Morphologic and molecular changes in the placenta: what we can learn from environmental exposures

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In mammals, the extraembryonic tissues, which include the placenta, are crucial for embryonic development and growth. Because the placenta is no longer needed for postnatal life, however, it has been relatively understudied as a tissue of interest in biomedical research. Recently, increased efforts have been placed on understanding the placenta and how it may play a key role in human health and disease. In this review, we discuss two very different types of environmental exposures: assisted reproductive technologies and in utero exposure to endocrine-disrupting chemicals. We summarize the current literature on their effects on placental development in both rodent and human, and comment on the potential use of placental biomarkers as predictors of offspring health outcomes. (Fertil Steril® 2016;106: 930–40. ©2016 by American Society for Reproductive Medicine.)

Key Words: Placenta, endocrine disrupting chemicals, assisted reproductive technologies, epigenetics

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The vitality of the placenta is essential to normal development of mammalian offspring. The placenta is the gestational interface between mother and fetus and is required for exchange of gases, nutrients, and waste products. The placenta also provides pregnancy-induced hormones, growth factors, and immune protection for the fetus. It is well recognized that compromised maternal health and genetic lesions of the conceptus can result in placental insufficiency and associated fetal growth defects. Moreover, environmental insults, the topic of the present review, can contribute to placental dysfunction and compromised offspring outcomes.

More recently, it has become appreciated that a healthy placenta is essential for the lifelong health of the mother and offspring. In fact, the Developmental Origins of Health and Disease (DOHaD) hypothesis, which posits that environmental stresses or exposures during development can increase the disease risk later in life, likely has equal contributions from the fetus and placenta (1). With the growing interest in DOHaD and the recognition that the placenta may play an important role in offspring programming, it is not surprising that there are increased efforts focused on placental biology (2). Studies on human placenta, however, lag behind those in other mammals. Given its critical role in mammalian development, the placenta is remarkably variable among mammals (3). Nevertheless, there are notable similarities between the human and the rodent placenta, which enables studies of rodent and human placenta to be compared (4). This review will highlight how the environment can modify the placenta in both rodent and human. Specifically, we focus on the iatrogenic changes induced by assisted reproductive technologies (ART) and changes that occur after developmental exposure to endocrine-disrupting chemicals (EDCs). Whether any of the reported changes following either environmental perturbation can serve as a reliable biomarker, and surrogate for fetal health, requires further investigation.

THE PLACENTA AS A BIOMARKER OF OFFSPRING HEALTH

Morphologic, physiologic, and/or molecular changes in the placenta may serve as biomarkers of offspring health and risks. Currently, morphology and function are assessed by means of gross morphology, histology, and imaging techniques. Advanced imaging could allow for more accurate, real-time assessments of placental function and fetal health, possibly improving prognoses and informing interventions. Moreover, investigations of

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molecular biomarkers have relied on omics-based techniques. In addition to transcriptomic and proteomic characterization, epigenomic studies of normal and abnormal placentas would provide insight into mechanisms underlying altered gene expression in functionally compromised placentas. Stepping beyond the central dogma, metabolomic and secretomic studies would also add to a more comprehensive understanding of placental function.

Because the environment comprises a broad array of potential insults, identifying a specific biomarker associated with a given insult is daunting. Instead, identifying biomarkers of response that reflect changes in biologic function as a consequence of an exposure may ultimately be more informative (5). Although response biomarkers mask the specific insult that is responsible for the placental change, the tendency for different environmental stimuli to converge and affect a more limited number of molecular pathways suggests biomarkers of response may ultimately be more relevant and predictive of fetal health.

ASSISTED REPRODUCTIVE TECHNOLOGY AS AN ENVIRONMENTAL EXPOSURE

ART is not traditionally considered to be an environmental exposure. Nevertheless, ART procedures consist of fertilization outside the body in an artificial culture environment and many other procedures, such as hormone stimulation, gamete/embryo freezing, embryo culture, cell biopsy, and embryo transfer, that are not inherent to mammalian reproduction. These manipulations have the potential to disrupt the normal biologic processes in embryos and cause damage via oxidative, thermal, and mechanical stress (6). One major biologic process that coincides with the timing of ART procedures is the epigenetic reprogramming of the genome. It has been proposed that ART procedures disrupt this crucial reprogramming, leading to epigenetic perturbations that can affect the embryo and the extraembryonic tissues.

In the United States, the number of ART cycles has increased by 25% in the past decade, and the number of babies born has risen from 49,458 in 2004 to 66,706 in 2013 (7). However, even as reproductive medicine advances, ART is still associated with pregnancy complications, including low birth weight and abnormal placentation (8). Although the patients' infertility status may contribute to these complications, there is now abundant evidence supporting that ART procedures themselves can cause these effects. Indeed, experimental studies using the gametes and uterine environment of fertile animals provide evidence that ART procedures can induce adverse effects.

Although the vast majority of ART babies are born healthy, there is concern that ART children display symptoms indicative of increased risk for diseases later in life (9). As ART continues to advance and become more available, iatrogenic effects should be minimized to ensure healthy pregnancies and limit adverse health outcomes for ART-conceived children. In the following section, we summarize the current knowledge of identifiable changes in the placenta with ART in both experimental and clinical studies.

ART: Morphologic Changes

Several studies have shown that ART increases term placental weight in mice (10–15). Intriguingly, the procedure of transferring blastocyst stage embryos alone can increase overall placental weight, strongly suggesting that relatively brief procedures can contribute to placental phenotypes (14). In addition to overall increased placental weight, mouse IVF placentas also exhibit disproportionate overgrowth of the junctional zone, a tissue that secretes factors that may influence the growth of the placental vasculature (12–16). This disproportion is observed in E12.5 IVF concepti, meaning this morphologic change is already detectable soon after placental formation (16). It is unclear if increases in placental weight and changes in placental cell composition are evidence of a direct adverse effect of ART procedures impairing placental development or are evidence of compensatory mechanisms. If changes in cell composition are the result of compensatory mechanisms, the fact that they occur so early suggests that stress signals are already affecting the early embryo before placental formation. Importantly, increased placental weight with the use of ART was almost always associated with a significant reduction in fetal weight (11–15). In some instances, fetal weight was unchanged, which may be influenced by the genetic background of the embryo (14, 15). Although reduced fetal weight may be indicative of reduced placental efficiency, it is not clear if reduced fetal weight is due to impaired placental function or if ART procedures also directly affect fetal growth processes.

Most studies in humans report at least one type of morphologic difference in ART placentas, but the exact phenotypes are not consistent among studies. Increased placental weight, placental:fetal ratio, placental thickness, abnormal umbilical cord insertion, and abnormal placental shape have been observed with the use of ART in term singletons (17–22). In a study comparing placentas from ART or spontaneously conceived pregnancies from either fertile or subfertile patients, only ART placentas exhibited increased placental thickness and increased incidence of hematomas (22), suggesting that the placental pathologies are the result of ART procedures rather than patients' infertility status. One study also noted edema and microcalcifications in ART placentas (23). The incidence of other placental pathologies, including gross malformations, infarcts, fibrin deposition, chorioamnionitis, fibrinoid necrosis, lesions, and syncytial knots have not been observed (18, 20). Importantly, in addition to differences in gross morphology and noticeable placental pathologies, ART placentas may display more subtle degenerative alterations. For example, in one study, ultrastructural changes in syncytiotrophoblasts were detectable only with the use of transmission electron microscopy (24).

ART: Genomic Imprinting and Global Methylation Levels

There is compelling work showing that ART can affect genomic imprinting in both mice and humans. Imprinted genes, which are genes that display monoallelic expression