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Oxidative stress and the evolutionary origins of preeclampsia

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ABSTRACT

In this speculative paper, I consider the relationship between oxidative stress and the evolution of placentation in eutherian mammals. I argue that epitheliochorial placentation, in which fetal tissues remain separated from maternal blood throughout gestation, has evolved as a protective mechanism against oxidative stress arising from pregnancy, particularly in species with unusually long gestation periods and unusually large placentas. Human beings comprise an unusual species that has the life history characteristics of an epitheliochorial species, but exhibits hemochorial placentation, in which fetal tissues come into direct contact with maternal blood. I argue that the risk of preeclampsia has arisen as a consequence of the failure of human beings to evolve epitheliochorial placentation.

1. Introduction

In many mammalian species, pregnancy involves deep invasion by placental tissues – which are of fetal origin – into the wall of the uterus, generating intimate and complex interactions between the physiologies of mother and offspring during gestation. Human beings have an invasive form of placentation in which fetal cells invade the inner third of the myometrium and take control of the local maternal circulatory system by transforming her uterine spiral arteries into inelastic tubes no longer subject to maternal vasodilatory control (Lyall, 2005). The apparent necessity of this relatively deep invasion of the uterine wall during human gestation has been held to predispose human beings to diseases related to inadequate (and excessive) invasion (Crosley et al., 2013; Elliot and Crespi, 2015; Pijnenborg et al., 2008; Rosenberg and Trevathan, 2007; Robillard et al., 2003), most prominently preeclampsia (in which inadequate invasion and a consequent failure to remodel the maternal vasculature is a universal feature). Hence, the existence of preeclampsia in human beings represents an evolutionary conundrum—given what must be a vast reproductive cost of preeclampsia to human populations over historical times, how has the condition been retained by natural selection? What benefits of deeply invasive placentation could outweigh such costs?

Invasive placentation, in the sense described here, is hemochorial placentation. In species with hemochorial placentas (including monkeys, apes, rodents, rabbits, many bats and insectivores, and several African shrew-like mammals) the fetal placental tissues breach maternal blood vessels, causing maternal blood to wash directly over the surface of the placenta and through its complex sinuses before being returned to uterine veins. Direct contact between circulating maternal blood and fetal tissues (which bear antigens of paternal and hence foreign origin) gives rise to a range of complex immunological and physiological complications, likely including preeclampsia. Yet, many mammalian species exhibit quite different forms of placentation which appear to evade such complications entirely. Species with epitheliochorial placentas (including ruminants, whales, and the lower primates) have the least invasive form. The placenta not only fails to breach maternal blood vessels, but it never even breaches the epithelial tissues lining the wall of the uterus. Maternal blood in such species is generally bound with maternal blood vessels, and fetal tissues never come into contact with it. Species with endotheliochorial placentas (including almost all carnivores, along with some bats, South American mammals and some African mammals) lie somewhere between these two extremes: the placenta invades past the maternal epithelium, but does not invade maternal blood vessels, such that maternal blood and fetal tissues are always separated by the endothelium of maternal capillary walls. It is noteworthy that neither preeclampsia nor any condition very similar to it has been observed in a species with epitheliochorial or endotheliochorial placentation.

Historically, epitheliochorial placentation has been regarded as a "primitive" condition from which more advanced mammalian species with deeply invasive placentation have arisen. However, the expansion of studies of comparative placentation into ever more exotic taxa (reviewed in Elliot and Crespi, 2009), combined with statistical models of the evolutionary process (Elliot and Crespi, 2008, 2009; Carter and Enders, 2004; Vogel, 2005; Wildman et al., 2006; Mess and Carter, 2006), strongly suggest that the opposite is the case. At the present time, it seems likely that the earliest

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true placental mammals had already been characterized by hemochorial or endotheliochorial placentas, and that the epitheliochorial form of placentation is a relatively recent evolutionary novelty that has arisen multiple times, independently, in several taxonomic groups. The human hemochorial placenta, then, is in some respects actually a "primitive" one, and its lineage can be traced back without break to the earliest mammalian species that lived 200 million years ago.

In this speculative paper, I assess the evidence that epitheliochorial placentation may provide a protective effect against preeclampsia. I pay specific attention to oxidative stress during placentation, a factor that appears to play a major role in the pathogenesis of preeclampsia. I argue – on the basis of life history – that human beings and other apes may have "the wrong type" of placenta when viewed in the context of mammals as a whole, and suggest that the invasive hemochorial human placenta might not be an adaptive evolutionary strategy at all, but perhaps reflects nothing more than a "frozen accident", a suboptimal phenotype that is maintained not by evolutionary selective advantage, but by constraints imposed upon placentation by the contingencies of developmental biology. My view is that the central evolutionary problem of human pregnancy is not, "why is the human placenta so invasive?", but rather "why is the human placenta not epitheliochorial?"

