

Placental Weight in Pregnancies With Trisomy Confined to the Placenta

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Abstract

Objective: Mosaicism with trisomy confined to the placenta is present in ~1% of ongoing pregnancies at the time of chorionic villus sampling. Some studies have found reduced fetal growth in confined placental trisomy. The objective of this study was to assess placental weight and fetoplacental weight ratio in pregnancies with trisomy confined to the placenta, and to correlate them with the level of trisomy in the three major placental lineages.

Methods: We conducted a retrospective study of 69 pregnancies with prenatally diagnosed mosaic trisomy in which the trisomic cells were confined to the placenta. Placental weight and fetoplacental weight ratio were compared to those of matched controls, and placental weight was also analyzed for associations with the type and level of trisomy. Placental pathology was also reviewed.

Results: The pregnancies with mosaic trisomy were found to have lower placental weights than matched controls, but normal fetoplacental weight ratios. Placental weight was not associated with the type or level of trisomic cells in the three placental lineages at term (chorionic plate, chorionic villus mesenchyme, and trophoblast). There were no pathognomonic findings on routine placental pathology of the trisomic placentas.

Conclusion: Although placental weight was reduced (with normal fetoplacental weight ratio) in pregnancies with trisomy confined to the placenta, the level of placental trisomy was not correlated with placental weight. Thus, trisomy may alter placental function rather than have a direct hypoplastic effect on placental growth. More in-depth studies beyond routine pathology are required to identify how trisomy affects placental function.

Résumé

Objectif : Le mosaïcisme en présence d'une trisomie confinée au placenta est constaté chez ~1 % des grossesses en cours au moment du prélèvement des villosités chorionales. Certaines études ont constaté une baisse de la croissance fœtale dans les cas de

trisomie confinée au placenta. La présente étude avait pour objectif d'évaluer le poids placentaire et le rapport poids fœtal-poids placentaire chez des grossesses dont la trisomie était confinée au placenta, ainsi que de corrélérer ces valeurs avec le degré de trisomie au sein de trois principales lignées placentaires.

Méthodes : Nous avons mené une étude rétrospective portant sur 69 grossesses qui présentaient une trisomie en mosaïque (diagnostiquée pendant la période prénatale) dans le cadre de laquelle les cellules trisomiques étaient confinées au placenta. Le poids placentaire et le rapport poids fœtal-poids placentaire ont été comparés à ceux de témoins appariés; le poids placentaire a également été analysé en vue d'en déceler les associations avec le type et le degré de trisomie. La pathologie placentaire a également fait l'objet d'une analyse.

Résultats : Il a été établi que les grossesses présentant une trisomie en mosaïque comptaient des poids placentaires plus faibles que ceux des témoins appariés, mais que leurs rapports poids fœtal-poids placentaire étaient normaux. Le poids placentaire n'était pas associé au type ni au degré des cellules trisomiques au sein des trois lignées placentaires à terme (plaque chorionale, axe mésenchymateux de la villosité chorionale et trophoblaste). L'examen pathologique placentaire systématique des placentas trisomiques n'a généré aucun résultat pathognomonique.

Conclusion : Bien que le poids placentaire ait été réduit (s'accompagnant d'un rapport poids fœtal-poids placentaire normal) pour ce qui est des grossesses présentant une trisomie confinée au placenta, le degré de trisomie placentaire n'était pas en corrélation avec le poids placentaire. Ainsi, la trisomie peut altérer la fonction placentaire plutôt que d'exercer un effet hypoplasique direct sur la croissance placentaire. Un plus grand nombre d'études approfondies allant au-delà de l'examen pathologique systématique s'avèrent requises pour identifier la façon dont la trisomie affecte la fonction placentaire.

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INTRODUCTION

Trisomy mosaicism with the trisomic cells predominantly or completely confined to the placenta occurs in ~1% of pregnancies at the time of chorionic villus sampling, at 10–12 weeks' gestation.¹ Although such pregnancies are usually associated with normal fetal growth,^{2,3} reduced fetal growth has been associated with trisomy 16⁴ and with high

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levels of trisomic trophoblast⁵ in prenatally diagnosed trisomy mosaicism. Furthermore, studies of pregnancies marked by intrauterine growth restriction have shown an association with chromosome abnormalities such as trisomy in the placenta when examined postpartum.^{6–12} There are few data, however, on placental weight or fetoplacental weight ratio in pregnancies with confined placental trisomy.

