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Abnormal Placentation Associated with Infertility as a Marker of Overall Health

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Abstract

Infertility and the fertility treatments utilized are associated with abnormal placentation leading to adverse pregnancy outcomes related to placentation, including preterm birth, low birth weight, placenta accrete and placenta previa. This may be due to the underlying genetics predisposing to infertility or the epigenetic changes associated with the fertility treatments utilized, as specific disease states leading to infertility are at increased risk of adverse outcomes, including placental abruption, fetal loss, GDM, and outcomes related to placentation, as well as the treatments utilized including in vitro fertilization (IVF) and NIFT (non-IVF fertility treatment). Placentation defects, leading to adverse maternal and fetal outcomes, which are more pronounced in the infertile population, occur due to changes in trophoblast invasion, vascular defects, changes in the environmental milieu, chronic inflammation and oxidative stress. These similar processes are recognized as major contributors to lifelong risk of cardiovascular and metabolic disease for both the mother and her offspring. Thus, abnormal placentation, found to be more prevalent in the infertile population, may be the key to better understand how infertility affects overall and long term health.

Keywords

infertility; placentation; overall health; epigenetics; genetics; IVF; NIFT

Introduction

Infertility is associated with abnormal placentation leading to adverse pregnancy outcomes related to placentation. Infertile couples who conceive spontaneously without treatment are at higher risk of preterm birth and low birth weight.[1] More specific states associated with infertility are also associated with abnormal placentation. Women with uterine factors that contribute to infertility and pregnancy loss, such as mullerian anomalies and myomas requiring surgery, are at increased risk of placenta accrete and placenta previa.[2] Endometriosis, a condition associated with infertility, has also been implicated in pregnancy complications due to abnormal placentation, such as preterm birth, preeclampsia, IUGR, and placenta previa.[3–6] Women with Polycystic Ovary Syndrome (PCOS) leading to ovulatory

dysfunction and infertility are at increased risk of developing gestational diabetes (GDM) as a result of the fetal-placental unit straining the metabolic balance of these women. These women are at additional risk of suboptimal placental function and abnormal placentation. [7–10] Further, mothers with GDM are independently at risk for placental disorders, including altered placental structure, function and hypertrophic growth. [11–13]

Fertility treatments themselves are associated with dysfunctional placentation leading to placentation related adverse pregnancy outcomes.[1] However, it remains unclear if it is the fertility treatment or the more pronounced infertility requiring more aggressive treatment that leads to adverse outcomes. For example, pregnancies conceived using assisted reproductive technologies (ART), the majority of which utilize in vitro fertilization (IVF), are at increased risk for low birth weight and small for gestational age babies, preeclampsia, placental abruption, placenta previa, retained placenta and preterm labor and delivery, compared to pregnancies conceived spontaneously.[14–21] In addition, couples utilizing other types of fertility treatments, also known as non-IVF fertility treatments (NIFT), are at increased risk of adverse outcomes, including placental abruption, fetal loss, GDM, and outcomes related to placentation.[15, 22]

These pregnancy outcomes associated with dysfunctional placentation are associated with long-term health consequences for the mother. Since dysfunctional placentation is more pronounced in the infertile population, it may be the key that links infertility to overall long term health.[22] Therefore, in this review, we will address the mechanisms of normal placental development, followed by dysfunctional placental development leading to preeclampsia, IUGR, placental abruption, placenta previa, and GDM, including their association with both the underlying infertility as well as the fertility treatments utilized. Finally, we will focus on the impact of abnormal placentation on short-term maternal well-being, as well as long term consequences on maternal health.

Normal Placental Development

The placenta is composed of two principle tissue sources: the trophectoderm, or outer epithelium, which differentiates into villous and extravillous trophoblasts (EVT), and an underlying vascular network and stroma derived from embryonic mesoderm. Arising from the tips of the placental anchoring villi, invasive EVTs migrate and penetrate through the maternal decidua, endometrium, and the inner third of the myometrium. This invasion continues into the lumens of spiral arterioles and veins to establish a vascular connection. [23, 24] EVTs then transdifferentiate into an endothelialized trophoblast cell type, expressing many cell surface markers characteristic of endothelial cells. Alterations in extracellular matrix proteins result in arteries that are dilated, non-vasoactive vessels that allow greater transport of maternal blood to the intervillous space.[24–26]

Mechanisms for Abnormal Placentation

Formation of the vascular interface is directly related to trophoblast differentiation and relies on complex interactions between EVT-expressed adhesion molecules, the uterine

extracellular matrix, and vasculature.[27–29] Variance from the normally established vascular connection leads to changes in placental blood flow and to adverse outcomes.

