Progress in the understanding of the pathophysiology of immunologic maladaptation related to early-onset preeclampsia and metabolic syndrome related to late-onset preeclampsia

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Among mammalian species, human reproduction has 2 outstanding features. The human hemochorial placentation is characterized by a very deep endovascular trophoblast invasion in the spiral arteries, reaching deep into the myometrium. This requires an agonistic direct cell-cell interaction between the maternal immune system and semi-allogeneic trophoblast. The second feature is preeclampsia, a heterogeneous syndrome, a uniquely human condition. The human female is one of the few mammals exposed to her partner's semen on multiple occasions before conception. Regulatory T cells, especially paternal antigen-specific regulatory T cells, play an important role in the maintenance of pregnancy. Sexual intercourse increases the number of dendritic cells in the uterus that play an important role in the induction of paternal antigen-specific regulatory T cells. Paternal antigen-specific regulatory T cells maintain pregnancy by inducing tolerance. In the decidua basalis of preeclamptic cases, clonal regulatory T cells are reduced; these would normally monoclonally expand to recognize fetal or paternal antigens. Programmed cell death-1 expressed on T cells regulate cytotoxic T-cell activity and protect the fetus against maternal rejection. Programmed cell death-1 expression on clonal cytotoxic T cells is reduced in preeclampsia especially in early-onset preeclampsia, making the fetus and placenta vulnerable to attack by cytotoxic T cells. These phenomena can explain the epidemiologic phenomenon that preeclampsia is more common in couples using condom contraception, with shorter cohabitation periods, first pregnancies, first pregnancies in multiparous women when they change partner, and pregnancies after assisted reproduction using donated gametes.

In contrast to its importance in early-onset preeclampsia, shallow trophoblast invasion does not play a role in the development of preeclampsia, that is, immune maladaptation does not seem to be involved. Late-onset preeclampsia (>34 weeks' gestation), representing 80% to 90% of preeclampsia in most developed countries with a "Western lifestyle," is strongly associated with maternal cardiometabolic variables (metabolic syndrome). Although the underlying pathophysiology might be quite different, syncytiotrophoblast stress is the final common pathway leading to the maternal syndrome among the subtypes of preeclampsia by causing an imbalance between proangiogenic factors (placental growth factor and vascular endothelial growth factor) and antiangiogenic factors (soluble fms-like tyrosine kinase-1 and soluble endoglin). Low-dose aspirin, started before 16 week's gestation, will prevent up to 60% of early-onset preeclampsia but will not prevent late-onset preeclampsia. Optimizing prepregnancy weight and controlling gestational weight gain may be the most effective ways to prevent preeclampsia.

Key words: immunology, inositol phosphoglycan P-type, maternal-fetal graft paradox, placental dysfunction, preeclampsia, primipaternity, regulatory T cells

Introduction

Although many theories have been proposed, it is now widely but not universally accepted that syncytiotrophoblast (STB) stress is the fundamental pathway leading to maternal syndrome.[1–3] In early-onset preeclampsia, shallow endovascular trophoblast invasion in the spiral arteries, leading to ischemia or reperfusion and inflammatory injuries, seems to be the most important pathway leading to STB stress.[2–6] In late-onset preeclampsia, the much more common phenotype of the syndrome, STB stress seems to be primarily related to maternal constitutional and lifestyle-related factors, such as cardiometabolic fitness.[7] Many recent studies have demonstrated that imbalances between proangiogenic (vascular endothelial growth factor [VEGF] and placental growth factor [PlGF]) and antiangiogenic(soluble fms-like tyrosine kinase-1 [sFlt-1] and soluble endoglin [sEng]) factors play a pivotal role in the pathophysiology of preeclampsia.[6] The imbalance between these proangiogenic vs antiangiogenic factors is detectable long before the clinically detectable onset of preeclampsia. The sFlt-1-to-PlGF ratio

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measurement is currently used in several countries assisting clinicians in the management of patients with preeclampsia.[6,8,9]

