Placental Abnormalities and Preeclampsia in Trisomy 13 Pregnancies

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Summary

Women who are carrying a trisomy 13 fetus are prone to have an abnormal placenta as well as to develop preeclampsia in the second and third trimesters. This article provides a comprehensive review of placental abnormalities, such as small placental volume, reduced placental vascularization, a partial molar appearance of the placenta and placental mesenchymal dysplasia, and preeclampsia associated with trisomy 13 pregnancies. The candidate preeclampsia-causing genes on chromosome 13, such as sFlt1, COL4A2 and periostin, are discussed. [Taiwan J Obstet Gynecol 2009;48(1):3–8]

Key Words: COL4A2, periostin, placental abnormalities, preeclampsia, pregnancy, sFlt1, trisomy 13

Introduction

Women who are carrying a trisomy 13 fetus are prone to have an abnormal placenta as well as to develop preeclampsia in the second and third trimesters. This article provides a comprehensive review of the placental abnormalities, such as small placental volume, reduced placental vascularization, a partial molar appearance of the placenta and placental mesenchymal dysplasia, and preeclampsia associated with trisomy 13 pregnancies.

Placental Abnormalities Associated with Trisomy 13 Pregnancies

Placental abnormalities associated with trisomy 13 include small placental volume, reduced placental vascularization, a partial molar appearance, and placental mesenchymal dysplasia.
for fetal karyotyping at 11–13\textsuperscript{6} gestational weeks (median, 12 weeks), Wegrzy\v{n} et al [4] found that in trisomies 13 and 18, the mean placental volume was significantly smaller than that of the normal cases, and the volume was below the 5\textsuperscript{th} centile of the normal range in 39\% of cases. However, in trisomy 21 and Turner syndrome, the mean placental volume was not significantly different from that of the normal pregnancies.

**Reduced placental vascularization**

Feinberg et al [5] reported a pregnant multipara who presented with severe preeclampsia, fetal trisomy 13, the histopathologic findings of abnormal trophoblastic invasion into the uterine spiral arteries with inadequate trophoblastic remodeling of the maternal uterine vasculature and an absence of normal physiologic changes in the spiral arteries. In a study of 25 chromosomally abnormal early ongoing pregnancies presenting with fetal aneuploidy (10 cases of trisomy 21, nine of trisomy 18, three of triloploidy, two of monosomy X and one of trisomy 13) and 25 controls of chromosomally normal pregnancies, Jauniaux and Hustin [6] found that the placentas of the aneuploid group was systemically associated with trophoblastic hypoplasia, stromal edema or cavitation, reduced vascularization and ramification of the main villous trunks. In a study of placental vascularization using three-dimensional power Doppler ultrasound at 11–13\textsuperscript{6} gestational weeks in 100 normal control pregnancies and 25 aneuploid pregnancies (13 cases of trisomy 21, eight of trisomy 18, two of trisomy 13, one of triloploidy and one of Turner syndrome), Rizzo et al [7] found that the flow indices were significantly reduced in cases with trisomies 13 and 18 compared with normal cases. However, the flow indices in cases with trisomy 21 were not significantly different from normal cases.

**A partial molar appearance of the placenta**

Partial moles have been well known to be associated with diandric triloploidy. Partial molar appearance has been reported to present on prenatal ultrasound associated with fetal trisomy 13. Jauniaux et al [8] first reported the diagnosis of partial mole in a pregnancy with trisomy 13 at 21 gestational weeks and thought that the villous edema was more likely related to insufficient development of the villous vasculature in some placental areas. In that case, the villous trophoblasts were microscopically normal, and the maternal serum human chorionic gonadotropin (hCG) level was within the normal range during pregnancy and follow-up after delivery. Curtin et al [9] reported a case of trisomy 13 associated with preeclampsia and abnormal ultrasound mimicking a triploid partial mole. Histologic examination of the placenta in that case showed villous hydrops but no evidence of trophoblastic hyperplasia. Has et al [10] reported three cases of trisomy 13 with partial molar appearance of the placenta in the second trimester. The placentas had poor vascularization and focal villous edema but no trophoblastic hyperplasia. The total hCG levels were normal during and after the pregnancies.