Two major, interdependent factors determine maternal blood flow to the placenta: size of the placental bed and successful trophoblast invasion/ spiral artery remodeling. The number of spiral arteries that communicate with the intervillous space determines placental bed size. Shallow, inadequate trophoblast invasion and poor spiral artery remodeling contribute to poor maternal blood flow to the placenta and underlie perfusion complications of pregnancy. [30–32]

Placental thickness and heterogeneity have also been linked to adverse perinatal outcomes. [33, 34] Data from mouse models suggest that the placentae from fetuses from IVF are significantly different in size compared to naturally conceived controls. [35] Chorionic villus weight at sampling is negatively associated with hypertension which is more common in women conceived with infertility. [36]

Pathophysiology and Outcomes of Abnormal Placentation

Abnormal placentation includes conditions such as placental abruption, placenta previa, and the placenta accreta spectrum. These conditions often lead to adverse pregnancy outcomes and preterm delivery. In addition, conditions such as preeclampsia and IUGR also contribute to preterm delivery as well as low birth weight, and an underlying feature of all these adverse outcomes is inappropriate trophoblast invasion.

Placenta previa and accreta

Excessive trophoblast invasion leads to abnormal adherence of the placenta beyond the decidua and into the myometrium. These cases of placenta accreta, which are often found in combination with placenta previa, occur more frequently in women who have had prior uterine surgery.[2] The migrating trophoblast is more readily exposed to the myometrium and the underlying vasculature in these cases. The loss of normal anatomic planes and the excessive vascular remodeling of the radial and arcuate arteries leads to invasive vascular connections.[2] This has an impact on maternal morbidity in the short term, with high rates of hemorrhage, blood transfusion and peripartum hysterectomy.[37] Adverse neonatal outcomes such as preterm birth, low birth weight, small for gestational age, reduced five-minute Apgar scores, and neonatal intensive care unit admissions are also elevated in women with placenta accreta.[37] All of these immediate adverse outcomes have a significant impact on long-term maternal and child health.

Placental abruption

Ranging from small and chronic to catastrophic and lethal, placental abruption is the partial or complete separation of a normally located placenta from the uterus prior to delivery. Regardless of presentation, the underlying abnormality in placental abruption is the pathologically high incidence of vascular abnormalities in the placental bed due to defective and shallow trophoblast invasion of the decidua. On placental biopsy of abruption placentas, 60% of uteroplacental arteries have an absence of physiologic transformation.[38] This results in decreased placental blood flow, dysfunctional endothelial responses to vasoactive

substances, and overall ischemia.[39] In 33% of the cases, abnormalities, including vessel occlusion with surrounding myometrial hemorrhage, are seen in vessels deep in the myometrium.[38] In these cases, signs of vasculopathy can be seen like atherosclerosis, narrowing, necrosis, and thrombosis similar to patients with established vascular disease.[38, 40] This suggests that though the defective trophoblast invasion may lead to suboptimal vascular remodeling and pregnancy complications, there are significant underlying maternal contributors to the pathology that may be indicative of underlying vascular disease.[41]