Women at the time of their first pregnancy are 10 to 15 years older than at the start of even the 20th century and mostly had lengthy sexual relationships before conceiving. Currently, late-onset preeclampsia (>34 weeks' gestation) is by far the most commonly encountered phenotype of preeclampsia. Couple-specific immune maladaptation, one of the topics reviewed in this study, plays only a very minimal role in late-onset preeclampsia. In late-onset preeclampsia, the main drivers seem to be increased maternal body mass index (BMI), increased gestational weight gain (GWG), and other clinical characteristics composed of metabolic syndrome and maternal age. The fact that late-onset preeclampsia is by far the most common phenotype led some researchers to conclude that preeclampsia is caused by a "poor" prepregnancy cardiovascular or metabolic status—and indeed for the term phenotype of the syndrome. This special issue has a separate study on these conflicting viewpoints—the placenta "villain or victim"[7] with the ancestral discussion between the seed (trophoblastic implantation) and soil (maternal predispositions to vascular diseases), the cited contradictors even proposing the preceding "soil" to replace the "seed,"[10,11] that is, they argue that it is lack of cardiometabolic fitness that causes the disease.[7]

In our opinion, these viewpoints are not mutually exclusive, so we proposed "the seed and the soil." Research, particularly more than the past 15 to 20 years, has taught us about the heterogeneity of this major obstetrical problem. In this aspect, Redman's papers deserve reevaluation.[2,3] Late, researchers have learned to heed his message. We believe that understanding that immunomaladaptation induces shallow placentation, which is a "seed" of preeclampsia, and metabolic syndrome, such as symptoms during the late pregnancy period, which is a "soil" induce hypertension and proteinuria (Figure). The seed and soil are thought to interact with each other to develop preeclampsia.

We hope this review article improves our understanding of the pathophysiology of preeclampsia.

Preeclampsia—the immune maladaptation hypothesis

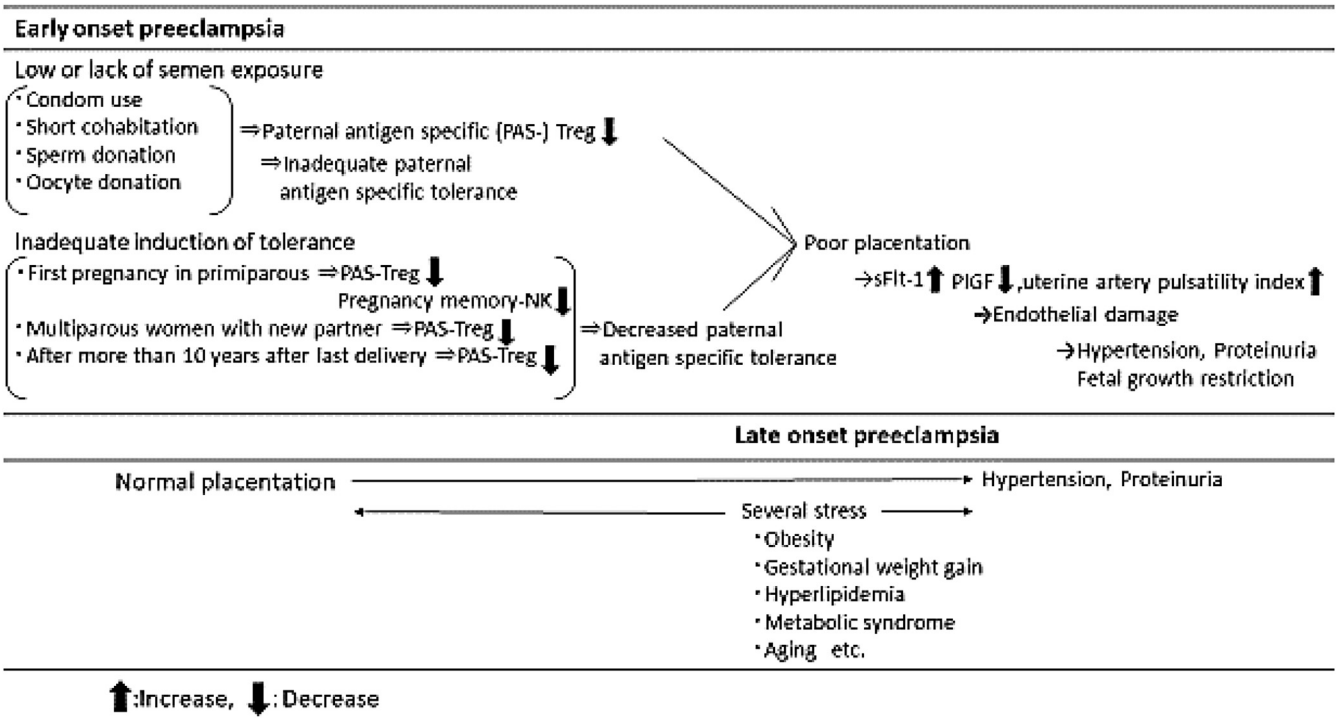
Although many studies are supporting the immune maladaptation hypothesis, there are also epidemiologic studies that question its validity. Nowadays, prepregnancy maternal constitutional factors, particularly obesity, play major roles in the pathophysiological pathways leading to late-onset preeclampsia, by far the most common preeclampsia phenotype. It might be this type of preeclampsia that was primarily studied in the published large Scandinavian and US studies arguing against the immune maladaptation hypothesis.[12]In these studies, the authors showed that the incidence of preeclampsia in multiparous women increased with the number of years since the last delivery; after a birth interval of 10 years, the incidence of preeclampsia in multiparous women was the same as in primigravid women. The authors concluded that in women with a new partner, it was the more prolonged birth interval that explained the increased rate of preeclampsia and not the primipaternity effect, that is, no immune maladaptation. It could well be that these authors studied primarily the term preeclampsia (gestational ages are not provided in these studies). However, more recently, it was demonstrated that the effect of prolonged birth interval on the preeclampsia risk could also be explained by immune maladaptation. Paternal antigen-specific regulatory T (PAS-Treg) cells remain in the body after delivery and have a life span. Therefore, the number of these Treg cells decreases after 10 years from the last pregnancy.[13] Therefore, >10 years after delivery, the risk of developing preeclampsia is equivalent to that of primiparous women, even in multiparous women (Figure).

