Preeclampsia: A multi-stress disorder
C.W.G. Redman
Nuffield department of obstetrics and gynaecology, John Radcliffe hospital, university of Oxford, OX3 9DU Oxford, United Kingdom

1. Preeclampsia is a complex disease

Preeclampsia affects about 2 to 3% of all pregnancies. It is an important cause of maternal death worldwide, the first cause of iatrogenic prematurity and a leading cause of fetal growth restriction [1]. As many other familial conditions, such as hypertension, obesity or type II diabetes, it is a common complex disease. Despite familial patterns of occurrence, genome wide association scans identify common genes that paradoxically explain only a very small proportion of overall heritability. Interactions with the environment are known to be important. Preeclampsia has the unique feature of maternal interactions with her fetus. There is substantial evidence that paternal genes contribute to the occurrence of preeclampsia in a partner specific way [2], which adds to the complexity of the genetic background to the disease.

2. Preeclampsia is defined as a syndrome

A syndrome is a phenotypic definition with no specific diagnostic attribute. Instead, a cluster of features must occur together to allow the diagnosis to be made. The components of a syndrome are set by consensus; there is no scientific validity. All of the so-called “definitions” of preeclampsia are, ultimately, unsatisfactory attempts to describe what is observed in clinical terms. The features are non-specific and therefore have other potential causes. A syndrome cannot be precisely defined in terms of causation and is not equivalent to a disease with a defined pathogenesis. This lack of precision impedes progress and understanding. Moreover although new discoveries may add to diagnostic discrimination, there is no reason to expect the eventual recognition of a single specific diagnostic feature that will make clinical management simpler [3].

3. Preeclampsia arises from disturbed uteroplacental perfusion

The placenta is a fetal tissue with two circulations: fetal via the umbilical vessels and maternal from about 40 spiral arteries supplied by the uterine arteries. On the maternal side, there is no microcirculation. The spiral arteries open directly into the intervillous space, which is, in effect, a large arteriovenous shunt.

The spiral arteries are extensively remodeled from weeks 8 to 18 of pregnancy such that their distal ends lose their smooth muscle and become widely dilated and unresponsive to vasoconstrictive stimuli. This process, called placentation, modifies the quality but not the quantity of maternal blood flow as it enters the intervillous space to be non-pulsatile and at low pressure. In preeclampsia, the remodeling is incomplete. The ensuing high pressure flow causes hydrostatic damage to the placental villi and perfusion by intermittent pulses of fully oxygenated arterial blood; the latter is presumed to lead to fluctuations in oxygen delivery that predispose to oxidative stress. The placental problem, at least at this stage, is neither hypoxia nor reduced flow but oxidative stress and physical disruption of the placental villous architecture. The maternal syndrome is driven by the ensuing maternal interactions with a compromised placenta. What is seen to be the disease is in fact the maternal response to the placental problems.

4. The two stage model of preeclampsia

The two stage models of preeclampsia are widely accepted (Fig. 1). The first stage, poor placentation, occurs in the first half of pregnancy when there are no clinical features of the disorder. However, at this time Doppler’s analysis of flow velocity waveforms in the uterine arteries detect changes that reflect the downstream spiral artery pathology and identify a group of pregnancies with a high risk of preeclampsia: typically of early onset (<34 weeks) rather than of late onset disease [4]. The second stage, the clinical disease, arises from factors released by the oxidatively stressed placenta (see below).
5. By what mechanism is placentation disturbed in women who get preeclampsia?

The short answer is that nobody knows. But the hypothesis is that it relates to interactions between the maternal immune system in the decidua and paternally derived antigens expressed by the fetus on trophoblast (the placental cell at the fetomaternal frontier). It is proposed that, after implantation, appropriate recognition of trophoblast stimulates decidual immune cells (natural killer and T cells) to release trophic substances (cytokines and growth factors) that promote deep placentation. Decidual NK cells are a rich source of such factors [5]. Failure of such recognition would lead to poor placentation. Partner-specific immunoregulation may even begin preconception by uterine exposure to sperm and seminal fluid which both express the full range of paternal HLA and other antigens (Fig. 1). Such responses have been demonstrated in animal species [6]. These hypothetical early stages of the disease would account for the first pregnancy preponderance of preeclampsia and its association with a short interval between first coitus and conception [7]. It is argued that a brief partnership does not allow immunoregulation to be fully developed so predisposing to poor placentation in the ensuing pregnancy.

6. Poor placentation, placental stress and the integrated stress response

The maladapted spiral arteries that result from poor placentation expose the placenta to hydrostatic and oxidative stresses from utero-perfusion that is both at high pressure and intermittent. Low-level oxidative activity is an intrinsic part of normal inflammatory signaling. But intense oxidative activity overcomes antioxidant defenses, whereupon oxidative stress ensues, which causes biochemical damage within and around cells. Nitrosative stress is a closely related process, extending the biochemical damage by the formation of toxic peroxynitrites. Oxidative stress promotes inflammation in various ways, in some instances: it can activate NF-κB, a transcription factor, central to the inflammatory response and a cellular sensor of stress [8]; secondly, it generates oxidatively modified molecules, which are pro-inflammatory, for example, oxidized low density lipoproteins (LDL). These are thought to contribute to atherosclerosis, an inflammatory process [9]; thirdly it may lead to apoptosis or necrosis. Apoptosis, programmed cell death, is a physiological form of cell death, which arouses a minimal inflammatory response. Necrosis, being pathological, is highly pro-inflammatory.