Preeclampsia

Preeclampsia is a pregnancy-specific multisystem syndrome that presents with hypertension and proteinuria after the midtrimester. The pathophysiology of preeclampsia begins in the first trimester when invasion of trophoblast in the decidua and remodeling of the spiral arteries takes place. Preeclampsia, is thought to arise due to a two step dysregulation that begins with defective adhesion molecule expression by EVT's.[42, 43] Disordered trophoblast invasion of spiral arteries begins as early as 6–8 weeks gestation and leads to hypoperfusion of the placenta and oxidative stress.[44–46] The second stage then involves an overactive maternal immune response and clinical syndrome. The oxidative stress stimulates release of reactive oxygen species (ROS), cytokines, antiangiogenic factors, and microparticles that are risk factors for cardiovascular disease (CVD) in later life.[47–49] Though vascular connections are abnormal, invasion in the first trimester sets the foundation for abnormalities in later pregnancy. Defective remodeling can be found in both decidual and myometrial portions of the vessels. The mean external myometrial spiral artery diameter in the third trimester of a normal pregnancy is 500 μm as compared to approximately 200 μm in preeclamptic patients.[50] This abnormal remodeling alters the flow rate of blood into the intervillous space as well as the consistency of the blood flow. Both of these changes lead to fluctuations in the supply of oxygen to the placenta. Inadequate placental perfusion results in hypoxia-reperfusion type injuries which in turn can lead to modifications of lipids and proteins, mitochondrial and endoplasmic reticulum stress and apoptosis/necrosis.[51] In contrast to normal pregnancy, where particles are discarded from the placenta by apoptotic mechanisms necrotic trophoblast debris activates endothelial cells and stimulates the release of pro-inflammatory cytokines. [52]The release in cytokines and antiangiogenic proteins increases the ratio between the antiangiogenic factor soluble fms-like tyrosine kinase-1 (sFlt-1) and the proangiogenic placental growth factor (PlGF), which is thought to contribute to a systemic endothelial response, manifested clinically as preeclampsia and is also seen in IUGR.[53, 54]

To prevent hypertension in normal pregnancy, there is an increase in vasodilation that results, due to a systemic increase in vasodilator production.[55, 56] Failure of systemic vascular endothelial function is seen in the endothelial cells of women with preeclampsia. [57] A maternal anti-angiogenic state, in part due to placental anti-angiogenic factors, has emerged as one of the most important mechanisms underlying this generalized endothelial dysfunction.[48, 58–60] The insufficient drop in vascular resistance combined with generalized endothelial cell dysfunction lead to the clinical features. The underlying maternal cardiovascular profile and her handling of factors produced by an oxidatively stressed placenta, however appear to play a role in the development, timing, onset and

severity of the disease.[61] This endothelial dysfunction likely contributes to overall long-term health and cardiovascular disease.

Intrauterine Growth Restriction

The ultimate structural and functional changes that trophoblast invasion and spiral artery remodeling bring about are critical for delivering low pressure, high blood flow without impedance. This demand is especially important in later pregnancy as the fetus undergoes exponential growth. Doppler studies of the umbilical arteries in normal pregnancy indicate a progressive fall in fetoplacental vascular resistance as reflected by increasing end diastolic flow velocity.[62] Pregnancies complicated by severe IUGR and abnormal umbilical artery Dopplers demonstrate a significant reduction in gas-exchanging villi and decreased villous angiogenesis, thought to lead to increased trophoblast turnover.[63] These placentas have reduced intervillous space volume, poorly developed peripheral villi, and thicker trophoblastic epithelium that decrease the nutrient exchange area and compromise the exchange functions of the placenta.[64]

Doppler ultrasound studies of the umbilical artery and uteroplacental circulation in the first and second trimesters have demonstrated that increased impedance to flow in these vessels is associated with an increased risk for subsequent development of IUGR[65, 66] as well as preeclampsia and preterm delivery.[67] Three-dimensional ultrasound assessment of placental volume has found that reduced volume in the first and second trimesters, is associated with the subsequent development of IUGR[68–70] and when combined with uterine artery Doppler velocimetry is able to identify women at risk for subsequent development of pregnancy complications.[71]

Preterm labor

Commonly associated with preeclampsia, similar disease processes have been described in preterm labor.[72] While intrauterine inflammation is thought to be one of the principal contributors to the onset of preterm parturition, there is also a subset of patients with preterm labor that have placental vascular lesions. Approximately 30% of patients with preterm labor have failure of physiologic transformation of the uterine spiral arteries. Histologically, the vascular lumen is narrow and cytotrophoblasts have not invaded the muscular wall.[73] A similar number have failure of physiologic transformation of the myometrial segment of the spiral arteries.[73] As in the case of preeclampsia, these vessel lumens fail to expand and suboptimal perfusion leads to a pathologic state. Why the same pathologic states lead to two different clinical outcomes has yet to be established, but may provide insights into the pathophysiology of both conditions.

