Adverse Intrauterine Environment and Gamete/Embryo-Fetal Origins of Diseases

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Abstract

The 'fetal origins of adult disease (FOAD)' hypothesis proposes that developmental programming during gestation may influence adult health and disease [1]. It suggests a process where events occurring at critical, or sensitive, periods of fetal development, permanently alter structure, physiology, or metabolism. These changes predispose affected individuals to diseases in later life.

Barker and his colleagues were the first to develop the concept of FOAD based on significant associations between low birthweight and the risk of chronic diseases in adulthood, including coronary artery disease, hypertension and stroke, type 2 diabetes, and osteoporosis. Several other groups confirmed associations between birthweight and adult health in other populations. These adverse intrauterine environments include gestational diabetes mellitus (GDM), intrauterine undernutrition and pre-eclampsia, which are common and severe gestational complications. Furthermore, certain antenatal nutritional disturbances can increase the risk of diseases later in life without affecting fetal growth. In this chapter, we will discuss the evidence related to adverse intrauterine environment and embryo-fetal origins of diseases.

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3.1 Gestational Diabetes Mellitus and Adult Disease

GDM is a common medical complication of pregnancy. It is defined as any degree of glucose intolerance that was not present, or recognized, prior to pregnancy. GDM affects between 2 and 5 % of pregnant women [2]. Intrauterine hyperglycemia has detrimental effects on both mother and fetus. There is increasing evidence that women with GDM are at increased risk of cardiovascular disease, type 2 diabetes and other metabolic diseases of their offspring compared with women without GDM [3, 4]. The FOAD hypothesis proposes that although occurring in response to a transient phenomenon, these adaptations become permanent if they occur during critical periods of early development. Since the fetus is dependent on nutrients from the mother, offspring of GDM adapting to an increased nutrient supply, may be at risk of metabolic diseases in later life. For the same reason, intrauterine undernutrition and intrauterine growth restriction (IUGR) may permanently alter the endocrine and metabolic status of the fetus, thus interfering with physiological functions in later life.

3.2 Intrauterine Undernutrition/Intrauterine Growth Restriction

Undernutrition is still a considerable public health problem in developing countries. Maternal undernutrition can affect several physiological functions of the newborn. Normal fetal growth takes place in two different stages: the first stage, embryonic life, consists of the proliferation, organization, and differentiation of the embryo, whereas the second stage, fetal life, consists of the continued growing and functional maturation of different tissues and organs of the fetus. Clinically, intrauterine growth retardation (IUGR) describes newborns with a birthweight below the 10th percentile for their gestational age with pathological restriction of fetal growth due to adverse genetic or environmental influences. The offspring develop type 2 diabetes mellitus, cardiovascular diseases and metabolic syndrome in adult life, especially when followed by rapid postnatal ‘catch-up’ growth. Fetal malnutrition not only induces adaptations necessary for fetal survival and health, but also undermines future health if the postnatal environment is unfavourable.

3.2.1 Studies in Human

Many epidemiological studies show that impaired fetal growth resulting from IUGR was associated with the development of arterial hypertension and cardiovascular disease, dyslipidemia, glucose intolerance or even type 2 diabetes and visceral adiposity during adult life [5–11]. All are features of the metabolic syndrome and contribute to morbidity and mortality in later life. These studies were undertaken in the UK, and subsequently confirmed in other countries such as Holland, South

Africa, India and other developing countries [5, 12–15]. Short stature, premature adrenarche and polycystic ovarian syndrome (PCOS) are also endocrinological associations of IUGR [16].

3.2.2 Epidemiological Studies

Intrauterine growth restriction is associated with increased risks of ischaemic heart disease and hypertension in later life. Vascular endothelial dysfunction has been implicated in hypertension, insulin resistance, type 2 diabetes and atherosclerosis. An increase in stiffness of large arteries causes a rise in systolic blood pressure and isolated systolic hypertension [17, 18]. Altered structure and numbers of small arteries and capillaries may also play a significant role in the development of increased peripheral resistance.

