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DEBATE

Pre-eclampsia

Why pre-eclampsia?

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Genetic conflicts in pregnancy

In a recent paper, Haig (1993) applied the evolutionary theory of parent–offspring conflict (Trivers, 1974), to the fetal–maternal relationship. Basic to this view is the recognition that the interests of the genes of the mother do not necessarily agree with the interests of the genes of the offspring, as the genes active in the fetus, essentially a combination of 'own' (maternal) and 'strange' (paternal) genes, will be selected to promote anything that is necessary to serve their fetus' development, whilst the genes active in the mother will be selected to guard the interests of the mother. Hence, according to Haig, any fetal–maternal relationship is characterized by 'genetic conflict'.

To prevent 'escalation' of this conflict, the mother and the fetus should interact adequately, that is, they should send adequate signals to each other and respond accordingly. This, however, clearly does not always proceed impeccably, as there are various conditions in which there is obviously no optimal tuning between the maternal and fetal interests. One of these conditions is pre-eclampsia, a principle cause of maternal mortality and of iatrogenic pre-term delivery, which may contribute to neonatal deaths from immaturity (MacGillivray, 1983). As the signs of pre-eclampsia generally disappear quickly once pregnancy is terminated (Redman, 1991), pre-eclampsia can be regarded as an inadequate response of the mother to the presence of her conceptus. This raises various questions, to be discussed in this paper, the most relevant ones being: (i) to what is the mother responding?; (ii) what is the nature of this response?; and (iii) why is this type of response so common in the human?

Pre-eclampsia

Pre-eclampsia is a disease which in the Western world affects ~6% of all pregnancies (though preferably first pregnancies; MacGillivray, 1958). It is clinically defined by hypertension and proteinuria (Redman and Jefferies, 1988), but the disease may also be associated with abnormalities of the central nervous system and the blood (Redman, 1990), as well as with disseminated intravascular coagulation (DIC) (Bonnar *et al.*, 1971). DIC may result in renal lesions which may eventually cause renal failure (Easterling and Benedetti, 1989). Also the liver may be affected (Steegers *et al.*, 1995); in a special group of pre-eclamptic patients, abnormal liver function is associated with haemolysis and thrombocytopenia (HELLP syndrome; Tomsen, 1995).

In pre-eclamptic pregnancies, the fetus may suffer from insufficient transfer of gasses and nutrients and exhibit growth retardation (Heyborne *et al.*, 1992), because in such pregnancies there is generally a poor placental circulation, due to defective invasion by the trophoblast of the uterine spiral arteries (Gerretsen *et al.*, 1981), or to atherotic changes in these vessels (Redman, 1991). Accordingly, hypertension in pre-eclampsia has been interpreted as the result of the fetus' attempt to increase the placental perfusion in order to improve its condition (Haig, 1993). Other symptoms of pre-eclampsia, however, are not so easily interpreted as being in the interest of one of the parties, as most of them are detrimental to both.

Aetiology of pre-eclampsia

Not much is known about the aetiology of pre-eclampsia. Hence, the question, asked above, to what factor(s) pre-eclampsia is the response, can not unequivocally be answered. The current, generally accepted concept regarding the cause of pre-eclampsia is that the disease is due to endothelial cell dysfunction (Rodgers *et al.*, 1988; Roberts *et al.*, 1989; Rappaport *et al.*, 1990; Burrows *et al.*, 1994); this endothelial cell dysfunction is both apparent from morphological parameters, e.g. endotheliosis and ultrastructural changes in placenta bed and uterine boundary vessels (Shanklin and Sibai, 1989; Roberts *et al.*, 1990) and biochemical parameters, e.g. a disturbance of the prostacyclin/thromboxane A_2 balance (Roberts *et al.*, 1989), increased levels of factor VIII-related antigen (Fournie *et al.*, 1981), aberrations in endothelin and elastase (Greer *et al.*, 1991) and inhibition of vascular relaxation (Gryglewski *et al.*, 1986). This, however, raises the question how this endothelial cell dysfunction is brought about. Some authors claim that sera of pre-eclamptic patients contain factors cytotoxic to endothelial cells (Musci *et al.*, 1988; Rodgers *et al.*, 1988; Roberts *et al.*, 1989); other authors suggest that pre-eclampsia is the maternal response to a pathogenic factor of trophoblastic origin (Smarason *et al.*, 1993).

