Placental Abnormalities and Preeclampsia in Trisomy 13 Pregnancies

Chih-Ping Chen[1,2,3,4,5]*

[1]*Department of Obstetrics and Gynecology, Mackay Memorial Hospital,* [2]*Department of Medical Research, Mackay Memorial Hospital, Taipei,* [3]*Department of Biotechnology, Asia University,* [4]*School of Chinese Medicine, College of Chinese Medicine, China Medical University, Taichung, and* [5]*Institute of Clinical and Community Health Nursing, National Yang-Ming University, Taipei, Taiwan.*

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.

Correspondence to: Dr Chih-Ping Chen, Department of Obstetrics and Gynecology, Mackay Memorial Hospital, 92, Section 2, Chung-Shan North Road, Taipei, Taiwan.
E-mail: cpc_mmh@yahoo.com
Accepted: January 12, 2009

Small placental volume

Small placentas with reduced placental vascularization have been associated with trisomy 13. In a pathologic analysis of trisomy 21 (16 fetuses), trisomy 18 (25 fetuses) and trisomy 13 (seven fetuses), Arizawa and Nakayama [1] found a tendency for heavy placentas in trisomy 21 and a tendency for light placentas in trisomy 18 and trisomy 13, when compared with the standard weight. They also found that human placentas in the presence of trisomies 13, 18 and 21 had immature or dysmature villi. Placentas in pregnancies with trisomies 13, 18 and 21 have been shown to have different lesions of hypotrophy, immaturity, hydrops, trophoblastic cysts and mineralization of the trophoblastic basal lamina [2]. In a study that compared first-trimester placental volume in 17 chromosomally abnormal pregnancies (nine cases of trisomy 21, four of trisomy 18, two of trisomy 13, and one each of Turner syndrome and 48,XXY,+21) and 2,846 normal pregnancies, Metzenbauer et al [3] found that the placental volume in the chromosomally abnormal group was significantly lower than that in the normal cases. In a study that measured placental volume using three-dimensional ultrasound in 500 consecutive singleton pregnancies (417 cases of normal karyotypes, 45 of trisomy 21, 17 of trisomy 18, 10 of Turner syndrome, and six of trisomy 13) immediately before chorionic villus sampling

for fetal karyotyping at 11–13^{+6} gestational weeks (median, 12 weeks), Wegrzyn 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 5th 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 triploidy, 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^{+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 triploidy 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 triploidy. 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 β-hCG, an elevated level of maternal serum α-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, triploidy 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 β-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 α-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 of anchoring villi, in cytotrophoblasts that had penetrated into the placental bed, 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 periostin 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

1. Arizawa M, Nakayama M. Pathological analysis of the placenta in trisomies 21, 18 and 13. *Nippon Sanka Fujinka Gakkai Zasshi* 1992;44:9–13. [In Japanese]
2. Labbé S, Copin H, Choiset A, Girard S, Barbet JP. The placenta and trisomies 13, 18, 21. *J Gynecol Obstet Biol Reprod (Paris)* 1989;18:989–96. [In French]
3. Metzenbauer M, Hafner E, Schuchter K, Philipp K. First-trimester placental volume as a marker for chromosomal anomalies: preliminary results from an unselected population. *Ultrasound Obstet Gynecol* 2002;19:240–2.
4. Wegrzyn P, Faro C, Falcon O, Peralta CF, Nicolaides KH. Placental volume measured by three-dimensional ultrasound at 11 to 13+6 weeks of gestation: relation to chromosomal defects. *Ultrasound Obstet Gynecol* 2005;26:28–32.
5. Feinberg RF, Kliman HJ, Cohen AW. Preeclampsia, trisomy 13, and the placental bed. *Obstet Gynecol* 1991;78:505–8.
6. Jauniaux E, Hustin J. Chromosomally abnormal early ongoing pregnancies: correlation of ultrasound and placental histological findings. *Hum Pathol* 1998;29:1195–9.
7. Rizzo G, Capponi A, Cavicchioni O, Vendola M, Arduini D. Placental vascularization measured by three-dimensional power Doppler ultrasound at 11 to 13+6 weeks' gestation in normal and aneuploid fetuses. *Ultrasound Obstet Gynecol* 2007;30:259–62.

