

Preeclampsia and the Systemic Inflammatory Response

Christopher W. G. Redman^{*,†} and Ian L. Sargent^{*,†}

Normal pregnancy is associated with a systemic inflammatory response. The response is exacerbated in preeclampsia and can account for its clinical features. Many of the physiologic changes of normal pregnancy are part of an acute-phase reaction, which is generated by an inflammatory response. The placenta is the proximal cause of these problems. There are several possible placental factors that may evoke the inflammatory responses that currently are being investigated. The special susceptibility of obese women, or those with diabetes or chronic hypertension, to preeclampsia is explained by the chronic systemic inflammatory responses that these women have. The clinical implications of these concepts are discussed.

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Inflammatory responses are more primitive than classic immune responses. They are fast, stereotyped, and relatively nonspecific. The adaptive immune system responds more slowly but is more flexible in its ability to generate antigen-specific responses. An inflammatory response is not necessarily stimulated by antigenic stimulation. In the context of pregnancy there is little evidence that the systemic inflammatory responses that are discussed in this article are a form of fetal rejection.

The inflammatory system responds to danger signals,¹ which may be exogenous (from pathogens) or endogenous (from products of trauma, ischemia, necrosis, or oxidative stress). The responses involve inflammatory leukocytes (granulocytes, macrophages, and natural killer lymphocytes) and a cooperating inflammatory network comprising the endothelium, platelets, and humoral components such as complement (Table 1). This review concerns the systemic inflammatory response in pregnancy and preeclampsia. Such generalized responses inevitably involve several parts of the inflammatory network, especially the circulating inflammatory leukocytes and endothelium.

In addition, systemic inflammation has complex effects on metabolism. The complete range of events stimulated by systemic inflammation is called the *acute-phase response*, which

in fact includes both acute and chronic changes. It varies in different situations and comprises alterations in circulating acute-phase proteins with or without fever, anemia, leukocytosis, or metabolic adaptations, especially involving liver and adipose tissue.² Acute-phase proteins are classified as positive, those that increase with systemic inflammation (eg, C-reactive protein [CRP]), or negative, those that decrease (eg, albumin).

Oxidative stress is particularly associated with a systemic inflammatory response.³ It is a disequilibrium between antioxidant defenses and production of reactive oxygen species in favor of the latter. Unrestrained oxidative stress causes cell damage and death through oxidative chain reactions triggered by superoxide anion.

Normal Pregnancy Evokes a Systemic Inflammatory Response

Normal pregnancy evokes a mild systemic inflammatory response. The changes do not imply that pregnant women are in any sense ill. The response, which varies from woman to woman, is wide-ranging and by the third trimester involves inflammatory leukocytes, endothelial activation, the acute-phase response, and metabolic features of systemic inflammation (Table 2). Some of the responses, which are considered to be physiologic adaptations of pregnancy, are in fact components of the acute-phase response such as decreased

*Department of Obstetric Medicine, University of Oxford, Oxford, UK.

†Nuffield Department of Obstetrics and Gynaecology, John Radcliffe Hospital, Oxford, UK.

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Table 1 Components of the Inflammatory or Innate Immune System

Inflammatory leukocytes
Granulocytes
Monocytes
Natural killer lymphocytes
Certain B cells producing natural antibodies
Endothelium
Platelets
Coagulation cascade
Complement system
Cytokines and chemokines
Adipocytes
Hepatocytes

plasma albumin levels⁴ or increased plasma fibrinogen levels.⁵ There are many such examples (summarized by Redman and Sargent⁶). The classic acute-phase reactant, CRP, has not been studied in detail during pregnancy. There is a small increase of circulating CRP, which begins in the first trimester,⁷ when the long-recognized leukocytosis of pregnancy is established.⁸

As pregnancy advances, the systemic inflammatory response strengthens and peaks during the third trimester. The evidence for this concept was strengthened by detailed flow cytometric analyses of circulating inflammatory leukocytes.^{9,10} These changes are associated with increases in circulating inflammatory cytokines in the second half of pregnancy (several reports, for example Vince et al¹¹). In sum, normal pregnancy is a state of mild systemic inflammation, with evidence for an acute-phase reaction and activation of multiple components of the inflammatory network.