Leptin, a major adipokine secreted by adipose tissue, regulates food intake and energy expenditure. Tzschoppe et al. [19] compared placental leptin synthesis and leptin-binding capability in venous cord blood between IUGR newborns (<10th percentile), and, appropriate-for-gestational age neonates (AGA, 10–90th percentile). They found that placental leptin synthesis was significantly higher in IUGR infants compared to AGA infants, and, leptin-binding capability in venous cord blood was increased in IUGR newborns. Reduced biologically-active leptin levels may contribute to perturbed regulation of appetite. IUGR may also affect the development of adipocytes. Development of obesity is associated with increased adipocyte differentiation, adipocyte hypertrophy, and/or upregulation of lipogenic genes. As an adipogenic transcription factor, PPARG2 promotes adipocyte differentiation and lipid storage [20]. Therefore, IUGR individuals may demonstrate dysregulation of appetite, and abnormal activation of adipocytes, contributing to development of obesity.

Ten per cent of children born small for gestational age (SGA) remain short, which constitutes a significant proportion of adults with short stature. Growth hormone (GH) trials in the USA and in Europe led to the approval of GH for treatment of short stature in SGA infants. GH treatment reduces body fat while promoting lean body mass, with a 40 % drop in circulating high molecular weight adiponectin and a 30 % lowering of follistatin. The change in adiponectin may explain the decrease in insulin sensitivity when GH is given. Follistatin inhibits myostatin, so a decline in follistatin might be expected to reduce muscle mass. On the other hand, it promotes adipogenesis and thus the decline contributes to the reduction in fat mass that occurs in response to GH [16].

Reproductive endocrinology is also disturbed in IUGR infants. Young women are at increased risk of polycystic ovarian disease and early menarche. Leptin has effects upon GnRH secretion and is a risk factor for early development of puberty and potentially menarche. Young women who are overweight are more likely to suffer early puberty. The insulin-resistance and dyslipidaemia that follows SGA birth in young women may yield a hyperandrogenic state, resulting in premature pubarche followed by PCOS in adolescence. Controlled trials of metformin to

determine its effect on the clinical course of premature pubarche also demonstrate that early metformin can prevent or delay manifestations of hyperandrogenism, including PCOS [16].

3.2.3 Experimental Studies

Insulin resistance is one of the most common adult outcomes associated with IUGR infants. Preterm SGA infants have lower insulin sensitivity than preterm, AGA infants in the first few months of life [21]. Epidemiological studies demonstrate that IUGR infants were more likely to suffer from glucose intolerance as adults. A key fetal adaptation to poor fetal nutrition is upregulation of insulin receptors without upregulation of insulin signalling in fetal skeletal muscle [21]. However, postnatally in IUGR infants there is upregulation of both insulin receptors and insulin signalling pathways. At birth, SGA infants have low concentrations of circulating insulin and insulin-like growth factor-1 (IGF1). In 48 h after birth, they are more insulin-sensitive, and, have high plasma non-esterified fatty acid (FFA). They then undergo a period of accelerated postnatal growth associated with increased insulin sensitivity. This early period of increased insulin sensitivity and accelerated growth precedes subsequent development of insulin-resistance later in life [21].

Endothelial dysfunction in adults is another common outcome in IUGR infants. Leeson et al. [22] found that low birthweight was associated with reduced, endothelium-dependent dilatation in children aged 9–11 years. Cardiovascular risk factors showed no relationship to flow-mediated dilation, but an inverse relationship with HDL cholesterol levels. The inverse relationship with blood HDL cholesterol concentrations might imply a role for the lipid environment in the origin of the defect; endothelial dysfunction being a consequence of a primary defect in lipid metabolism. Flow-related, vasodilatation was impaired in low birthweight children relative to normal birthweight at age x years [23]. Endothelium-dependent vasodilation of normal birthweight children was 1.5 times that of low birthweight children at the same age [24]. In low birthweight children, the maximal hyperaemic response was reduced, whereas the acetylcholine response was unaffected [24]. Although Goodfellow [23] found no evidence of a correlation between birthweight and serum concentrations of von Willebrand factor, a marker of endothelial cell activation, in fit young adults, a smaller study found higher concentrations in low birthweight subjects [25].

Martin [24] reported that low birthweight children showed increased carotid artery stiffness compared with normal birthweight controls at age 9 years. Another study of 281 young adults demonstrated that low birthweight was related to increased carotid, femoral and brachial artery stiffness [26]. Changes in the architecture or the number of peripheral arterioles and capillaries have been implicated in the aetiology of increased peripheral vascular resistance in hypertension, which could partially contribute to the observed relationship between the resistance index (RI) and birthweight [27, 28].