Infertility and Abnormal Placentation

Conditions leading to infertility may be involved with abnormal placentation and trophoblast invasion.[22, 74, 75] The etiology of recurrent pregnancy loss may also come back to the trophoblast. Premature loosening of trophoblast connections and consequent premature and disorganized flow of maternal blood into the intervillous space has been associated with

recurrent spontaneous abortion.[61] In these cases, increased levels of placental oxidative stress and trophoblast degeneration have been noted.[76, 77]

Endometriosis, a condition commonly associated with infertility, has also been implicated in second- and third- trimester pregnancy complications, such as preterm birth, preeclampsia, IUGR, and placenta previa.[3–6] Different mechanisms including an imbalance of endocrine and inflammatory markers, bleeding from endometriotic implants, as well as molecular and functional abnormalities of the eutopic endometrium may lead to defective deep placentation and decidualization of the endometriotic tissue.[78–81] Based on low quality evidence, there seems to be an increased rate of spontaneous abortion with a relative risk (RR) of 1.31 (95% CI 1.07–1.59) for women with endometriosis compared to women without,[82] but overall there is insufficient evidence support an association between endometriosis and miscarriage. [83]

Uterine etiologies contributing to infertility that leads to surgery increases one's risk for abnormal placentation leading to adverse outcomes. Excessive trophoblast invasion leads to abnormal adherence of the placenta beyond the decidua and into the myometrium, which occurs more frequently in women who have had prior uterine surgery. This leads to placenta accreta, which are often found in combination with placenta previa. The migrating trophoblast is more readily exposed to the myometrium and the underlying vasculature in these cases. The loss of normal anatomic planes and the excessive vascular remodeling of the radial and arcuate arteries leads to invasive vascular connections.[2]

PCOS is another condition leading to infertility with short- and long- term consequences. Pregnant women with PCOS have an increased risk of pregnancy and neonatal complications that is not attributable to use of ART.[84] The common denominator among these adverse outcomes is defective trophoblast invasion and placentation.[85, 86] Hyperandrogenic mothers appear to be most at risk and it is postulated that testosterone acts directly on trophoblast invasion and on placenta morphology and function.[87–89]

Women with PCOS have a chronic low-grade inflammation and the metabolic dysfunction which is enhanced in pregnancy.[90] Elevated lipid concentrations, ROS, and inflammatory markers induce endothelial dysfunction.[91] This leads to physiologic abnormalities, remodeling of spiral vessels with reduction in the uterine artery impedance, reduced depth of endovascular trophoblast invasion, and ultimately abnormal placentation.[89, 91]

Histologic studies evaluating both macroscopic and microscopic changes in the placenta of women with PCOS found a significant reduction in the placental weight, thickness, density and volume in patients with PCOS.[87] Subclinical alterations varied according to the PCOS phenotype and the local microvascular and inflammatory damage was similar to that observed in non-pregnant women with PCOS [88, 90]

Epigenetic Influence on Placentation

Epigenetics is the study of modifications in gene expression without alteration of the genetic code itself, and it is a field that has been gaining increased acceptance as an important regulator of human health and disease. Epigenetic modifications can arise from direct DNA

methylation, imprinting, post-translational modification of histone proteins and chromatin remodeling, or from non-coding RNA.[92] Gametogenesis and the pre-implantation embryonic period are two points wherein the epigenome is entirely reprogrammed,[93] and this peri- conception and peri-implantation period has the potential to significantly alter gene expression. In fact, aberrations in methylation have been found to negatively affect placentation.[94] Both rodent and human choriocarcinoma cell line studies have shown that specific patterns of methylation are important for normal placental function.[95, 96] In addition, other post-translational modifications due to oxidative stress lead to placental pathology.[97–99] During normal gestation, ROS generation is increased and is necessary for proper physiology.[100] However, when levels of ROS outweigh the anti-oxidant host defenses, epigenetic changes occur and pathology results. Differential DNA methylation has been identified in first trimester placenta during placentation in pregnancies conceived with IVF compared to NIFT conceptions, possibly due to the environmental conditions during embryogenesis or other environmental conditions, including an altered hormonal milieu. [101] Some of these changes may be attributed to specific transcription factors, including GATA3, that lead to altered invasion and migration or other regulators affected by environmental exposures to the embryo and developing placenta.[74]

