The Placenta
From Development to Disease

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The Placenta - friend not foe

The placenta is central to the survival of the fetus. Placental dysfunction, whether from disease or maldevelopment, therefore threatens the fetus and its mother. Disruption to normal placental function can disrupt fetal development in ways that are not apparent until long after birth. The crucial role of the placenta for fetal well being, the developmental origins of human adult disease and cardiovascular health, and maternal placental syndromes is now being unravelled.

The Placenta: From Development to Disease examines research into placental function and its clinical implications to provide a springboard for improving clinical practice and enhancing medical research. Influential information is extracted from the compelling narrative by the use of ‘take home’ features including:

- Clinical Pearls – pointing to important issues in clinical practice
- Research Spotlights - highlighting key insights into placental understanding
- Teaching Points – explaining basic concepts for novice readers

The Placenta: From Development to Disease is ideal for both experienced clinicians and researchers and those new to the field. Anyone who needs to understand the central importance of the placenta in the well being of their maternal and fetal patients should read this book.

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The Placenta
From Development to Disease
To Brian, Emily and Allison for their unwavering support

To Peggy, my childhood sweetheart and wife

To the memory of my grandmother, Fengtong Zhao
The Placenta
From Development to Disease

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Preface

The human placenta is central to the important events that influence not only development and growth of the fetus but also the risks for multiple adult diseases in both the mother and offspring. Diabetes mellitus, obesity, and cardiovascular disease, among others, have origins in utero where the placenta plays a pivotal role. Our goal as editors of *The Placenta: From Development to Disease* was to create a comprehensive, yet succinct, resource for new investigators and clinicians, while also providing a manual for senior investigators and experienced clinicians who mentor trainees at all educational levels.

With this ambitious goal in mind, we selected topics of interest to both clinicians and researchers. We first introduced the contemporary concepts about the placenta’s central position in the developmental origins of human adult disease (DOHAD) and in the cardiovascular health and maternal placental syndromes (CHAMPS). We then described the developmental biology of the placenta and the further dissection by molecular analyses for the structure and function of this organ, including assessments of metabolic, secretory and transport functions. We have highlighted key techniques used to study the placenta, both in the laboratory and in the clinical setting. Indeed, our authors provide some chapters with step-by-step instructions for study of the placenta by newcomers. From there we move to specific clinical disorders that influence pregnancy outcomes, underscoring the pivotal role the placenta plays in each. We conclude with topics that are at the forefront of clinical and research applications, including proteomics, stem cell development, and prenatal diagnosis by analysis of cell-free RNA and DNA from trophoblast.

The chapters are designed to be reader friendly, and the clinical pearls, research spotlights, and teaching points are targeted at the novice. For seasoned investigators, we hope the overviews of topics outside their area of research and the technique chapters will be especially useful for training. For experienced clinicians, we aimed to heighten awareness of the diverse functions performed by the placenta and to provide insights into how the placenta can be a window to current and future disease(s).

Most importantly, *The Placenta: From Development to Disease* would not be possible without the committed efforts of the authors of the chapters. Clinicians and investigators; students, trainees, and postdoctoral fellows; and junior and senior investigators from around the world—all have contributed to this endeavor. We owe tremendous gratitude to each of them for their insightful contributions, their attention to deadlines, and their willingness to allow us to edit their chapters, sometimes brutally, for uniformity of style. Without these talented authors, we as editors would not have been able to produce a book with the breadth and depth, yet succinct writing style, that we feel has blossomed. Last but certainly not least, we thank the publishers at Wiley-Blackwell for their recognition of the importance of the placenta as a subject for a book and for their editorial support throughout this endeavor.

Sincerely,

Helen Kay
D. Michael Nelson
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PART I

Fetal Origins of Adult Disease/Programming
CHAPTER 1
Maternal Undernutrition and Fetal Programming: Role of the Placenta

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Introduction

What is developmental origins of health and disease (DOHaD)?

DOHaD is an area of research that emerged following retrospective cohort studies of David Barker and colleagues during the late 1980s. These investigators studied the association of geographical distribution of heart disease in the United Kingdom to a person’s birthplace, irrespective of the place where individuals develop disease [1]. Their data suggested that environment in early life causes permanent changes in fetal physiology that predisposes the adult to disease later in life. Association of early undernutrition with low birth weight is a major component of fetal programming of the Barker hypothesis. The key contention of the Barker hypothesis is that the undernourished fetus is programmed to exhibit a “thrifty phenotype,” and this predisposes to a lifetime of increased food intake and fat deposition. Such individuals develop obesity, diabetes, and hypertension as adults, due to alterations in homeostatic regulatory mechanisms as a fetus.

