References and Notes

1. E. A. Stewart, *Lancet* **357**, 293 (2001).
2. S. Cramer, B. Patel, *Am. J. Clin. Pathol.* **94**, 435 (1990).
3. M. S. Rein *et al.*, *Obstet. Gynecol.* **77**, 923 (1991).
4. N. Christacos, P. Dal Cin, C. C. Morton, B. J. Quade, paper presented at the 53rd Annual Meeting of the American Society of Genetics, Los Angeles, CA, 2003.
5. E. P. Henske, *Genes Chromosomes Cancer* **38**, 376 (2003).
6. P. Dal Cin *et al.*, *Genes Chromosomes Cancer* **36**, 205 (2003).
7. G. P. Flake, J. Andersen, D. Dixon, *Environ. Health Perspect.* **111**, 1037 (2003).
8. J. Andersen, R. L. Barbieri, *J. Soc. Gynecol. Investig.* **2**, 663 (1995).
9. K. Cesen-Cummings, J. A. Copland, J. C. Barrett, C. L. Walker, B. J. Davis, *Environ. Health Perspect.* **108** (suppl. 5), 817 (2000).
10. D. Linder, S. M. Gartler, *Science* **150**, 67 (1965).
11. C. C. Morton, *Environ. Health Perspect.* **108**, 775 (2000).
12. A. A. Sandberg, *Cancer Genet. Cytogenet.* **158**, 1 (2005).
13. C. P. Pavlovich, L. S. Schmidt, *Nat. Rev. Cancer* **4**, 381 (2004).
14. C. L. Walker, D. Hunter, J. I. Everitt, *Genes Chromosomes Cancer* **38**, 349 (2003).
15. J. Wei, L. Chiriboga, M. Mizuguchi, H. Yee, K. Mittal, *Mod. Pathol.* **18**, 179 (2005).
16. J. D. Cook, C. L. Walker, *Curr. Mol. Med.* **4**, 813 (2004).
17. K. L. Gross *et al.*, *Genes Chromosomes Cancer* **41**, 183 (2004).
18. J. D. Cook, C. L. Walker, *Semin. Reprod. Med.* **22**, 105 (2004).
19. A. Al-Hendy, E. J. Lee, H. Q. Wang, J. A. Copland, *Am. J. Obstet. Gynecol.* **191**, 1621 (2004).
20. M. Shozu, K. Murakami, M. Inoue, *Semin. Reprod. Med.* **22**, 51 (2004).
21. M. S. Rein, R. L. Barbieri, A. J. Friedman, *Am. J. Obstet. Gynecol.* **172**, 14 (1995).
22. K. Kawaguchi *et al.*, *Am. J. Obstet. Gynecol.* **160**, 637 (1989).
23. I. Sozen, A. Arici, *Fertil. Steril.* **78**, 1 (2002).
24. N. Chegini, in *Cytokines in Human Reproduction*, J. A. Hill, Ed. (Wiley, New York, 2000), pp. 133–162.
25. X. Luo, L. Ding, J. Xu, N. Chegini, *Endocrinology* **146**, 1097 (2005).
26. W. H. Catherino *et al.*, *Genes Chromosomes Cancer* **40**, 204 (2004).
27. E. A. Stewart, R. A. Nowak, *Obstet. Gynecol.* **92**, 624 (1998).
28. E. A. Stewart, R. A. Nowak, *Hum. Reprod. Update* **2**, 295 (1996).
29. J. D. Cook *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **102**, 8644 (2005).
30. J. C. Tsibris *et al.*, *Cancer Res.* **59**, 5737 (1999).
31. C. E. Rothwell, E. J. McGuire, R. A. Martin, F. A. De la Iglesia, *Fundam. Appl. Toxicol.* **18**, 353 (1992).
32. B. Romagnolo *et al.*, *J. Clin. Invest.* **98**, 777 (1996).
33. S. A. Carney *et al.*, *Lab. Invest.* **82**, 719 (2002).
34. J. Condon *et al.*, *Biol. Reprod.* **67**, 506 (2002).
35. M. S. Soloff *et al.*, *Mol. Hum. Reprod.* **10**, 685 (2004).
36. G. Pron *et al.*, *Fertil. Steril.* **79**, 120 (2003).
37. J. Hindley *et al.*, *Am. J. Roentgenol.* **183**, 1713 (2004).
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Supporting Online Material