Immune maladaptation is involved in the causation of shallow trophoblast invasion in the spiral arteries, resulting in placental dysfunction and fetal growth restriction (FGR). Early-onset preeclampsia is typically associated with FGR (Figure). Recognition of the role of immune maladaptation is relevant for the practicing obstetrician as follows:

1. A more prolonged period of sperm exposure provides a partial protection against early-onset preeclampsia. All women with changing partners are strongly advised to use condoms to prevent sexually transmitted diseases. However, a certain period of sperm exposure within a stable relation, when pregnancy is aimed for, is associated with a partial protection against preeclampsia.[14,15]
2. According to the primipaternity concept, a multiparous woman with a new partner should be approached as being a primigravid women.[14,15] All primigravid pregnant women and multiparous women with a new partner should be asked about the length of their sexual relationship with the father of the pregnancy.[16,17]
3. Artificial donor insemination, oocyte donation, and embryo donation are associated with an increased risk of developing pregnancy-induced hypertensive disorders.[16,17]

It should be noted that the role of a "new father" (primipaternity) is associated with not only an excess risk of preeclampsia but also lower infant birthweight. In addition, in this aspect, multiparous women with a new partner behave similarly to primigravid women.[18] It has been observed for 160 years, without proper explanations, that primiparous women gave birth to slightly lighter babies than multiparous women.[18] We have recently shown that when comparing birthweights, primipaternity-multiparous women have 100- to 150-g lighter babies on average than their multiparous counterparts (after adjustment for preeclampsia, smoking, alcohol, and maternal BMI). Considering the human pregnancy as a "maternal-fetal graft paradox," it makes sense to assume that the first establishment of a "couple's symbiosis" might be less successful in first pregnancies. In subsequent pregnancies, the tissue habituation (including some

FIGURE
Pathogenesis of early and late-onset preeclampsia



When there was no or little semen exposure, PAS-Treg cell induction was insufficient, resulting in insufficient immune tolerance to the fetus and poor placentation. In primiparous women, the number of PAS-Treg cells was lower than that in multiparous women and no pregnancy memory NK cells resulting in poor placentation. In multiparous women with a new partner, the risk of poor placentation was increased because of inadequate induction of the new partner's PAS-Treg cells. In multiparous women >10 years after delivery, memory PAS-Treg cells were decreased year by year. Therefore, the risk of preeclampsia in these cases were similar to that in primiparous women. In these cases, serum sFlt-1 was elevated, and PlGF was decreased because of poor placentation. In addition, the pulsatility index levels in the uterine arteries were increased. The combination of these factors resulted in vascular endothelial dysfunction, which led to hypertension, proteinuria, and FGR by 34 weeks' gestation. In contrast, in late-onset preeclampsia, placentation was normal in early pregnancy, but hypertension and proteinuria developed after 34 weeks' gestation because of the addition of stressors that trigger preeclampsia, such as obesity, much gestational weight gain, hyperlipidemia, metabolic syndrome, and aging.