The placenta is a multifunctional organ that synthesizes, metabolizes, and transports nutrients required by the fetus. The placenta is also a source of hormones that influence fetal, placental, and maternal metabolism and the course of fetal development. By virtue of these roles, the placenta plays a pivotal role in fetal programming.

Scope of problem

Four hundred thousand children in the United States alone are born annually with low birth weight resulting from intrauterine growth restriction (IUGR). IUGR is variably defined, but a common definition is a fetal weight below the 10th percentile for gestational age as determined by antenatal ultrasound (hence the phrase IUGR) or by newborn birth weight percentiles (hence the phrase small for gestational age). IUGR babies exhibit aberrant development and require higher neonatal intensive care. In addition to the short-term risks, the long-term risk of developmental programming includes metabolic disorders later in life. Up to 63% of adult diabetes, hypertension, and heart disease may be attributed to low-birth-weight conditions in conjunction with an accelerated newborn-to-adolescent weight gain and obesity. Therefore, the DOHaD field is increasingly recognized as an important contributor to the epidemic of obesity and metabolic syndrome in Western populations.
PART I
Fetal Origins of Adult Disease/Programming

Why should we care?
We as scientists
The DOHaD field is now unequivocally established, yet still in its infancy. There is still a lack of specific mechanisms to explain the effects for most of the epidemiological observations described for adult human disease. Fetal growth is directly related to placental growth and placental phenotype, which are regulated by the genetic background. We as scientists have great potential to study the signals for fetal nutrient demand that control placental transfer capacity. Importantly, there are great opportunities to dissect molecular mechanisms that regulate placental nutrient transfer in early pregnancy and that program nutrient transfer closer to term.

We as clinicians
Clinicians should aim to identify IUGR placentas and fetuses early enough to institute appropriate monitoring, and ideally, interventions that can limit adverse outcomes for the offspring. Examination of the maternal diet prior to and during pregnancy together with early detection of "placental disease" may help improve outcomes in IUGR.

We as patients with a "placental disease"
Patients should improve life style, including a healthy diet, physical exercise, and prenatal care to optimize fetal and neonatal outcomes.

Importance of maternal nutrients for fetal development
During normal pregnancy, the primary determinant of fetal growth is the concentration of nutrients in the maternal circulation and the blood supply to the placenta. Glucose, amino acids (AA), and fatty acids (FA) are among the nutrients vital for fetal growth and development. Collectively, the data show that deficiency of nutrients in the mother causes alterations in placental nutrient transport and reduced body weight in the offspring.

Glucose
The majority of fetal glucose derives from maternal metabolism of carbohydrate in the diet. Glucose supply to the fetus is a facilitated process mediated by members of the glucose transporter (GLUT) family. Four isoforms GLUT1, GLUT3, GLUT4, and GLUT8 have been identified in human and rodent placentas. Glucose deprivation leads to hypoglycemia. This suggests that less glucose availability affects fetal growth. In rats, severe maternal glucose deprivation reduces placental transfer and fetal uptake of glucose, which results in fetal growth restriction.

AA
Fetal AA come from maternal AA pools derived from the diet. Fetal concentrations of nearly all AA are greater than maternal concentrations, suggesting that the placenta actively transfers AA from the maternal compartment to the developing fetus. Essential AA must be supplied in food, while nonessential AA are synthesized by the fetus from essential AA. Several AA transporter systems have been identified in human and rat placentas. Abnormalities in AA transport may be the reason that total AA concentrations are lower than controls in IUGR babies.

Fatty acids
FA content and character in fetal plasma directly correlates with the FA composition of maternal plasma and with the maternal diet. Essential FA cannot be synthesized and are dietary essentials (e.g., linoleic and linolenic acid). Essential FA in human pregnancy are transported from maternal to fetal circulations as triglyceride-rich lipoproteins, which are hydrolyzed by placental lipases. This results in free FA (FF) release, which are transported by saturable plasma membrane FA-binding proteins, FA translocase, and a family of FA transport proteins. Low birth weight in both human and rat pregnancy correlates with low intake of essential FA.

Factors affecting placental capacity for nutrient transfer
Multiple factors interact to influence the placental delivery of nutrients to the fetus. Size, histopathology, blood flow, transporter abundance, and organ consumption are factors responsive to environmental changes. Key studies...
address placental size, morphology, and transport abundance.