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Fig. S1

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REVIEW

Latest Advances in Understanding Preeclampsia

Christopher W. Redman* and Ian L. Sargent

Preeclampsia is a relatively common pregnancy disorder that originates in the placenta and causes variable maternal and fetal problems. In the worst cases, it may threaten the survival of both mother and baby. We summarize recent work on the causes of preeclampsia, which reveals a new mode of maternal immune recognition of the fetus, relevant to the condition. The circulating factors derived from the placenta, which contributes to the clinical syndrome, are now better understood. This brief review on preeclampsia does not cover all aspects of this intriguing condition but focuses on some new and interesting findings.

Preeclampsia is a potentially dangerous complication of the second half of pregnancy, labor, or early period after delivery, characterized by hypertension, abnormal amounts of protein in the urine, and other systemic disturbances (*1*). The condition affects about 2.5 to 3.0% of women. It has the potential to kill either mother or baby or both, even in the developed world (although rarely). Eclampsia is an end stage of the disease characterized by generalized seizures. Preeclampsia cannot be prevented, so it is managed by screening symptomless women and inducing delivery when necessary. It is one of the most common reasons for induced preterm delivery.

Risk factors for preeclampsia have been analyzed in a recent systematic review (*2*). These factors include a previous history of preeclampsia, primiparity, obesity, family history of preeclampsia, multiple pregnancies, and chronic medical conditions such as long-term hypertension or diabetes (*2*). Paradoxically, cigarette smoking reduces the risk (*2*). Thrombophilia, an inherited tendency to overactive coagulation, may also be a consideration. Although preeclampsia may develop at any time after 20 weeks of gestation, early onset disease is more severe and characterized by a higher rate of small size for gestational age neonates as well as a higher recurrence rate than with later onset disease.

It is generally agreed that preeclampsia results from the presence of a placenta (*3*) and, in particular, the trophoblast cells that are found only in this tissue. Multinucleate syncytiotrophoblast, which forms the epithelial layer of the villi, is one subset of trophoblast that is in direct contact with maternal blood. Mononuclear extravillous cytotrophoblast form a tissue interface in the lining of the uterus, the decidua. The clinical syndrome arises from secondary systemic circulatory disturbances that can be ascribed to generalized maternal endothelial dysfunction. There are two broad categories, maternal and placental. In placental preeclampsia, the problem arises from a placenta that is under hypoxic conditions with oxidative stress. (*4*) Maternal preeclampsia arises from the interaction between a normal placenta and a maternal constitution that is susceptible to, or suffers from, microvascular disease, as with long-term hypertension or diabetes (*5*). Mixed presentations, combining maternal and placental contributions, are common.

Placental Preeclampsia

Placental preeclampsia appears to progress in two stages: preclinical and clinical (Fig. 1C). This variant arises from poor development of the early placenta and its maternal blood supply, called poor placentation. In the second stage, an increasingly hypoxic placenta causes the maternal signs of the condition, including hypertension and proteinuria as well as clotting and liver dysfunction. In severe, particularly early onset disease (before 34 weeks gestation), the fetus may suffer increasing nutritional and respiratory insufficiency, asphyxia, or death.

In the second two trimesters of pregnancy, the placenta requires increasing access to the maternal blood supply. This is created by extensive remodeling of maternal spiral arteries, which are the end arteries of the uteroplacental circulation that deliver blood directly into the placental intervillous space. Remodeling depends on one of the subtypes of the trophoblasts, which differentiates into tumor-like cells (extravillous cytotrophoblasts) that invade the lining of the pregnant uterus from weeks 6 to 18 of gestation (*6*).