However, this type of suggestion shifts the problem, as it may be asked why in one pregnancy there are cytotoxic or pathogenic trophoblastic factors circulating in the blood, while in other pregnancies there are no such factors. Moreover, these hypotheses do not explain the fact that pre-eclampsia notably affects the first pregnancies of a woman with her partner (Need, 1975); nor do they explain the observation that pre-eclampsia is more frequent in molar pregnancies (Page, 1939), in which the 'conceptus' contains paternal genes only (Kajii and Ohama, 1977), and in triploid-13 pregnancies (Feinberg *et al.*, 1991; Tuohy and James, 1992). Also, it should be explained why more male than female fetuses are involved in pre-eclamptic pregnancies (James,

1987) or why pre-eclampsia seems to be more frequent in pregnancies in which the conceptus is entirely 'strange' to the mother due to oocyte donation (Pados *et al.*, 1994). A similar problem presents with respect to the observation that also familial factors are implicated in the aetiology of pre-eclampsia (Adams and Finlayson, 1961; Symonds, 1986) and that there seems to be an environmental component in the genesis of pre-eclampsia as well, as the incidence of pre-eclampsia is higher in urban areas (Zemel *et al.*, 1990). Finally, it remains to be explained why pre-eclampsia is over-represented in women with a recent history of urinary tract infection (Hill *et al.*, 1986).

Pre-eclampsia as a disease involving non-specific host defence

Various authors drew attention to the possible role of the cytokine, tumour necrosis factor-α (TNFα), in the pathogenesis of pre-eclampsia (Stark, 1993; Inoue *et al.*, 1994; Todt *et al.*, 1996). Indeed, many of the features of pre-eclampsia might result from the actions of TNFα, a potent activator of endothelium (Munro *et al.*, 1991), of which the plasma concentrations are, on average, elevated in pre-eclampsia (Vince *et al.*, 1995). Also, there is evidence that the endothelial damage underlying the disease, is caused by oxygen-free radicals (Dekker and Kraayenbrink, 1991; Stark, 1993; Many *et al.*, 1996). These toxic oxygen products may be produced by activated leukocytes (Harlan, 1987; Lyall *et al.*, 1994; Faas *et al.*, 1995).

In addition, it has been demonstrated recently that in pregnant rats (and only in pregnant rats) a pre-eclampsia-like disease can be induced when (on day 14 of pregnancy) the animals are treated with a very low dose (0.2 μg, i.e. one-tenth of the ED_{50} for termination of pregnancy) of the potent pro-inflammatory, TNFα-inducing (Cybulski *et al.*, 1988) agent, endotoxin (Faas *et al.*, 1994a). Not only did endotoxin-treated pregnant animals exhibit the classical signs of pre-eclampsia until the end of pregnancy (day 21), including hypertension, proteinuria and DIC (endotoxin-induced DIC, it had been demonstrated previously, was probably caused by inactivation by oxygen-free radicals of the anti-thrombotic ecto-enzyme ADP-ase (Poelstra *et al.*, 1990), which is present in both the glomerular basement membrane of the kidney (Visscher *et al.*, 1993) and in the placenta (Bakker *et al.*, 1992); the animals also exhibited an inflammatory response, characterized by influx of activated (i.e. oxygen-free radicals producing) polymorphonuclear leukocytes and macrophages into various organs, including the kidneys; this influx of inflammatory cells lasted until parturition (Faas *et al.*, 1995).

Moreover, treatment of diseased pregnant rats with the anti-inflammatory drug, aspirin, attenuated the clinical signs of the disease as well as the inflammatory response of the glomeruli of the kidneys (Faas *et al.*, 1994b, 1997); the oxygen-free radical scavenger, superoxide dismutase, had a similar effect (Faas, 1995). Together, these data suggest that in the rat there is a causal relationship between the endotoxin-induced, pregnancy-specific persistent inflammatory response and the clinical signs of the pre-eclampsia-like disease; that oxygen-free radicals play an important role in the genesis of the syndrome and that in the pregnant condition, even a relatively weak pro-inflammatory stimulus may elicit a strong, persisting inflammatory response.

On the basis of the above evidence, we propose (and this may be the answer to the second question) that like the endotoxin-induced pre-eclampsia-like disease of the rat, human pre-eclampsia, too, should probably be regarded as a pregnancy-specific inflammatory response (Faas *et al.*, 1995a,b). This is not to suggest that pre-eclampsia is caused by endotoxin, although the observation that expression of the endotoxin receptor, CD-14, on granulocytes and monocytes is significantly increased in normally pregnant women compared to non-pregnant controls (C.W.G.Redman, personal communication) is remarkable, and may explain the association between pre-eclampsia and urinary tract infection.