Size

Placental size affects the capacity for nutrient transport through changes in surface area, and placental weight correlates with fetal weight at term in many species. Timing, duration, and etiology of nutritional restriction yield variable phenotypes for placental mass. The Dutch Famine of 1944–45 reflects a highly cited example of this premise. Exposure to famine only during the first trimester of pregnancy enhanced placental weight at delivery without any impact on newborn weights when compared to control women, resulting in an increased placental-to-birth-weight ratio. In contrast, women subjected to starvation in their third trimester of pregnancy had reduced weight placentas and low-birth-weight newborns but an unaltered ratio of placental-to-birth-weight as compared with nonstarved women [1]. These results suggest that human placental adaptations in early pregnancy can overcome some environmental stressors such that fetal nutrition is maintained in late gestation. Collectively, these data suggest the placenta may compensate for insults to minimize fetal growth restriction. The histomorphology of the placenta ultimately determines placental function.

Histomorphology

Small placentas exhibit altered histopathology and ultrastructure compared to normal size placentas. Notably, the maternal undernutrition that yields IUGR in human pregnancy generates placentas with a reduced surface area for nutrient exchange, a lower volume density of trophoblasts, and increased placental apoptosis at term. In IUGR placentas, absent or reversed end-diastolic flow in the umbilical artery, as assessed by Doppler velocity waveform analysis, is indicative of poorly branched and capillarized vili, and thickened exchange barrier. In these placentas, vascular resistance occurs as a result of inadequate trophoblast invasion of the spiral arteries. In contrast, in less severe IUGR, positive end-diastolic umbilical artery flow is associated with a normal stem artery development, increased capillary angiogenesis, and adequate terminal villous development. Thus, the thicker placental exchange barrier and the increased placental vascular resistance in severe IUGR may correspond to alterations in placental structure directly involved in fetal programming of cardiovascular disease.

These structural alterations in the human placenta are mirrored in the guinea pig exposed to global maternal undernutrition compared to control diets. The nutrient deprived gestations exhibit a labyrinthine placenta with a 70% lower surface area and a barrier thickness 40% higher in late gestation. A reduction in the length of the labyrinthine vessels and decreased expression of vascular endothelial adhesion molecules in the murine placenta in response to maternal protein malnutrition are compatible with the possibility that alterations in maternal nutrition changes placental vascular function [2]. These histopathological changes predispose to lower nutrient transfer to the fetus. Our work in the rat exposed to maternal undernutrition showed enhanced apoptosis in junctional and labyrinthine zones of the placenta [3], suggesting that both hormone production and maternal-fetal exchange are impaired. Taken together, these data indicate that restriction of nutrients impairs the functional capacity of the placenta disproportionately compared to the reduction in placental weight alone.

Clinical Pearl

Doppler velocimetry techniques may be used to detect increased placental vascular resistance and predict adverse pregnancy outcome.

Transport abundance

Reductions in maternal-fetal nutrient transfer may derive from an inadequate maternal supply, inadequate placental blood flow, impaired placental transport, or a combination of these processes. Maternal nutritional status affects transporters in the placenta, which is time-dependent. For example, rats fed 50% less food during the last week of gestation have lower than control glucose levels in maternal plasma, a lower maternal-to-fetal glucose concentration gradient, and downregulation of GLUT3 expression, suggesting a mechanism for placental glucose transport dysfunction. These changes suggest that transport-mediated mechanisms may effectively reduce fetal levels of glucose. Placental transport of AA is affected by the activity and location of AA transporters systems. In humans, circulating essential AA concentrations are decreased in growth-restricted human fetuses, likely from reduced AA transport activity. In rats, maternal protein restriction downregulates placental nutrient transport prior to the onset of fetal growth restriction, suggesting that a
reduced placental supply of AA is a causal factor for IUGR, not simply a consequence of this malady. Undernourished women exhibit placental and offspring deficiency in essential FA, leading to altered placental FA metabolism and IUGR. These placenta not only have decreased levels of arachidonic acid and docosahexaenoic acid, but also show an altered ratio of both these FA relatives to their essential FA precursors, linoleic and α-linolenic, consistent with abnormal metabolism [4].

Taken together, these studies show the pivotal role played by the placenta in assuring that multiple nutrients are available to sustain normal fetal growth.

Placental nutrient synthesis and metabolism

Uteroplacental tissues in humans, ruminants, and equids metabolize glucose derived from the maternal circulation. Placental glucose consumption is reduced during short periods of maternal undernutrition, but this reduction has no effect on the partitioning of glucose between the uteroplacental and fetal tissues in humans [5]. Conversely, prolonged maternal hypoglycemia induces uteroplacental tissues to use less of the more limited supply of glucose available, thereby sparing glucose for the fetus. These adaptations correlate with reduced GLUT1 expression, offering a mechanism for the effect. The placenta metabolizes glucose to lactate during normal pregnancy [5], and this event increases the maternal-to-fetal concentration gradient for glucose. Placental lactate production decreases in response to maternal undernutrition in sheep, making glucose less readily available for fetal consumption [5].