NK cells, natural killer cell; *PAS-Treg cell*, paternal antigen-specific regulatory T-cell; *PlGF*, placental growth factor; *sFlt-1*, soluble fms-like tyrosine kinase-1.

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permanent changes in uterine vasculature) has already been boosted by a first pregnancy.[18,19] In the discussion of the immunology of preeclampsia workshop 2018 paper[20] (Tables 1 and 2), the current authors stated that "with the hemochorial placenta, women would have to face a potentially serious immunologic 'attack' at the fetomaternal interface." To prevent rejection, mammals have acquired an immunologic tolerance mechanism. However, inadequate tolerance can lead to complications, such as preeclampsia and poor placentation-induced FGR (Figure).

The observation of an inverse relationship between the duration of sexual cohabitation and incidence of preeclampsia suggests that long-term sperm exposure may be important for human implantation success[19,20] This makes physiological sense as the human female is one of the few mammals exposed to her partner's semen on multiple occasions before conception. From an evolutionary perspective, it can be argued that induction of PAS tolerance through repeated sperm exposure may have reproductive advantages, perhaps by promoting the implantation and survival of embryos conceived in long-term relationships (Figure). In terms of evolution, the relatively high incidence of preeclampsia represents a reproductive disadvantage in humans compared with other mammals. During all human history, in developing countries nowadays and until the 1950s in developed countries, eclampsia accounted for at least 1% of human births.[20] Robillard et al[20,21] postulated that the existence of the clinical syndrome preeclampsia-eclampsia required mankind to adapt to a tremendous reproductive burden. Considering semiallogenic trophoblastic implantation, we are facing 2 specific human features: (1) preeclampsia or eclampsia is confined to humans and (2) the very deep trophoblastic invasion characteristic of normal human placentation. The

TABLE 1
Summary of major advances in immunology of reproduction these last 3 decades

Major advances in immunology of reproduction	
• Lack of HLA-G in preeclampsia (1990s) • Role of cytokines (Th1 or Th2 paradigm) (1990s) • Immunologic role of seminal fluid (TGF-β) (Tremellen, & S. Robertson (1998) • Pivotal role of NK cells (implantation and angiogenesis) B.A. Croy, A. Moffett, S. Hiby (2000–2004) • Dysregulation of angiogenic factors by complement activation (Girardi et al, 2006) • Role of hyperglycosylated HCG (deepness of implantation) (Cole, 2007) • Immunologic animal model for preeclampsia (Girardi, 2008) • Pivotal role of T Reg cells (Saito, 2010)	Redman and Sargent,[3] 2009

Adapted from Robillard et al.[17] Copy of the original Table with permission of the JRI. All references are found in reference [17].

HCG, human chorionic gonadotropin; *HLA-G*, human leukocyte antigen G; *NK*, natural killer; *TGF-β*, transforming growth factor β.

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The concept that preeclampsia may be an immunologic disorder dates back to the beginning of the 20th century.[22,23] In the early 1950s, Medawar[24] proposed the concept of the "fetus as an allograft." Since then, it has been assumed that implantation of the fetal placenta would be controlled by a maternal immune response mediated by T cells (adaptive immune system) recognizing paternally derived alloantigens expressed by the placenta, although initially missing the importance of the innate immune system. The focus of research in the remainder of the 20th century was focused on the adaptive immune system. The pivotal involvement of the innate immune system in the immunology of reproduction was only recognized at the beginning of the 20th century.

trophoblast normally invades the spiral arteries into the myometrium, with semiallogeneic endovascular trophoblast cells physiologically replacing the maternal endothelial cells in these spiral arteries (hemochorial placenta) and disrupting the vascular smooth muscle layer. This agonistic maternal cell-fetoplacental cell interaction necessitated a high degree of active tolerance toward the semiallogeneic placental tissue, compared with other mammals. Robillard et al[17,20,21] postulated that the major difference between the human fetus and their mammal counterparts is the size of its brain requiring about 60% of total fetal nutritional needs during the extraordinary phase of brain development in the second and third trimester of pregnancy and hypothesized that the large size of the human fetal brain would require the deep endovascular trophoblast invasion, which increases the maternal blood flow to intervillous spaces. According to this hypothesis, such a deep invasion of the trophoblast can only occur on the basis of major immunogenetic compromises in terms of maternal-paternal tissue tolerance (Table 1 and 2).

