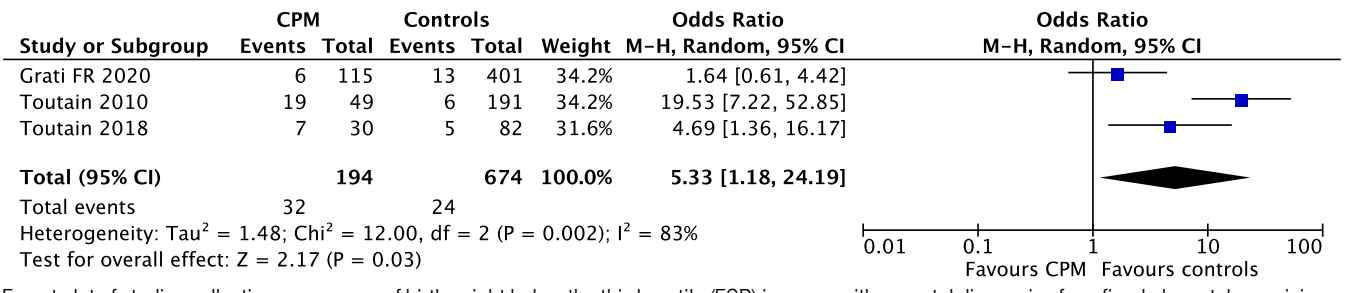
Heterogeneity was explored through subgroup analyses for type of chromosomal abnormality involved in CPM when data were available. Any remaining heterogeneity could not be examined because of limited available data.

Comment

Principal findings

This meta-analysis suggests that pregnant women prenatally diagnosed with CPM have a higher risk of delivering small neonates compared with the unaffected matched control population, by 2.5-fold for SGA neonates and 5-fold for BW below the third centile. The rate of SGA neonates increases to 12% and 17% relative to that of an average of approximately 6% in the unaffected control group, according to pooled crude and sensitivity analyses, respectively. The rate of BW below the third centile increases to 16% relative to an average of 4% in the unaffected control group. Subgroup analysis revealed that the risk of

FIGURE 4
Forest plot of BW < 3rd in CPM cases vs controls



Forest plot of studies collecting occurrence of birthweight below the third centile (FGR) in cases with prenatal diagnosis of confined placental mosaicisms and normal controls.

FGR, fetal growth restriction.

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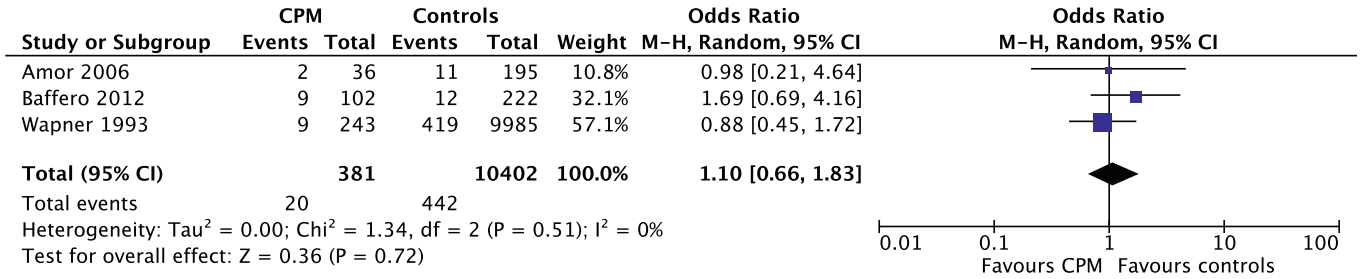
FIGURE 5
Forest plot of LBW in CPM cases vs controls



Forest plot of studies collecting occurrence of birthweight <2500 g (LBW) in cases with prenatal diagnosis of confined placental mosaicisms and normal controls.

LBW, low birthweight.

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delivering SGA neonates is 3-fold higher in the non-T16 CPM and 11-fold higher in the T16 CPM group compared with that of controls, and the rate of SGA neonates increases to 14% in the non-T16 CPM and to 45% in the T16 CPM group relative to an average of approximately 6% in the control group.