The placenta synthesizes some of the AA required for fetal growth. For example, fetal glycine in sheep and human placentas are from endogenous synthesis. Serine derived from the fetus is converted in the placenta to glycine, and this AA is released back to the fetus. Interestingly, explant cultures from IUGR human placentas accumulate less serine in vitro than normal term villous explants. Besides placental synthesis of AA, uteroplacental tissues metabolize AA, supplying the fetus with essential AA [5].

The placenta synthesizes significant concentrations of FA in humans, sheep, and pigs. FA synthesis in term human placentas is lower than its oxidation. IUGR placentas commonly show a deficiency in oxidative enzymes, resulting in excess lipid peroxidation and free radical formation, both of which are harmful to maternal endothelial cells when released.

Collectively, these data show that placental nutrient synthesis and metabolism influence fetal growth and development.

Placental hormone synthesis and metabolism

The placenta releases hormones into both the maternal and fetal circulations, and synthesis and secretion of these hormones are responsive to environmental changes. Human placental lactogen, progesterone, insulin-like growth factors (IGF), and glucocorticoids play critical regulatory roles in fetal homeostasis.

Human placental lactogen and progesterone influence maternal metabolism to favor glucose delivery to the fetus [6]. Concentrations of both hormones are lower in undernourished mothers, and this may contribute to limited delivery of glucose to the fetus. This suggests that changes in placental endocrine dysfunction may be a cause and not a consequence of altered fetal growth.

<table>
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<th>Clinical Pearl</th>
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<td>Maternal plasma concentration levels of lactogen and progesterone may be used to predict adverse outcomes for the offspring.</td>
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The IGF family of hormones modulates growth, cell division, and differentiation. The action of the IGFs is regulated by IGF-binding proteins (IGFBPs), and together may modulate fetal growth. IGF-I is mitogenic for placental stromal fibroblasts and has insulin-like effects to increase AA transport in human placental cells. The ovine placenta clears IGF-I from the umbilical circulation when fetal IGF-I concentrations are high but secretes IGF-I when fetal concentrations are low. Fetal IGF-I concentrations positively correlate with fetal body weight to suggest that hormone production, metabolism, or both adjust to conditions prevailing in utero to yield optimal fetal growth. IGF-II modulates trophoblast development at the feto–maternal interface. Disturbances in IGF-II expression and activity associate with IUGR in human pregnancy [7].
CHAPTER 1 Maternal Undernutrition and Fetal Programming: Role of the Placenta

Research Spotlight
There are fetal sex differences in the IGF axis. IGF-II concentrations in umbilical cord serum from male neonates are significantly higher than those in female neonates, and cord plasma IGF-I and IGFBP-3 are higher in female neonates than in males.

Glucocorticoids are key regulators of organ development and maturation. The placenta is not a site for synthesis of glucocorticoids, but the placental 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) converts active glucocorticoids to inactive metabolites. This enzyme is affected by exogenous exposure to glucocorticoids and by fetal and maternal glucocorticoid concentrations. The human 11β-HSD2 enzyme is localized to the syncytiotrophoblast and is thus positioned to limit glucocorticoids transfer to the fetus. Extended periods of maternal undernutrition downregulates placental 11β-HSD2 activity, increasing placental exposure to glucocorticoids. This leads to fetoplacental growth restriction and abnormalities in cardiovascular and metabolic function in the adult offspring. Therefore, changes induced by elevated glucocorticoids may have beneficial effects on offspring viability, but they also impact negatively on fetal growth and development. [8] Thus, 11β-HSD2 enzyme plays a vital role to protect the fetus from exposure to excess maternal glucocorticoids.

Maternal undernutrition increases placental vascular resistance, and this subjects the fetal heart to an excess workload. This observation provides a direct link between altered placental structure and programming the risk for cardiovascular diseases in IUGR fetuses. The placenta functions as a nutrient sensor and directly regulates the nutrient supply available for fetal growth. Genomic imprinting is an epigenetic phenomenon whereby the expression of a gene depends on the parent of origin. For example, IGF-I is an imprinted gene and is crucial to fetal development as described above. IGF-I is downregulated in placentas exposed to nutrient restriction [7]. Moreover, a placenta-specific transcript (P0) for the IGF-II gene is expressed exclusively in the labyrinthine trophoblast of the mouse, and deletion of this transcript yields diminished placental growth, reduced placental nutrient transfer, and fetal growth restriction. Methylation of DNA restricts the genes available for transcription in cells. Maternal undernutrition affects the methylation status of the placental IGF-II gene and, in so doing, may control placental supply of maternal nutrients to the fetus. Imprinted genes in the placenta may be modified by perturbations of the maternal environment and altered fetal programming results. Moreover, the placenta strongly influences fetal endocrinology and metabolism. A well-documented example is rise in fetal glucocorticoid levels that follows decreased activity in placental 11β-HSD2. The adverse effects of excess fetal glucocorticoids on fetal development of the hypothalamic pituitary axis may program the fetus to be at higher risk for metabolic diseases as an adult.