8. Jauniaux E, Halder A, Partington C. A case of partial mole associated with trisomy 13. *Ultrasound Obstet Gynecol* 1998; 11:62–4.
9. Curtin WM, Marcotte MP, Myers LL, Brost BC. Trisomy 13 appearing as a mimic of a triploid partial mole. *J Ultrasound Med* 2001;20:1137–9.
10. Has R, İbrahimoğlu L, Ergene H, Ermis H, Başaran S. Partial molar appearance of the placenta in trisomy 13. *Fetal Diagn Ther* 2002;17:205–8.
11. Moscoso G, Jauniaux E, Hustin J. Placental vascular anomaly with diffuse mesenchymal stem villous hyperplasia: a new clinico-pathological entity? *Pathol Res Pract* 1991;187:324–8.
12. Jauniaux E, Nicolaides KH, Hustin J. Perinatal features associated with placental mesenchymal dysplasia. *Placenta* 1997; 18:701–6.
13. Cohen MC, Roper EC, Sebire NJ, Stanek J, Anumba DOC. Placental mesenchymal dysplasia associated with fetal aneuploidy. *Prenat Diagn* 2005;25:187–92.
14. Sander CM. Angiomatous malformation of placental chorionic stem vessels and pseudo-partial molar placentas: report of five cases. *Pediatr Pathol* 1993;13:621–33.
15. Chen CP, Chern SR, Wang TY, Huang ZD, Huang MC, Chuang CY. Pregnancy with concomitant chorangioma and placental vascular malformation with mesenchymal hyperplasia. *Hum Reprod* 1997;12:2553–6.
16. Arizawa M, Nakayama M. Suspected involvement of the X chromosome in placental mesenchymal dysplasia. *Congenit Anom (Kyoto)* 2002;42:309–17.
17. Müngen E, Dundar O, Muhcu M, Haholu A, Tunca Y. Placental mesenchymal dysplasia associated with trisomy 13: sonographic findings. *J Clin Ultrasound* 2008;36:454–6.
18. Bower C, Stanley F, Walters BN. Pre-eclampsia and trisomy 13. *Lancet* 1987;2:1032.
19. Evers J, Seelen J, Blankenborg G. Severe toxemia, hydramnios and trisomy 13–15. *Ned Tijdschr Verloskd Gynaecol* 1967;67: 395–7.
20. Boyd PA, Lindenbaum RH, Redman C. Pre-eclampsia and trisomy 13: a possible association. *Lancet* 1987;2:425–7.
21. Thornton JG, O'Donovan P, Stigter R, Williams J, Sullivan LG. Pre-eclampsia and trisomy 13. *Lancet* 1987;2:794.
22. Tuohy JF, James DK. Pre-eclampsia and trisomy 13. *Br J Obstet Gynaecol* 1992;99:891–4.
23. Heydanus R, Defoort P, Dhont M. Pre-eclampsia and trisomy 13. *Eur J Obstet Gynecol Reprod Biol* 1995;60:201–2.
24. Pedersen BW, Grønlund A. Severe pre-eclampsia and fetal trisomy 13 in a multiparous woman. *Ugeskr Laeger* 2003;165: 2108–9. [In Danish]
25. Bdolah Y, Palomaki GE, Yaron Y, et al. Circulating angiogenic proteins in trisomy 13. *Am J Obstet Gynecol* 2006;194:239–45.
26. Kendall RL, Wang G, Thomas KA. Identification of a natural soluble form of the vascular endothelial growth factor receptor, FLT-1, and its heterodimerization with KDR. *Biochem Biophys Res Commun* 1996;226:324–8.
27. Shibuya M. Structure and function of VEGF/VEGF-receptor system involved in angiogenesis. *Cell Struct Funct* 2001;26: 25–35.
28. Kita N, Mitsushita J. A possible placental factor for preeclampsia: sFlt-1. *Curr Med Chem* 2008;15:711–5.
29. Maynard SE, Min JY, Merchan J, et al. Excess placental soluble fms-like tyrosine kinase 1 (sFlt1) may contribute to endothelial dysfunction, hypertension, and proteinuria in preeclampsia. *J Clin Invest* 2003;111:649–58.