The innate immune system: the role of natural killer cells

In a landmark study in 2000, Croy et al[25] demonstrated that the natural killer (NK) cells were the key regulators of adequate implantation and the endovascular trophoblast invasion were critically involved in the remodeling of spiral arteries in mice. The mouse findings were later confirmed in humans.[26,27] NK cells represent the predominant population of lymphocytes in the decidua, and T and B cells are rare. NK cells express inhibitory and activatory killer cell immunoglobulinlike

TABLE 2
Biologic puzzle of human reproduction for mammalian zoologists and proposed explanation

Anthropological mysteries on human "extravagant" sexuality disconnected with reproduction (Diamond, 1997)[70,71]	Evolutionary adaptation of human reproduction and "extravagant" sexuality
• Incredibly low fertility rate (20%–25% at the youngest age) • Loss of estrus • Concealed ovulation • No sperm competition at conception • Society, nuclear families, "universality" of marriage • Common parental care (birds and not mammals) • Testis size of human males (too big compared with other primates without sperm competition) • Menopause	• "Necessity" in humans because of big fetal big brain • A deeper trophoblastic implantation (nutritional exchanges ×2 per body size) • Hominids have hemochorial placentas: intimate cohabitation between maternal and paternal (trophoblast) tissues. No physical barrier on the maternal side. Therefore, major immunologic issues of "compatibility tolerance" • Maternal habituation to specific paternal tissues through sperm exposure of (1) big testes and (2) low fertility rate (impregnation) • Loss of estrus (impossible with a 25% fertility rate) • Concealed ovulation: to remain constantly "attractive"

The human "extravagant sexuality" might be an adaptation allowing a safe trophoblastic (very aggressive) implantation. Adapted from Robillard et al.[21]

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receptors (KIR) capable of recognizing human leukocyte antigen (HLA) class I molecules. Uterine NK cells influence both extravillous trophoblast invasion and maternal placental bed vascular remodeling by producing a series of cytokines involved in angiogenesis and vascular stability, such as VEGF, PlGF, and angiopoietin. Moffett-King et al[26] changed our understanding of the importance of the HLA-C−NK cell receptor interaction. HLA-C loci are dimorphic for residues 77 to 80, and these 2 HLA-C groups interact with different NK cell receptors. There is great diversity of NK KIR haplotypes in humans with variations in the number of genes and polymorphisms at individual loci. All women express KIR on decidual NK cells for both groups of HLA-C alleles, and as HLA-C is polymorphic, each pregnancy will involve different combinations of paternally derived fetal HLA-C expressed on extravillous trophoblast and maternal KIRs. Mothers lacking most or all activating KIRs (AA genotype) when the fetus had HLA-C2 genotype, belonging to the HLA-C2 group, are at a substantial risk of preeclampsia.[27]

The main problem in the discovery by Croy et al[25] and Moffett-King et al[26] was that NK cells did not seem to have an immunologic memory like T cells, and the epidemiologic studies indicated that "pregnancy memory" must exist to explain that subsequent pregnancies with the same male partner are protected against preeclampsia. More recently, it was shown that even NK cells may have "memory." Wohl et al[28] demonstrated that decidual NK cells "remember" a first pregnancy. NKG2 is a key molecule that recognizes HLA-E expressed on extravillous trophoblast. NKG2 expression on uterine NK cells is overexpressed in multiparous women. This overexpression is specific to decidual NK cells and independent of age (gestational week). This activation leads to a higher expression of pregnancy supporting factors, such as VEGF-α. Furthermore, these precursors of pregnancy memory NK cells seem to be present in the endometrium, especially "activated" by pregnancy.[28] These reports suggested that NK cells play an important role in placentation, and spiral arterial remodeling but shallow placentation alone cannot cause preeclampsia in mouse[29] and human[30] and cannot explain the epidemiologic risk factors for preeclampsia described previously. For example, pregnancy memory NK cells can explain the successful placentation and reduce the risk of preeclampsia in the next pregnancy with the same partner but cannot explain the increased risk of preeclampsia in the first pregnancy when the partner change in multiparous women.