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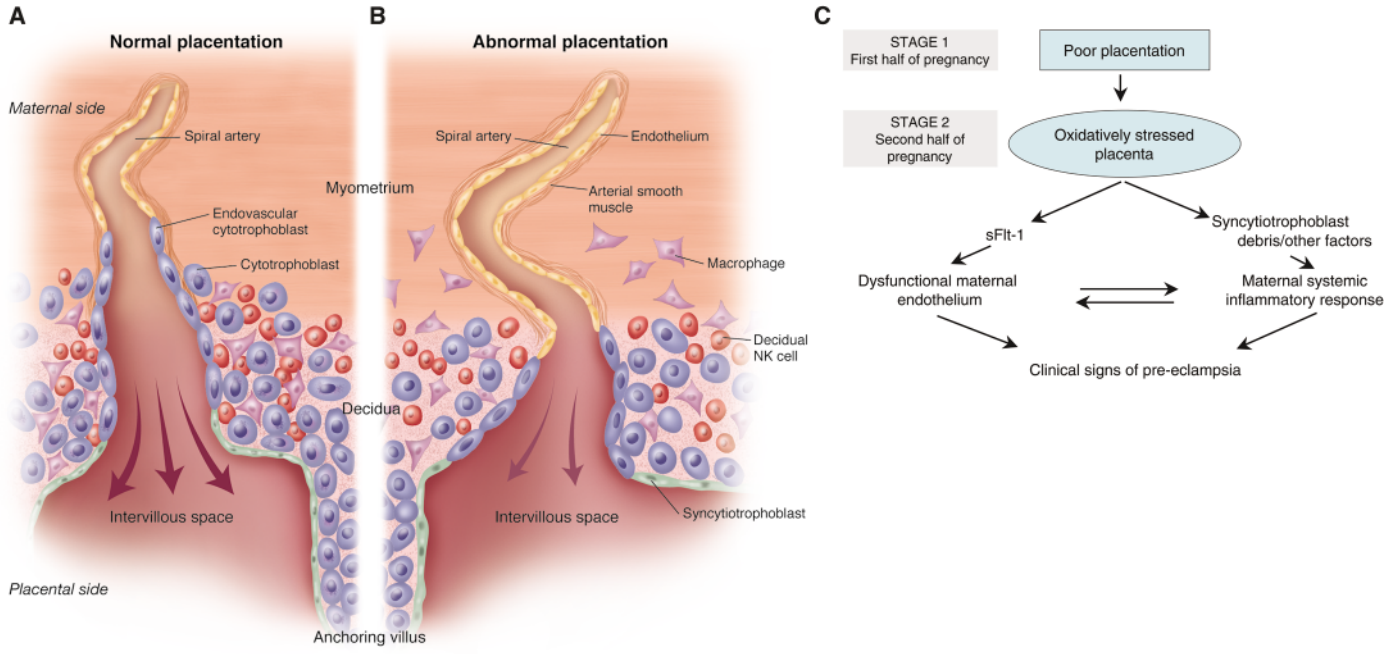

Fig. 1. Poor placentation and preeclampsia. Normal placentation (**A**) and poor placentation (**B**) at 15 to 16 weeks of pregnancy. The placenta is linked to the maternal decidua by anchoring villi. During normal placentation, cytotrophoblasts (blue) cross these placental-maternal bridges and invade the maternal decidua and adjacent spiral arteries. They penetrate the walls of the arteries and replace part of the maternal endothelium (yellow), stimulating remodeling of the arterial wall such that the smooth muscle is lost and the artery dilates. In the decidua, they are confronted by many NK cells (red) and some macrophages (purple). During normal pregnancy, these immune cells facilitate deep invasion of cytotrophoblasts into the myometrial segments (A) and promote extensive spiral artery remodeling. In the preclinical stage of preeclampsia, invasion is restricted (B) with impaired arterial remodeling. (**C**) The two stages in development of preeclampsia.