30. Zhou Y, McMaster M, Woo K, et al. Vascular endothelial growth factor ligands and receptors that regulate human cytotrophoblast survival are dysregulated in severe preeclampsia and hemolysis, elevated liver enzymes, and low platelets syndrome. *Am J Pathol* 2002;160:1405–23.
31. Vuorela P, Helske S, Hornig C, Alitalo K, Weich H, Halmesmäki E. Amniotic fluid—soluble vascular endothelial growth factor receptor-1 in preeclampsia. *Obstet Gynecol* 2000;95:353–7.
32. Koga K, Osuga Y, Yoshino O, et al. Elevated serum soluble vascular endothelial growth factor receptor 1 (sVEGFR-1) levels in women with preeclampsia. *J Clin Endocrinol Metab* 2003;88:2348–51.
33. Sugimoto H, Hamano Y, Charytan D, et al. Neutralization of circulating vascular endothelial growth factor (VEGF) by anti-VEGF antibodies and soluble VEGF receptor 1 (sFlt-1) induces proteinuria. *J Biol Chem* 2003;278:12605–8.
34. Tsatsaris V, Goffin F, Munaut C, et al. Overexpression of the soluble vascular endothelial growth factor receptor in preeclamptic patients: pathophysiological consequences. *J Clin Endocrinol Metab* 2003;88:5555–63.
35. Bdolah Y, Sukhatme VP, Karumanchi SA. Angiogenic imbalance in the pathophysiology of preeclampsia: newer insights. *Semin Nephrol* 2004;24:548–56.
36. Chaiworapongsa T, Romero R, Espinoza J, et al. Evidence supporting a role for blockade of the vascular endothelial growth factor system in the pathophysiology of preeclampsia: Young Investigator Award. *Am J Obstet Gynecol* 2004;190: 1541–50.
37. Hertig A, Berkane N, Lefevre G, et al. Maternal serum sFlt1 concentration is an early and reliable predictive marker of preeclampsia. *Clin Chem* 2004;50:1702–3.
38. Karumanchi SA, Bdolah Y. Hypoxia and sFlt-1 in preeclampsia: the "chicken-and-egg" question. *Endocrinology* 2004;145: 4835–7.
39. Levine RJ, Maynard SE, Qian C, et al. Circulating angiogenic factors and the risk of preeclampsia. *N Engl J Med* 2004;350: 672–83.
40. Levine RJ, Thadhani R, Qian C, et al. Urinary placental growth factor and risk of preeclampsia. *JAMA* 2005;293:77–85.
41. Thadhani R, Mutter WP, Wolf M, et al. First trimester placental growth factor and soluble fms-like tyrosine kinase 1 and risk for preeclampsia. *J Clin Endocrinol Metab* 2004;89: 770–5.
42. Venkatesha S, Toporsian M, Lam C, et al. Soluble endoglin contributes to the pathogenesis of preeclampsia. *Nat Med* 2006;12:642–9.
43. Wikström AK, Larsson A, Eriksson UJ, Nash P, Nordén-Lindeberg S, Olovsson M. Placental growth factor and soluble FMS-like tyrosine kinase-1 in early-onset and late-onset preeclampsia. *Obstet Gynecol* 2007;109:1368–74.
44. Moore Simas TA, Crawford SL, Solitro MJ, Frost SC, Meyer BA, Maynard SE. Angiogenic factors for the prediction of preeclampsia in high-risk women. *Am J Obstet Gynecol* 2007; 197:244.e1–8.
45. Baumann MU, Bersinger NA, Mohaupt MG, Raio L, Gerber S, Surbek DV. First-trimester serum levels of soluble endoglin and soluble fms-like tyrosine kinase-1 as first-trimester