Be that as it may, the question arises why pregnant individuals are so sensitive to pro-inflammatory stimuli, including the omnipresent endotoxin, and why the inflammatory response, once evoked in the pregnant individual, is so violent, persistent and life-threatening to both mother and child. It is likely that the phenomenon, dangerous though it potentially is, serves an important biological aim. In this view, pre-eclampsia must be regarded as the pathological variant of a physiological process which is associated with reproduction. The fact that this pathological variant, pre-eclampsia, seems to be restricted to primates [pre-eclampsia has also been observed in the patas monkey (Palmer *et al.*, 1979) and the lowland gorilla (Baird, 1981)], while, as far as we know, not affecting pregnant females of other orders, might suggest that the increased sensitivity of pregnant individuals to pro-inflammatory stimuli has a particular significance for the reproductive strategy of primates and therefore of humans. This may provide an answer to the third question.

Pre-eclampsia as a consequence of the human reproductive strategy

Longer than in any other species, the human child makes its presence felt as it needs its parents' (and the groups to which it belongs) care for many years, before it is able to look after itself. In addition, the next child is already born before the previous one is independent of parental care. This implies that humans should be able to effectively control both the quantity and the quality of their offspring. Indeed, humans are so-called 'K-breeders', i.e. their reproductive strategy aims to produce a limited number of young in which the parents do much investment (Stearns, 1976).

The need to limit the number of offspring, however, seems to conflict with the human reproductive potential, because the human female is a fertile individual (ovulation each month; continuous willingness to mate), and so is the male. However, in the course of evolution, mechanisms have evolved by which limitation of the number of offspring could be achieved. First, women may practise fertility control by prolonged breast feeding (Howie and McNeilly, 1982). Furthermore, there is a very significant post-implantation pregnancy loss rate, which has been estimated by Miller *et al.* (1980) to be at least 43% and by Roberts and Lowe (1975) to be even higher (78%). Also the decreasing fertility of women from the age of ~35 years onward (Gindoff and Jewelewicz, 1986; Meldrum, 1993), and the defin-

itive end of fertility at about 50 years (menopause) contributes to the limitation of the number of offspring and enables the woman to invest more in fewer young (Williams, 1957; Rogers, 1993).

The need for a small number of 'high-quality offspring', however, raises a serious problem, as the human species appears to have evident problems with producing 'high-quality zygotes': according to Hertig *et al.* (1952) and Edwards (1986) more than half the (fertilized) eggs are abnormal. Although this may be one of the adaptations to reduce fertility, it can only be functional if this is accompanied by a very sophisticated mechanism for adequate selection and elimination of zygotes which are less fit. That in the human species such a mechanism apparently operates is illustrated by the fact that in spite of the many abnormal zygotes, the vast majority of the children that are born, are normal in every respect. Post-implantation pregnancy loss, therefore, may be part of the human reproductive strategy and be the necessary consequence of adequate selection and subsequent elimination of unfit zygotes.

This may present the clue to pre-eclampsia; elimination of the majority of zygotes occurs at or shortly after implantation (Roberts and Lowe, 1975; Miller *et al.*, 1980). In various species (mice, horses) it has been observed that implantation is associated with a local influx of inflammatory and immune-competent cells (Enders and Liu, 1991; Robertson *et al.*, 1992; Seamark *et al.*, 1992; McMaster *et al.*, 1993) which are capable of producing a variety of cytokines, including TNFα (e.g. Cybulski *et al.*, 1988; Jokhi *et al.*, 1994). The production of cytokines in association with implantation is a physiological phenomenon. Implantation, however, demands acurately tuned co-operation between the endometrium and the blastocyst and depends on an adequate balance within a complex cytokine network (Hill, 1992; Salomonsen, 1992; Chard, 1995; Edwards, 1995; Vinatier and Monnier, 1995). Thus, it has been demonstrated that some cytokines, e.g. leukemia inhibitory factor (Chaouat *et al.*, 1995; Polan *et al.*, 1995; Cullinan *et al.*, 1996), interleukin (IL)-1 (Simón *et al.*, 1995; Psychoyos *et al.*, 1995) and IL-10 (Krishnan *et al.*, 1996) promote implantation, while other cytokines, e.g. interferon (IFN)-γ, IL-10 and TNFα can cause fetal loss (Inoue *et al.*, 1994; Krishnan *et al.*, 1996; Todt *et al.*, 1996). It is in the interest of the fetus to regulate the cytokine network in such a way that it (the fetus) is not directly attacked; to this end the fetus also redirects the maternal immunity away from cell-mediated immunity towards enhanced humoral responsiveness (Wegmann *et al.*, 1993).