Placental and fetal growth are closely linked. Postulated mechanisms relating the placenta to poor fetal growth include decreased efficiency of nutrient transfer through the placenta and increased resistance of placental vessels,¹³ as well as reduced uterine perfusion secondary to impaired trophoblast invasion.¹⁴ An altered placental growth pattern can also affect the fetoplacental weight ratio; for example, thicker placentas show lower ratios than thin placentas.¹³ In addition, fetoplacental weight ratio increases with gestational age.¹⁵

We undertook a retrospective analysis of prenatally diagnosed cases of trisomy mosaicism confined to the placenta, taken from an ongoing study of trisomy mosaicism.^{5,16–22} Placental weight and fetoplacental weight ratio were measured and compared to those of matched controls to determine if placental trisomy differentially affects fetal and placental growth. Associations between placental weight and the level of trisomy in three placental lineages assessed postpartum (chorionic plate, chorionic villus mesenchyme, and trophoblast) were also investigated. Our hypothesis was that trisomic placental cells would cause a direct hypoplastic effect on placental growth, such that (1) a higher level of placental trisomy would correlate with lower placental weight and (2) fetal growth would be reduced only as a secondary effect, resulting in an increased fetoplacental weight ratio.

METHODS

We carried out a retrospective study of all 69 singleton pregnancies that met the chosen inclusion criteria from the ongoing study of trisomy mosaicism at the University of British Columbia.

The inclusion criteria for pregnancies comprised prenatal diagnosis via CVS, with no trisomy detected in the amniotic

fluid (via amniocentesis), in fetal or neonatal blood lymphocytes (via cordocentesis or postnatal blood draw), or in the amnion (postnatally), in order to select for cases where the trisomy was likely to be completely confined to the placenta. The final inclusion criterion was the availability of placental weight data.

Some cytogenetic and clinical data from 28 of the cases have been previously published^{5,17–22}; all data from the other 42 cases are unpublished. Placental weight or fetoplacental weight ratio from any of the cases has not been previously published. Twenty-five cases (36%) were derived from C&W; the other 44 cases (63%) were referred from other centres.

The following trisomies were identified by CVS:

trisomy 16 (n = 13), trisomy 7 (n = 10), trisomy 2 (n = 9), trisomy 12 (n = 6), trisomy 8 (n = 3), trisomy 9 (n = 4), trisomy 10 (n = 4), trisomy 15 (n = 3), trisomy 13 (n = 2), trisomy 17 (n = 2), trisomy 18 (n = 2), trisomy 22 (n = 2), trisomy 4 (n = 1), trisomy 11 (n = 1), trisomy 20 (n = 1), trisomy 21 (n = 1), and multiple trisomy (n = 5). In all cases of trisomy 7 where testing for the origin of the chromosomes 7 in the diploid infant was performed (n = 5) (in order to rule out Russell-Silver syndrome from uniparental disomy), the result was normal biparental inheritance. None of the trisomy 15 cases (n = 3) had testing of origin (to test for Prader-Willi syndrome or Angelman syndrome from uniparental disomy).

It is important to note that placentas may have been more likely to be forwarded for inclusion in the ongoing study if abnormalities (IUGR or fetal anomalies) were present. In 63 of the 69 cases, the phenotype of the child was known; excluding digital and facial dysmorphism (because such data were not consistently reported), 89% of the cases (56/63) did not have anomalies. There was one case each of imperforate anus, hypospadias, hip dysplasia, hydronephrosis, and possible ventricular septal defect, as well as two familial phenotypes (familial benign megalencephaly and familial hip dysplasia).

Gestational age and birth weight were collected from the UBC Department of Medical Genetics medical records for the local cases, or from referring physicians for the referred cases. Placentas from both the local and referred cases were weighed at C&W in the same manner: the cord and membranes were trimmed, excess superficial blood was washed off, and then the trimmed placentas were weighed on the same scale. Where available, data from placental pathology were also collected.

Since the level of trisomic cells can vary widely between tissues and between sites within a placenta,²³ postpartum placental sampling was performed using multiple sites and an

ABBREVIATIONS

C&W	Children's and Women's Health Centre of British Columbia
CVS	chorionic villus sampling
IUGR	intrauterine growth restriction
UBC	University of British Columbia

Table 1. Level of placental trisomy and placental weight

		Placental weight		<i>P</i>
		Below the reference population mean ²⁵	Above the reference population mean ²⁵	(Mann-Whitney test, z-approximation)
	Chorionic plate	25.6 ± 34.3% (n = 44)	39.3 ± 39.0% (n = 12)	> 0.05
% trisomic cells	Chorionic villus mesenchyme	31.2 ± 34.9% (n = 46)	32.9 ± 35.6% (n = 15)	> 0.05
	Trophoblast	16.4 ± 31.4% (n = 29)	15.1 ± 25.3% (n = 11)	> 0.05

average level of trisomy was calculated in each of three tissue lineages of the placenta: chorionic plate, chorionic villus mesenchyme, and trophoblast. Samples of chorionic plate and samples of chorionic villus mesenchyme were each cultured and analyzed by conventional cytogenetic analysis, in which 5–15 cells were examined from each of 1–3 sites. In addition, as previously reported from our centre, a mixed trophoblast suspension was isolated by short-term (20–30 minutes) collagenase digest of chorionic villi followed by FISH for the chromosome involved, typically on 500–1000 nuclei from 1–3 sites.^{23,24} Since the cut-off for diagnosing the presence of trisomy by FISH (done on control samples) was determined by different methods during the time period (> 3 standard deviations below the mean, or the procedure from Lomax et al.²⁴), 10% was arbitrarily chosen as the cut-off; that is, all sites with < 10% of nuclei having 3 signals were all coded as 0%. A table with a full description of each mosaic trisomy case (including previous references, and clinical and cytogenetic data) is available upon request.