3.2.4 Animal Studies

Several animal models demonstrate that maternal undernutrition during the neonatal period can affect offspring. Among these various models, many similarities of adult offspring phenotypes are observed including raised blood pressure, insulin resistance and increased adiposity, which are hallmarks of the metabolic syndrome [11, 29].

Intrauterine growth retardation in animals can be induced by both prolonged modest changes in maternal diet, and, by more severe changes in uterine blood supply. The effect of maternal protein restriction in rodents on the phenotypes of offspring has been assessed, including insulin resistance, dyslipidaemia and hypertension. In both rats and sheep, low newborn weight has been associated with an increased risk for type 2 diabetes with abnormal insulin secretion and glucose intolerance [30, 31]. Nevertheless, the effect of IUGR on whole body insulin sensitivity and metabolic activity in adult rats which were fed either a normal protein diet or a low protein diet during pregnancy and 2 weeks of lactation, suggests that IUGR results in improved insulin sensitivity without 'catch-up' growth. Animal models also suggest that leptin deficiency, or leptin resistance, may result in the pathogenesis of the metabolic syndrome in IUGR offspring [32, 33]. IUGR rat offspring showed significantly increased expression of PPARG both as newborns and as adults. Further, the expression of adipogenic transcription factors regulating PPARG was also upregulated in both groups. Maternal protein restriction also leads to endothelial dysfunction in isolated small arteries from adult rat offspring [34, 35]. Small resistance arteries of adult offspring exposed prenatally to a 50 % reduction in maternal protein intake appeared to demonstrate endothelial dysfunction, although dilatation in the aorta was normal. Reduced endothelium-dependent vasodilatation of cerebral microvessels in offspring of dams fed a low-protein diet [36].

Hypoxia-induced IUGR has long-term effects on cardiac susceptibility to ischaemic-reperfusion injury that are independent of sex and age [37]. This group also identified a mismatch in glucose metabolism, resulting in proton accumulation in the post-ischaemic myocardium of IUGR offspring as a potential mechanism [37]. There have been few studies of arterial distensibility in models of maternal nutrient restriction. However, loss of diurnal variation in heart rate and blood pressure in adulthood has resulted from maternal undernutrition followed by postnatal overnutrition [38].

Are adverse outcomes in IUGR infants gender-specific? Food-restricted (FR) male rats develop increased hepatic triglyceride and cholesterol content with elevated sterol regulatory element-binding protein-1c, fatty acid synthase, and lipoprotein lipase expression [39]. However, FR females have decreased hepatic cholesterol levels., and, plasma lipid levels in FR males and females did not differ significantly. These data suggest that intrauterine events may result in sex-dependent, altered lipid metabolism with an increased risk in male rats.

3.2.5 Underlying Mechanisms

Lifelong programming of the ACTH/hypothalamic–pituitary–adrenal (HPA) axis has been proposed as a mechanism to explain the association between low-birthweight infants and later development of metabolic syndrome and hypertension in adult life. Increased cortisol levels due to alterations in the regulation of the ACTH/glucocorticoid axis may be one mediating mechanism. Indeed, infants born after significant exposure to stressful conditions are often SGA and have blunted HPA axis responses to stressors compared to AGA infants. These findings are consistent with animal models showing that adverse intrauterine conditions can result in blunted cortisol responses to acute stressors and may provide a mechanism for adult susceptibility to disease for SGA infants [40].

The predictive-adaptive response (thrifty phenotype) hypothesis proposes that the fetus makes adaptations in the early developmental period based on the predicted postnatal environment. If prenatal and postnatal environments match, the physiological settings achieved through the processes of developmental plasticity will leave the organism well prepared for the postnatal environment and the organism will cope adequately with postnatal cues. A mismatch between prenatal and postnatal environments renders the organism more susceptible to later disease [41]. Any evidence to support this hypothesis?