2. Oxidative stress in placentation and preeclampsia

Oxidative stress arises during pregnancy either from an excessive production by the placental metabolism of reactive oxygen species (ROS), or from an inadequate supply of antioxidant substances to dispose of or suppress formation of these harmful free radicals (Wisdom et al., 1991; Myatt and Cui, 2004; Burton and Jauniaux, 2004, 2011; Laízíar, 2012). The majority of ROS are thought to result from mitochondrial activity under hyperoxia (in which case, there are more electrons traveling along the mitochondrial electron transport chain and hence a greater chance of "leakage" of electrons onto molecular oxygen to generate the reactive superoxide ion) or hypoxia (in which case a shortage of molecular oxygen results in an accumulation of electrons). However, ROS can also be formed in the endoplasmic reticulum and other membranes (especially in highly secretory cells), by the enzyme NADPH oxidase (which is a particularly important source in early pregnancy) (Raijmakers et al., 2006), and by other enzymatic systems. ROS cause cellular stress by directly damaging DNA, proteins and lipids, and through their effects on intracellular signaling pathways that can give rise to a wide range of cellular responses, including proliferation, growth arrest, senescence and cell death (Martindale and Holbrook, 2002).

Reactive oxygen species are important signal transducers in normal placentation. In early pregnancy, embryos require low oxygen tension to cause development, through pathways activated by hypoxia-inducible factor, of blood, vasculature, placentas and nervous systems (Burton et al., 2003; Simon and Keith, 2008). Low oxygen tension in early pregnancy is also an important promoter of placental angiogenesis (Pereira et al., 2015). At this time, the embryo is supported by secretions from endometrial glands rather than from the maternal circulation (Jauniaux et al., 2000; Burton et al., 2002), but the breaching of maternal blood vessels in the first trimester results in direct access to oxygenated maternal blood and a precipitous oxidative insult (Jauniaux et al., 2000). Under low oxygen tension trophoblast maintains a proliferative phenotype, but under high oxygen tension trophoblast differentiates along a pathway leading to a highly invasive phenotype that is important in carrying out the remodeling of the endometrium in normal pregnancy (Genbacev, 1997). The formation of ROS under high oxygen tension is thought to be involved in several of the mechanisms by which trophoblast cells sense the degree of local oxygenation and program cell behavior accordingly (De Marco and Caniggia, 2002) and is involved in causing the fusing of cytotrophoblast cells into the syncytiotrophoblast (Frendo et al., 2001). Mounting evidence suggests that placental oxidative stress, in general, increases throughout the duration of pregnancy (Toescu et al., 2002; Qanungo and Mukherjea, 2000), although the concentration of oxygen declines after the initial hyperoxia (Soothill et al., 1986; Burton, 2009).

Medical research has provided evidence of increased oxidative stress of placental tissues, particularly the invasive cytotrophoblast, in preeclampsia (Sikkema et al., 2001; Many et al., 2000). Furthermore, the degree of oxidative stress appears to be correlated with the severity of preeclampsia (Chamy et al., 2006; Uotila et al., 1993). It is thought that inadequate differentiation of cytotrophoblast down the invasive pathway yields insufficient or unsuccessful remodeling of spiral arteries (characteristic of some but not all cases of preeclampsia), resulting in various forms of oxidative stress in the mature placenta (Roberts and Hubel, 1999). These effects are not thought to be a consequence merely of inadequate oxygenation. Instead, it is proposed that a lack of constancy in the concentration of oxygen may be more significant in generating oxidative stress (Burton and Jauniaux, 2004) by causing ischemia–reperfusion injuries. In this scenario, ROS are generated rapidly during reoxygenation following a local episode of transient hypoxia (Hung et al., 2001), causing apoptosis of trophoblast cells and the release of cellular debris and other materials into the maternal circulatory system (Redman and Sargent, 2000; Hung et al., 2002; Hung and Burton, 2006) and generating maternal endothelial inflation and damage. To the extent that the severity of preeclampsia may depend upon the mother's ability to resist harmful substances emitted by oxidatively stressed placentas, pregnancy has been regarded as a "stress test" for the vascular health of a mother's body (Sattar and Greer, 2002).

3. Placental structure and oxidative stress

I hypothesize that the epitheliochorial placenta provides a structure in which the maternal circulatory system is buffered from direct exposure to ROS and other stressors emitted by the fetal trophoblast by maternal cell layers, including epithelium, connective tissue and endothelium. Maternal blood vessels supplying the epitheliochorial placenta are typical of mammalian vasculature in general in that they exhibit a progressive reduction of vessel diameter as the vessel approaches its target cells (Brosens et al., 1967). The situation in the hemochorial placenta is quite different, with vessels becoming progressively larger and less tense, resulting in very low peripheral resistance at the point at which maternal blood is deposited directly into the trophoblastic lacunae (Moll et al., 1975; Moffett and Loke, 2006). The hemochorial placenta thus appears to be adapted for direct transfer of materials between fetal and maternal bloodstreams, giving rise to a risk of the transfer in the opposite direction of harmful substances, while the epitheliochorial placenta often depends on the direct secretion of materials from mother to fetus, the separation of blood mitigating against maternal danger. For example, iron is taken up by fetuses with hemochorial placentation directly from maternal blood in the form of transferrin, but must be actively secreted by uterine glands in the form of an iron-rich glycoprotein, uteroferrin, in species with epitheliochorial placentation (Carter, 2012). Similarly, while some substances, such as glucose, appear to be able to diffuse across the several cell layers separating maternal blood and fetal blood in epitheliochorial placentation, other substances are transferred in the form of "uterine milk", an evolutionary novelty in epitheliochorial species (Hansen