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Predisposing Factors to Abnormal First Trimester Placentation and the Impact on Fetal Outcomes

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Abstract

Normal placentation during the first trimester sets the stage for the rest of pregnancy and involves a finely orchestrated cellular and molecular interplay of maternal and fetal tissues. The resulting intrauterine environment plays an important role in fetal programming and the future health of the fetus, and is impacted by multiple genetic and epigenetic factors. Abnormalities in placentation and spiral artery invasion can lead to ischemia, placental disease and adverse obstetrical outcomes including preeclampsia, intrauterine growth restriction, and placental abruption. Although first trimester placentation is affected by multiple factors, preconception environmental influences such as mode of conception, including assisted reproductive technologies which result in fertilization in vitro and intrauterine influences due to sex differences are emerging as potential significant factors impacting first trimester placentation.

Keywords

first trimester placentation; abnormal placentation; trophoblast; assisted reproductive technology; IVF; NIFT; sex differences

Introduction

The common thread to many pregnancy-associated pathologies is that their biologic foundation is laid in the first trimester of pregnancy. The process of placentation and trophoblast differentiation occurs throughout the first trimester of pregnancy and requires a complex interplay of multiple factors including maternal immune tolerance, expression of cytokines, growth factors, and autocrine/paracrine/juxtacrine mediators, as well as a receptive decidua that allows for extravillous trophoblast invasion and spiral artery remodeling [1] [2]. Abnormal placentation and failure of first trimester trophoblast invasion into the placental bed are at the core of the pathogenesis of preeclampsia [3] [4] and placental perfusion-related intrauterine growth restriction (IUGR), both of which contribute significantly to preterm delivery [5, 6]. A multitude of factors can impact abnormal

placentation leading to adverse fetal outcomes including genetics and epigenetic changes, due to the environment. Specifically, preconception environmental influences due to mode of conception, such as in vitro fertilization (IVF) through assisted reproductive technologies (ART) and intrauterine environmental influences due to fetal sex differences are evolving as significant factors impacting first trimester placentation.

In this review, we will start off by exploring the mechanisms of normal placentation, implications of intrauterine fetal programming, and the impact of genetics and epigenetics on placentation. We will then review the pathophysiology and outcomes of abnormal placentation, including preeclampsia, IUGR, placental abruption, previa, and accreta. Lastly, we will focus on two specific environmental influences, mode of conception and ART as well as fetal sex differences, both of which are evolving as potential factors affecting early placentation.

Normal Placentation: Trophoblast invasion and spiral artery remodeling

Normal trophoblast invasion involves cell attachment to the extracellular matrix, breakdown of the extracellular matrix by proteases including the gelatinases [7] and urokinase plasminogen activator (uPA), and invasion and reattachment [2] [8] [9]. Extravillous trophoblast invasion into the maternal decidua and inner third of the myometrium are tightly regulated by growth factors, cytokines, and immune cells. Trophoblasts are highly invasive cells that are most invasive earlier in gestation, with a 50% decrease in invasiveness from 8-10 weeks to 12-14 weeks gestation age, emphasizing the importance of these early events in establishing placentation [10] [11]. Additionally, adequate trophoblast invasion is also required for spiral artery remodeling. The superficial portions of the spiral artery musculoelastic vessel walls are replaced with extravillous trophoblasts, which allow for vascular dilation and increased oxygen and nutrient delivery to the intervillous space [4]. Shallow, inadequate trophoblast invasion and poor spiral artery remodeling contribute to poor maternal blood flow to the placenta and underlying complications of pregnancy [1] [12].

Although establishment of placentation occurs during the first trimester, many studies of abnormal placentation have used placental samples obtained at the time of birth to identify possible causative factors. For example, differential expression of genes involved in angiogenesis, cell-to-cell contact and regulation of response to low oxygen levels, including multiple members of the VEGF family, have been identified in term placentas [13] [14]. While term placentas are undoubtedly important in understanding the later manifestations of these pregnancy-related complications, assessment of first trimester placental tissue is of vital importance for investigating the underlying causes. More recent studies have used early placental samples, often cultured chorionic villous explants from elective first trimester terminations, and less commonly chorionic villus samples [15]. Optimization of isolation techniques for multiple platform testing have been developed for more widespread use of chorionic villi, which will likely lead to a better understanding of early placentation in ongoing pregnancies (Akhlaghpour, submitted). Additionally, animal models and *in vitro* studies using trophoblast and various different cell lines have been invaluable to understand underlying mechanisms leading to disease. [1] [16] [17] [18].