markers for late-onset preeclampsia. *Am J Obstet Gynecol* 2008;199:266.e1–6.
46. Sela S, Itin A, Natanson-Yaron S, et al. A novel human-specific soluble vascular endothelial growth factor receptor 1: cell-type-specific splicing and implications to vascular endothelial growth factor homeostasis and preeclampsia. *Circ Res* 2008;102:1566–74.
47. Lunell NO, Lewander R, Mamoun I, Nylund L, Sarby S, Thornstrom S. Uteroplacental blood flow in pregnancy induced hypertension. *Scand J Clin Lab Invest* 1984;169(Suppl): 28–35.
48. Genbacev O, Zhou Y, Ludlow JW, Fisher SJ. Regulation of human placental development by oxygen tension. *Science* 1997;277:1669–72.
49. Podjarny E, Baylis C, Losonczy G. Animal models of preeclampsia. *Semin Perinatol* 1999;23:2–13.
50. Caniggia I, Mostachfi H, Winter J, et al. Hypoxia-inducible factor-1 mediates the biological effects of oxygen on human trophoblast differentiation through TGFβ(3). *J Clin Invest* 2000;105:577–87.
51. Rajakumar A, Whitelock KA, Weissfeld LA, Daftary AR, Markovic N, Conrad KP. Selective overexpression of the hypoxia-inducible transcription factor, HIF-2, in placentas from women with preeclampsia. *Biol Reprod* 2001;64: 499–506.
52. Fisher SJ. The placental problem: linking abnormal cytotrophoblast differentiation to the maternal symptoms of preeclampsia. *Reprod Biol Endocrinol* 2004;2:53.
53. Nagamatsu T, Fujii T, Kusumi M, et al. Cytotrophoblasts up-regulate soluble fms-like tyrosine kinase-1 expression under reduced oxygen: an implication for the placental vascular development and the pathophysiology of preeclampsia. *Endocrinology* 2004;145:4838–45.
54. Stepan H, Faber R. Elevated sFlt1 level and preeclampsia with parvovirus-induced hydrops. *N Engl J Med* 2006;354:1857–8.
55. Griffin CA, Emanuel BS, Hansen JR, Cavenee WK, Myers JC. Human collagen genes encoding basement membrane α1(IV) and α2(IV) chains map to the distal long arm of chromosome 13. *Proc Natl Acad Sci USA* 1987;84:512–6.
56. Killen PD, Francomano CA, Yamada Y, Modi WS, O'Brien SJ. Partial structure of the human α2(IV) collagen chain and chromosomal localization of the gene (*COL4A2*). *Hum Genet* 1987;77:318–24.
57. Bjørn SF, Hastrup N, Lund LR, Danø K, Larsen JF, Pyke C. Co-ordinated expression of MMP-2 and its putative activator, MT1-MMP, in human placentation. *Mol Hum Reprod* 1997; 3:713–23.
58. Pang ZJ, Xing FQ. Expression profile of trophoblast invasion-associated genes in the pre-eclamptic placenta. *Br J Biomed Sci* 2003;60:97–101.
59. Johnson MP, Fitzpatrick E, Dyer TD, et al. Identification of two novel quantitative trait loci for pre-eclampsia susceptibility on chromosomes 5q and 13q using a variance components-based linkage approach. *Mol Hum Reprod* 2007;13:61–7.
60. Zintzaras E, Kitsios G, Harrison GA, et al. Heterogeneity-based genome search meta-analysis for preeclampsia. *Hum Genet* 2006;120:360–70.
61. Parimi N, Tromp G, Kuivaniemi H, et al. Analytical approaches to detect maternal/fetal genotype incompatibilities that increase risk of pre-eclampsia. *BMC Med Genet* 2008;9:60.
62. Galewska Z, Bańkowski E, Romanowicz L, Gogiel T, Wolańska M, Jaworski S. Preeclampsia-associated reduction of cathepsin D activity in the umbilical cord. *Clin Chim Acta* 2005; 351:177–84.
63. Takeshita S, Kikuno R, Tezuka K, Amann E. Osteoblast-specific factor 2: cloning of a putative bone adhesion protein with homology with the insect protein fasciclin I. *Biochem J* 1993;294:271–8.
64. Sasaki H, Roberts J, Lykins D, Fujii Y, Auclair D, Chen LB. Novel chemiluminescence assay for serum periostin levels in women with preeclampsia and in normotensive pregnant women. *Am J Obstet Gynecol* 2002;186:103–8.