The trophoblasts penetrate the maternal decidual spiral arteries, which are obstructed before 9 weeks of gestation by invasive trophoblast plugs (*4*, *7*) when placental perfusion is minimal. Before this time, the fetus is engaged in organogenesis and is especially vulnerable to teratogenic damage from free radicals. After 9 weeks, the uteroplacental arteries recanalize from the placental periphery, a process that is completed by 12 weeks. The associated increase in placental oxygenation is a watershed for trophoblast growth and differentiation and marked by the sudden appearance of markers of oxidative stress in the placenta (*7*). From then on, invasive cytotrophoblasts in decidual tissue extensively remodel the spiral arteries, including their distal myometrial segments, such that they lose their smooth muscle and become greatly dilated (Fig. 1). The presence of trophoblasts in the lumina (endovascular cytotrophoblasts), walls, and surrounding interstitial tissues (interstitial cytotrophoblasts) of the ends of the spiral arteries appears to be critical for this process. Endovascular trophoblasts express markers of endothelial cells, including angiogenic factors and their receptors, and replace the endothelial lining of the arteries with a pseudoendothelium forming intriguing compound vessels, part fetal and part maternal (*6*).

By 20 weeks, this process is more or less complete such that the maternal circulation can supply the expanding intervillous space of the placenta; by full term, a huge fetal surface formed from the microvilli (the terminal leaflets of the branching umbilical circulation, covered in the syncytiotrophoblasts) can come into direct contact with maternal blood. Hence, extravillous cytotrophoblasts play a critical role by expanding the vascular capacity of the uteroplacental circulation. In many cases of placental preeclampsia, trophoblast invasion is inhibited, the arteries are poorly remodeled, and the capacity of the uteroplacental circulation is too small. This is called poor placentation, which is established before 20 weeks and before clinical signs appear (*3*). It is impossible to study this process prospectively, but it has been inferred from studies of placental bed biopsies at delivery. In addition, poor placentation does not always cause overt preeclampsia but has been associated with small size for gestational age fetuses.

Immunological Considerations

In preeclampsia, invasive trophoblasts fail to gain full access to maternal supply lines. New work suggests that trophoblast signaling to decidual immune cells is weak and fails to stimulate collaboration, essential for placentation (*8*, *9*). It has long been considered that preeclampsia may be a form of maternal immune rejection of the genetically foreign fetus. Many have sought maternal T cell recognition of fetopaternal human lymphocyte antigens (HLAs) without success, because trophoblasts do not express the necessary strong transplantation antigens, HLA-A, -B, or -D (*10*). Invasive cytotrophoblasts that infiltrate maternal territory during placentation express a unique combination of HLAs, namely HLA-C, -E, and -G (*10*). Of these, only HLA-C is polymorphic signaling paternal (foreign) alloantigens. In the decidua, the invading trophoblasts meet many maternal lymphocytes. These are not classical T cells but mainly NK (natural killer) cells with an unusual phenotype when compared to circulating NK cells (10), which is associated with high cytokine production rather than cytolytic activity. Of outstanding importance is the fact they express receptors that recognize the exact combination of HLAs displayed by invasive cytotrophoblasts. The invasive cytotrophoblasts and the decidual NK cells are closely apposed to each other in the first trimester decidua but disappear by full term (*11*). Because the NK cells express an unusual array of receptors that bind to the unique combination of HLAs expressed by the intermingling cytotrophoblast and NK cells, it is likely they engage in a some form of immune recognition (*10*).