In utero programming impacts health of offspring

The implications of abnormalities in placentation and fetal growth *in utero* have been shown to have a long-term impact on the health of the fetus. The concept of fetal/development origins of adult health and disease, known as the 'Barker Hypothesis' has been well established [19]. Conditions that impact the intrauterine environment such as poor maternal nutrition, poor placentation, and pre-eclampsia, result in fetal reprogramming which can manifest in low fetal birth weight, alterations in neonatal body composition, and changes in placental shape and size [20] [21]. These factors have in turn been linked to adult disease later in life. Multiple large epidemiologic studies have found associations with a variety of adult-onset diseases including metabolic syndrome, atherosclerosis, coronary artery disease, type 2 diabetes mellitus, stroke, and obesity [22] [23] [19] [20]. For example, infants born from pregnancies complicated by preeclampsia have been shown to have an increased risk for cardiovascular disease and stroke [24]. Another large epidemiologic study found low birth weight to be a predictor of all cause mortality in women and premature death in men [25]. Additionally, numerous rodent and sheep models exist demonstrating the physiologic and molecular mechanisms underlying these different disease processes [22]. While the underlying mechanisms of these adult diseases are variable and complex, it is clear that early placentation and fetal programming play an important role.

Impact of genetics and epigenetics on placentation and pregnancy outcome

Genetics

The placenta is the main source of nutrition for the fetus, and regulation of genes that impact placental growth and nutrient transfer, as well as their interaction with the environment, play an important role in fetal health [26]. The maternal, paternal, and fetal genome all impact placentation for both imprinted and non-imprinted genes. Haig's 'parental genetic conflict' postulates a conflict between maternal drive to balance allocation of resources between the mother and offspring and the paternal drive to maximize extraction of maternal resources for the benefit of the offspring [27] [28] [26]. Paternally derived genes stimulate placental invasion and intrauterine growth while maternally derived genes tend to have the opposite effect [29] [30]. Additionally, non-imprinted genes from the fetus and placenta, with one gene copy derived from each parent, also play an important role in placentation [1].

Multiple studies have found a link between maternal and paternal heritability and adverse pregnancy outcomes. Both men and women who were small for gestational age (SGA) themselves are more likely to parent a child with SGA, and these women are more also likely to develop pre-eclampsia during pregnancy [31] [32]. Maternal type-I diabetes mellitus has also been shown to confer a 4-fold increased risk of pre-eclampsia [33]. Additionally, paternal genetics play a role in increased risk of pre-eclampsia in women who become pregnant by a partner who has fathered a pregnancy complicated by preeclampsia with another women [34]. While these are population-based studies, they show epidemiologic evidence of a link between parental genetics and pregnancy outcomes.

Epigenetics and imprinted genes

Epigenetics, the study of genetic reprogramming leading to changes in gene expression and phenotypes by various types of regulation such as DNA methylation, histone modifications, and non-coding RNAs, has been a large focus of recent research [35]. Many human diseases and conditions have been linked to aberrant DNA methylation or mutations in DNA pathways, including hyper- and hypo-methylation of gene promoters, CpG islands, as well as global changes to the epigenome [36] [37] [38]. These epigenetic modifications play an important role in the regulation of placentation. Placentation has been described as displaying many similarities to tumorigenesis, including rapid cell division, migration and invasion, and escape from immune detection, with significant overlap in multiple proto-oncogenes, growth factors, hormones and pathways essential for both cancer cell and trophoblast function [39] [40]. Several studies have shown epigenetic modifications of tumor suppressor and tumor-associated genes, including the *APC* gene, *Maspin* gene, and the *Wnt/b-catenin* pathway, in human placentas [41] [42] [43].

During preimplantation development of the mammalian embryo, DNA methylation of non-imprinted genes undergoes post-fertilization global reprogramming, first with demethylation followed by *de novo* methylation [44]. The *de novo* methylation occurs at the blastocyst stage, and is mostly restricted to the inner cell mass, leaving the trophectoderm relatively demethylated compared with the embryonic lineage [45]. These specific patterns of demethylation and *de novo* methylation are important for normal placental function, as studies in rodents and choriocarcinoma cells lines have shown disruption of trophoblast proliferation and invasion after administration of DNA methylation inhibitors [46] [47]. Various exposures during the preimplantation period such as *in vitro* culture of embryos and peri-implantation period such as sex hormone exposure also cause epigenetic alterations [48] [49] [50] [51].