The Systemic Inflammatory Response in Normal Pregnancy Is Not a Form of Maternal Immune Rejection of the Fetus

The systemic inflammatory response of pregnancy does not imply that there is alloimmune recognition of the fetus with either antigen-specific tolerance or, conversely, immune rejection.

The major interface between mother and fetus, the large syncytiotrophoblast layer, expresses no known polymorphic major histocompatibility (HLA) antigens. Histocompatibility antigens are the targets for immune rejection that are executed by cytotoxic T cells. However, because the placental hemochorial surface is a syncytium, it is unclear how it could be susceptible to cytolytic attack from single T cells. By nature, this huge unicellular layer would be too large. However, the concept of maternal immune rejection of the foreign fetus persists, despite the lack of a rationale or specific evidence.

The inflammatory immune system can be activated in ways other than by activated antigen-specific T cells. However, it is not yet known how normal pregnancy provokes a mild maternal systemic response. That it arises from the pla-

centa is self-evident. However, it appears to be heralded in the luteal phase of the menstrual cycle even before there is a placenta.²¹

Preeclampsia is Associated With a More Extreme Maternal Systemic Inflammatory Response Than Occurs in Normal Pregnancy

Preeclampsia is recognized as a syndrome, a cluster of features that together define the disorder, among which new hypertension and proteinuria are given prominence. In clinical terms, the disease varies in time of onset, speed of progression, degree to which the mother or fetus or both are endangered, and the pattern of maternal organ involvement. The diversity of these features includes not only the classic pregnancy-induced hypertension and proteinuria, but abnormalities in liver and clotting function and several different forms of crisis other than the classic one of eclampsia. These features arise from the sum of the circulatory disturbances caused by systemic maternal endothelial cell dysfunction or activation,²² which as already stated represents part of the inflammatory response. Subsequent work from many investigators has strengthened the hypothesis. Pathologic alterations in the endothelium can be seen in the kidney as glomerular endotheliosis.²³

The concept of an endothelial disorder recently has been broadened as a result of the work described by Sacks et al⁹ and its interpretation.¹⁰ The contribution of endothelial dysfunction can be viewed in a larger context as part of the inflammatory network. Activated leukocytes will activate endothelium and vice versa.^{24,25} Hence, it is inevitable that, on average, all the markers of inflammation that already are changed in normal pregnancy (see earlier) are affected more

Table 2 The Systemic Inflammatory Response in Normal Pregnancy and Preeclampsia

Inflammatory Marker	Significant Change in Normal Pregnancy Relative to Nonpregnancy	Significant Change in Preeclampsia Relative to Normal Pregnancy
Leukocytosis	(8)	(16)
↑ Leukocyte activation	(9)	(9)
↑ Complement activation	(12)	(17)
↑ Clotting activation	(13)	(18)
↑ Activation of platelets	(14)	(19)
↑ Systemic endothelial activation	(15)	(20)

NOTE. Some of these features are not shown by all women with preeclampsia, which is a variable condition. Numbers in parentheses refers to relevant references.

severely in preeclampsia (Table 2). The inflammatory changes may progress to the point of decompensation, that can account for the different crises of the condition such as eclampsia, HELLP syndrome and so on.

An important rat model of preeclampsia depends on using a classic pro-inflammatory stimulus, namely a single administration of endotoxin to pregnant rats at 14 days. This causes new hypertension and proteinuria, which persists until the end of pregnancy. The same dose has no effect on nonpregnant animals.²⁶

The Continuum Between Normal Pregnancy and Preeclampsia

It is a new concept that the processes generating preeclampsia are an intrinsic part of normal pregnancy and that the systemic inflammatory response of preeclampsia is not a different condition but a more extreme part of the spectrum common to all pregnancies. Preeclampsia develops when the systemic inflammatory process causes maternal systems to decompensate.¹⁰ The disorder is not a separate condition but simply the extreme end of a continuum. This concept has important implications for prediction, screening, studies of genetic susceptibility, and treatment and can explain why preeclampsia is impossible to distinguish clearly in terms of any definition, diagnostic test, or pathologic lesion from normal pregnancy.