It may be suggested here that only healthy zygotes are able to regulate the local inflammatory response so that they are not harmed by it. There may, however, be zygotes which are less successful in this respect, e.g. zygotes with evident chromosomal abnormalities, or zygotes which, for some other reason, are 'too strange'. Also, there may be circumstances which by themselves may have nothing to do with the fetus, e.g. a recent urinary tract infection, lack of anti-oxidant capacity (vitamin E and C?) or certain environmental conditions in which the mother finds herself, which break the delicate balance between the various cytokines, rendering the inflammatory response more violent than it should be. In those circumstances there may be an unintended attack on the fetus, without, however, necessarily causing its elimination.

In those cases in which the conceptus is subjected to a non-fatal inflammatory attack, the blastocyst will implant, though probably in a defective manner, as elevated levels of TNFα, produced by inflammatory cells, interfere with implantation (Inoue *et al.*, 1994; Todt *et al.*, 1996). This defective implantation will further affect the conceptus' ability to regulate the mothers' host defence response. The mother, then, remains pregnant and will be subjected to an increasingly more violent, non-adequately regulated inflammatory response and be exposed to the products of her own activated inflammatory cells, including oxygen-free radicals, and possibly also to products, shed into the circulation by the placenta. The inflammatory response will not stop, unless pregnancy is terminated. Activated inflammatory cells will circulate in the mother and in the placenta, damaging the endothelium and the sub-endothelial matrix, detoriating the functions of the kidneys, the liver, the lungs, the brain and also of the placenta. Eventually, the mother will develop the clinical signs of pre-eclampsia.

Conclusions

We propose that pre-eclampsia is the consequence of an unsuccessful attack of the maternal non-specific host-defence on the implanting conceptus. The result of this attack is not elimination of the conceptus, but defective implantation and a lasting arousal of the maternal inflammatory response. As pregnancy proceeds, the fetus will need increasingly more oxygen and nutrients; however, there is impaired perfusion of the placenta, and the fetus will be in ever greater distress. As a result, the fetus will send increasingly stronger signals to the mother; this may not only lead to an increase in maternal blood pressure (Haig, 1993), but also to a further dysregulation of the inflammatory response of the mother. In serious forms of pre-eclampsia, this may ultimately result in both a critical condition of the fetus, and in extensive damage of the maternal endothelium, leading to severe dysfunction of various maternal organs such as the kidneys, the liver and, in the case of eclampsia, the brain.

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From birds and bees to babies? Can theories on genetic conflict aid the clinician?

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One of the more seemingly perverse examples of parental behaviour occurs in a bird species known as the white-fronted bee-eater. In this species, older males actively disrupt the breeding attempts of their sons who may subsequently become helpers at the nest of the harassing father (Emlen and Wrege, 1992). Among many social insects such as honeybees, specialized female worker castes have abandoned reproduction in order to help their mothers' reproductive efforts (Hamilton, 1964; Dawkins, 1989). Under certain adverse conditions a human fetus may launch a high risk and potentially lethal biochemical assault on its mother, in order to maximize its chances of survival to term (Haig, 1993; Schuiling *et al*., 1997). The diversity of behavioural interactions between parents and offspring of non-viviparous species, such as birds and bees, is paralleled (if not amplified) in the maternal–fetal interactions underlying mammalian pregnancy. According to Haig (1993), much of the biochemistry, physiology and pathology associated with human pregnancy can productively be interpreted in the light of an evolutionary theory that he has nominated the 'genetic conflict' theory of pregnancy. If this theory is accepted as being correct then, given its breadth, it may be expected to radically alter our perception of the maternal–fetal relationship at all levels of analysis and should, by extension, contribute to the understanding and treatment of pregnancy-associated pathology. The question that we wish to address in this article is to what extent such benefits are likely to accrue. But first:

Is the theory correct? Undoubtedly, the general answer is yes. For our purposes, the seminal work of Hamilton (1964), on the genetics of social behaviour is the starting point. Hamilton's rule approximates to: an individual is predicted to behave altruistically towards another individual to an extent which is in direct proportion to the degree to which the individuals are genetically related. This rule encapsulates the idea that the evolution of cooperative behaviour is greatly facilitated among relatives. Moreover, in certain situations, in which genetic relatedness is increased by haplo–diploid breeding systems (e.g. honeybees), or in which certain ecological factors are influential (e.g. bee-eaters), extreme forms of altruism may evolve. In genetic terms, foregoing or delaying one's own reproductive efforts to aid those of a relative must count as one of the most altruistic acts imaginable. However, these diverse behaviours can generally be rationalized (via Hamilton's rule) as attempts by all of the interacting parties to maximize their fitness within the constraints of their particular genetic or ecological systems. If we view female worker honeybees as industrious paragons of altruistic virtue, and older male bee-eaters as selfish saboteurs, then we are applying misleading and irrelevant value judgments, which are best discarded before such arguments are applied to human pregnancy.