In addition to global methylation changes, imprinted genes have been shown to play an important role in development and physiology of the placenta [52] [53]. Genomic imprinting is an epigenetic modification by which there is silencing of one allele depending on the parental origin, resulting in mono-allelic expression of the imprinted gene [54]. The importance of imprinted genes in the placenta is highlighted by the large number of imprinted genes that are expressed in placental tissue relative to other types of adult tissue [54] [55]. Numerous imprinted genes in the placenta have been identified including those involved in placental morphology and function such as *Phlda2* and *Peg10*, and genes involved in nutrient supply, including *Igf2*, which impacts diffusion permeability of the placenta and has important implications for placental and fetal growth [56] [57] [58].

Adverse fetal outcomes associated with abnormalities in early placentation

Ultimately, abnormal placentation results in impaired uteroplacental perfusion, chronic hypoxia, and placental ischemia [59]. These in turn lead to clinically important adverse obstetrical outcomes including preeclampsia, intrauterine growth restriction (IUGR), and placental abruption, which collectively contribute to over half of preterm deliveries [60]

[61]. Preterm birth is the single most common cause of neonatal mortality, resulting in an estimated 1.1 million neonatal deaths every year [62]. Preterm birth is associated with increased risk for neonatal morbidity including infection, respiratory distress syndrome, pulmonary hypoplasia, and neurological complications [63] [20].

Preeclampsia

Preeclampsia is a pregnancy-specific vascular disorder characterized by development of hypertension and proteinuria in the second half of gestation. Preeclampsia affects between 2-5% of pregnancies and is a leading cause of maternal and perinatal morbidity and mortality worldwide [64] [59]. Early onset preeclampsia at <34 weeks is associated with a 7-fold increase in impaired fetal growth, likely indicating a more severe disease associated with poor placentation [65]. While the pathophysiology is not well defined, it is generally accepted that the pathogenesis manifests in early pregnancy and involves poor differentiation of invasive trophoblasts, shallow placental implantation, and lack of physiologic dilation of the spiral arterioles. Placental perfusion becomes inadequate and eventually leads to endothelial activation with systemic vasoconstriction [66] [67].

Numerous underlying etiologies have been proposed to contribute to preeclampsia including abnormal angiogenesis and placental ischemia, immunologic maladaptation, and genetics [68]. Anatomic alterations in preeclamptic placentas have been seen including a decreased in placental surface area [69] and increased placental maternal vascular lesions when compared to controls [70]. Changes in maternal serum growth factors including fms-like tyrosine kinase 1 (sFlt-1), placental growth factor (PlGF), and vascular endothelial growth factor (VEGF) have been observed to precede any clinical manifestations of disease [71]. Hypoxia-induced dysregulation of trophoblast invasion mediated by hypoxia inducible factor (HIF) has also been shown to play a role [72]. While epidemiologic data has clearly shown a strong maternal and paternal genetic component, no clearly defined inheritance pathway or specific gene has been identified [68]. Ongoing genetics research using microarray, transcriptome profiling, genetic linkage studies, and pathway analysis in both trophoblast and decidual tissue is being done to further explore susceptibility genes to preeclampsia [73].

Intrauterine growth restriction

Intrauterine growth restriction (IUGR) is failure of the fetus to reach its predetermined growth potential, and is defined as estimated fetal growth below the 10th or 5th percentile [74]. Fetal growth restriction is associated with increased fetal morbidity and mortality, with earlier and more severe growth restriction associated with increased neonatal compromise. Although the most common etiology of IUGR is placental disease, other factors including chromosomal abnormalities, smoking, and infection also contribute [73]. IUGR related to placental compromise likely has a similar underlying endothelial disease and abnormal placentation that is associated with preeclampsia. Similar aberrant changes in placental morphology with poor villous growth and decreased surface area, abnormalities in placental growth factors, and hypoxia-mediated changes are seen in both IUGR and preeclampsia [75] [66] [76]. Despite these similarities, the underlying risk factors appear to be divergent between with two diseases. There is a strong relationship between preeclampsia and elements of metabolic syndrome, including obesity, insulin resistance, and hyperlipidemia,

that is not seen with unexplained IUGR, leading to the inference that while the final pathway may be similar the underlying causes are different [66] [77]. Additionally, data is more limited on genetic predisposition and recurrence risk for IUGR compared with preeclampsia, likely in part related the more diverse causes contributing to fetal growth restriction [59].