If adverse events take place during intrauterine life, especially during a specific crucial window of developmental plasticity, epigenetic modifications may alter the expression of genes. This may drive metabolic pathways towards survival in the short term, but has detrimental long-term impact during adult life [41, 42]. Non-genomic changes may take place during the crucial window of developmental plasticity [43]. Shifts in the transcriptional activity of DNA may produce sustained metabolic adaptations. Within tissues and organs that control metabolic homeostasis, a range of phenotypes can be induced by sustained changes in maternal diet via modulation of genes that control DNA methylation or histone acetylation, or through small non-coding RNAs activity [44, 45]. The phenotypic effects of epigenetic modifications during development may not manifest until later life, especially if they affect genes modulating responses to later environmental challenges, such as high-fat diet [41].

Lambertini et al. [46] showed widespread epigenetic changes in IUGR infants, and, suggested the possibility that a specific signature in the epigenome may characterise IUGR infants. However, the relationship between the programming of specific genes and alterations in subsequent growth and metabolism is obscure. Einstein's group [47] identified epigenetic alterations that may provide a mechanism linking IUGR with T2DM later in life. They identified 56 candidate loci near genes controlling growth such as those involved in the cell cycle. Reductions in DNA methylation in the HNF4A promoter region may be responsible for maturity onset diabetes while, epigenetic changes in the H19/IGF2 locus may be a site related to human IUGR [47].

In recent years, it became clear that the onset of puberty is also regulated by genes that underlie epigenetic modification. The onset of puberty is accompanied by

alteration of DNA methylation and histone modification of transcriptional repressors, contributing to activation of genes that are known to be critically involved in the onset of puberty. Genome-wide analysis of hypothalamic DNA methylation reveals profound changes in methylation patterns associated with the onset of female puberty [48].

DNA methylation and histone acetylation are potential explanations for the mechanisms involved in fetal origins of adult diseases. Micro-RNA's also represent a possible mechanism. miR-16 and miR-21 expression are markedly reduced in the placenta of growth-restricted infants [49]. The potential role of miR-21 is intriguing because it targets genes that affect apoptosis and the cell cycle. Traditional genetic inheritance may also play a role. Genetic variations affecting the insulin axis might influence both birthweight and subsequent development of T2DM, and, explain transgenerational effects. Finally, epigenetic modifications are frequently tissue-specific, so findings in the placenta may not apply to muscle, adipose tissue or pancreatic cells [16].

3.3 Preeclampsia

Preeclampsia is a syndrome defined by the hypertension and proteinuria, which typically occurs after 20 weeks of gestation and resolves after delivery. Depending on ethnicity, the incidence of preeclampsia ranges from 3 to 7 % in nulliparae and 1 % to 3 % in multiparae. Overall, 10–15 % of maternal deaths are directly associated with preeclampsia and eclampsia. Although this multisystem disorder constitutes a major cause of maternal mortality as well as perinatal morbidity and mortality worldwide, the mechanisms underlying the development of preeclampsia are not yet understood [50].

Pre-eclampsia is not just an isolated disease of pregnancy. It also increases the vulnerability of offspring to adult diseases, including cardiovascular diseases, obesity and cancer. Offspring of pregnancy complicated by preeclampsia tend to be thinner, have higher blood pressures [51–53], and, they are more likely to suffer stroke and epilepsy [54, 55]. However, the daughters of women with preeclampsia during pregnancy have higher risks of breast cancer [56]. Explaining these disparate associations has been speculative rather than derived from a consistent, unifying hypothesis.

3.3.1 Studies in Human

Pre-eclampsia is associated with an increased risk of hospitalization for a number of diseases among non-SGA children born at term including infectious and parasitic diseases, diseases of the blood and blood-forming organs, endocrine, nutritional, and metabolic diseases, diseases of respiratory system, and, congenital malformations. SGA is associated with an increased risk of several diseases in adult life [57].

Davis et al., using the available BP data, found that children exposed to preeclampsia in utero have approximately 2–3 mmHg higher SBP (systolic BP) during childhood and young adult life [58]. Long-term follow-up studies demonstrate a doubling of risk from stroke [54]. Debbie et al. also confirmed that conclusion, and supported the view that preeclampsia and gestational hypertension were risk factors specific for higher blood pressures in offspring [59]. The key biological pathways relevant to the cardiovascular health of offspring are therefore likely to have additional effects, on other features of stroke risk, beyond clinic blood pressure measures alone.