Although the NKG2 expression reflects NK cell memory of previous pregnancies, this "memory" is not partner specific and thus does not explain the epidemiologic studies supporting the immune maladaptation hypothesis.

The paramount immunologic role of semen for induction of paternal antigen-specific regulatory T cells

Treg cells play a central role in the maintenance of allogenic pregnancy by inducing PAS tolerance.[31−33] Seminal plasma priming induces the PAS-Treg cells.[34,35] PAS-Treg cells clonally proliferate after pregnancy.[36] Indeed, clonally expanded Treg cells, a surrogate marker for PAS-Treg cells, are decreased at decidua basalis of preeclamptic cases but not in miscarriages.[37] Treg cells are a specialized subpopulation of T cells that act to suppress the immune response, thereby maintaining homeostasis and self-tolerance. Sperm exposure does protect against developing preeclampsia.[14,15] Actual partner-specific exposure to the sperm cells seems to be important for that matter. Deposition of semen in the female genital tract provokes a cascade of cellular and molecular events that resemble a classic inflammatory response. Dendric cells (DCs) are antigen-presenting cells, and they present antigens to T cells. The number of DCs increase in the uterus during implantation, promote decidualization and angiogenesis, and are known to be essential for implantation.[38] Seminal plasma priming induces the increased number of immature DCs that induce tolerance in the uterus.[35,39,40] These immature type of DCs flows into the uterus from the lymph nodes or tissues other than the uterus and peaks 3.5 days after mating just before implantation in mice.[39] In contrast, the mature type of DCs moves into uterine draining lymph nodes and is thought to induce the development of PAS-Treg cells.[35] These Treg cells move to the uterus just before the implantation, resulting in successful implantation and establishing the implantation by inducing tolerance to the semiallograft fetus.[37,38] The in vitro study revealed that uterine DCs after mating induce PAS-Treg cells.[35] No such result was obtained for uterine DCs after mating with male mice lacking seminal plasma after seminal vesicle removal.[35] Therefore, exposure to seminal plasma is important in the induction of PAS tolerance. These results can explain the risk of preeclampsia in women with condom use and short cohabitation.[14,15]

The critical seminal factor seems to be seminal vesicle-derived transforming growth factor beta 1 (TGF-β1). Seminal vesicle-derived TGF-β1 is secreted predominantly in a latent form. Seminal plasmin and uterine factors transform the latent form into bioactive TGF-β1.[41] Intrauterine insemination of TGF-β1 in vivo results in an increase in granulocyte-monocyte colony-stimulating factor (GM-CSF) production that is sufficient to initiate an endometrial leukocytosis comparable with that seen following mating.[42] The introduction of TGF-β1 into the uterus in combination with paternal ejaculate antigens favors the growth and survival of the semiallogenic fetus, as evidenced by increases in fetal and placental weights in animal studies, in 2 ways. First, by initiating a postmating inflammatory reaction, TGF-β1 increases the ability for taking the paternal antigens contained within the ejaculate. Second, TGF-β1 and the subsequent postcoital inflammatory response initiate a strong type 2 (Th2) immune deviation and suppress type 1 (Th1) immune deviation that induces fetal rejection. The processing of an antigen by antigen-presenting cells in an environment containing TGF-β1 is likely to initiate a Th2 phenotype within these

TABLE 3
Immunologic tolerance comparisons of the risk factors between preeclampsia and miscarriage

Variable	Preeclampsia		Miscarriage
	Early onset	Late onset	
Impairment of paternal antigens-specific tolerance			
First pregnancy in primigravida	Yes	Weak	No
First pregnancy in multipara cases with new partner	Yes	Weak	No
Impairment of seminal plasma priming			
Use of condoms	Yes	Weak	No
Short cohabitation	Yes	Weak	No
Artificial insemination by donor	Yes	Weak	No
Complete allografted fetus			
Oocyte donation	Yes	Weak	Yes