Intervention strategies targeting the placenta to prevent altered fetal growth, fetal programming, or both should dissect in more detail how placental growth, nutrient transport function, and placental oxidative stress are modulated by maternal administration of IGFs or pharmacological levels of methyl donors. Targeted upregulation of the activity of placental 11β-HSD2 may also beneficially modulate feto-placental health.

<table>
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<th>Research Spotlight</th>
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<tr>
<td>Synthetic glucocorticoids such as dexamethasone and betamethasone are not extensively metabolized by placental 11β-HSD2, possibly due to protection from their 9-halogen group.</td>
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Collectively, these studies show that hormone synthesis and metabolism by the placenta are affected by maternal nutritional status and that the biological effects of the hormones influence fetal growth and development.

Mechanisms of placental programming
The placenta regulates fetal development by regulating nutrient transfer to the fetus and by controlling the bioavailability of specific hormones important to fetal growth and development. The placenta therefore plays a pivotal role in mediating the programming effects of suboptimal conditions during development. Mechanisms likely involved in programming the effects of maternal undernutrition include modulation of placental vascular resistance, regulation of the nutrient supply, genomic imprinting, and metabolism of glucocorticoids.

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PART I

Fetal Origins of Adult Disease/Programming

Figure 1.1 The role of the placenta in fetal programming resulting in diseases of adulthood.

Summary

Maternal nutrition during pregnancy is an important determinant of optimal fetal development, pregnancy outcome, and ultimately, life-long health. Barker’s epidemiological studies have stimulated new ideas about both in utero development and risks for adult diseases. Animal models of programming have shown that most fetal organs are vulnerable to the effects of maternal undernutrition during critical periods of development. Importantly, these studies show that programming the placenta, as illustrated in Figure 1.1, may mediate effects on the fetus.

Maternal undernutrition reduces fetal growth in part by impairing placental development and function. Placental alterations include decreases in placental weight, altered vascular development, reductions in glucose, AA, and FA transport, and hormone synthesis and metabolism. The plasticity of the placenta allows this pivotal tissue to respond to exogenous insults and to compensate for many environmental influences. Moreover, maternal diet may alter the placental genome through gene imprinting, an effect that may affect future generations. When the placental response is not sufficient to maintain fetal growth, IUGR results and suboptimal outcomes result (Table 1.1). The elucidation of further roles for the placenta in fetal programming will increase our understanding of DOHaD and hopefully will provide new strategies to prevent and treat suboptimal fetal development in the future.

Teaching Points

1. Fetal programming may occur following natural or experimental environmental changes in both humans and animals.
2. Maternal undernutrition-mediated fetal programming results in different outcomes depending on species, sex, and type of diet. It is dependent on time and length of insult.
CHAPTER 1 Maternal Undernutrition and Fetal Programming: Role of the Placenta

Table 1.1 Consequences of maternal nutrient restriction on adult offspring.

<table>
<thead>
<tr>
<th>Natural or Controlled Diet</th>
<th>Species</th>
<th>Adult Offspring Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor living conditions: Low-birth-weight baby</td>
<td>Human</td>
<td>Coronary heart disease, hypertension, obesity</td>
</tr>
<tr>
<td>Twin pregnancies: The growth restricted baby</td>
<td>Human</td>
<td>Non-insulin-dependent type II diabetes mellitus</td>
</tr>
<tr>
<td>Food restriction due to increased litter size</td>
<td>Pig</td>
<td>Hypertension, glucose intolerance</td>
</tr>
<tr>
<td>Guinea-pig</td>
<td>Guinea-pig</td>
<td>Glucose intolerance, insulin deficiency</td>
</tr>
<tr>
<td>Global nutrient restriction</td>
<td>Ovine</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Sheep</td>
<td></td>
<td>Hypertension, smaller livers, females have</td>
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<td></td>
<td></td>
<td>reduced progesterone secretion during the</td>
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<td></td>
<td></td>
<td>luteal phase of their estrous cycles and markedly</td>
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<tr>
<td></td>
<td></td>
<td>reduced fertility</td>
</tr>
<tr>
<td>Guinea-pig</td>
<td></td>
<td>Glucose intolerance, insulin deficiency</td>
</tr>
<tr>
<td>Rat</td>
<td></td>
<td>Hypertension, glucose intolerance, hypertension,</td>
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<tr>
<td></td>
<td></td>
<td>hypercholesterolemia, obesity</td>
</tr>
<tr>
<td>Rat-like hamster</td>
<td></td>
<td>Delay in physical and neurodevelopment</td>
</tr>
<tr>
<td>Protein deprivation</td>
<td>Rat</td>
<td>Glucose intolerance, relative insulin resistance,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>hyperinsulinemia, hypertension</td>
</tr>
<tr>
<td></td>
<td>Mice</td>
<td>Longevity affected</td>
</tr>
<tr>
<td>Global mineral (calcium, copper, iron, magnesium, zinc) or vitamin</td>
<td>Rat</td>
<td>Glucose intolerance, insulin resistance, obesity</td>
</tr>
<tr>
<td>restriction</td>
<td></td>
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<tr>
<td>Chromium restriction</td>
<td>Rat</td>
<td>Obesity</td>
</tr>
<tr>
<td>Low-sodium diet</td>
<td>Rat</td>
<td>Hypertension and reduced creatine</td>
</tr>
<tr>
<td>Iron deficiency</td>
<td>Rat</td>
<td>Hypertension</td>
</tr>
</tbody>
</table>