Male and female offspring have similar outcomes except that males exposed to mild or severe preeclampsia have an increased prevalence of congenital malformations of the genital organs [57]. Males, born at term exposed to severe preeclampsia, had an increased risk of diseases of the blood and blood-forming organs, and, disorders of the immune system. While females exposed to severe preeclampsia or eclampsia had an increased risk of cerebral palsy, and, diseases of the musculoskeletal system and connective tissue [57].

3.3.2 Epidemiological Studies

Pre-eclampsia and IUGR result from inadequate formation of spiral arteries that may compromise the flow of nutrients and oxygen to the fetus, and, similarly reduce transportation of waste from the fetus. Offspring of preeclampsia pregnancies do not have higher risks of obesity. Moreover, after adjusting for parental BMI, there is an inverse association between preeclampsia and the BMI of offspring, as mothers experiencing preeclampsia are more likely to have higher BMI [51, 60]. However, in preeclampsia pregnancy, there is no difference in height between offspring of preeclampsia and normotensive pregnancies [57, 60, 61].

Offspring of preeclampsia pregnancies have lower risks of developing breast or prostate cancer, possibly due to abnormal intra-uterine exposure to sex hormone. Trichopoulos [62] hypothesized that the developing breast is influenced by the fetal environment, particularly variations in hormone concentrations, which could mediate subsequent breast cancer development. Trichopoulos [62] also proposed that increased concentrations of oestrogens in pregnancy increase the probability of future occurrence of breast cancer in daughters. Maternal, urinary estriol excretion declines late in preeclamptic pregnancies [63]. However, circulating maternal estrogens near delivery do not seem to be lower in preeclampsia [64, 65]. The limited data are not consistent with lower umbilical cord blood estriol, estradiol, and estrone concentrations in preeclampsia. Vatten et al. [65] found higher concentration of AFP in cord blood in pregnancies complicated by severe preeclampsia, and, they indicated that elevated AFP levels are associated with reduced breast cancer risk among female offspring. The authors attributed their findings to an anti-oestrogenic effects of AFP [65]. It has also been suggested that exposure to elevated androgen concentrations mediate the associations of preeclampsia with lower breast cancer risk [66]. Low expression of the aromatase gene, or a small or impaired placenta, as

found in preeclampsia, increases the release of androgens from the placenta late in pregnancy when the fetal adrenal gland, the source of dehydroepiandrosterone (DHEA)-sulfate, undergoes rapid growth. Elevation of androgen, accompanied by low sex-hormone binding globulin in fetal blood, might confer long-term protection against breast carcinogenesis by antagonizing the effect of estrogens on ductal development in the fetal breast. Other factors, such as some angiogenic factors, growth factors and endocrine factors may contribute to these associations [56, 67, 68].

3.3.3 Experimental Studies

Women with a history of preeclampsia are at increased risk of type 2 diabetes in later life. However, some studies demonstrate that birthweight is more important than preeclampsia in the development of type 2 diabetes. There is also a strong relationship between babies who have been small for gestational age and subsequent development of type 2 diabetes [69]. Tenhola et al. [70] measured mean concentrations of serum total LDL, HDL, cholesterol, triglycerides, fasting insulin, blood glucose, serum cortisol and dehydroepiandrosterone sulfate in offspring of pre-eclampsia pregnancies and offspring of non-preeclamptic pregnancies. There was no difference between these two groups, however, SGA children of preeclampsia pregnancies had the highest concentrations of serum total LDL and cholesterol. The concentrations of LDL and cholesterol are higher than AGA children of preeclamptic pregnancies, or, in SGA or AGA children of non-preeclamptic pregnancies - even though the differences were not significant [70]. Pre-eclampsia is positively associated with offspring BP after adjustment for family adiposity, suggesting IUGR may mediate this association. Another perinatal cohort study examined whether IUGR and childhood growth trajectory may mediate the association between pre-eclampsia and childhood SBP at 7 years of age. Results demonstrate that preeclampsia-eclampsia was significantly associated with higher SBP, independent of IUGR [52]. This finding suggests that other mechanisms may be involved, such as genetic transmission and placental-fetal vascular impairment [51, 52]. Jayet et al. [53] showed that offspring of mothers with preeclampsia displayed marked vascular dysfunction in the pulmonary and systemic circulations, as evidenced by 30 % higher pulmonary artery pressure, and, 30 % lower flow-mediated dilation (FMD) of the brachial artery. Moreover, oxidative stress was increased in offspring of women with preeclampsia, and, suggests that it might represent an underlying mechanism. Finally, pulmonary artery pressure during nitric oxide inhalation remained significantly higher in offspring of mothers with preeclampsia than in control subjects, suggesting that a structural defect, possibly related to remodelling of the pulmonary vascular wall, also contributes to pulmonary hypertension. Thus, preeclampsia leaves persistent defects in the systemic and pulmonary circulation of the offspring. This predisposes offspring to exaggerated hypoxic pulmonary hypertension during childhood and may contribute to premature cardiovascular disease later in life.