Placental Abruption

Placental abruption is complete or partial separation of the placenta prior to delivery and occurs in ~1% of deliveries. Risk factors for placental abruption include maternal age, hypertension, cigarette smoking, and drug use and likely emerges as a result of placental under-perfusion or a chronic hypoxic insult to the placenta [59] [78]. Placenta abruption has a similar mechanism to other ischemic placental disease, such as preeclampsia and IUGR, including abnormalities in extracellular matrix remodeling, angiogenesis, and inflammation [79]. At least one study has shown lower birth weight and lower placental weight in preterm abruption compared with term abruption, indicating potentially distinctive etiologies, in which preterm abruption is more closely tied to ischemic placental disease [80].

Predisposing factors for abnormal placentation

Assisted Reproductive Technology

Pregnancies conceived using assisted reproductive technologies (ART) have been shown to have higher rates of low birth weight and small for gestational age babies, preeclampsia, placental abruption, placenta previa, preterm labor and delivery, and cesarean delivery than pregnancies conceived spontaneously, and also have increased risks for perinatal mortality [81] [82] [83] [84] [85] [86]. Epigenetic modifications, more specifically imprinting disorders such as Beckwith-Wiedemann Syndrome, Angelman Syndrome, and retinoblastoma, although rare, also may be associated with ART [87] [88]. Understanding these ART-associated risks is becoming increasingly important as the number of babies conceived using *in vitro* fertilization (IVF) grows, with ART currently contributing to 1.5% of live births in the U.S [89].

Sequele of abnormal placentation have been associated with IVF pregnancies. Singleton infants born to women who have undergone ART have been shown to have an increased risk of low or very low birth weight compared with spontaneous conceptions [82] [90]. Animal models found that mouse pups conceived using IVF had significantly delayed fetal development and altered placentation compared to fetuses conceived spontaneously [91]. Moreover, the same group found decreased placental nutrient transport efficiency in mice conceived by IVF with down-regulation of select glucose transporters and system A amino acid transporters, as well as altered metabolic homeostasis [92] [93]. Differential placental steroid metabolism has also been shown when comparing IVF versus spontaneous pregnancies, which is hypothesized to affect passage of hormones to the fetus, potentially contributing to adverse outcomes. [94].

Human studies have also identified increased placental-related obstetrical complications. Women using IVF with donor oocytes have shown an increased risk of preeclampsia [95] [96] [97]. While some of these studies do not adequately control for confounding factors

including advanced maternal age and multiple pregnancy rate, even the studies that best control for these factors continue to show this association, potentially indicating an aberrant maternal immune response leading to poor placental invasion [97]. Multiple other examples of placental abnormalities associated with IVF have been shown in the literature including increased risk of placenta accreta with IVF, specifically with cryopreserved embryo transfer, and increased risk of retained placenta in advanced maternal age patients undergoing IVF [98] [99]. However, abnormal placental location in the late first trimester has not been demonstrated, and thus placental abnormalities leading to complications may occur at the molecular level in IVF conceptions [100] [101]. More recently, differences in global gene expression in first trimester placentas have been identified in pregnancies conceived with IVF compared to spontaneous conceptions as well as in pregnancies from couples with infertility conceived using non-IVF fertility treatments (NIFT). Microarray analysis identified a large number of differentially expressed genes in IVF vs. spontaneous pregnancies (157 genes, 112 up-regulated, 45 down-regulated). Additionally, there were 374 genes differentially expressed in NIFT vs. spontaneous pregnancies (247 up-regulated, 127 down-regulated) of which 45 genes (30 up-regulated and 15 down-regulated) were overlapping with the IVF vs. spontaneous comparison (Figure 1).

It is important to distinguish whether the risks of ART result from the procedures themselves or from the underlying infertility and its causes. We have demonstrated that pregnancies conceived using fertility treatments do not have an increased incidence of cytogenetic abnormalities or chromosomal mosaicism compared with those conceived spontaneously, regardless of treatment, either IVF or non-IVF fertility treatment (NIFT) [102] [101]. In addition, of the 157 differentially expressed genes in IVF and 374 differentially expressed genes in NIFT compared to spontaneous conceptions, 45 genes were overlapping suggesting that the underlying infertility may be a contributing factor (Figure 1). Other studies have also attempted to address this question, looking exclusively at infertile couples with matched sibling IVF and spontaneous gestations. These studies also provide evidence that perhaps the underlying infertility significantly contributes to adverse outcomes [103] [90]. However, various aspects of the ART procedures themselves may contribute to adverse outcomes including embryo culture conditions, epigenetic changes, and embryo transfer into a hyper-stimulated endometrium [35] [104] [51] [50]. Recent studies have shown an increased risk for low birth weight and pregnancy complications related to abnormal placentation with embryo transfer into a hyper-stimulated endometrium exposed to high levels of estradiol resulting in a shift toward frozen embryo transfer into a more physiologic endometrium [105] [106]. Teasing out the underlying contribution between infertility and ART procedures themselves remains a topic of ongoing debate and is the currently the focus of much research.