Without considering individual chromosomes involved in CPM, the risk of LBW and PTB was similar for both the CPM and the unaffected control groups, whereas the risk of HD may be doubled (only 2 studies included).

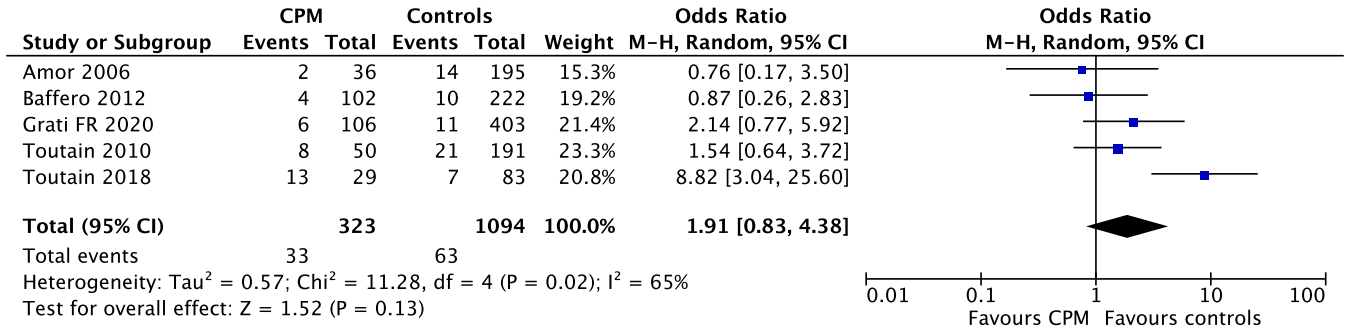
The paucity of reporting for all other obstetrical and neonatal outcomes hindered any further conclusions and indicated a need for future studies reporting extensive information on pregnancy and perinatal outcomes for pregnancies with CPM.

Comparison with existing literature

Given the controversial involvement of CPM in FGR, the aim of our study was to investigate the relationship between CPM and obstetrical and neonatal outcomes to provide optimal patient counseling and appropriate subsequent follow-up when CPM is diagnosed antenatally. Our results suggest a moderate increase in the risk of SGA neonates (pooled OR and sensitivity analysis) and FGR (BW below the third centile) at birth in the CPM vs the unaffected control pregnancies, potentially implying a relevant association between genomic imbalances confined to the placenta and impaired placental function. These results are supported by the recent work of Del Gobbo[49] that found a higher prevalence of CPM in term placentae of SGA euploid infants compared with that of non-SGA controls from uncomplicated pregnancies, concluding that placental genomic imbalances may underlie up to 18% of SGA cases in their population, as demonstrated by previous studies.[6,7]

An increased risk for fetal growth impairment from our analysis is in line with Eggenhuizen's first systematic review investigating CPM that showed a 71.7% rate of prenatal FGR and a 42% rate of BW <10th centile in pregnancies affected by CPM involving any of the autosomal chromosomes.[21] However,

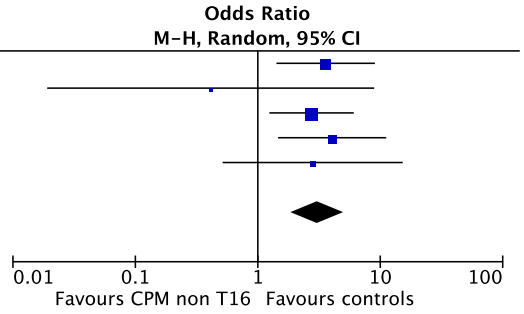
FIGURE 6
Forest plot of PTB in CPM cases vs controls



Forest plot of studies collecting occurrence of preterm birth at <37 weeks' gestation in cases with prenatal diagnosis of confined placental mosaicisms and normal controls.

Spinillo. Pregnancy outcome of confined placental mosaicisms. Am J Obstet Gynecol 2022.