A published reference population for placental weight was chosen, consisting of gestational age-stratified mean placental weights from 787 singleton pregnancies in Providence (Rhode Island), in which cord and membranes were trimmed and “excessive blood” washed from the crevices.²⁵ A published reference population for fetoplacental weight ratio was also chosen, involving gestational age-stratified mean fetoplacental weight ratios for 15 047 singleton pregnancies collected from Kuopio (Finland).²⁶ In this Finnish reference population, the placentas were washed clear of excess blood, and although cord and membranes were not trimmed before weighing, they used a correction factor (trimmed weight = 0.854 × untrimmed weight) derived from >1500 placentas at their centre.

For each mosaic trisomy case (both local and referred), two controls matched for maternal age (± 5 years) and for parity (0, 1, or ≥ 2) were selected by reviewing medical records at C&W of routine deliveries that had occurred on the same

date or on the previous or following day. For some trisomy mosaic cases, no data for maternal age (n = 5) or parity (n = 20) were available; in these cases, the controls were chosen randomly with respect to maternal age or parity. After matching, there was no difference in mean parity between the trisomic cases (1.14 ± 1.06) and the matched controls (1.06 ± 1.07) (Mann-Whitney test, z-approximation, *P* > 0.05). However, even after matching, maternal age was slightly higher in the trisomic group (37.8 ± 3.5 years) than in the matched controls (35.3 ± 4.4 years) (Welch’s approximate *t* test, *P* < 0.001), which is not surprising as trisomy is associated with advancing maternal age.

Gestational age, placental weight, and birth weight for the controls were also collected from C&W medical records. The placentas were weighed according to the routine practice in the C&W labour and delivery unit: they were weighed untrimmed, and superficial excess blood was not washed clear before weighing.

We used a published reference population for placental weight and fetoplacental weight ratio for the matched controls consisting of gestational age-stratified mean placental weights and fetoplacental weight ratios from 29 902 singleton pregnancies collected in Detroit. In this population, placentas were also untrimmed and not washed clear of excess blood.²⁷

Statistical analyses were carried out using SPSS version 10.0 for Windows (SPSS Inc, Chicago IL) and the Vassar WebSite for Statistical Computation (<http://faculty.vassar.edu/~lowry/VassarStats.html>). Two-tailed tests were utilized.

The study was approved by the ethics committees of UBC and the Children’s and Women’s Health Centre of British Columbia.

RESULTS

Placental weights of the mosaic trisomy cases were clearly lower than the means from their reference population²⁵;

Table 2. Chromosome-specific comparisons for placental weight

Chromosome	Placental weight		
	Below the reference population mean ²⁵	Above the reference population mean ²⁵	% Below
Trisomy 16	11	2	85
Trisomy 7	9	1	90
Trisomy 2	7	2	78
Other trisomy	26	11	70

$\chi^2 = 2.32, P > 0.05$

53 cases had placental weights below the mean and 16 had placental weights above the mean (binomial test, z-approximation, $P < 0.001$).

In contrast to the mosaic trisomy cases, the placental weights of the matched controls were slightly greater than their reference population²⁷; 57 controls had placental weights below the mean and 81 had placental weights above the mean (binomial test, z-approximation, $P = 0.05$).

Neither the mosaic trisomy cases nor matched controls had fetoplacental weight ratios that were significantly different from their corresponding reference populations. Of the mosaic trisomy cases, 34 had fetoplacental weight ratios below and 35 above the mean; of the matched controls, 66 had fetoplacental weight ratios below the mean and 72 above the mean (binomial test, z-approximation, $P > 0.05$).

Placental weight and birth weight were significantly correlated with each other in both the mosaic trisomy cases ($r = 0.60$, $P < 0.001$) and the matched controls ($r = 0.61$, $P < 0.001$).

In the cases of mosaic trisomy, placental weight below the reference population mean²⁵ was not associated with a higher level of trisomy in the chorionic plate, chorionic villus mesenchyme, or trophoblast (Table 1) (Mann-Whitney test, z-approximation, $P > 0.05$).