The NK receptors KIRs (killer immunoglobulin-like receptors) recognize polymorphic HLA-C. The multigene KIR generates numerous haplotypes that differ in both gene content and allele combination. Some haplotypes inhibit NK cell function (cytokine production in these cells), whereas others are stimulatory, depending on both the KIR pheno-

type of the NK cells and the HLA-C phenotype of the stimulating cells. There are a large number of possible combinations. However, there are two broad classes of HLA-C haplotypes (C1 and C2). The KIRs bind more strongly to C2 than C1. KIR haplotypes also form two groups. The simpler A group codes mainly for inhibitory KIR. The more complex B group has additional genes for stimulating NK cells (*9*). Preeclampsia is substantially more prevalent in women who are homozygous for the inhibitory A haplotypes (AA) than in women homozygous for the stimulator B genes (BB). The effect is strongest if the fetus is homozygous for the HLA-C2 haplotype (9). In short, placentation is better and preeclampsia less common if trophoblast strongly simulates uterine (maternal) NK cells. However, this activation has not yet been confirmed in vitro. Whether this interaction between trophoblasts and NK cells can help to explain why preeclampsia is more common in first pregnancies, long suggested to be an immune phenomenon, remains to be seen.

Placental Factors That Might Cause the Maternal Syndrome

In the two-stage model, a hypoxic and dysfunctional placenta is considered to release factors into the maternal circulation that cause the clinical features of this condition (Fig. 1C). These appear to arise from a generalized systemic inflammatory response (*12*), of which endothelial dysfunction is a prominent component. Several candidate factors have been suggested (*12*); none of them are yet proved to be causative in vivo. The strongest is the soluble receptor for vascular endothelial growth factor (VEGF)–1, also known as sFlt1 (soluble fms-like tyrosine kinase 1). It binds vascular endothelial growth factors and placental growth factor and deprives the systemic endothelium of essential survival factors. It is therefore antiangiogenic, as has been confirmed in animal and human studies [summarized in (*12*)].

Infused neutralizing monoclonal antibody to VEGF mimics the anti-angiogenic action of sFlt1, which has been exploited to treat metastatic colorectal or renal cancer. It also causes hypertension and proteinuria, the typical features of preeclampsia [summarized in (*13*)]. It has been recently reported that preeclamptic women have higher circulating sFlt1 concentrations than do normal pregnant control women and also more anti-angiogenic activity in their sera. Moreover, infusion of sFlt into experimental rats elicits endothelial lesions in the glomeruli of the kidneys (glomerular endotheliosis) that are pathognomic of preeclampsia (*13*). sFlt1 is not specific to pregnancy, but the factor is secreted into maternal blood by trophoblasts, which are stimulated by hypoxia. It therefore has the necessary attributes of a trophoblast-derived factor that disrupts the maternal endothelium, which is a primary target for preeclampsia (*1*). However, it may not be the sole cause, nor is it raised in every affected woman. The term "preeclampsia" describes a syndrome (a cluster of clinical features) not a disease and may encompass separate conditions that look alike to the clinician. The condition is varied in its presentation, features, and outcomes. It is hard to conceive how one factor can explain the entire spectrum. Another suggested candidate is neurokinin B (*14*). There are also many other circulating trophoblast factors that are increased in preeclampsia, and their role in the disease is undefined.

Preeclampsia is associated with a systemic inflammatory response (*15*), but so is normal pregnancy, although to a lesser extent. Many parts of the inflammatory network are involved (inflammatory leukocytes, endothelium, clotting cascade, platelets, and acute phase reactants) yielding minor systemic changes that have previously been considered to be part of the physiology of normal pregnancy. These features are intensified in the third trimester, even more so in preeclampsia, and could contribute to some, if not all, of its maternal disturbances. The causes of the systemic inflammation are not known. One intriguing feature is that the placenta releases what can be described as trophoblast debris into the maternal circulation. This comprises syncytiotrophoblast membrane microparticles, cytokeratin fragments, soluble RNA and DNA of fetal origin, and even cytotrophoblast cells (*15*). This debris is proinflammatory and increased in amounts in preeclampsia, so its disposal probably imposes a maternal inflammatory burden.