3. Placental development during pregnancy has a major impact on pregnancy outcome. Thus, small-for-gestational-age placentas are more likely to result in offspring with metabolic diseases later in life.
4. Genetic imprinting has a major role in placental development. Maternal undernutrition during pregnancy significantly decreases placental 1P(2), which negatively affects placental growth.
5. Glucocorticoid treatment changes placental handling and fetal delivery of lactate and selected AA. Glucocorticoids also impact placental expression of GLUT1 (GLUT1) and GLUT5 in a dose- and time-dependent manner in both human and rat placentas.


References

CHAPTER 2
Cardiovascular Health and Maternal Placental Syndromes
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Introduction
Pregnancy is a time of great maternal metabolic, anatom-ical, and physiological challenges in order to adapt the mother to the needs of the developing fetus. Adverse maternal outcomes and, in particular, placental complications can occur if the mother or fetus fails to rise sufficiently to these challenges. The maternal placental syndromes (MPS) encompass a spectrum of diseases associated with placental dysfunction, including the hypertensive disorders of pregnancy, placental infarction, and fetal growth restriction (FGR) secondary to placental insufficiency. Although their etiology is both multifactorial and incompletely understood, these conditions share some common pathological mechanisms and predisposing risk factors. Increasing evidence suggests that these women are more likely to develop cardiovascular disease (CVD) in later life. This chapter explores the relationships between the predisposition of women who develop these MPS and their future cardiovascular health.

Maternal placental syndromes
Hypertensive disorders of pregnancy
Hypertension is the most common medical problem encountered in pregnancy and remains an important cause of maternal and fetal morbidity and mortality worldwide. Although both chronic and gestational hypertension have significant adverse effects on pregnancy outcomes, the development of preeclampsia (PE) is associated with the highest risk. PE is a multisystem disorder complicating 2–3% of pregnancies and is characterized by hypertension and proteinuria. The risks to the fetus from PE include growth restriction, iatrogenic preterm delivery, hypoxic-neurologic injury, perinatal death, and long-term risks associated with low birth weight and prematurity.

Although the pathogenesis of PE is not fully understood, endothelial dysfunction, as part of a generalized inflammatory reaction, is a hallmark of PE and involves the maternal circulation to the placenta and the maternal systemic vasculature. Healthy pregnancy is associated with a state of relative systemic inflammation, and therefore, PE may represent the culmination of the maternal systemic inflammatory responses engendered by the pregnancy itself. Notably, all the inflammatory changes of normal pregnancy are exaggerated in PE, and features of the disease include not only endothelial dysfunction but a wider stress response, including the acute phase response and metabolic effects of dyslipidemia and increased insulin resistance (IR). Physiologically, this may be an attempt by the mother to compensate for the deficient placental function.
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There is increasing support for the theory that PE is, fundamentally, two separate pathological processes that occur based on the gestational age at onset of disease. This concept remains an area of ongoing research. More than 80% of all cases comprise the late-onset type, which is generally associated with a normally grown baby with normal placentation manifested by normal or only slightly altered behavior of the uterine spiral arteries. In contrast, early onset disease represents a smaller, but more severe, subset of cases. Early onset PE is associated with abnormal placentation, inadequate and incomplete trophoblast invasion of maternal spiral arteries, increased vascular resistance in the uterine arteries and within the placental bed, as well as FGR. As a consequence of poor placentation, oxidative and endoplasmic reticulum (ER) stress of the placenta occur to yield endothelial dysfunction and inflammation. The early onset disease is a subgroup associated with severe complications, and this fact has made this phenotype the focus of much basic and clinical research.

Clinical Pearl
Early onset PE is associated with a much higher incidence and severity of fetal and maternal complications and requires increased antenatal surveillance in order to optimize administration of steroids and timing of delivery.