Preeclampsia, Oxidative Stress, and Other Metabolic Changes

Preeclampsia is associated with increased markers of oxidative stress in placental tissue. It already has been mentioned that inflammation and oxidative stress are related closely. The oxidative stress of preeclampsia is not localized to the placenta but is disseminated in the maternal circulation²⁷ and is an expected part of the systemic inflammatory response. Just as normal pregnancy is associated with increased circulating markers of oxidative stress, the more intense systemic inflammatory response of preeclampsia is matched by evidence for greater systemic oxidative stress.²⁷ Of great clinical relevance is the fact that antioxidants, including the antioxidant vitamins that have a potential use in preventing preeclampsia,²⁸ also have anti-inflammatory actions.³

There is not agreement about the occurrence in preeclampsia of the other metabolic changes that have been associated with systemic inflammation. There is modest evidence for a more intense acute-phase response, in relation to certain markers (see Redman and Sargent⁶ for a more detailed discussion). Serum CRP levels may be increased but it is difficult to separate the changes caused by preeclampsia from the chronic changes associated with risk features such as obesity.

The Role of the Placenta

It has been long known that the placenta is the cause of preeclampsia.³² An important placental pathology is an in-

sufficient uteroplacental circulation leading to placental hypoxia, oxidative stress, and, in the most severe cases, infarction. The insufficiency arises in part from poor placentation (see article, Abnormal Placentation and the Syndrome of Preeclampsia, by Fisher et al in this issue). There are also separate obstructive lesions of the spiral arteries called *acute atherosclerosis*.³⁴ However, these pathologies are not identified universally in all cases of preeclampsia.

How these placental problems generate the systemic problems of preeclampsia is a major research challenge. What is sought is one or more factors released from the syncytial surface of the placenta into the maternal circulation, which are pro-inflammatory.

A strong candidate is the soluble receptor for vascular endothelial growth factor also known as soluble fms-like tyrosine kinase (sFlt-1), which is produced by the placenta. By its antiangiogenic actions, an excess of sFlt-1 can cause systemic endothelial damage and dysfunction and hence a systemic inflammatory response, as described elsewhere in this issue.

It is possible that syncytiotrophoblasts could synthesize and release excessive amounts of pro-inflammatory cytokines. However, to date the evidence is not convincing.³¹ As an alternative, circulating inflammatory leukocytes may become activated in transit through the intervillous circulation by exposure to oxidized lipids or other factors.³²

The syncytial surface of the placenta, similar to other biological surfaces, renews itself by shedding apoptotic debris and cells.³³ Debris derived from syncytiotrophoblasts can be shown as microparticles in blood from normal pregnant women in the third trimester, which are increased in preeclampsia.³⁴ Trophoblast hypoxia induces apoptosis³⁵ and significantly more apoptosis can be detected in situ in samples taken from the hypoxic placentas of preeclamptic women.³⁶ Other forms of circulating syncytial debris including cytokeratin and soluble fetal DNA also are increased in preeclampsia (summarized by Redman and Sargent³⁷). We have proposed that its clearance comprises the systemic inflammatory stimulus in normal and preeclamptic pregnancies (reviewed by Redman and Sargent³⁷). Syncytial microparticles are directly damaging to endothelium³⁸ and activate neutrophils directly,³⁹ and our preliminary evidence is that they are also directly pro-inflammatory (Sacks et al and Branton et al, unpublished observations).

Shedding of debris from the syncytial surface would be expected to increase in 2 situations. The first is with increased placental size. It is a clinical fact that preeclampsia is predominantly a disorder of the third trimester, when the placenta reaches its greatest size. The placenta grows larger with multiple pregnancies, which also increases the likelihood of preeclampsia. The second situation would be associated with placental oxidative stress, as with the most severe preeclampsia, typically of early onset and associated with intense fetal growth retardation, in which the placentas are usually abnormally small. Here, it must be presumed that there is an alteration in the quality of the inflammatory stimulus generated by the placenta, for example, by an increased content of peroxidized lipids.