The hypoxic placenta of preeclampsia suffers oxidative stress, a disequilibrium between antioxidant defenses and production of reactive oxygen species in favor of the latter. Its markers are readily detected in the preeclampsia placenta. Such stress is probably the cause of the increased release of trophoblast debris by apoptotic processes, exacerbated further by necrosis (*16*), although this is not yet proved. This, and the evidence for systemic oxidative stress in preeclamptic women, has provoked an encouraging trial of antioxidant vitamins C and E for prophylaxis. This showed substantial alleviation of the maternal signs but not an improved perinatal outcome. Larger confirmatory trials are underway in several countries. If the initial benefit is confirmed, this could be a major advance in preventive management (*17*).

Maternal Preeclampsia

A similar low-grade systemic inflammatory response characterizes adults with arterial disease, hypertension, obesity, or diabetes, which are conditions that also strongly predispose to preeclampsia in young women. Such constitutions lead to "maternal preeclampsia," where the problem is more an abnormal maternal response than an abnormal pregnancy (5). In this regard, pregnancy may constitute a metabolic and vascular stress test, which reveals a woman's health in later life and which is consistent with the higher incidence of ischemic heart disease, stroke, and hypertension that becomes evident many years after an episode of preeclampsia (*18*). Although preeclampsia is familial, it does not depend on a single maternal or fetal gene. There are many candidate genes that cannot be described here but are reviewed elsewhere together with evidence for a new gene for a transcription factor expressed in the placenta that may be involved in the control of trophoblast invasion (*19*).

Survival of the Fittest?

In evolutionary terms, preeclampsia is perceived as a struggle between the different survival needs of maternal and paternal (fetal) genes or maternal-fetal conflict (*20*). It is suggested that preeclamptic hypertension is dictated by the fetus (placenta) to gain a greater share of the maternal circulation. The price in terms of risks of maternal death would seem to be evolutionarily acceptable.

References and Notes

1. K. Y. Lain, J. M. Roberts, *JAMA* **287**, 3183 (2002).
2. K. Duckitt, D. Harrington, *BMJ* **330**, 565 (2005).
3. C. W. Redman, *Placenta* **12**, 301 (1991).
4. G. J. Burton, E. Jauniaux, *J. Soc. Gynecol. Investig.* **11**, 342 (2004).
5. R. B. Ness, J. M. Roberts, *Am. J. Obstet. Gynecol.* **175**, 1365 (1996).
6. K. Red-Horse *et al.*, *J. Clin. Investig.* **114**, 744 (2004).
7. E. Jauniaux, B. Gulbis, G. J. Burton, *Placenta* **24** (suppl. A), S86 (2003).
8. S. E. Hiby *et al.*, *J. Exp. Med.* **200**, 957 (2004).
9. P. Parham, *Nat. Rev. Immunol.* **5**, 201 (2005).
10. A. Moffett-King, *Nat. Rev. Immunol.* **2**, 656 (2002).
11. H. Haller *et al.*, *J. Reprod. Immunol.* **23**, 41 (1993).
12. S. A. Karumanchi, Y. Bdolah, *Endocrinology* **145**, 4835 (2004).
13. S. E. Maynard *et al.*, *J. Clin. Investig.* **111**, 649 (2003).
14. N. M. Page *et al.*, *Nature* **405**, 797 (2000).
15. C. W. Redman, I. L. Sargent, *Placenta* **24** (suppl. A), S21 (2003).
16. B. Huppertz *et al.*, *Placenta* **24**, 181 (2003).
17. M. T. Raijmakers, R. Dechend, L. Poston, *Hypertension* **44**, 374 (2004).
18. N. Sattar, I. A. Greer, *BMJ* **325**, 157 (2002).
19. M. van Dijk *et al.*, *Nat. Genet.* **37**, 514 (2005).
20. D. Haig, in *Evolution in Health and Disease*, S. C. Stearns, Ed. (Oxford Univ. Press, Oxford, 1999), pp. 77–90.

10.1126/science.1111726