In essence, all interacting organisms (with the exception of clones) are predicted to compete for resources which enhance survival and reproduction. Conflict and cooperation are two sides of the same coin; indeed, it is perhaps better to think of a continuum extending from unrelated, conflicting individuals that are intent on eating one another (host-parasite and predator-prey interactions), and moving towards the increasing cooperation (decreasing conflict) associated with parent–offspring interactions, culminating in fully cooperative, genetically identical parthenogenetic clones, such as occur in aphids. If Trivers (1974)—the first to apply Hamilton's theory of kin selection to the parent–offspring relationship—and Haig (1993), choose the word 'conflict' rather than 'cooperation' for the titles of their respective articles, they are probably intentionally underlining the extent to which the genetic

differences between, and resultant divergent genetic interests of, parents and offspring have been neglected, rather than making an absolute statement about the position of (in Haig's case) human pregnancy on the conflict-cooperation continuum *per se*.

Given that conflict exists in human pregnancy, a question in two parts arises: what are mother and offspring arguing about, and how does the conflict manifest itself? The answer to the first part is implicit in Trivers (1974); for instance, conflict may occur over the amount of nutrients transferred through the placenta and during lactation, the timing of parturition and weaning, and the extent of post-natal care (if this influences future parental reproductive fitness). The theory predicts that maternal and fetal genes will favour different optimum amounts of parental investment, with fetal genes favouring a higher level of investment in the pregnancy than maternal genes (Trivers, 1974; Dawkins, 1989, for a popular exposition). The answer to the second part is comprehensively addressed by Haig (1993). It is not our intention to comment in detail on particular aspects of his argument. However, we note that it includes plausible explanations for the evolution of the extreme diversity of mammalian fetal membranes, the occurrence of the decidual reaction, and the complex hormonal regulation of many aspects of pregnancy and lactation. In terms of reinterpreting existing data, the article represents a veritable paradigm shift in the understanding of human gestational physiology.

Assessing the extent to which Haig's theory could lead more directly to medical research or therapeutic benefits is problematical. It may be useful to draw a parallel with evolutionary theories of ageing, which were proposed more than 40 years ago (Medawar, 1952; Williams, 1957). Although these theories may have reduced the amount of barren speculation pertaining to the possible existence and identification of one or a few over-riding mechanisms of ageing, we are not aware that they have greatly aided therapeutic research in the area. If evolutionary theories, as applied to humans, lack predictive power at the mechanistic level it is simply due to the extreme complexities of human physiology and the random nature of the mutations which fuel evolutionary innovation. With the possible exception of bacteria (Clark, 1991), it is unlikely that any model or theory currently exists for any organism that is capable of linking quantitative genetics with the details of physiology in a predictable manner. This may account for the relative paucity of specific suggestions for future research in Haig's (1993) article.

However, despite these problems (which probably impinge on all selective theories of physiological adaptation) we believe that the conflict theory of human pregnancy is nevertheless capable of directing the researcher, at least in a general sense. This is partly due to the fact that—in contrast to putative mechanisms of ageing, for example—a limited subset of genes and their products can readily be identified as being involved in maternal–fetal interactions. These include hormones produced by the placenta and secreted into the maternal bloodstream. In addition, theories of genetic conflict make some general predictions about physiology. For example, evolutionary escalatory 'arms races' between competing genetic entities (such as mother and fetus) may result in high levels of expression of some genes, with little apparent net benefit. Haig (1993) points to the placental lactogens in this context, which are abundantly produced by the placenta, rapidly degraded by the mother, and result in no observable abnormalities when the entire genetic locus is deleted in the fetus. Do these observations make them irrevelant as subjects for further study in relation to pathology? Not necessarily; it is probably worth speculating on the consequences of mutations in the pregnant mother which might impinge on her ability to degrade the placental lactogens in her bloodstream. Are all of her normal fetuses consequently aborted because they trigger a surveillance mechanism that exists to protect the mother from the dangers of abnormally aggressive placentation? We do not know, but the answer may well be found in the current or future clinical literature.

It is a truism that in order to arrive at the correct answers, the correct questions must be asked. We strongly believe that many illuminating questions about human pregnancy may be formulated within the context of the conflict theory. Ultimately, its influence may not be apparent in terms of direct medical advances (although we do not rule these out), but, rather, may be reflected in the extent to which it is taken up by those involved in researching the physiology of normal and abnormal pregnancy.

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