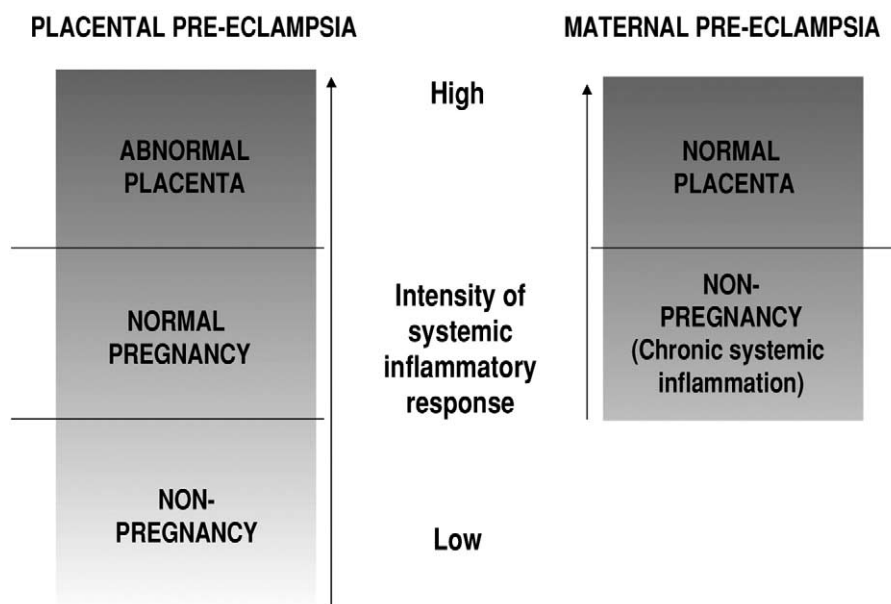


Figure 1 Placental and maternal preeclampsia. A hypothetical gray scale of increasing systemic inflammation is shown. In a completely normal woman, although normal pregnancy stimulates a systemic inflammatory response, it is not intense enough to generate the signs of preeclampsia. To do that requires the abnormal stimulus from an oxidatively stressed placenta (left-hand column: placental preeclampsia). In a woman with a chronic systemic inflammatory response associated with conditions such as chronic hypertension, diabetes, or obesity that predispose to preeclampsia, the starting point is abnormal enough such that even a normal placenta can stimulate a systemic response on an intensity to give the signs of preeclampsia (right-hand column: maternal preeclampsia). In clinical practice there are many mixed presentations, with both maternal constitution and placental ischemia contributing to the presentation.

Maternal Predisposing Factors

Some medical conditions are well known to predispose the patient to preeclampsia including obesity,⁴⁰ diabetes,⁴¹ and chronic hypertension.⁴² Low-grade systemic inflammation is a feature of all these conditions in men or nonpregnant women: obesity,⁴³ diabetes,⁴⁴ or chronic hypertension.⁴⁵ The effect of such medical problems is to increase the baseline of systemic inflammation on which the changes of pregnancy are superimposed (Fig 1). We propose that, in pregnancy, the decompensation from excessive systemic inflammation will happen earlier and at a lower threshold, accounting for the predisposition of affected women to preeclampsia.

Clinical Implications and Conclusions

Pregnancy imposes a substantial systemic inflammatory stress on all pregnant women in the second half of pregnancy. Preeclampsia occurs when this response is increased to the point of decompensation. The continuum between normal pregnancy and preeclampsia, and maternal and placental preeclampsia, are emphasized. The systemic inflammatory response of normal pregnancy generates many features that are considered to be physiologic responses to pregnancy but are best considered as components of an acute-phase response, for example, decreased plasma albumin levels, hypercoagulability, or leukocytosis.

The continuum of inflammatory responses in all pregnant

women approaching full term explains why preeclampsia is such a frustrating condition for clinicians. There is no clear frontier between normality and abnormality. Diagnosis is uncertain in many borderline cases. Indeed, seeking a diagnosis may not be useful because essentially there is not a separate condition to diagnose. Instead, the clinical imperative is to recognize potential or actual danger for the mother. The various signs of the disorder identify rough positions on the spectrum between normality and preeclampsia. These are action points for clinical responses that are needed at each stage according to the perception of danger for the mother. Hence, a definition of preeclampsia is not a fundamental statement about pathology but a critical statement about management milestones.

Chronic systemic inflammation in women who are obese, chronically hypertensive, or diabetic, combined with the added stimulus from that of even a normal pregnancy explains the special susceptibility of these women to the pregnancy disorder. These women can be labeled as having maternal preeclampsia. In this presentation the problem is in the woman not in the pregnancy. Other women have what is best designated as placental preeclampsia, in which the woman is normal but the pregnancy (ie, the ischemic placenta) is not. There are many mixed presentations and it is part of the art of practice to disentangle the 2 contributions as much as is possible.

