Introductory Chapter: Environmental, Genetic, and Epigenetic Risk Factors in Adverse Pregnancy and Birth Outcomes

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1. Introduction

It is well established that pregnancy complications and adverse birth outcomes are important public health concerns in both developed and developing countries. Prenatal development refers to the process in which an embryo and later fetus develop during gestation. Each pregnancy can be divided into three trimesters of approximately 3 months each. A normal, full-term pregnancy lasts about 40 weeks. During the 40 weeks of pregnancy, the embryo and fetus are heavily influenced by environment (**Figure 1**).

The human placenta is the highly specialized organ of pregnancy that is responsible normal fetal growth and development [1]. It plays an important role in substance exchange between the

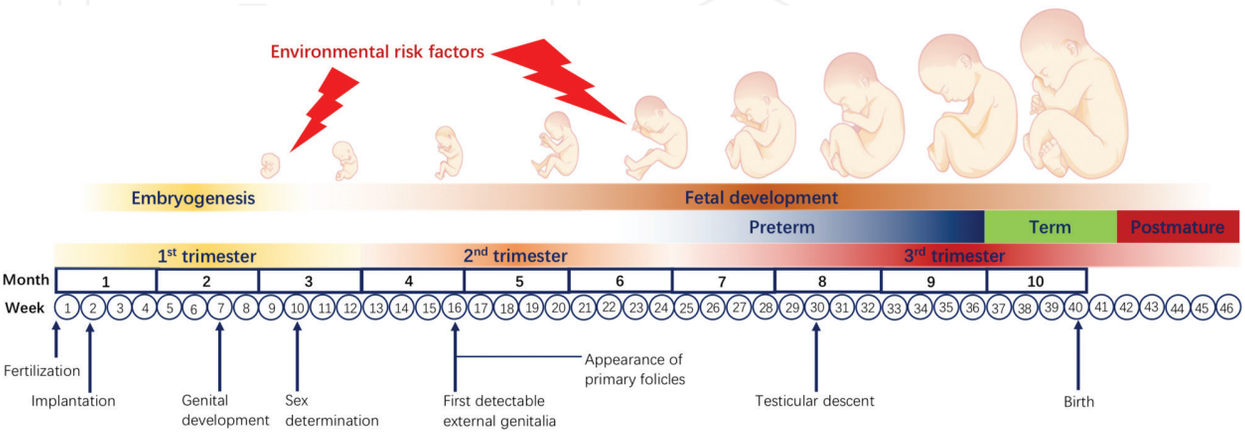

Figure 1. The embryo and fetus are heavily influenced by environment during the 40 weeks of pregnancy.

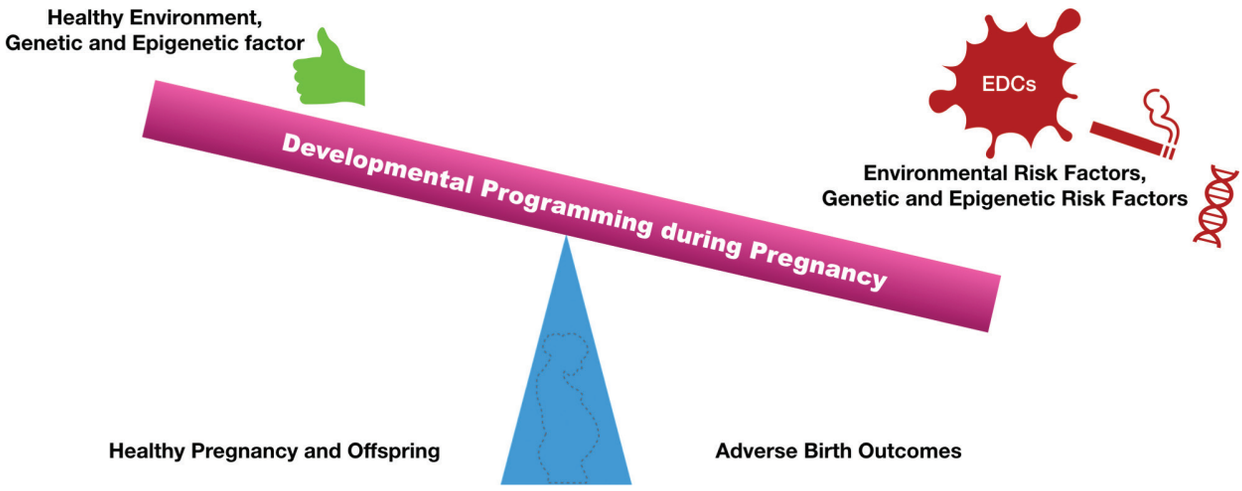

Figure 2. Several risk factors may affect fetal growth and development during pregnancy.