Infertility and Fertility Treatments

Increased rates of low birth weight, placental abnormalities, preeclampsia, and preterm labor are more common in pregnancies conceived using IVF compared to pregnancies conceived spontaneously.[14–21] Ovulation induction has also been associated with increased placental abruption, fetal loss after 24 weeks gestation, and GDM.[102] Women utilizing fertility treatment have a significant maternal morbidity including hemorrhage, hypertension, renal, pulmonary, cardiac, and infectious morbidities.[75, 103] This, therefore, makes infertile women and women receiving fertility treatment a particular group of interest.

While ART is not traditionally considered to be an environmental exposure, IVF and ART procedures include fertilization outside the body, micromanipulation, and other procedures, such as hormone stimulation, gamete/embryo freezing, embryo culture, cell biopsy, and embryo transfer, that are not present in spontaneous conceived pregnancies. These conditions lead to epigenetic changes and differential gene expression in the placenta.[104–107] In addition, these manipulations have the potential to disrupt the normal biologic processes in embryos and cause damage via oxidative, thermal, and mechanical stress.[104, 108, 109]

Animal studies have demonstrated that appropriate demethylation can be altered through controlled ovarian hyperstimulation and can result in developmental failure.[110] Both IVF and controlled ovarian hyperstimulation are stimulated conditions wherein the hormonal milieu is altered. Human chorionic gonadotropin, progesterone, and estradiol are three key pregnancy-associated hormones that are found in high concentrations at the maternal–fetal interface at the time of vessel remodeling. It is thought that these hormones may control EVT movement and thus act as regulators of vessel remodeling.[111]

In pregnancies that result from fresh IVF cycles, the embryo and fetus are exposed to supra-physiologic estrogen levels. The elevated estrogen exposure is associated with higher rates of low birth weight and IUGR[112] and epigenetic changes are thought to be involved. *GATA3*, a transcription factor expressed in trophoblast, is involved in trophoblast differentiation and subsequent placental development. It is downregulated in the presence of elevated estradiol and which leads to impaired trophoblast cell migration and invasion.[74] This data provides insight into molecular mechanisms behind why supra-physiologic estrogen environments lead to adverse outcomes.

It is important to distinguish whether these observed changes in infertile patients are the result of ART or if they arise from the underlying infertility. Infertile couples who conceive spontaneously without treatment are at higher risk of preterm birth and low birth weight.[1] Infertility, however, is only a symptom of underlying pathology. Comparing placentas from ART or spontaneously conceived pregnancies to fertile and subfertile patients, only the ART placentas were found to have increased placental thickness and increased incidence of hematomas,[113] which suggests that the placental pathologies result from ART procedures rather than patients' infertility. Other placental pathologies, such as gross malformations, infarcts, fibrin deposition, fibrinoid necrosis, lesions, and syncytial knots have not been observed,[114, 115] but it is possible that ART placentas may display more subtle alterations. One study, for example, detected ultrastructural changes in syncytiotrophoblasts, but only with the use of transmission electron microscopy.[116]

Effects on the Fetus/Child

Placental abnormalities can lead to hypoperfusion and oxidative stress, both of which have long-term effects for the neonate and developing child into adulthood. Long-term follow-up studies have found that children born to women with preeclampsia and hypertensive disorders of pregnancy have higher risk of diabetes mellitus and CVD in later life.[117–119] Endothelial function is significantly reduced in both mothers and children after preeclampsia[120] and this is consistent with the fact that offspring have also increased levels of cardiovascular risk factors such as higher blood pressure,[121–123] body mass index,[121, 122] and increased risk of stroke in adulthood.[124] In addition, maternal hypertensive diseases of pregnancy are also a risk factor for adverse neurocognitive and psychological outcomes.[125, 126]