In placental preeclampsia there is a clinically 'silent' prodromal stage when the uteroplacental circulation fails to develop fully as a result of poor placentation (see article, "Ab-

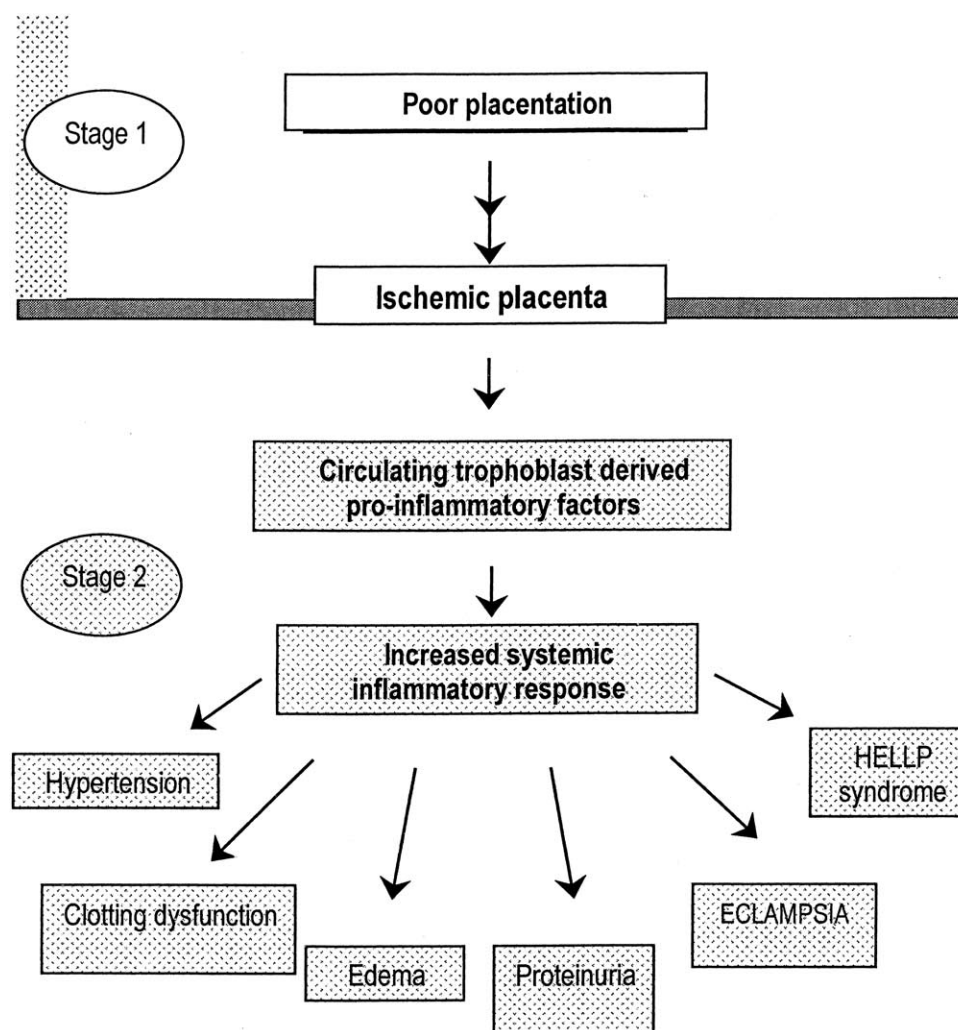


Figure 2 The 2 stage evolution of preeclampsia. Other types of preeclampsia that do not depend on poor placentation but on excessively large placentas or increased maternal susceptibility to the inflammatory stresses of an otherwise normal pregnancy will not depend on the first stage as depicted here.

normal Placentation and the Syndrome of Preeclampsia”, by McMasters et al in this issue and Figure 2). This is a separate condition which may or may not lead to clinical preeclampsia (37). There are also other causes of uteroplacental ischemia (acute atherosclerosis) or of excessive placental inflammatory stimulation. In addition, chronic maternal conditions that cause long-term systemic inflammation may yield the clinical features of preeclampsia in association with a normal pregnancy and placenta.

In conclusion, we have reviewed the evidence for a systemic inflammatory response that characterizes normal pregnancy and the mounting evidence that this is exaggerated in preeclampsia and could be the cause of the maternal illness. How this occurs (eg, by enhanced placental production of sFlt-1, placental microfragments, or other factors) and how an exaggerated systematic inflammatory response of relatively short duration can cause the many features of the disorder, remains to be elucidated in detail.

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