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Review

Pre-eclampsia: Definitions, paternal contributions and a four stage model

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ABSTRACT

It is 40 years since I started researching pre-eclampsia. Much has changed but some old problems persist. These include the debate of how to define a syndrome, the inheritance and genetics of pre-eclampsia, why primiparae are so susceptible and is primipaternity important? If it is, in a multiparous pregnancy (after changing partners), the old hypothesis that pre-eclampsia is the outcome of failed maternal immunoregulation to accommodate nature's transplant – the fetus – must be confronted. These points are briefly reviewed and a four stage model of pre-eclampsia derived.

1. Introduction

These are exciting times for pre-eclampsia research. Never have there been so many new insights into pathogenesis, or possibilities for better diagnosis or prediction. This issue gives a taste of the great progress that is being made. The contributors all gave presentations at the 2009 meeting in Oxford of the European ISSHP, which celebrated the advances that they are currently making.

It is difficult to envisage from the view point of 2009–10, how much has changed since 1970, when I first began to research pre-eclampsia. Enormous progress in understanding cell biology, genetics and molecular biology has transformed the potential for progress. In 1970, cytokines had yet to be discovered. There were no monoclonal antibodies; nor was there flow cytometry. ELISA measurements and immunoassays for prostaglandins were just becoming available. Powerful techniques such as genomic, proteomic and metabolomic analysis (industrial in their scope and ability to generate discovery) were as unimaginable then as they are routine now. Genetic modification of experimental animals was not possible.

Despite accelerating progress, some very basic problems remain. In this short introduction three will be briefly discussed: the definition of pre-eclampsia, its heritability, and why primiparae are especially susceptible to pre-eclampsia. The staging of pre-eclampsia is described and a four stage model proposed.

2. Defining pre-eclampsia

Pre-eclampsia is a syndrome, in effect recognized as a phenotype. A syndrome is defined by consensus, not by insight into pathogenesis. Hence there is no gold standard. There is no absolute way of deciding if one definition is better than another. It depends on the use, to which it is to be put. Clinicians want definitions that highlight the need for intervention. They should be simple, useable by relatively inexperienced personnel and not costly to implement. Researchers want consistency so that studies can be compared. This has led to two types of definition for such different purposes. Clinical definitions may be broader, for example that of the Australasian Society for the Study of Hypertension in Pregnancy [1]. Pre-eclampsia is defined as gestational hypertension combined with onset of maternal renal, hepatic, haematological or neurological dysfunction or of fetal growth restriction. This brings together cases with a common need for increased clinical vigilance but not necessarily with the same condition. Laboratory and related clinical research seeks to be more precise and, with exceptions, applies the more conventional criterion of new hypertension and proteinuria that resolves after delivery, purportedly features of the pregnancy not of the woman. Precision is sought by strict application of

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the criteria. But there are uncertainties that may not be acknowledged and undermine such efforts. Blood pressure measurements have large sampling and measurement errors. Urine dipstick assessments are notoriously imprecise, subjective and influenced by variable dilution of the urine. Urinary protein loss may fluctuate in the short term (hour by hour) in pre-eclampsia, which is not typical of proteinuria of other renal conditions [2]. Quantification by protein–creatinine ratios is better than nothing but not as exact as it may seem. Cases may be missed simply because enough readings are not recorded. A further issue is that the development of pre-eclampsia may be censored by spontaneous or induced delivery. Pregnancies are often ended by induced delivery near term for gestational hypertension. A recent trial suggests that this is beneficial [3]. Without intervention an unknown proportion of such women would progress to pre-eclampsia, which otherwise would not be revealed. Spontaneous labour may have the same effect: progression to pre-eclampsia may be censored by the natural ending of pregnancy. This is especially true of spontaneous preterm labour where the impact of censorship is potentially greater.

Better definitions are not easy to envisage. Progress will probably be made if subtypes of pre-eclampsia are discriminated such as early and late onset disease [4], or placental and maternal pre-eclampsia [5]. It is possible that the HELLP syndrome, at least in its most florid form, is another subtype. On the other hand, poor placentation, which has the advantage of possible tissue diagnosis, includes some forms of fetal growth restriction without hypertension [6]. The next ten years may see three or four new definitions emerge that are more specific and replace the present unsatisfactory phenotype which has dominated the subject for more than the last 50 years. This development is long overdue.