One purpose of this paper is to highlight the fact that responses to tissue or cellular stresses, placental or systemic in the mother, are not compartmentalized, but tend to occur together as an integrated stress response.

The endoplasmic reticulum (ER) is an intracellular compartment where proteins and lipids are synthesized and calcium is stored. ER stress is the consequence of perturbation of these functions; in particular, it comprises a range of physiological responses that allow homeostasis to be restored [10], which is part of the integrated stress response [11]. The responses include inhibition of most new protein synthesis and, in extreme circumstances, cell death by apoptosis. Because cellular stress responses do not occur in isolation, oxidative stress causes ER stress [12] and conversely ER stress causes oxidative stress [13]. Moreover, oxidative and inflammatory stress is very closely linked. In preeclampsia placentas, abnormal ER stress [14], oxidative and nitrosative stress [15] and inflammatory activation [16] have all been observed. Moreover, apoptosis and necrosis (the end stages of these stresses) are significantly more common features of the preeclampsia placenta [15–17].
10. Normal pregnancy is associated with a systemic inflammatory response

Normal pregnancy evokes a systemic inflammatory response, especially towards the end of the third trimester [3]. This manifests in several ways, summarized previously [26], including activation of monocytes and granulocytes, and of the endothelium. It is associated with evidence of increasing systemic oxidative stress as pregnancy advances in terms of several circulating markers particularly oxidized lipids [26]. In preeclampsia, these changes are more intense.

11. Preeclampsia is not just an endothelial disorder

Circulating markers of oxidative stress are increased in preeclampsia relative to normal pregnancy. In parallel, the inflammatory changes of normal pregnancy are exaggerated. This, of course, involves the endothelium but also other components of the inflammatory network, including inflammatory leukocytes [27]. There is no question that the features of the disease that are clinically most prominent derive from dysfunctional endothelium. But the stress response is wider: there are associated changes such as the acute phase response and metabolic responses triggered by systemic inflammation.

12. Acute phase response

The acute phase response, which also may also be a chronic response, is a variable reaction to inflammation, local or systemic. It comprises changes in circulating plasma protein concentrations and other phenomena such as fever or leukocytosis and metabolic adaptations. Proteins linked to the acute phase response, acute phase proteins, are synthesised in the liver. They are classed as positive, if they increase with systemic inflammation, or as negative, if they decrease. In preeclampsia, many acute phase proteins change as part of an acute phase response. These comprise increases in angiotensinogen, fibrinogen, various other clotting proteins including plasminogen, complement components including C3, alpha-1-antitrypsin, caeruloplasmin, soluble phospholipase A2 and alpha1-acid glycoprotein [28]. Albumin, an example of a negative acute phase reactant, is reduced. However CRP is not a prominent acute phase reactant in preeclampsia.

13. Other metabolic responses

Systemic inflammation has other effects on metabolism, specifically involving central adipose tissue. The pro-inflammatory cytokine, tumour necrosis factor-α (TNF-α), induces insulin resistance, inhibits lipogenesis and stimulates lipolysis [29], which releases free fatty acids (FFAs), of which circulating levels are increased in preeclampsia [30]. Obesity, which is a risk factor for preeclampsia [31], is characterized by a systemic inflammatory response in non-pregnant individuals. Adipose tissue is not simply an energy store but a rich source of pro-inflammatory cytokines and other metabolic mediators (adipokines). Visceral, rather than subcutaneous, fat is more important in this context. Adipocytokines secrete TNF-α, interleukin-6 and plasminogen activator inhibitor-1 and many related factors, and are the principal source of leptin. Leptin is secreted during acute inflammation and has an important action on immune cells, all of which express the leptin receptor. An
inflammatory response is amplified in obese individuals because of the pro-inflammatory output from adipose tissue [32] and this may account for the increased susceptibility of obese pregnant women to preeclampsia.

In summary, the evidence for involvement of the entire systemic inflammatory network in preeclampsia justifies the conclusion that the disorder is more than endothelial dysfunction and comprises oxidative, inflammatory and metabolic stresses.

14. Implications of these concepts for clinical care

Preeclampsia is probably the most common cause of secondary hypertension in clinical practice. The wide range of clinical and laboratory features can all be traced back to a systemic inflammatory response caused by the placenta. There are maternal and placental components in the maternal syndrome. Even a normal pregnancy imposes an inflammatory stress on a mother; if she has an underlying predisposition such as chronic hypertension, obesity, type II diabetes or metabolic syndrome, even a relatively normal pregnancy may cause a maternal syndrome in a highly susceptible individual.

Since the origins of the disorder lie in immune events starting prepregnancy or in very early pregnancy, it is unlikely that measures, (antihypertensive, antiplatelet or antioxidant therapies) aimed at suppressing maternal responses to the inflammatory pressures of a placenta, will effectively prevent the onset of the condition. For the moment, only a well-timed delivery, with removal of the causative condition, is guaranteed to curtail the condition.

Disclosure of interest

The author declares he has no conflicts of interest concerning this article.

References