Decreases in methylation of insulin-like growth factor 2 has been found in cord blood of preeclamptic pregnancies.[127] This suggests that epigenetic regulation and the intrauterine environment might be among the mechanisms behind the association between intrauterine exposure to preeclampsia and risk for metabolic diseases. Additionally, there is increasing evidence that offspring conceived via IVF display a level of vascular dysfunction similar to that seen in children of mothers with preeclampsia without IVF.[128, 129] A 2015 randomized control trial found that antioxidant administration to IVF children improves nitric oxide bioavailability and vascular responsiveness in the systemic and pulmonary circulation.[130] These findings indicate that in young individuals, ART-induced vascular dysfunction is subject to redox regulation and is reversible. Animal studies also suggest that IVF leads to endothelial dysfunction and increased stiffness in offspring, which translates

into arterial hypertension *in vivo*, suggesting underlying epigenetic modifications.[128] These offspring have also been found to have significantly elevated activity of enzymatic regulators of cardiovascular and metabolic physiology providing evidence that postnatal cardiovascular and metabolic health are directly affected by IVF. [131]

Maternal Health Consequences

In addition to fetal well-being, the placenta is an important mediator of maternal health. Pregnancy complications result, in part, due to the underlying pathologies previously described. There are also more severe maternal morbidities (SMM) such as hemorrhage, embolism, stroke, acute myocardial infarction, and others that may occur. SMM, though overall low in number, is on the rise and has long term health implications.[132] Women of very advanced maternal age are not only at increased risk of GDM, hypertensive disorders, operative and cesarean deliveries,[133, 134] but those who conceive with the use of IVF, are at increased risk of retained placenta, suggesting that placentation abnormalities may contribute to maternal morbidity, and this may be more pronounced in women with infertility.[135] Additionally, fertility treatments (IVF and NIFT combined) have been associated with an increased risk of SMM in analyses adjusted for maternal age, race, obesity, and co-morbidities.[75]

Late manifestations of placentation disorders primarily result in the form of CVD and metabolic effects, though there is some data to support an association with other diseases. Preeclampsia has been associated with increased end-stage renal disease later in life[136, 137] and subclinical hypothyroidism.[138, 139] Both conditions are associated with CVD: kidney disease and CVD are closely interrelated in that disease of one organ can cause dysfunction of the other and abnormal thyroid hormone levels damages endothelial cells and can have cardiovascular effects.[140]

Placental and pregnancy complications that lead to downstream maternal health effects are primarily indicators or contributing factors to long-term cardiovascular sequelae. The American Heart Association considers a history of preeclampsia or a hypertensive disorder of pregnancy a major risk factor for development of CVD.[141] Women with a history of preeclampsia are at increased risk of developing hypertension (RR 3.70, 95% CI 2.70–5.05) and on average 7.7 years earlier than a woman without a history of preeclampsia.[142, 143] These women are also a nearly 2-fold increased risk of ischemic heart disease, stroke, and venous thromboembolism.[142] Overall risk of death from CVD is increased 9 to 10-fold in women with early onset preeclampsia (<34 weeks gestation) and two-fold in women with preeclampsia onset >34 weeks of gestation.[144]

Impaired endothelial function and vasodilatation remote from pregnancy has been seen in several studies evaluating women with a history of preeclampsia and early onset IUGR. [145–148] These women have higher levels of glucose, insulin, and unfavorable lipids compared to women with normal pregnancies.[149] Epidemiologic studies suggest that the increased risk of late cardiovascular morbidity reflects an underlying predisposition and that preeclampsia results in permanent arterial changes, which in turn lead to downstream CVD. [150–153]

Non-invasive vascular function tests have received considerable attention as they have been found to relate more closely with endothelial function and future CVD risk than conventional blood pressure measurements.[154] Of these tests, flow-mediated dilation (FMD), a measure of conduit artery endothelial function, has become an established technique for assessing endothelial dysfunction in the brachial artery and predicting future cardiovascular risk.[155, 156] Pregnancy is normally associated with increased FMD, reflecting enhanced endothelial function,[157] however, a recent review and meta-analysis reported significantly lower FMD in women with preeclampsia both before and after the onset of preeclampsia as well as three years postpartum.[158] These results indicate that endothelial dysfunction precedes the onset of preeclampsia and persists after pregnancy. They also suggest the potential of FMD to predict preeclampsia, and represent a possible mechanism for future cardiovascular risk in these women.[158] Other assessments of vascular reactivity are under investigation and show promise, but further research is needed.