FIGURE 7
Subgroup analysis - Forest plot of SGA in CPM non-t16 vs controls



Forest plot of subgroup analysis of birthweight below the 10th centile in all CPM after exclusion of trisomy 16 vs in unaffected controls with no CPM.

CPM, confined placental mosaicism.

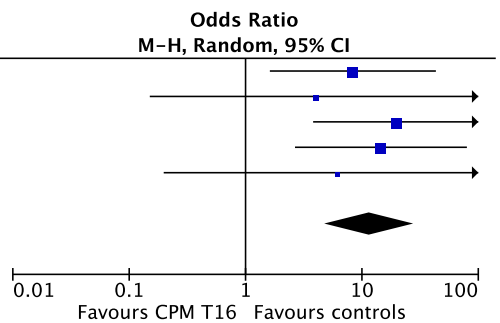
Spinillo. Pregnancy outcome of confined placental mosaicisms. Am J Obstet Gynecol 2022.

Eggenhuizen et al[21] did not perform quantitative pooling of outcome data by meta-analysis. An association was shown between T16 CPM and adverse pregnancy outcomes, especially FGR.[35,47,48] Consequently, the higher proportion of T16 CPM included in Eggenhuizen's review as compared with that included in our meta-analysis well explains the differences in the effects found on rates of SGA neonates (Eggenhuizen's paper with 100/300 [33.3%] CPM cases involving chromosome 16 and a 63.1% SGA rate vs the current work with 31/708 [4%] CPM cases involving chromosome 16 with a 45.1% SGA rate).[21]

In our work, subgroup analysis by type of CPM (T16 CPM and non-T16 CPM) demonstrated that the risk of delivering SGA neonates is increased 3-fold in non-T16 CPM, and 11-fold in T16 CPM, supporting the concept of a greater detrimental impact of T16 CPM on fetal growth. All other prespecified outcomes could not be explored through subgroup analyses by type of CPM because of insufficient data in the original studies.

Interestingly, in our meta-analysis the risk of PTB at <37 weeks of gestation in CPM pregnancies was comparable with that of unaffected controls, implying that neonatal morbidity related to prematurity is probably not increased when CPM is considered as a whole, regardless of the individual chromosome involved. Unfortunately, a distinction could not be made between spontaneous and iatrogenic PTB in our meta-analysis because of lack of data. Notably, Eggenhuizen reported PTB at <37 weeks in 31% of CPM cases, with 43 of 71 PTB cases being T16 CPM, whereas Grati et al found an increased risk of spontaneous PTB and BW below the third centile exclusively in T16 CPM, with reassuring results for CPM other than T16,[31] as also previously reported by Amor et al[29] and Baffero et al.[30] The greater proportion of PTB found in the systematic review by Eggenhuizen et al[21] may be once again explained by the large proportion of T16 CPM included in their analysis, given the reported relationship between T16 CPM and adverse obstetrical outcomes such as preeclampsia.[34,47]

FIGURE 8
Subgroup analysis - Forest plot of SGA in CPM t16 vs controls



Forest plot of subgroup analysis of birthweight below the 10th centile in trisomy 16 CPM vs in unaffected controls with no CPM.

CPM, confined placental mosaicism.

Spinillo. Pregnancy outcome of confined placental mosaicisms. Am J Obstet Gynecol 2022.

According to our analysis, CPM seemed to play a relevant role in the growth of fetuses given that they were not reaching their full growth potential at birth, but had a limited effect on PTB and LBW.

Because stillbirth and IUFD were scantly reported in the included studies (Table 1), pooled crude meta-analysis for such rare events was not considered appropriate given that it would have been difficult to estimate the magnitude of risk.

Whereas the risk of stillbirth related to CPM seemed to be increased in older studies,[24,50] more recent studies[30,31] demonstrated that the occurrence of stillbirth with CPM was similar to that of controls (Grati et al reported 1 stillbirth in T16 CPM and 1 in controls; Baffero et al found no cases neither in CPM or controls). Similarly, the risk of IUFD at <24 weeks of gestation was difficult to estimate because of the wide variety in reporting this specific outcome, particularly when addressing gestational age of pregnancy loss. Baffero[30] and Wolhstenholme[27] found a slight increase in the risk of fetal loss in CPM vs the greater risk reported in older studies,[23,24] whereas Grati[31] and Roland[22] confuted this finding.