Eero Kajantie et al. [54] found that children from pregnancies complicated by severe pre-eclampsia were thin at the age of 2 years. This is consistent with the

reported association between thinness at 2 years of age, and, later hemorrhagic and thrombotic stroke. This association was not the result of the children's living conditions after birth as assessed by the father's occupation. This led to the suggestion that the association was a consequence of fetal undernutrition leading to thinness at birth that persisted through infancy. Statistical analysis showed the association between people exposed to pre-eclampsia with increased risk of hemorrhagic or thrombotic stroke was independent of the babies' birthweight or gestational age at birth. Babies from pregnancies complicated by pre-eclampsia had reduced brain circumferences, probably as a consequence of impaired brain growth in uterus[54]. The investigators speculate that stroke may originate through reduced brain growth in utero as a consequence of fetal undernutrition. Given the redistribution of cardiac output in favor of the brain, one of the fetal brain-sparing responses, may permanently change the structure of the cerebral arteries. They speculated that stroke might originate in two ways in pre-eclampsia, either through reduced brain growth or impaired brain growth leading to "brain sparing" responses.

Wu et al. [55] reported that prenatal exposure to pre-eclampsia was associated with an increased risk of epilepsy in children born after 37 weeks of gestation. The mechanisms underlying the associations between them were unclear, but probably because pre-eclampsia may cause fetal brain ischemia and vascular fetal brain lesions. Pre-eclampsia has been shown to be an important risk factor for neonatal encephalopathy [71]. The association may be mediated by placental dysfunction. The fact that preeclampsia was associated with an increased risk only in children who were born after 37 weeks of gestation reflects that other causes of preterm birth outweigh the effect of preeclampsia or indicates that the pathology related to preeclampsia needs gestational time to increase the susceptibility to epilepsy, or, the fetal brain may be more susceptible later in pregnancy [54].

3.3.4 Animal Studies

In pre-eclampsia, the spiral arteries inadequately remodel so that uterine flow is reduced by 50 % and there is chronic placental ischaemia or, at best, intermittent flow that induces an ischaemia/reperfusion phenomenon [72]. Reactive oxygen species (ROS) and cytokines released from the ischaemic placenta trigger systemic oxidative and inflammatory reactions. The placenta also overexpresses anti-angiogenic factors that inhibit the normal function of pregnancy-related proangiogenic factors, including VEGF (vascular endothelial growth factor) and PlGF (placental growth factor). The combination of these factors may stimulate systemic endothelial dysfunction that is consistently found during symptomatic pre-eclampsia in the mother.

Offspring of pre-eclamptic pregnancies develop from the first trimester onwards within an environment of placental insufficiency and restricted oxygen supply. By the start of the second trimester the offspring are confronted with elevated circulating anti-angiogenic factors, which antedate the later emergence of the clinical pre-eclamptic syndrome and systematic maternal inflammatory, oxidative

and dysfunctional endothelial states [5]. To mimic the human syndrome an animal model needs to develop the cardinal features of pre-eclampsia, which include pregnancy-specific hypertension, proteinuria and associated alterations in vascular function and biomarkers. Although a variety of models exist that are based on different aspects of the pathophysiology of pre-eclampsia, no model has been able to successfully mimic all the pathophysiological features of pre-eclampsia, or, to accurately replicate the first trimester origin of the human condition.

Mechanical reduction in maternal uterine artery blood flow by unilateral or bilateral uterine artery ligation in animal models induces a pregnancy-specific increase in maternal blood pressure [73]. If uterine perfusion I reduced at 14 days of gestation, changes in resting BP are consistently pronounced in the offspring throughout life. When uterine perfusion takes place later in gestation, despite resulting in growth restriction, either no increase in BP or modest changes in later life was observed [73]. However, early ligation of uterine vessels has been associated with the full range of features of preeclapsia in dams, including disordered antiangiogenic factors and vascular dysfunction.