Fetal growth restriction
FGR is the failure of the fetus to reach its genetically predetermined growth potential due to adverse genetic or environmental factors. The clinical impact of increased perinatal mortality and morbidity is further exaggerated in the presence of prematurity. Although the etiology is multifactorial, placental insufficiency is the most common cause. Diagnosis of placental insufficiency can be based on ultrasound parameters, but FGR is often a diagnosis of exclusion. Currently, no in utero treatment can improve or reverse established growth restriction, and management is based on antenatal surveillance to determine judicious timing of steroid administration and the gestational age at delivery. In normal pregnancy, there is effective first trimester invasion of maternal trophoblasts, resulting in the formation of a low-impedance and high-capacitance circulatory interface between the maternal and fetal circulations. The fetus, however, is vulnerable to nutrient deprivation even in the presence of minor placental insufficiency or abnormal placental development.

Epidemiology
There is increasing epidemiological evidence to suggest that adverse pregnancy outcomes such as PE, preterm delivery, and low birth weight are associated with increased risk for the affected women for CVD in later life. In a retrospective cohort study in Scotland using discharge data of almost 130,000 women, PE was associated with a twofold increased risk of subsequent ischemic heart disease (IHD) (RR 2.0; 1.5–2.5) [1]. More alarmingly, if a woman had a combination of PE, preterm delivery, and a baby of low birth weight, she has a risk of IHD or death seven times that of controls (95% CI 3.3–14.5). A recent meta-analysis combining eight studies (2,346,997 women), with a mean follow-up of 11.7 years, demonstrated a relative risk of 2.16 (1.86–2.52) of IHD in women with PE, substantiating previous evidence [2]. This doubling of risk remains robust even after adjusting for pre-pregnancy hypertension, diabetes mellitus, obesity, dyslipidemia, metabolic syndromes, and smoking. Furthermore, there is an inverse relationship between birth weight and the incidence of adult CVD, with offspring birth weight also inversely related to maternal CVD, suggestive of an intergenerational influence. Although low birth weight may result from preterm delivery or FGR, both are independently associated with an increased risk of maternal cerebrovascular disease and CVD, with double the risk of developing CVD if the mother delivered a baby in the lowest birth weight quintile for gestational age [1]. These epidemiological links are biologically plausible as women who develop either MPS or CVD share many features such as endothelial dysfunction, inflammation, and oxidative stress. Common risk factors, either genotypic or phenotypic, appear to underlie both conditions. We have previously proposed a model whereby pregnancy with its concomitant digression into a metabolic syndrome is a “stress test” of maternal metabolic response (Figure 2.1) [3]. Women who develop adverse pregnancy outcomes such as PE or FGR make greater excursions into metabolic disturbances during pregnancy and are predisposed to metabolic and vascular disease in later life.
PART I  Fetal Origins of Adult Disease/Programming

Figure 2.1  Risk factors for vascular disease are identifiable during excursions into the metabolic syndrome of pregnancy. (Reproduced by permission of Sattar N and Greer IA (2002) Pregnancy complications and maternal cardiovascular risk: Opportunities for intervention and screening? British Medical Journal 325(7356): 157–60.)

Research Spotlight

Women with a combination of PE, preterm delivery, and SGA are up to seven times more likely to develop CVD. The use of adverse pregnancy outcome history as part of risk assessment for future CVD requires evaluation.

Maternal placental syndromes—common pathology?

FGR and early onset PE are associated with infarction of the placenta and are different clinical manifestations of placental insufficiency that have common features in the placental pathology. Both conditions exhibit abnormal histopathology of spiral arteries in the basal plate. Notably, both conditions also share multiple predisposing maternal risk factors, including race, pre-existing hypertension, inflammation, and nongestational diabetes. Interestingly, the latter characteristics are also important risk factors for CVD in later life. The manifestation of different clinical phenotypes despite similar placental pathology may be due to a variable maternal response products released from a stressed placenta. Alternatively, the similarities in placental pathology may be more apparent than real, and the placental dysfunction in the two phenotypes may indeed be different. Contributions from both maternal and placental factors likely determine the ultimate clinical manifestations (Figure 2.2).