Considering that the definition of fetal defects was not standardized in the included studies, indications for TOP were not always clearly stated,[27] TOPs were not constantly reported, and sometimes they were actually excluded from the original cohort,[22] pooled analysis for structural fetal anomalies was not performed. Although Amor, Baffero, and Grati described a rate of birth defects similar to that of controls,[29−31] Eggenhuizen et al[21] interestingly reported a 24.2% rate of structural fetal anomalies with CPM, mostly T16 CPM (21 of 38). Although screening for fetal defects with advanced US is advisable in CPM,[51] adequately powered prospective studies with inclusion of UPD assessment should further elucidate this issue.

The relationship between placental disorders and hypertensive conditions in pregnancy is extensively noted in literature,[52,53] thus we attempted to assess the incidence of the latter in CPM gestations; we observed that, although only 2 studies reported this outcome, the risk of developing HD in CPM pregnancies may be increased, as already extensively reported for T16 CPM.[30,31]

Similarly, NICU admission at birth was only reported in 2 studies,[30,31] and therefore it was not possible to proceed with quantitative analysis. Other pregnancy complications were only occasionally reported.

Strengths and limitations

This meta-analysis investigated obstetrical and neonatal outcomes of CPM pregnancies confirmed with fetal or neonatal karyotype evaluation. The complexity of this meta-analysis is strictly related to the rarity of CPM and to the enormous advances of diagnostic genetic testing and work-up together with the evolution of US machines that are presently routinely used in clinical practice.

Hence, the long study interval (1989−2021), the limited sample size, the heterogeneity of the population (owing to variability of criteria for matching controls, indications for invasive prenatal diagnosis, and characteristics of the population), and unavailability of clear information concerning TOPs are all potential sources of bias.

Our meta-analysis is based on retrospective matched cohort studies, although the quality of included studies was generally scored high. Unavailability of clean separated data of individual studies made it difficult to adjust for potential confounding factors of investigated outcomes (such as maternal age, indication for CVS, smoking, maternal diseases, parity) that must be considered when heterogeneous data are pooled for meta-analysis.

However, heterogeneity of the analysis of rates of SGA neonates was reduced by sensitivity analysis of studies with higher quality and by subgroup analysis for established risk factors of fetal growth impairment such as the presence of CPM trisomy 16.[35,48] For other outcomes, subgroup and sensitivity analyses were not feasible, and great variation in heterogeneity may be a reflection of the nonstandardized nature of observational studies.

Clinical considerations

Antenatal counseling and management of CPM pregnancies are challenging. According to the results of our analysis, we can assume an overall good prognosis of CPM pregnancies when T16 is excluded, no congenital anomaly is detected by fetal US, and euploid fetal AF is confirmed. Nevertheless, residual risk of low-level TFM exists,[3,5] and long-term or neurodevelopmental outcomes were not available from the literature. However, our results suggest the need for third-trimester surveillance because of the higher risk of SGA and FGR for CPM pregnancies. We suggest that an early third-trimester scan (26−28 weeks) evaluating estimated fetal weight and Doppler studies would be appropriate in CPM to screen for early FGR and SGA, with assessment at 36 weeks in all cases. Additional assessments would be offered on the basis of the overall risk of SGA or preeclampsia, as defined by well-established mathematical models.[54,55]

To improve patient counseling, stratification of risk on the basis of the individual chromosomes and the subtype of mosaicism involved is recommended in future research. There is robust evidence, in fact, that T16 CPM is strongly associated with adverse pregnancy and postnatal outcomes (high risk of FGR or SGA neonates, PTB, congenital abnormalities).[35,47,48] Moreover, recent research showed that type III CPM carries a greater risk of growth restriction and residual TFM.[25] In addition, our results show an 11-fold increase in the risk of SGA neonates for T16 CPM compared with controls.