The pathogenesis of pre-eclampsia may be described in two stages. The initial stage indicates abnormal placental implantation, followed by transition to the second stage of endothelial dysfunction. Placental insufficiency is likely to lead to offspring of pre-eclamptic pregnancies developing in an environment of significant hypoxia from early in the pregnancy [74]. Early placental development takes place under low oxygen environment as this predates the formation of an effective maternal-fetal circulation, while abnormal placentation in pre-eclampsia is likely to result in significantly lower oxygen delivery to the fetus for the majority of gestation [75]. In mice, exposure to anoxic circumstances induces hypertension, proteinuria, IUGR, renal pathology and elevations in maternal soluble endoglin (sEng). When the data from models of pregnancy hypoxia are collected, there is a striking lack of consistent reports of elevated BP in the offspring, suggesting that hypoxia alone is insufficient to induce the long-term effects of pre-eclampsia, or, that the levels of hypoxia currently used are not representative of the levels offspring are exposed to during development [76].

Many studies show an increase in levels of circulating anti-angiogenic factors including sFlt-1 and sEng [77, 78]. sFlt-1 inhibits the normal function of pregnancy-related angiogenic factors, including VEGF and PlGF [77]. Overexpression of sFlt-1 in rats induces hypertension, proteinuria and glomerular endotheliosis, even in non-pregnant rats. Lu et al. [79] found gender-specific impacts on weight and BP in offspring. Male offspring born to sFlt-1–treated pregnant mice have significantly lower birthweights than male offspring of the control group, while there was no significant difference in the post-weaning weight in female offspring. Furthermore, mean, systolic, and diastolic BP were significantly higher in male offspring born to sFlt-1–treated mothers, while no differences existed in female [80]. In maternal under-nutrition models, the increase of BP is more pronounced in male offspring than female.

The specific role of systemic maternal endothelial dysfunction is relatively easier to study in animal models. These models are based either on systemic

inhibition of eNOS (endothelial NO synthase) by administration of L-NAME (NG-nitro-larginine methyl ester) or by eNOS knockout [81]. The mice consistently show abnormal endothelial function and, through selective breeding of an eNOS-knockout mother with a wild-type male, an experimental scenario can be produced to study the effect of maternal endothelial dysfunction on the in utero development of an eNOS-heterozygous offspring. These offspring have higher BP during adulthood than the genetically similar offspring bred from a wild-type mother and an eNOS-knockout father, who differ only in that their in uterine development was in a wild-type mother with normal endothelial responses [81]. The study indicates that the maternal eNOS genotype influences both blood pressure and behavior of offspring, possibly because developmental programming associated with intrauterine growth retardation. In addition, prenatal exposure to glucocorticoids can induce adult cardiovascular and metabolic physiological dysfunction in gender-specific patterns [82, 83]. Male embryos may be more susceptible to maternal environment and cannot adapt successfully. This gender sensitivity may be attributable to differences in the hormonal status between the two different genders where females may have a protective effect in relation to hypertension and epigenetic factors.

3.3.5 Underlying Mechanisms

The mechanisms underlying pre-eclampsia or eclampsia include chronic uterine ischemia, dysfunction of the nitric oxide system, insulin resistance, hypersensitivities of the autonomic nervous and rennin-angiotensin systems, activation of a systemic inflammatory response, and activation of circulating proteins that interfere with angiogenesis. In pre-eclampsia, exposure to the abnormal intra-uterine circumstances leads to vascular structural remodeling, that persists into post-natal life. In animal models, there is also evidence of increased aortic stiffness, as well as greater elastic fibre content in the vessel wall [84]. By adult life, 16-month-old offspring of hypoxic dams exhibit distinct vascular structural changes with oedematous and necrotic aortic endothelium and disarranged proliferative smooth muscle cells [85]. Other studies of rat model offspring have also identified an increased propensity to develop arterial internal elastic lamina lesions, an early atherosclerotic process, at 8 and 16 weeks of age [86]. These observations underline development of an early atherogenic phenotype, as a potential link between pre-eclampsia exposure and later cardiovascular disease. Consistent with the observations in above animal studies, offspring of pre-eclamptic pregnancies also show an increased intima-media thickness with aortic arterial thickening already evident at birth [87]. In an sFlt-1 overexpressing model, sFlt-1 as a splice variant of the VEGF receptor Flt-1 seems to be involved centrally in the pathogenesis of preeclampsia. The high levels of circulating sFlt-1 in early pregnancy predict later onset of preeclampsia. These increased levels of sFlt-1 are accompanied by reduced levels of free VEGF and PlGF in the maternal circulation, suggesting that sFlt-1 inhibits VEGF and PlGF. This prevents them from binding their endothelial cell receptor, resulting in