Women who have had a preterm delivery from any cause may also be at higher risk of developing CVD. A population-based study comparing the incidence of cardiovascular morbidity in a cohort of women who delivered preterm compared to those that delivered at term and found a linear association between the number of preterm deliveries and future risk for cardiovascular related hospitalizations.[159] Another cohort study in Finnish women, found that maternal CVD mortality was inversely related to the birthweight of offspring and women having premature deliveries were also at increased CVD risk.[160]

Increased insulin resistance, pro-inflammatory activity, endothelial dysfunction, and abnormal lipid profiles persist postpartum in women with adverse pregnancy outcomes and are potential early manifestations of metabolic syndrome.[161–165] Women with PCOS who often have pre-existing insulin resistance and compensatory hyperinsulinemia are particularly at risk. Women with both preeclampsia and IUGR are also a high risk group with up to 20% of women meeting criteria for metabolic syndrome several months postpartum.[166] Patients with metabolic syndrome and patients with PCOS, independent of BMI, are at an increased risk for type 2 diabetes.

Women with infertility are at increased risk of developing GDM. A large, prospective cohort study demonstrated that women with infertility due to ovulation disorders (including PCOS) were 52% more likely to develop GDM and women with unexplained infertility had a 45% greater risk compared to women without a history of infertility. No association was found between endometriosis or male factor infertility and GDM risk.[167]

A history of GDM predisposes women to metabolic syndrome. These women have been found to have atherogenic lipid profiles and signs of early vascular dysfunction at 3 months postpartum compared to women without prior GDM.[168–170] A history of GDM predisposes women to type 2 diabetes compared to women with normoglycemic pregnancies (RR 7.43, 95% CI 4.79–11.51) and this risk doubles from RR 4.69 in the first five years after delivery to 9.34 more than five years after delivery.[171]

In addition, women with GDM are at elevated risk of developing CVD, and at a younger age, than women without a history of GDM.[159, 172–174] Hyperglycemia and insulin

resistance are key players in the development of atherosclerosis and its complications. The alterations in vascular homeostasis due to endothelial and smooth muscle cell dysfunction are the main features of vasculopathy resulting from diabetes and this favors a pro-inflammatory/thrombotic state.[175] The ROS produced from metabolic abnormalities play a major role in precipitating micro- and macro- vascular disease through endothelial dysfunction and inflammation.

A recent study found that placental global DNA hypermethylation is associated with GDM independent of established risk factors.[176] Several prior studies, have also found higher levels of DNA methylation in diabetic patients.[177–180] Studies in animals support a positive association between a diabetic metabolic state and global DNA methylation that connect diabetes, oxidative stress, and global DNA hypermethylation.[181, 182] Differential methylation has also been identified in placentas of pregnancies conceived from couples with infertility utilizing different fertility treatments.[104, 109] In fact, we identified differential methylation in pregnancies conceived with different fertility treatments even as early as the late first trimester, during placentation,[101] suggesting that differential methylation states may predispose to adverse pregnancy outcomes, such as GDM that has long term health implications. Further studies are needed to determine methylation patterns that may predict disease.

Conclusion

A multitude of factors (Fig. 1), including genetic and epigenetic factors leading to infertility and the need for fertility treatments can impact placentation. Changes in trophoblast invasion, vascular defects, changes in the environmental milieu, chronic inflammation and oxidative stress are associated with placentation defects leading to adverse maternal and fetal outcomes, which are more pronounced in the infertile population. Similar processes that lead to abnormal placentation are recognized as major contributors to lifelong risk of cardiovascular and metabolic disease for both the mother and her offspring. Thus, abnormal placentation may be the key to better understand how infertility affects overall and long term health.

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Figure 1:

The genetic and epigenetic influences of infertility on placental development, to overall long term health sequelae in maternal and fetal health.