Major implications based on the current literature indicate that, when CPM is suspected, detailed anatomic US to detect structural anomalies must be performed at a fetal medicine center by expert operators,[51] especially when chromosomes 2, 7, 8, 13, 15, 16, 21, and 22 are involved. Stratification of the risk according to the chromosome involved can only be explored from case series or case reports from the available literature. A higher risk of fetal involvement and

adverse outcomes can be presumed when trisomy 7,[56,57] 13,[58] 15,[59–61] 16,[34,47] 21,[62] and 22[63,64] are involved, whereas in case of trisomy of chromosome 2[39,65] or 8[38,66] expert US assessment is recommended given the good prognosis when the fetus is structurally normal. For most chromosomes, insufficient numbers of cases with adequate clinical follow-ups make it difficult to draw any conclusion. In addition, UPD after trisomic rescue exists and can result in phenotypic effects, depending on the presence of imprinted gene(s) on the involved chromosome (commonly 6, 7, 11, 14, 15, or 20).[11] Hence, in case of imprinted chromosomes, UPD analysis is recommended to exclude specific syndromes, regardless of the presence of structural abnormalities. Genetic counseling is therefore advised when CPM is diagnosed antenatally.

Given that direct analysis of CVS and NIPT both involve the trophoblastic cell lineage, genome-wide cell-free DNA (cfDNA) has the potential to diagnose rare autosomal trisomy (RAT)—defined as any autosomal trisomy other than 21, 13, 18—that is mostly attributable to CPM.[31,64,67] Recently, NIPT rather than CVS has been suggested to be more sensitive for detecting CPM because the entire placental trophoblast sheds cfDNA into the maternal circulation, and CPM restricted to a small part of the placenta could be missed by CVS sampling.[68]

However, despite a great theoretical potential and unquestionable safety, the clinical benefit of detecting RAT through genome-wide cfDNA remains uncertain because of lack of robust studies, and currently no professional society recommends genome-wide cfDNA testing.[69–71] We believe that further research on this topic must be encouraged within large prospective cohorts involving solid and reliable methods for the study of cfDNA, advanced equipment, and staff expertise.

Furthermore, recent evidence of a higher prevalence of mosaicism when using CMA owing to its higher resolution and possibility to detect mosaic CNVs will be debated in the near future.[15,72]

In addition, reassuring pregnancy outcomes following mosaic embryo transfer will surely contribute to further knowledge of biological mechanisms involved in chromosomal mosaicism of human blastocysts.[73,74] Confirmation of cytogenetic anomalies of CVS in term placentae and data collection of CPM histologic placental lesions should be addressed in future studies to confirm a direct relationship between CPM and abnormal placentation.

The paucity of available data regarding CPM outcomes should stimulate future research with larger and prospective studies to elucidate a potential remarkable relationship between chromosomal aberrations confined to the placenta and fetal growth. Possible research questions will address the role of maternal serum biomarkers for assessing the risk of placental dysfunction in CPM or for raising the suspicion of CPM when reduced fetal growth is observed. Further research may also investigate appropriate methods of sampling and genetic analysis of the placenta after delivery in case of unexplained FGR and of third-trimester screening for fetal growth either when CPM is confirmed or highly suspected by positive NIPT result.

Conclusions and implications

Pregnant women with prenatally diagnosed CPM carry a higher risk of delivering SGA neonates compared with unaffected controls (3-fold risk increase for CPM excluding trisomy 16 and 11-fold risk increase for CPM trisomy 16), whereas data on other obstetrical or neonatal disorders were not sufficient to be analyzed. The extent to which standard traditional approaches to placental insufficiency are enough in the context of CPM (fetal growth assessment with Doppler studies, cardiotocography, maternal assessment for HDs and indicated delivery with timing defined by the disease severity) should be explored in future studies (Video 1).