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responding T cells.[42] By initiating a Th2 immune response toward paternal ejaculate antigens, seminal TGF-β1 may inhibit the induction of Th1 responses against the semiallogenic conceptus that are thought to be associated with poor placental development and fetal growth. Decidual macrophages, present in an immunosuppressive phenotype from the moment of implantation,[43] may inhibit NK cell lytic activity through their release of molecules, such as TGF-β1, interleukin 10 (IL-10), and prostaglandin E2 (PGE2). Under the influence of the local cytokine environment, antigen-presenting cells, such as macrophages and DCs, may take up, process, and present ejaculate paternal antigen to T cells in the draining lymph nodes.[39] In addition, sperm assists in promoting female immune tolerance by eliciting uterine cytokine expression through a toll-like receptor 4–dependent signaling.[44]

The involvement of the balance of regulatory T cells and cytotoxic T cells in preeclampsia

The establishment of pregnancy depends on a balance between the induction of tolerance by Treg cells and immunologic rejection of the fetus by cytotoxic T cells.[31–33] Treg cells play a central role in the induction and maintenance of feto-maternal tolerance.[31–33] Decreased Treg cells are observed in both preeclampsia[32] and miscarriage,[33,45] whereas epidemiologic risk factors are different between preeclampsia and miscarriage (Table 3). Because of 16,000 polymorphisms, the diversity of HLA antigens in humans, identification of PAS-Treg cells and cytotoxic T cells are extremely difficult. Therefore, researchers assumed that Treg cells and cytotoxic T cells that specifically recognize paternal or fetal antigens have the same T-cell receptor repertoire sequence and are clonally increased. Tsuda et al[37] and Morita et al[46] purified Treg cells and cytotoxic T cells into a single cell and analyzed the mRNA expression of T-cell receptors to identify clonal Treg cells and cytotoxic T cells. Treg cell volume was reduced in miscarriage cases with normal fetal karyotypes, whereas clonal Treg cells in the decidua basalis were similar to those in normal pregnancy. Importantly, clonal Treg cells significantly reduced preeclampsia.[37] Assuming that clonal Treg cells are PAS-Treg cells, the result explained that first pregnancy, that is, primigravida or multigravida with a new partner after a short cohabitation period, is at risk of preeclampsia but not miscarriage (Table 3). Clonal decidual cytotoxic T cells increased in the late pregnancy period, but there was no difference in clonal cytotoxic T-cell rates between preeclampsia and normal pregnancies.[46] Immunosuppression-induced molecules, such as programmed cell death-1 (PD-1) and lymphocyte activation gene 3 (LAG-3), which are expressed on cytotoxic T cells, reduce cytotoxic activity and are beneficial in maintaining pregnancy.[47] When the immunosuppressive PD-1 expression rate was examined in clonal cytotoxic T cells, PD-1 was expressed on most cytotoxic T cells in normal pregnancy, but this rate was reduced in preeclampsia.[48] These data suggest that decreased PAS-Treg cells and decreased PD-1 expression on clonal cytotoxic T cells induce fetal rejection in preeclampsia. Indeed, increased cytotoxic T-cell response to paternal antigens is observed in preeclampsia.[49]

PAS-Treg cells increase in second pregnancy with the same partner, but this increase is not second pregnancy with a "new partner" in mice.[36] This explains that a first pregnancy with a new partner is a risk of preeclampsia in humans (Figure).[50,51]

As mentioned above, immunologic maladaptation is deeply involved in the pathogenesis of preeclampsia, but there are still some issues that need to be resolved. Decreasing Treg cell levels in mice increases the susceptibility to preterm birth and leads to FGR without an increase in the uterine artery pulsatility index, which is a hallmark of preeclampsia. Interestingly, these mice did not develop preeclampsia.[52,53] Therefore, it is unclear whether the decrease in PAS-Treg or PD-1 expression on PAS cytotoxic T cells is a direct cause of preeclampsia. However, the trophoblast

invades the uterus much more shallowly in mice than in humans, and the gestational period is only 20 days in mice. Therefore, experimental results in mice cannot be directly applied to human. In addition, as it is difficult to amplify PAS-Treg cells in vitro for the treatment of preeclampsia, agonistic antibodies against PD-1 may be a candidate for the therapy.