mother and the fetus during pregnancy. Many chemicals can transfer across the placenta and influence the development of the embryo and fetus [2]. The fetus is unable to detoxify substances efficiently because of their weak capability to detoxify toxic chemicals. Additionally, there are many different factors which can cause abnormalities of the placenta, such as environmental risk factors [3], genetic risk factors [4], and epigenetic risk factors [5]. Several studies have demonstrated that placental disorders are associated with pregnancy complications and adverse birth outcomes, including gestational diabetes mellitus (GDM), preeclampsia, miscarriage, preterm birth, stillbirth, macrosomia, and fetal growth restriction (FGR) [6–9]. The cause of pregnancy complications and adverse birth outcomes remains largely unknown but accumulating evidence have proved that environmental risk factors, genetic risk factors, and epigenetic risk factors may play important roles in the etiology and susceptibility of these diseases (**Figure 2**).

The pathogenesis of adverse pregnancy and birth outcomes is multifactorial, involving complex interactions between environmental influences, genetics, and epigenetic mechanisms. This introductory chapter mainly discusses the evidence linking several kinds of risk factors and adverse pregnancy and birth outcomes, such as environmental risk factors, genetic risk factors, and epigenetic risk factors.

2. Environmental impacts on prenatal development

The environment can have an important influence on fetal development. Variety of chemicals have been reported to be present in urine, blood, and amniotic fluid, which indicated that pregnant women around the world are highly exposed to chemicals [10–12]. Additionally, several studies also have shown that a wide range of chemicals has been detected in cord blood and fetal tissues, including bisphenol-A (BPA), phthalates, pesticides, and heavy metals [10, 13].

Environmental risk factors have a deleterious effect on prenatal development leading to problems including premature birth, stillbirth, and low birth weight [14–16]. While environmental hazards pose a definite threat to the developing fetus, they do not always cause adverse effects. The harmful health effect of environmental risk factors is determined by the timing of

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the exposure, the dose/duration of the exposure, genetic susceptibility, and gene-environment interactions [17, 18]. The fetus is particularly vulnerable to environmental hazards that disrupt developmental processes during relatively narrow developmental periods. For example, a birth cohort study of 1390 women found that arsenic concentrations in the third trimester, but not in the first and second trimesters, were negatively associated with birth weight and birth length [19]. Therefore, the timing of exposure during pregnancy is an important factor that may influence the outcome of exposure.

Multiple environmental risk factors, such as exposure to endocrine disrupting chemicals (EDCs), smoking, air pollution, can have a range of impacts on the health of a growing fetus [20, 21]. EDCs have the potential to interfere with endogenous hormone action. Several studies have suggested adverse endocrine disruptive effects of EDCs on the fetus, such as miscarriage, low birth weight, hypospadias, cryptorchidism, and other birth defects [20, 22]. For example, BPA is an EDC that is ubiquitous in modern environments, which provides great potential for exposure of the developing fetus. Links between BPA and endocrine disruption has been implicated in the etiology of several kinds of adverse reproductive outcomes [23, 24]. There is a large body of evidence showing that maternal smoking during pregnancy and secondhand smoking exposure can result in placental problems (previa and/or abruption), miscarriage, stillbirth, premature birth, and FGR [25, 26]. However, quitting smoking (even during pregnancy) greatly reduces the risks of these problems [25].

Although a large number of studies have examined the association between environmental risk factors exposure during pregnancy and adverse pregnancy and birth outcomes, the molecular mechanism of environment-induced adverse pregnancy and birth outcomes is still not fully understood. Thus, further researches are needed to investigate the molecular mechanisms underlying environment-induced adverse pregnancy and birth outcomes.

3. Genetic risk factors and pregnancy complications and adverse birth outcomes

It has been estimated that single nucleotide polymorphisms constitute approximately 90% of all genetic variations in the human populations. Over the past few decades, a number of epidemiologic studies, using both the candidate gene and genome-wide approach, have examined associations between genetic variants and the risk of pregnancy complications and adverse birth outcomes, such as GDM, preeclampsia, preterm birth, small for gestational age, and birth defects [18, 27–30]. Several genetic loci in genes have been identified to be associated with risks of pregnancy complications and adverse birth outcomes [27–29].