Fetal sex differences

There is considerable evidence that male infants are more likely to be born prematurely than female infants, and have higher rates of neonatal mortality [107] [108] [109], although not all studies have replicated these findings [110]. Male infants that are born prematurely may also be more likely to suffer from respiratory distress syndrome and pulmonary hypoplasia in the neonatal period [107] [108], and as a result suffer from associated neurological

complications, with increased rates of mild and moderate encephalopathy and intraventricular hemorrhage [111] [112]. While the mechanisms underlying these apparent sex differences have not been fully elucidated, potential etiologies include genetic and epigenetic regulators, hormone exposure, and inflammation/immune function. These mechanisms have an impact starting very early in gestation with the preimplantation embryo and last throughout placentation [113] [114].

Studies have identified global sex-specific differences in gene expression in placentas of male and female neonates [115]. Sex of the embryo impacts both fetal and placental chromosomal make-up, the rate of embryo development, fetal and placental growth, and the ability of the placenta to adapt to maternal stressors such as fetal hypoxia [116] [117] [118]. These differences in gene expression and regulation may be related to epigenetic phenomena, sexually dimorphic regulation of autosomal gene loci, or to X-linked genes [114]. The hormonal milieu during the first trimester, including effects of androgen on the trophoblast androgen receptors, has been hypothesized to play a role in sex-specific outcomes [119]. However, more recent data has found that testosterone may be more potent in female than male placentas, and is less likely to impact placental function [113]. Immune function and cytokine expression have also been found to be sex specific, with more severe chronic inflammation found in male preterm placentas compared with female preterm placentas [120]. More recently, we conducted RNA sequencing looking at differential gene expression in first trimester placentas and identified 25 differentially expressed transcripts as a function of sex in a small sample size. Of these differentially expressed genes, 15 were from autosomes and 10 from the allosomes (X or Y chromosomes). Of note, genes most differentially expressed from the allosomes can be used for identifying sex of the placenta in the research setting (Table 1). Even with a small sample size, significant differences were identified and further studies are underway to confirm these findings in larger sample sizes.

Conclusion

Abnormal placental function, originating during the first trimester, can lead to ischemic placental disease and has important implications for adverse obstetrical outcomes and the future health of the fetus. Parental and fetal genetics, as well epigenetics, impact the physiology and function of the placenta and play a role in the etiology of preeclampsia and IUGR. In addition, fetal sex-specific differences in gene expression and reprogramming cause differences in placental function and infant morbidity. Lastly, as mode of conception may be implicated with altered placental physiology and adverse obstetrical outcomes related to placentation and the prevalence of pregnancies conceived with fertility treatments, including NIFT and IVF, are increasing, further studies are needed to determine if it is the fertility treatments utilized or the genetics of the underlying infertility.

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Figure 1.
Differentially expressed genes in first trimester placentas based on mode of conception.

Differentially expressed genes from the allosomes in first trimester male and female placentas.

Table 1

Gene Name	Abbr	Chromosome	Log Fold Change	P-Value
DEAD Box Helicase 3, Y-Linked	DDX3Y	ChrY	5.98	5.68×10^{10}
Ubiquitously Transcribed Tetraatricopeptide Repeat Gene, Y-Linked	UTY	ChrY	5.41	5.83×10^8
Lysine (K)-Specific Demethylase 5D	KDM5D	ChrY	4.80	8.01×10^5
Protocadherin 11, Y-Linked	PCDH11Y	ChrY	4.71	3.41×10^5
Ubiquitin Specific Peptidase 9, Y-Linked	USP9Y	ChrY	4.65	3.71×10^4
Zinc Finger Protein, Y-Linked	ZFY	ChrY	4.62	1.84×10^4
Testis-Specific Transcript, Y-Linked 15	TTY15	ChrY	4.53	1.81×10^4
Protocadherin 11 Y-Linked	PCDH11Y	ChrY	2.01	9.65×10^6
Haloacid Dehalogenase-Like Hydrolase Domain Containing 1	HDHD1	ChrX	-1.20	2.79×10^5
X Inactive Specific Transcript (non-protein coding)	XIST	ChrX	-4.34	8.00×10^5