T helper (Th) cells play a central role in modulating systemic immune responses. Th cells are classified into Th1 cells, which activate cell mediators by their effective cytokines, such as IL-2 and IFN-Y, and Th2 cells, which induce humoral immunity by their effective cytokines, such as IL-4, IL-5, IL-9, IL-10, IL-13, and IL-25. Th17 cells induce inflammation by IL-17. The balance of Th1, Th2, and Th17 and Treg is important for a successful pregnancy.[48,54] Predominant Th1 and Th17 cell immunities and decreased Treg cells are observed in preeclampsia.[48,54,55] These immune conditions induce excessive inflammation, which may induce endovascular dysfunction resulting in the development of preeclampsia.[56] Treg cells suppress the activation of Th1 and Th17 cells.[48] Therefore, a combination of Th1 and Th17 cells activation and a decrease in Treg cells may be responsible for the development of preeclampsia.

What is the interaction between immunologic alterations and the placental metabolic syndrome in preeclampsia?

Recently, the risk between preeclampsia and metabolic syndrome is becoming clear[57,58] (Figure). In this study, we introduced the role of inositol phosphoglycans (IPGs) in the pathogenesis of preeclampsia. An interaction between an imbalance of circulating angiogenic factors and some second messengers of insulin (ie, IPGs may result in the "placental" insulin resistance occurring in preeclampsia).[56,59] IPGs promote trophic effects of insulin, enhancing protein synthesis, cell growth, differentiation, and cell survival and are derived from the fetal or placental unit.[60] The lipidic form of IPGs, with proinflammatory "endotoxin"-like effects, is transferred from the fetal or placental unit to the maternal circulation by a more permissive placental plasma membrane with a thinner glycocalyx and less tight junctions as a result of immunologic alterations. This lipidic form of IPGs, such as IPG P-type, may contribute to endothelial damage and atherosis.[59] Inflammation and ischemia and reperfusion injuries result in glycocalyx shedding that, along with diminished tight junctions, provide a vector mechanism for the leakage IPGs from the fetal or placental unit into the maternal circulation.[59,61] Furthermore, the possibility for IPGs to be detected in maternal urine during preeclampsia several weeks before the clinical onset of the disease in early- and late-onset types of the disease[62,63] may represent, along with other candidate urinary biomarkers, a valid cheap tool for early diagnosis and screening in particular in low-income countries.[63] Although the sFlt-1-to-PlGF ratio has been used to predict early-onset preeclampsia,[8,9] urinary IPGs are useful in predicting late-onset preeclampsia.

What about prevention of preeclampsia

To date, we have strong evidence that early-onset preeclampsia, the dangerous but relatively rare form of preeclampsia in terms of maternal and fetal morbidities, can be prevented up to 62% of cases by aspirin 150 mg/d when started before 16 weeks' gestation.[64] Taking aspirin from the early pregnancy period may reduce the degree of shallow placentation (ie, a seed of preeclampsia) and prevent the development of the disease. However, what about the far more common problem of late-onset preeclampsia? Although typically associated with a benign perinatal outcome, this entity may be a more important cause of maternal morbidity and mortality than early-onset preeclampsia. Besides calcium supplementation, what can we do to drastically reduce the rate of term preeclampsia?

Here, we would like to propose a potential "new" promising approach. Recently, 2 different teams from 2 different parts of the world (United States and Reunion Island, Indian Ocean)[65,66] have described that late-onset preeclampsia (and much less early-onset preeclampsia) is largely and specifically linearly associated with rising maternal BMI (Figure). Further research is urgently required to properly understand the main drivers and pathways on how cardiometabolic syndrome lead to late-onset preeclampsia.[59] Optimizing prepregnancy weight would probably represent an important primary preventative strategy. Recently, we demonstrated that having a high BMI does not automatically translate into a high risk of term preeclampsia. In a large population cohort study, we demonstrated that patients with obesity could decrease their risks by optimizing their GWG.[67–69] Large randomized control studies are required to evaluate if these observational data can be replicated in a prospective trial.

In summary, our understanding of the pathophysiology of preeclampsia has dramatically improved. Immune maladaptation is involved in the development of early-onset preeclampsia. Low-dose aspirin reduces the risk for early-onset preeclampsia, but not the risk for late-onset preeclampsia. In contrast, obesity and metabolic syndrome are associated with late-onset preeclampsia, but this is not an established method for its prevention. Broad and sustained public education toward healthy prepregnancy weight and possibly subsequently optimizing GWG may have the potential to greatly reduce late-onset preeclampsia. ■

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