3. Genes and familial aspects

Another continuing question concerns the familial nature of pre-eclampsia, which has been known for many years. That identical twins have discordant histories more often than not [7] points to a complex genetic disorder. This is consistent with the fact that the search for relevant pre-eclampsia genes has been perhaps less rewarding than anticipated. Such is the experience of genome wide studies of many other common complex conditions, such as obesity [8]. The genetics of pre-eclampsia are likely to be even more complicated because two genetically disparate individuals, mother and fetus, are involved. There is good evidence that paternal genes, expressed by the fetus, contribute to the occurrence of pre-eclampsia, which raises the intriguing question of how a mother accommodates immunologically to her fetus, an unresolved issue for nearly 60 years. In pre-eclampsia the relevant clinical observations have been of the added risks conferred by primiparity and primipaternity.

4. Primiparity and primipaternity

It is well known that primiparity is a risk factor for pre-eclampsia. The issue of primipaternity was first suggested by Need [9] and Feeney and Scott [10], in studies that suggested that changing partners increased susceptibility to pre-eclampsia in multiparous women. But the association has subsequently been discounted by showing that it is better explained by the confounding of a long inter-pregnancy interval, which appears to reduce the protection that a previous pregnancy confers [11]. Nevertheless, primipaternity has been shown to be important in relation to a completely different time course, namely that of a short interval between first coitus and conception by a specific partner [12]. In this context primipaternity in multiparous women becomes important: it suggests that sperm or semen induce immunoregulatory responses that are advantageous for a later pregnancy by the same partner. In mice, seminal plasma (more than sperm) is pro-inflammatory and primes the maternal immune system to partner-specific antigens; pre-conceptual exposure to seminal fluid also appears to improve reproductive importance in certain animal species [13,14]. Seminal fluid induces maternal regulatory T cells in local draining lymph nodes [15], which inhibit inappropriate cell- and antibody-mediated responses. Without such cells, out-bred (but not syngeneic) murine pregnancies fail [16]. Although their relevance to human pregnancy is less well defined it is known that, in human pregnancy, they are induced by an HLA-C mismatch between mother and fetus as are T suppressor cells [17,18]. Such observations suggest that regulatory T cells are a crucial part of maternal adaptation to the 'fetal transplant' and rationalise the apparent benefit of pre-conceptual exposure to paternal antigens by coitus.

These mechanisms depend on classical T-cell functions. But the most abundant decidual immune cells are natural killer (NK), which are in direct contact with invasive, extra-villous cytotrophoblast (evCT). evCT express Human Leukocyte Antigens (HLA)-C, -E and -G, whereas syncytiotrophoblast, in contact with maternal blood, is immunologically bland, devoid of all HLA [19]. Of these, only HLA-C is polymorphic [20] and signals fetal paternity to the mother. What is fascinating is the complexity of the HLA-C receptors that are expressed by decidual NK cells, especially the KIR (killer immunoglobulin-like receptors), which will interact with paternal HLA-C on evCT. KIR genes are as polymorphic as, or even more polymorphic than, HLA genes. The potential interactions between HLA-C2 (extra-villous cytotrophoblast) and KIR (decidual NK cells) and the patterns observed in reproductive failure including pre-eclampsia indicate that pregnancies where the father has endowed the fetus with group-2 HLA-C are particularly at risk [21]. This relationship indicates how different fathers could bring varying risks to conceptions with the same mother.

The protective effect of a previous pregnancy might result from immunological 'memory'' a property previously associated with T and B cell functions but not NK cells. That fetal specific regulatory T cells are generated in HLA-C incompatible pregnancies could explain the apparent paternal specific protection gained from previous pregnancies by the same partner. The issue is not this simple because, as far as it is understood, the protection given by a previous pregnancy is partner specific, whereas maternal immune exposure to the fetus is haplotype specific, meaning that the maternal immune system is exposed