The results of our study are clinically relevant for counseling of affected pregnant women, predicting a good prognosis for most cases in which trisomy 16, UPD, and structural anomalies were excluded, and supporting careful monitoring of fetal growth, particularly in the third trimester for a timely detection of growth impairment. ■

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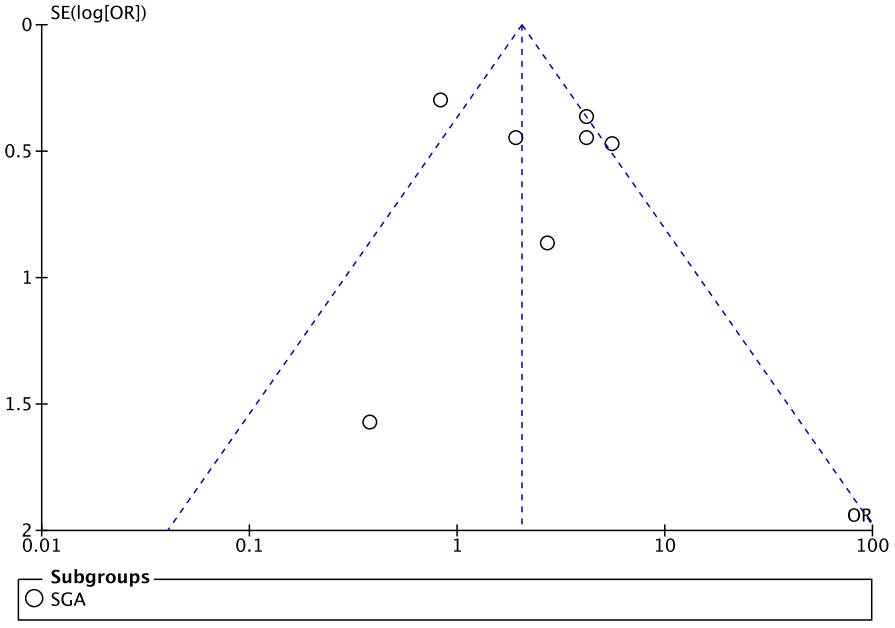
SUPPLEMENTAL FIGURE



Funnel plot of SGA.

SGA, small for gestational age.

Spinillo. Pregnancy outcome of confined placental mosaicisms. Am J Obstet Gynecol 2022.

SUPPLEMENTAL TABLE

Search strategy

MEDLINE
1. "mosaicism"[MeSH Terms] OR "confined placental mosaicism"[Title/Abstract] OR "mosaic"[Title/Abstract]
2. "fetal"[Title/Abstract] OR "fetus"[Title/Abstract] OR "prenatal"[Title/Abstract] OR "pregnanc*"[Title/Abstract]
3. "outcome*"[Title/Abstract] OR "small for gestational age"[Text Word] OR "birthweight"[Text Word] OR "stillbirth"[Text Word] OR "low birthweight"[Text Word] OR "preterm"[Text Word] OR "abortion"[Text Word] OR "miscarriage"[Text Word] OR "congenital"[Text Word] OR "premature"[Text Word]
4. 1 AND 2
5. 4 AND 3 (results 965)
EMBASE
1. "mosaicism"/exp OR "mosaicism" OR "confined placental mosaicism":ab,ti OR "mosaic":ab,ti
2. "fetal":ab,ti OR "fetus":ab,ti OR "prenatal":ab,ti OR "pregnanc*":ab,ti
3. "outcome*":ab,ti OR "small for gestational age"/exp OR "small for gestational age" OR "birthweight"/exp OR "birthweight" OR "stillbirth"/exp OR "stillbirth" OR "low birthweight"/exp OR "low birthweight" OR "preterm" OR "abortion"/exp OR "abortion" OR "miscarriage"/exp OR "miscarriage" OR "congenital"/exp OR "congenital" OR "premature"/exp OR "premature"
4. 1 AND 2
5. 4 AND 3 (results 2559)

Spinillo. Pregnancy outcome of confined placental mosaicisms. Am J Obstet Gynecol 2022.