abnormal angiogenesis and altered circulation at the utero-placental interface, and consequently poor perfusion of the placenta-fetal unit [79].

Exposed to hypoxia during late gestation, rat offspring manifest increased cardiac size, reduced left ventricular wall thickness, reduced cardiomyocte proliferation as well as epicardial detachment [88]. Since the epicardium is a major source of growth factors during cardiac development, this detachment of the epicardium in fetal life may be one potential mechanism of the myocardiac changes. Higher levels of apoptotic proteins and induction of HIF -1α are also involved in this process [89, 90]. In addition, maternal hypoxia can change cardiac collagen content of offspring, via a potential link between in utero hypoxia and later cardiovascular disease via alterations in cardiac ischaemia/reperfusion mechanisms. Rats exposed to hypoxia in late gestation had alterations in cardiac proton production and increased myocardial production of acetyl-CoA during reperfusion [37, 90]. In fetal life, such animals also have significant reductions in cardiac PKCε (protein kinase Cε), which may be secondary to increased methylation at the PKCε promoter site [91]. PKCε plays a critical role in cardioprotection during ischaemia [92].

Endothelial dysfunction is an early biological factor in the development of atherosclerotic vascular disease and predisposes to the development of left ventricular hypertrophy. Model offspring have enhanced vascular contraction in response to phenylephrine and a reduction in endothelium-dependent relaxation during early life. Experimental studies imply several potential mechanisms underlying vascular abnormality. In model offspring, both basal and acetylcholine-induced NO production is reduced in arterial segments. A characteristic feature of pre-eclampsia is a derangement of circulating anti-angiogenic factors. Persistent abnormalities in anti-angiogenic factors in the offspring may lead to persistent endothelial dysfunction in later life. Nevertheless, study of anti-angiogenic factors in children of 5–8 years of age has demonstrated no long term difference [93]. On one hand, it is possible that intrauterine exposure to anti-angiogenic factors causes altered in utero endothelial development and physiology. Consistently, sFlt-1 administered in vitro inhibits endothelial cell proliferation and tubule formation [94]. Additionally, HUVECs from pre-eclamptic donors appear to differ from normal in their response to oxygen levels. Under normal oxygen conditions, they develop a higher numbers of connections and shorter tubule lengths, creating networks similar to those seen when control cells were grown under hypoxic conditions [95]. These data indicate that endothelial cells from pre-eclamptic pregnancies may be fixed in a 'hypoxic' phenotype. On the other hand, it is possible that endothelial dysfunction represents a biomarker of other underlying metabolic abnormalities related to cardiovascular disease. Alternatively, the vascular changes may be inherited between mother and child. Polymorphisms in certain genes, such as those encoding eNOS, angiotensin converting enzyme and angiotensin, have been proposed as potential links underlying the development of the condition [96, 97]. During fetal life, adverse exposures may lead to heritable characteristics through programming of the epigenome, as the greatest level of active programming of the epigenome occurs during fetal life [98]. Hypoxia is a promising stimulus for epigenetic programming since it has been shown to induce a global decrease in transcriptional activity in the vascular endothelium [99].

3.4 Conclusions

Adverse intrauterine environments, including GDM, intrauterine undernutrition/IUGR and pre-eclampsia, adversely influence the responses of offspring to later challenges. Obesogenic diets or physical inactivity increase the risk of future disease predisposing to insulin resistance, type 2 diabetes, obesity and cardiovascular disease. Prevention of these disorders must begin in the uterus and continue throughout the life course. Special emphasis should therefore be given to optimal intrauterine milieu and to the avoidance of an obesogenic postnatal environment to reduce poor adult health outcomes.

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