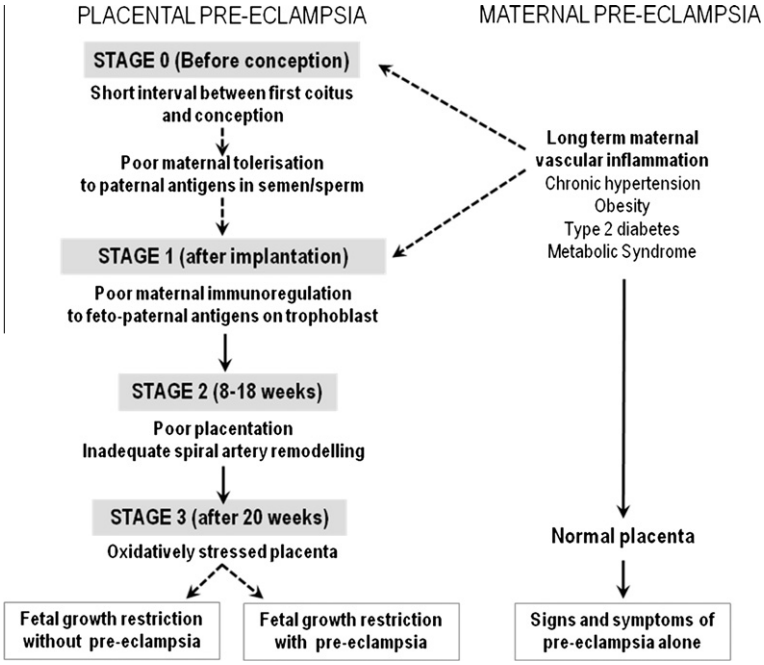

Figure 1. Placental pre-eclampsia is secondary to poor placentation which may have its origins in poor maternal tolerisation to paternal antigens expressed on trophoblast. The end stage is a dysfunctional placenta which causes varying degrees of fetal growth restriction (FGR). Note also that FGR can occur without a maternal syndrome. Maternal pre-eclampsia arises in women who have long term vascular inflammation secondary to various maternal conditions. The inflammatory burden of a normal placenta may be enough to cause signs of pre-eclampsia in the mother. Note that stage 0 may not always be present. Mixtures of placental and maternal factors are possible and when fully developed may account for some of the most serious cases of early onset disease. Stages 0 and 1 are as yet hypothetical, being based on circumstantial evidence only. Dotted arrows indicate pathways that may not be activated in all cases.

(and presumably tolerised) to only one half of the paternal genotype, as it is expressed in the placenta. In contrast, exposure to seminal antigens could give a broader exposure to feto-paternal antigens involving the whole paternal genotype. Protection from pre-eclampsia appears to be fully developed after one pregnancy rather than several pregnancies. This would be more consistent with broader rather than haplotype tolerisation.

In addition, current thinking has changed and it is now considered that NK cells may be able to retain memory; for example they can generate sustained immunity to cytomegalovirus [22]. Whether the decidual NK cells are reprogrammed by their exposure to foreign (fetal) HLA is not known. Nor is it known how these immune mechanisms contribute, if at all, to the protection from pre-eclampsia that women gain from a previous pregnancy by the same partner.

5. Two, three or four stage model for pre-eclampsia

The two stage model of the evolution of pre-eclampsia [23] now underpins much pre-eclampsia research. The clinical disorder is perceived as the end stage of an early failure of placentation and adaptation of the spiral arteries supplying maternal blood to the intervillous space. More recently Jauniaux et al. [24] suggested a three stage model, of which the first is inappropriate maternal immune adaptation to the fetus. Immune responsiveness to the fetus probably begins immediately after implantation. Decidual NK cells have already accumulated during the luteal phase of the preceding menstrual cycle and T cell reactivity is likely to be present at this time. Hence immunoregulation is probably activated very early in pregnancy. But even earlier, as already mentioned, pre-conceptual coitus and exposure to paternal seminal fluid and sperm may tolerise the mother to potential paternal antigens that his offspring will express. So, we recently have extended the model (Fig. 1) to four stages by including a pre-conceptual stage [25]. This is hypothetical at the moment since it is based on circumstantial rather than direct evidence. Roberts and Hubel [26] have pointed out that not all the stages are essential, for example some women with very high susceptibility, owing to underlying vascular inflammation, may develop the syndrome by entering the final stage directly (maternal pre-eclampsia). Poor placentation may cause fetal growth restriction without pre-eclampsia [5], so the earlier stages are not inevitably linked to the final stage. The pre-conceptual stage will only apply in those pregnancies with a short interval between first coitus and conception by the same partner.

6. Conclusion

We predicted in 1999 [27] that a single cause will not be found for pre-eclampsia or a single gene and it will be unlikely that a single screening test will efficiently predict

pre-eclampsia. Yet further, a single treatment or prophylactic measure is unlikely ever to be completely effective on its own. To date, no new discovery has altered this prediction. This does not mean that important progress has not been made and will continue to be made. Pre-eclampsia undoubtedly will come under greater control in due course but step by step, rather than by a dramatic coup. There are many challenges to keep pre-eclampsia researchers enthralled for the foreseeable future.

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