Several studies have found that gene polymorphism plays important roles in the susceptibility of pregnancy complications and adverse birth outcomes. A study conducted in the SCOPE pregnancy cohort found that the maternal and infant *FTO* (rs9939609) polymorphism AA genotype was significantly associated with increased risk of small for gestational age pregnancy and spontaneous preterm birth [31]. In a meta-analysis, Zhang et al. identified that nine polymorphisms in seven genes involved in the regulation of insulin secretion were significantly associated with risk of GDM. Among the nine polymorphisms, the rs7903146 in

TCF7L2 showed the strongest association with risk of GDM [27]. The *MTHFR* C677T polymorphism as a common genetic cause for hyperhomocysteinemia was associated with hypertension in pregnancy, preterm birth, and low birth weight [32, 33]. Nurk et al. examined the association between two polymorphisms of *MTHFR* gene (677C > T and 1298A > C) and pregnancy complications, adverse outcomes, and birth defects in 5883 women of the Hordaland Homocysteine Study. They found that the maternal carriage of the *MTHFR* 677C > T polymorphism was associated with the risk of placental abruption. However, they did not find significant associations between *MTHFR* polymorphisms and birth defects [34].

Though a large number of epidemiologic studies have examined the association between gene polymorphisms and adverse pregnancy and birth outcomes, a large portion of the results are inconsistent. Therefore, future studies with larger sample size, genomic-wide association studies (GWAS), and large-scale replications of identified associations are needed to illustrate the most significant genetic variants that associated with risk of adverse pregnancy and birth outcomes. Furthermore, as the genetic association of a polymorphism with adverse pregnancy and birth outcomes does not equate to a casual role, functional analysis should be performed to identify the causal variants.

4. Epigenetics and adverse pregnancy and birth outcomes

In addition to the sequence of the genome, the contribution of epigenetics to adverse pregnancy and birth outcomes is increasingly recognized. Epigenetics refers to heritable changes in gene expression patterns which do not alter DNA sequence. Epigenetics is now recognized as playing an important role in the etiology of human disease [7, 35, 36]. The main epigenetic mechanisms responsible for adverse pregnancy and birth outcomes are represented by DNA methylation, histone modifications, and noncoding RNA [37].

A growing body of evidence demonstrates that aberrant epigenetic modifications are associated with adverse pregnancy and birth outcomes [9, 38]. Using 1030 placental samples, Reichetzeder and colleagues reported that global placental DNA methylation was significantly increased in women with GDM [9]. In the study by Côté et al., maternal glycemia at the second and third trimester of pregnancy is correlated with variations in DNA methylation levels at *PRDM16*, *BMP7*, and *PPARGC1α* and with cord blood leptin levels [38].

The epigenetic signature inherited from the gametes is erased and established after fertilization [39]. The requirement of a high degree of spatial-temporal coordination of epigenetic changes during this process provides opportunities for disruption by environmental chemicals [40]. Unlike inherited genetic variation that is static through the course of a lifetime, epigenetic changes are sensitive indicators of the effects of acute and chronic environmental exposure [41]. Epigenetic mechanisms have been shown to be influenced by environmental factors. Abnormal epigenetic modifications represent an important mechanism for environmental factors influencing the risk of adverse pregnancy and birth outcomes. Exposure to EDCs during pregnancy has been shown to influence epigenetic programming of endocrine signaling and other important physiological pathways, thus further disrupt normal fetal development [42, 43]. The low-dose BPA administration to pregnant mice has been found to

cause hypomethylation at NotI loci that is involved in brain development [44]. Recent animal study has reported that prenatal exposure to di-n-butyl phthalate (DBP) can lead to marked changes in the epigenetic regulation of gene expression [45].

Previous studies have demonstrated that prenatal exposure to some EDCs (such as vinclozolin, methoxychlor, DBP, and DDT) may cause the transgenerational effect of adult disease [45, 46]. In recent years, a growing body of research has spotlighted the role of epigenetic mechanism in the transgenerational effect of prenatal exposure to EDCs [45–47]. Many of the environmentally induced epigenetic changes can be transmitted to future generations and associated with disease phenotypes in the unexposed individuals of subsequent generations. It has been reported that prenatal exposure to DBP may have the transgenerational effect of spermatogenic failure [45]. These adverse outcomes were accompanied by global DNA hypomethylation and spermatogenesis modulator gene (*Fstl3*) promoter hypomethylation, suggesting that prenatal DBP exposure can be imprinted through epigenetic alterations. Additionally, epigenetic markers may be useful as biomarkers for environmental exposure and disease and as potential targets for preventive and therapeutic interventions [48, 49].

This chapter puts an updated overview of the risk factors of adverse pregnancy outcomes and birth outcomes, transgenerational effect of prenatal environmental exposure on health in later life, and epigenetic mechanisms of environmental risk factor-induced adverse pregnancy outcomes and birth outcomes. By this way, these observations can be used to advise pregnant women or women of reproductive age to avoid such exposures and adopt a positive lifestyle to protect pregnancy and normal fetal development. Overall, avoidance of potential risk factors, identification of high susceptible women, and provision of personalized medical care are important in the healthcare management of pregnant women.

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