To assess for chromosome-specific effects, the mosaic trisomy cases were divided into four groups: trisomy 16 ($n = 13$), trisomy 7 ($n = 10$), trisomy 2 ($n = 9$), and other ($n = 36$). There was also no significant difference in placental weight between these groups (Table 2) ($\chi^2 = 2.32$, $P > 0.05$).

Twenty-three of the 25 local mosaic trisomy cases had assessment of placental pathology: of these, 52% (12/23) had some abnormality (Table 3), although the frequency and range of abnormalities were considered non-specific.

DISCUSSION

Although placental weight was significantly reduced in the cases with trisomy mosaicism confined to the placenta,

placental weight was not associated with the level of trisomy in any of the placental lineages (chorionic plate, mesenchyme, or trophoblast), and fetoplacental weight ratio was within normal limits. Therefore, the results of this study did not support the hypothesis that placental trisomy would have a direct hypoplastic effect on the placenta, which would have resulted in an association between placental weight and the level of placental trisomy and also increased fetoplacental weight ratio.

If placental trisomy does not have a direct hypoplastic effect on placental growth, then there must be an alternative explanation for the significant reduction in placental weight seen in the mosaic trisomy cases. It may be that placental trisomy first causes an alteration in placental function that reduces fetal birth weight. This decreased fetal growth may then in turn reduce placental growth through the mechanisms that regulate and balance fetoplacental growth in the general population, where birth weight and placental weight are known to be well correlated.²⁸ This is supported by the finding of normal fetoplacental weight ratios in the mosaic trisomy cases, and the fact that placental weight and birth weight were similarly correlated among both the mosaic trisomy cases and the matched controls ($r = 0.60$ and $r = 0.61$, respectively).

The lack of a pathognomonic finding in the placental pathology of mosaic trisomy pregnancies is consistent with previous studies.^{9,10} It is clear that more in-depth cellular and physiological studies are required to determine how placental function could be altered by trisomy. For example, recent studies in Down syndrome (trisomy 21) have suggested possible defects in syncytiotrophoblast formation and function,²⁹ and in extravillous trophoblast invasion and remodelling of the spiral arteries that could result in poor uteroplacental perfusion.³⁰

In addition, although significant differences between the involved chromosomes (trisomy 16, trisomy 7, trisomy 2, other trisomy) were not observed for placental weight in this study, larger sample sizes would be needed to address

Table 3. Placental pathologic findings

Case	Chromosome	Placental pathology
10	12	Normal
14	13	Normal
15	2	Normal
18	8/ 8,21	Lymphocytic villitis
19	16	Normal
		Minimal focal microscopic findings not considered sufficiently extensive to be of any clinical significance; e.g., focally increased perivillous fibrin, slight variation in villus maturity, focal congestion, a few hypervascular villi, a suggestion of very focal non-specific vessel villitis
20	2	Normal
24	2	Early acute chorioamnionitis
28	10	Focal old mural thrombus
32	8	(1) Placental infarcts; (2) Trophoblastic cysts; (3) Focal deciduitis of membranes; (4) Accessory lobe placenta
33	21	Decidual necrosis and inflammation – membranes and maternal surface
37	2,18,18	Normal
40	10	(1) Old infarct with decidual necrosis and thrombosis (abruption), at placental margin; (2) Hemosiderin deposition and macrophages at membranes
45	2	(1) Focal villitis of undetermined etiology; (2) Solitary intervillous thrombus
46	16	(1) Perivillous fibrinosis; (2) Old hemorrhage at membranes
48	4	Normal
49	13,18	Normal
50	7	Normal
56	22	(1) Increased intervillous fibrin; (2) Hemorrhage with early organization consistent with placental abruption
57	12	Perivillous fibrin deposition with no evidence of infarction
61	17	Normal
62	8	Normal
63	16	(1) Decreased fetal vascularization of chorionic surface; (2) Focal mural thrombosis fetal vessels; (3) Focal villus immaturity
65	9	Focally prominent fibrinosis
69	16	Normal

this conclusively. For example, there are well-established differences in the outcomes of pregnancies affected by mosaic trisomy, depending on the chromosome involved in the trisomy.⁵

This study has some other limitations. First, it was a retrospective study with possible selection bias. Second, although no association was observed between the level of placental trisomy and placental weight, trisomic placental cells may undergo significant apoptosis or necrosis during development, such that the level of placental trisomy assessed postpartum may not necessarily reflect trisomy levels during fetoplacental growth before birth. Third, placental weight is a crude, but convenient, marker of placental growth.

Nevertheless, this study does provide some insights into the role of the placenta in the pathogenesis of trisomic pregnancies.

CONCLUSION

The findings in this study did not support the hypothesis of a direct hypoplastic effect of placental trisomy on placental growth. Instead, placental trisomy may cause an alteration in placental function. Further studies are needed to delineate the mechanisms by which trisomy may affect placental function, and thus fetal growth.

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