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Trisomy 13-confined placental mosaicism: is there an increased risk of gestational hypertensive disorders?

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Trisomy 13, also known as Patau syndrome, is the third most common aneuploidy, occurring in approximately 1 in 5000–10,000 live births.[1] This condition is associated with holoprosencephaly, profound developmental delay, and is considered to be a life-limiting condition with less than 10% survival *ex utero*.[1] In addition to the neonatal implications, trisomy 13 is also associated with a well-documented 2–20-fold increased risk of hypertensive disorders of pregnancy with 25–40% of trisomy 13 pregnancies affected with a hypertensive disorders.[2,3] Possible hypotheses to explain the increase in hypertensive disorders of pregnancy include an increase in soluble fms-like tyrosine kinase-1 (sFLt-1) in trisomy 13 placentas compared with control placentas.[4] sFlT-1 is located on chromosome 13, and thus, women with a trisomy 13 fetus have more circulating sFlT-1.[4] sFlt-1 acts by inhibiting the pro-angiogenic effects of vascular endothelial growth factor and placental growth factor on vascular endothelial cells.

The sensitivity of cell-free DNA (cfDNA) screening for trisomy 13 is lower than for Down syndrome due to the GC content of chromosome 13. However, the specificity remains quite high. Because trisomy 13 is a rare aneuploidy, the positive predictive value following positive cfDNA result for trisomy 13 remains comparatively lower than for Down syndrome or trisomy 18. It is therefore common for a cfDNA result positive for trisomy 13 to be a false positive (i.e. diagnostic testing reveals a normal karyotype). Many of these false positives may be a result of confined placental mosaicism (CPM), though extensive cytogenetic analysis of the placenta after delivery is needed to confirm CPM.[5] CPM is more common for trisomy 13 compared with other aneuploidies, and there is empiric evidence supporting the relevance to fetal cfDNA.[6–8] After a high-risk cfDNA result for trisomy 21, 18, 13, and monosomy X, the likelihood of finding chorionic villus sampling mosaicism and the need for amniocentesis are, respectively, 2, 4, 22, and 59%.[9]

Given the increased risk of gestational hypertensive disorders with fetal trisomy 13, it is possible that women with false positive cfDNA result for trisomy 13 may be at increased risk of gestational hypertensive disorders as well because of CPM.[7]

We present a case series of six women with a cfDNA results screen positive for trisomy 13, who subsequently were found to have normal karyotypes or normal neonatal outcome. Four

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out of the five women (80%) for whom delivery information was available went on to develop gestational hypertensive disorders, one of which was severe and required preterm delivery. Further details regarding screening results, diagnostic testing results, and delivery details can be seen in Table 1. For the purposes of this series, the diagnosis of each gestational hypertensive disorder was made by the primary physician. However, these were also reviewed and validated by the study team using the International Society for the Study of Hypertension in Pregnancy guidelines.[10] This study was approved by the Institutional Review Board at the University of North Carolina at Chapel Hill.

Clearly, the distress a family faces in the setting of a positive screening test cannot be overlooked, especially in the setting of a life-limiting condition. Even after a normal amniocentesis and ultrasound, many families still feel a high degree of anxiety about their pregnancy. Many providers consider only the fetal risk in this setting, and thus, that risk appears resolved after diagnostic testing shows a normal karyotype. However, given the potential association with an increased risk for gestational hypertensive disorders, pregnancies should be monitored for signs and symptoms of gestational hypertensive disorders. Future prospective studies of maternal outcomes in the setting of false positive cfDNA results are needed to further understand the association between false positive cfDNA results, CPM, and hypertensive disorders of pregnancy.

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WHAT'S ALREADY KNOWN ABOUT THIS TOPIC

- Trisomy 13 (T13) pregnancies are associated with increased risk of gestational hypertensive disorders (GHDs).
- It is unclear if false positive cell-free DNA results for T13, which may be caused by confined placental mosaicism, are associated with increased risk for GHD.

WHAT DOES THIS STUDY ADD?

- Among six women with false positive cell-free DNA for T13, four developed GHD, raising the possibility that there may be an increased risk for GHD in women with false positive cell-free DNA results for T13.

Table 1

Cases of women with false positive cfDNA and outcomes

Case	Age/gravidity and parity	cfDNA technique	cfDNA result	CVS (result)	Amnio (result)	US (results)	GA at preX dx	GA at delivery	Pregnancy complications	Birth weight
1	35G2P0101	MPS	Aneuploidy suspected (borderline NCV value for chromosome 13)	Yes—47, XX+13[3]/46, XX[27][a]	Yes—46, XX	Normal	33/5	34/0 SVD	Severe PreX	8 lbs 6 oz
2	36G1	MPS	Results consistent with trisomy for chromosome 13	No	Yes 46, XY	Normal	36/6	37/0 LTCS	PreX	6 lbs 12 oz
3	37G6P2032	Targeted microarray	Aneuploidy detected for chromosome 13	No	Yes, nl FISH[b] and CMA	Normal	Postop day 1	39/0 LTCS	PreX	8 lbs
4	35G4P2012	MPS	Aneuploidy suspected (borderline NCV value for chromosome 13)	No	No	Normal	38/4	38/4 LTCS	gHTN	7 lbs 8 oz
5	37G1	MPS	Indeterminate for chromosome 13[c]	No	Yes—nl FISH[b] and CMA	Normal	Moved out of country at 33 wks			
6	35G1	MPS	Aneuploidy suspected (borderline NCV value for 13)	No	No	Normal	None	40 2/7LTCS	None	7 lbs 3 oz

cfDNA, cell-free DNA; MPS, massive parallel sequencing; NCV, normalized chromosome value; FISH, fluorescence *in situ* hybridization; CVS, chorionic villus sampling; Amnio, amniocentesis; US, ultrasound; GA, gestational age; preX, preeclampsia; dx, diagnosis; CMA, chromosome microarray analysis; wks, weeks; gHTN, gestational hypertension; SVD, spontaneous vaginal delivery; LTCS, low transverse cesarean delivery; BP, blood pressure; lbs, pounds; oz, ounce.

[a] Both euploid and trisomic cells were observed in two independent cultures using cell-type LTC (mesenchyme).

[b] All FISH were carried out using interphase *in situ* hybridization.

[c] The report reads: This result is likely caused by a segmental duplication or mosaic trisomy of the fetus or placenta. Copy number variant detection by microarray testing is recommended of the fetus to investigate these findings.