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Review

Vital and vulnerable functions of the primate placenta critical for infant health and brain development

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ABSTRACT

The placenta is essential to mammalian pregnancy with many roles beyond just nutrient supply, including both endocrine and immune functions. During the course of evolution, the placenta of higher primates has acquired some unique features, including the capacity to secrete corticotropin-releasing hormone (CRH). In addition, a placental receptor for IgG enables particularly high levels of protective maternal antibody to reach the fetus before birth. This paper reviews the placental biology of primates, and discusses its involvement in adrenocortical hormone activity during pregnancy, the transfer of maternal antibody, and finally the delivery of maternal iron to the fetus, which is needed for normal brain development. An understanding of these vital functions during a full-term, healthy pregnancy provides insights into the consequences of gestational disturbances, such as maternal stress, illness, and undernutrition, which have even larger ramifications if the infant is born premature.

1. Introduction

The evolution of mammals with their long period of internal development before birth is intimately associated with the placenta, especially its capacity to nurture the fetus and sustain pregnancy (O'Leary et al., 2013). As mammals evolved from the marsupial to eutherian stage, and longer gestations became common, the placenta took on additional roles. In addition to being essential for connecting the implanting embryo with the maternal blood supply, the placenta initiates hormone and immune changes in the gravid female needed to prevent rejection, and then continues to have myriad actions during the remainder of pregnancy (Murphy et al., 2006). The significance of the placenta is particularly prominent in primates. In both concrete and symbolic ways, it initiates and presages the continued importance of the mother-infant relationship and nursing during the postnatal period. A consideration of placental functioning provides insight into the intimate communication between mother and fetus required for a successful outcome and the birth of a healthy, resilient infant.

Across the Order Primates, which is comprised of over 650 species, one can identify progressive changes in placental structure and function, trends that help to understand important aspects of human pregnancy. When comparing prosimians to monkeys and apes, the placenta becomes more invasive, penetrating deeper into the uterine endometrium, reflecting the change from an epitheliochoreal placenta into the hemochorial placenta (Montiel et al., 2013). The epithelial barrier between maternal and fetal blood thins to a point where the capillaries are sufficiently proximal to permit some fetal white blood cells to cross into the mother, where they remain and can be active for years after birth (Bianchi et al., 1996; Stevens et al., 2004). This proximity also exposes the mother's own leukocytes to paternal antigens on fetal cells. That exposure required a more assertive regulation of the female's immune responses during pregnancy, another process implemented by the placenta, in part through the synthesis of syncytin and the release of immunomodulatory hormones like progesterone. Moreover, in higher primates, it includes a placental capacity to secrete CRH, which provides a way for the fetus to regulate its own pituitary-adrenal axis, and thus cortisol levels in circulation (Margioris et al., 1988; Smith, 1999). In addition, placental CRH has some endocrine effects in the maternal compartment (Sasaki et al., 1989), is involved in immune tolerance early in gestation, and helps later to initiate labor (Makrigiannakis et al., 2003). An inappropriate or premature surge of CRH can also mediate some of the harmful effects of intrauterine infections (Mazoub and Karalis, 1999; Uh et al., 2008). Later in the review, we also illustrate the relationship between cortisol levels present in the maternal and fetal compartments of monkeys during pregnancy.

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The hemochorial placenta is found in all monkeys, including the rhesus macaque, the primary species assessed in our research. This type of placenta is associated with a reduction in the number of offspring, with just one infant being common in monkeys and apes. The change in the placenta and decreased fecundity in the ancestors of Old and New World monkeys also coincided with a dramatic anatomical change in the reproductive tract, the shift from a bicornuate to a single, fused uterus. Even the subset of South American monkeys – the marmosets and tamarins that reverted back to having dizygotic twins – do so with a unicornuate uterus and hemochorial placenta. But it should be reiterated that singleton pregnancies predominate among most monkeys and apes. For example, in our breeding colony of rhesus monkeys, twinning is exceedingly rare. It has occurred only 2 times in over 4000 pregnancies across a span of 50 years, a statistic far below the current prevalence of twinning in humans (3.3%). Another notable feature of the primate pregnancy is its long length. Gestation became more prolonged as the body size of primates increased: from the 2-month pregnancy in a small prosimian like the mouse lemur, to the 5.5–6.0 month duration in most monkeys, and finally reaching 8-months in the great apes.

In addition to permitting the mother to gestate a larger and more precocial infant with an elaborated brain by birth, the extension of pregnancy afforded the opportunity for some other adaptations to become established. In the monkeys of Africa and Asia, as well as in the great apes, the placenta acquired a receptor for one isotype of maternal antibody, the immunoglobulin G class (IgG) (Leach et al., 1996). This placental feature enables a receptor-mediated transfer of maternal IgG, which accelerates during the final weeks of pregnancy (Coe et al., 1994; Roopenian and Akilesh, 2007). Thus, the full-term infant monkey has as much or higher IgG levels than its mother at delivery. The pediatric significance of this transfer of maternal antibody is that it engenders an extended period of passive immunity, protecting the young infant against many bacterial and viral pathogens to which the mother had been exposed. The evolution of placental antibody transfer in primates is considered in the third section of our review.