**Placental mesenchymal dysplasia**

Placental mesenchymal dysplasia is characterized by an enlarged hydropic placenta with multiple cysts and dilated chorionic vessels, histologic features of enlarged stem villi with loose connective tissue and cistern formation, and lack of trophoblastic proliferation and stromal trophoblastic inclusions [11–15]. Placental mesenchymal dysplasia may present the sonographic finding of multiple cystic areas within the placenta, a normal or slightly increased level of maternal serum \(\beta\)-hCG, an elevated level of maternal serum \(\alpha\)-fetoprotein and a diploid fetus [11,12]. Placental mesenchymal dysplasia has been a prominent prenatal sonographic feature of Beckwith-Wiedemann syndrome owing to overproduction of IGF-2 [13]. Placental mesenchymal dysplasia may be associated with chromosomal abnormalities such as trisomy 13, Klinefelter syndrome, triloploidy and Xp deletion [13,16,17]. In a review of 66 cases with mesenchymal dysplasia, Cohen et al [13] reported that approximately one quarter of the cases had Beckwith-Wiedemann syndrome, and among 36 cases karyotyped, four (11\%) had chromosomal abnormalities including 47,XY,t(1;13)(q32;q32),+13, 47,XXY, 69,XXX, and 46,XXp−. Cohen et al [13] found oligohydramnios, intrauterine growth restriction, a cystic hygroma, congenital heart defects, and a normal postnatal maternal serum \(\beta\)-hCG level a few weeks after delivery in the case of trisomy 13. Müngen et al [17] reported a case of trisomy 13 with the karyotype 46,XY,der(13)t(13;13)(q11;q11)[20]/47,XY,+13[11], normal levels of maternal serum \(\alpha\)-fetoprotein, hCG and unconjugated estriol, multiple hypoechoic lesions throughout the entire placenta, and a malformed fetus with postaxial polydactyly of the hands and an atrial septal defect. The histopathologic finding of the placenta was consistent with placental mesenchymal dysplasia.

**Preeclampsia Associated with Trisomy 13 Pregnancies**

Bower et al [18] found that the incidence of trisomy 13 was 2.3 of 10,000 births in pregnancies with preeclampsia in comparison with 0.5 of 10,000 births in pregnancies without preeclampsia. Evers et al [19] first
reported severe toxemia and polyhydramnios in a case with possible trisomy 13. Since then, numerous case studies of preeclampsia with trisomy 13 have been reported [5,18,20–25]. Boyd et al [20] studied 14 women who gave birth to trisomy 13 infants and matched them for age and parity to 28 normal controls, and found that there was a significant increase in the incidence of preeclampsia in the trisomy 13 group (5/14) compared with the controls (0/28). Thornton et al [21] reported that preeclampsia occurred in two out of five multiparous women who gave birth to trisomy 13 infants. Bower et al [18] reported that preeclampsia occurred in two out of nine cases of trisomy 13. Touhy and James [22] studied 25 women who gave birth to trisomy 13 infants and matched them for age, parity and date of delivery to 50 normal controls, and found that there was a significantly increase in the incidence of preeclampsia in the trisomy 13 group (6/25) compared with the controls (1/50).

Extra Copy of Candidate Preeclampsia-causing Genes on Chromosome 13

Reported candidate preeclampsia-causing genes on chromosome 13 include sFlt1, COL4A2 and periostin.

sFlt1

sFlt1 maps to 13q12 and encodes the placental soluble FMS-like tyrosine kinase 1 (sFlt1), which binds vascular endothelial growth factor (VEGF) with high affinity. sFlt1 is a splice variant of the VEGF receptor Flt1, lacking the transmembrane and cytoplasmic domains. FMS-like tyrosine kinase 1 (Flt1) (OMIM 165070), also known as vascular endothelial growth factor receptor 1 (VEGFR1), has an extracellular region with seven immunoglobulin (Ig)-like loops containing a ligand binding domain and a dimerization domain in the N-terminal, a transmembrane domain region, and a split tyrosine kinase domain [26]. Kinase insert domain receptor (KDR) (OMIM 191306), also known as vascular endothelial growth factor receptor 2 (VEGFR2), has an extracellular region with seven Ig-like loops in the N-terminal, a transmembrane domain region, and a split tyrosine kinase domain [26]. sFlt1 is a splicing Flt1 variant that is truncated at the C-terminus. sFlt1 has only six Ig-like loops and additional 31 amino acid stretch which is encoded in the 5′-region of intron 13. sFlt1 acts as a potent VEGF and placental growth factor (PGF) antagonist [26,27]. VEGF (OMIM 192240) and PGF (OMIM 601121) belong to the VEGF family, which is essential for angiogenesis, the maintenance of endothelial cell status, and vessel wall permeability [28]. VEGF exerts biologic effects by binding the receptor Flt1 or KDR, and PGF exerts biologic effects by binding the receptor Flt1. sFlt1 binds VEGF and PGF, and thus prevents VEGF and PGF from interacting with Flt1 and KDR [26,27].

In animal models, infusion of sFlt1 induces manifestation of preeclampsia [29]. Placental sFlt1 expression has been noted to be elevated in preeclampsia [30]. By using Affymetrix U95A microarray chips (Affymetrix, Inc., Santa Clara, CA, USA), Maynard et al [29] performed gene expression profiling of placental tissue from women with or without preeclampsia and found that sFlt1 mRNA was upregulated in the preeclamptic placentas, leading to increased systemic levels of sFlt1. Vuorela et al [31] found that sFlt1 levels in the amniotic fluid were elevated in preeclampsia. Maynard et al [29] also found that increased circulating sFlt1 in patients with preeclampsia was associated with decreased circulating levels of free VEGF and PGF. Many other studies have confirmed that alterations in circulating angiogenic factors play an important role in the pathogenesis of preeclampsia [32–46]. Bdolah et al [25] found that trisomy 13 pregnancies had increased circulating sFlt1/PGF ratios compared with trisomy 18 or trisomy 21 pregnancies, or normal karyotype pregnancies, and suggested that the increased risk of preeclampsia in pregnant women with a trisomy 13 fetus may be directly related to the alterations in the angiogenic profile.