Finally, we discuss another placental receptor, the transferrin receptor (TfR), which also has a transmission function that becomes prominent at the end of pregnancy. The TfR pulls increasing amounts of iron from the maternal blood stream into the fetal compartment. These iron stores in the neonate are critical for providing the iron needed to sustain rapid growth during the early postnatal period, and cannot be replaced after birth by the delimited iron available in breast milk. We have found that a low prenatal provision of maternal iron has many health consequences for the developing infant monkey. In addition to increasing the risk for iron-deficiency anemia, a low prenatal iron endowment will adversely impact the developing brain. The anemic infant monkey evinces reduced brain energetics, skewed monoaminergic neurotransmitter activity, and slower myelination due to the iron depletion in oligodendrocytes (Patton et al., 2012; Rao et al., 2013).

2. The placenta as an endocrine tissue

One of the first tasks for the implanting primate embryo, at not much more 100 cells, is to facilitate the survival of the corpus luteum and to ensure the continued secretion of progesterone in order to block menstruation. The syncytiotrophoblast, which will give rise to the placenta, is the source of the chorionic gonadotrophin (CG) that 'rescues' the corpus luteum. By extending the functional life span of the luteal body, it maintains high levels of progesterone until the placenta is large enough to produce sufficient amounts of its own estrogen and progesterone. Then, by mid-pregnancy, a luteoplacental shift will occur. Placental steroidogenesis becomes so pervasive at that point that a female monkey can be ovariectomized and her gravid state will be maintained normally until term. The primate placenta is also an active contributor to other hormone changes associated with pregnancy, including being the site for converting the dehydropiandrosterone-sulfate (DHEA-S) produced by the fetal adrenal into the estrogens found in the mother's blood stream. This estrogen has many functions, including synergizing with prolactin later in pregnancy to prepare the breast tissue for lactation. But early in the primate pregnancy, estrogen has another important action, which is to stimulate the maternal adrenal to secrete more cortisol. In the squirrel monkey, a primate that has high cortisol levels even when not pregnant, this estrogenic effect is so pronounced and quick that a precipitous cortisol rise can be used to index conception (Coe et al., 1986). One can also mimic estrogen's stimulatory action on the adrenal by administering it to adult males and tracking the resulting surge in cortisol and cortisol-binding globulin (CBG) levels over the next week.

Corticosteroids have important functions during pregnancy in many species. In some animals like sheep, the rising adrenal hormone levels at the end of gestation signal and initiate labor. The importance of cortisol in higher primates is also highlighted by the fact that the placenta acquired the ability to secrete CRH and thereby to directly influence pituitary-adrenal axis, primarily in the fetal compartment, but also in the maternal compartment (Sasaki et al., 1989). This unique ability to release CRH is associated with other critical placental actions, because it can stimulate the trophoblast production of syncytin. We have come to appreciate that syncytin helps to mediate the maternal immune tolerance for the fetus, and thus CRH indirectly contributes to the maintenance of pregnancy in this way. The evolutionary story behind placental syncytin is an interesting one – a capacity acquired by incorporating DNA inserts from ancestral viral infections into the early mammalian and primate genome – but those details go beyond the scope of this review (see: Dupressoir et al., 2012; Tolosa et al., 2013). Both CRH and cortisol levels in primates continue to rise significantly as pregnancy progresses and then serve other functions during the second half of pregnancy (Mastorakos and Ilias, 2003). Of clinical significance, an inappropriately early or large increase in CRH levels during the second or third trimester is a warning sign that the pregnancy will not go to term (Fahlbusch et al., 2012; Wadhwa et al., 1997). Further, there is now evidence that in a normal term delivery, CRH synergizes with oxytocin, pro-inflammatory cytokines, and prostaglandins to stimulate the myometrial contractions of labor as progesterone's tonic inhibition is withdrawn (Zoumakis et al., 1996; Jeschke et al., 2005; McLean and Smith, 2001).

The placenta fulfills another important role related to cortisol, which is to assist in the transfer of maternal cortisol to the fetal compartment and to regulate the amount that will cross (Campbell and Murphy, 1977). During the first half of gestation, the majority of the cortisol found in the circulation of fetal monkeys is actually of maternal origin (Althaus et al., 1986; Pepe and Albrecht, 1995). As pregnancy progresses, greater amounts are produced by the fetus, but that must wait until its tiny adrenal glands have increased to a sufficient size. Even when the developing adrenals can secrete enough cortisol and are responsive to ACTH from the fetal pituitary, this endogenous secretion by the fetus continues to be strongly influenced by how much corticosteroid is transferred. When the transfer of maternal cortisol is high, fetal cortisol synthesis and release are decreased as a counter-regulatory response. Although this reduction is adaptive, one collateral ramification of lessening fetal adrenal activity is that it simultaneously decreases the secretion of DHEAs, the placenta's primary substrate for estrogen.

The placenta has one other way to regulate cortisol levels in the fetal compartment, which is to enzymatically modify maternal