Wikström et al [43] reported that both early-onset and late-onset preeclampsia were associated with altered plasma levels of sFlt1 and PGF, and the alterations were more pronounced in early-onset preeclampsia. Moore Simas et al [44] found that maternal serum sFlt1 and sFlt1/PGF ratio were altered prior to preeclampsia onset, and suggested that serum sFlt1 and sFlt1/PGF ratio are useful for the prediction of preeclampsia in high-risk women. Baumann et al [45] found that both soluble endoglin (sEng) and sFlt1 serum concentrations in the first trimester were higher in women with subsequent preeclampsia than in controls, and suggested that sEng and sFlt1 are useful first-trimester serum markers to predict preeclampsia. sFlt1-14, a natural VEGF inhibitor, is a human-specific splice variant of Flt1 that contains 75 amino acids not present in sFlt1 and misses 31 highly conserved amino acids present in sFlt1. sFlt1-14 has been found to be upregulated in syncytial knots of the preeclampsia placenta, and it is the predominant VEGF-inhibiting protein produced by the preeclamptic placenta [46].

Preeclampsia, abnormal placentation and excess placental production of sFlt1

Maternal syndrome of preeclampsia has been thought to be secondary to abnormal placentation and excess
production of sFlt1 [38]. The hypoxic placenta produces sFlt1, and its overexpression leads to preeclampsia [28]. Increased maternal serum levels of circulating sFlt1 in trisomy 13 pregnancies have been noted in women who carry a trisomy 13 fetus and an abnormal placenta with an extra copy of the placental sFlt1 gene [25]. Decreased uteroplacental blood flows, placental insufficiency and placental hypoxia are associated with preeclampsia [47-52]. Placental ischemia and hypoxia have also been noted to induce excess sFlt1 production in preeclampsia [53]. An interesting example that elevated levels of sFlt1 may be triggered by various forms of placental pathology is the case report of elevated sFlt1 level and parvovirus-induced hydrops presented by Stepan and Faber [54]. In that case, ultrasonography at 24 gestational weeks revealed a hydropic placenta and generalized fetus hydrops; cordocentesis confirmed severe fetal anemia and parvovirus B19 infection, and the mother had elevated serum levels of sFlt1 and preeclampsia. However, with resolution of hydrops after intrauterine blood transfusion, the sFlt1 level fell and the signs of preeclampsia resolved.

**COL4A2**

**COL4A1** (OMIM 120130) maps to 13q34 and encodes the basement membrane α1 chain of type IV collagen [55]. **COL4A2** (OMIM 120090) maps to 13q34 and encodes the basement membrane α2 chain of type IV collagen [55,56]. Type IV collagen is associated with laminin, entactin and heparan sulfate proteoglycans to form the basement membranes that separate epithelium from connective tissues. Bjørn et al [57] found that type IV collagen messenger RNAs were highly expressed and co-localized in the extravillous cytotrophoblasts and co-localized in the extravillous cytotrophoblasts and in cytotrophoblastic cell islands. Pang and Xing [58] demonstrated greater than two-fold higher expression of 18 extracellular matrix molecular genes including the COL4A2 gene in preeclamptic placenta, and suggested that the abnormal expression profiles of extracellular matrix molecules might be associated with the pathogenesis of preeclampsia. The abnormal expression of the collagen IV gene may result in the ineffectiveness of basement membrane remodeling and subsequent shallow trophoblastic infiltration [59]. In a heterogeneity-based genome search meta-analysis for preeclampsia, Zintzaras et al [60] identified a novel candidate chromosome region of 13q33.1-13q34 for general preeclampsia. Johnson et al [59] have obtained strong evidence of linkage on 13q with a peak logarithm-of-odds score of 3.10 between D13S1265 and D13S173 (at about 123 cM), a critical region where COL4A1 and COL4A2 reside. In a study to detect maternal/fetal genotype incompatibility that increases risk of preeclampsia, Parimi et al [61] found that COL4A2 had a possible incompatibility effect. Galewska et al [62] reported decreased activity of cathepsin D activity in the preeclampsia umbilical cord, leading to reduced collagen degradation and subsequent accumulation of collagen in the umbilical cord and uterine arteries. The authors suggested that polymorphisms in collagen that impact expression levels or degradation by cathepsin D could influence the risk of developing preeclampsia.

### Periostin

**Periostin** or OSF2 (OMIM 608777) maps to 13q13.3 and encodes peristin or the osteoblast-specific factor 2 (OSF2), which has a sequence homology to insect adhesion molecule fasciclin I and may play a role in the adhesion process [63]. Sasaki et al [64] found that serum periostin concentrations were elevated in patients with preeclampsia compared with normotensive pregnant women, and that the periostin gene was expressed in the stroma cells of placenta. The authors suggested that human periostin may play a role in the pathogenesis of preeclampsia, and that release of adhesion molecule from the placenta could disturb adhesion interaction between cells and regulate the activation of leukocytes and endothelial cells, leading to inflammation.

### References

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