Patterns of placental disease

Failure of trophoblastic invasion and differentiation necessary for remodeling of the spiral arteries has long been implicated in both FGR and PE. The myometrial portion of the artery is most significantly affected with a graduated increase in severity from FGR cases that are normotensive to those that are hypertensive. This results in reduced placental perfusion, increased placental ischemia, and subsequent oxidative stress. Accumulation of lipid-laden macrophages surrounded by areas of fibrinoid necrosis in the spiral arteries is called acute atherosis, and this histopathology is comparable to atherogenesis in nonpregnant women (Figure 2.3). These plaques project into the vessel lumen to further restrict uteroplacental blood flow. Acute atherosis is more pronounced in the cases of PE associated with FGR compared to FGR alone. Indeed, placental morphological changes are more prominent in pregnancies complicated by PE with FGR than in PE alone. This is consistent with data that show that the mean birth weight is lower in pregnancies complicated by FGR secondary to PE than in the cases of unexplained
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Figure 2.3 Histology of acute atherosis in the spiral arteries within the decidua. The arterial lesion is histologically characterized by fibrinoid necrosis of the vessel walls (eosinophilic staining) with infiltration of foam cells into the damaged vessel wall. On light microscopy, it appears similar to that seen in atherosclerosis. (Reproduced by permission of PathologyOutlines.com, Inc., and Dr. Yan Lemeshev.)

FGR without PE. The placental pathology in both FGR and PE is explored in further detail in Chapters 31 and 32.

Metabolic syndrome of pregnancy

The common and disparate metabolic, pathological, and constitutional risk factors for the development of MPS and future CVD are examined in the following.

Obesity and insulin resistance

The prevalence of obesity has risen exponentially in the last 20 years. Obesity is a significant risk factor in the development of gestational hypertension and PE, with the risk of PE doubling for every 5–7 kg/m² increase in BMI. Although the contribution of increased adiposity to the pathogenesis of PE is not fully understood, the increased inflammation, IR, and endothelial dysfunction attributed to obesity are likely contributing factors.

In contrast, FGR is less common in obese women with normal glucose tolerance, as they have a tendency to have neonates with an increased percentage of body fat as well as a metabolic profile consistent with IR. However, in common with obese offspring, babies of low birth weight are more likely to suffer from metabolic diseases, such as type 2 diabetes and CVD in later life. The factors for this are unknown but are thought to be either secondary to genetic predisposition to IR or to in utero programming as a result of the adverse maternal metabolic environment.

Dyslipidemia

In PE, the hyperlipidemia of normal pregnancy is compounded by marked increases in free fatty acids (FFA) and triglycerides (TG). Increased TG drives production of small, dense LDL to enhance oxidative stress and to create an atherogenic environment where small, dense LDLs are preferentially ingested by the macrophages in the vessel wall of the spiral arteries. A reduction in HDL, cholesterol limits endothelial protection. Elevated FFA leads to systemic hyperinsulinemia, impaired peripheral insulin sensitivity, and endothelial dysfunction. Interestingly, there is no predisposition to dyslipidemia in women who develop unexplained FGR without PE.

Inflammation and endothelial dysfunction

Normal pregnancy evokes a systemic inflammatory response that is exaggerated in PE. The inflammation involves both the acute phase response of leukocytosis and the activation of complement and the clotting cascades. There are increases of proinflammatory cytokines, including TNF-alpha and IL-6, and PAI-1. Upregulation of the inflammatory response is also apparent in FGR, although not as exaggerated as that seen in PE. There is an increase in activation of circulating neutrophils together with an increase in placental and circulating levels of proinflammatory cytokines relative to uncomplicated pregnancies. Indeed, evidence of chronic inflammation in the placenta in pregnancies complicated by FGR is similar to that seen in preterm deliveries and PE.

Endothelial cells are key mediators of both local and systemic inflammatory responses. Features of endothelial dysfunction are accentuated in pregnancies complicated by both PE and FGR. There is upregulation of adhesion molecule expression on the endothelium, and these anchor margination leukocytes to facilitate perivascular accumulation. There are also abnormalities of uterine and brachial artery blood flow prior to the clinical manifestation of the phenotypes. These findings suggest that the endothelial dysfunction may precede both FGR and PE, albeit more pronounced in women who develop PE.
PART I
Fetal Origins of Adult Disease/Programming

Oxidative and endoplasmic reticulum stress
The ER is central to many cellular functions and is the major subcellular site for protein folding and trafficking. Failure of the ER’s adaptive capacity results in activation of the unfolded protein response (UPR), which intersects with inflammatory and stress signaling pathways. ER stress may thus be the link between inflammation and metabolic disease, including obesity, IR, and type 2 diabetes mellitus. ER stress is a major component of the pathophysiology in FGR and PE, resulting in reduced cell proliferation and increased apoptosis in placentae of both conditions [4]. ER stress and oxidative stress are closely linked as both are stimulated by vascular malperfusion and ischemia reperfusion. UPR generates reactive oxygen species (ROS), and together, they activate similar intracellular inflammatory signaling pathways such as the NF-κB pathways.

Research Spotlight
ER stress links inflammation and metabolic disease and is a major determinant of the pathophysiology of IUGR and PE [4].

Angiogenic factors
The altered release of placental factors into the maternal circulation as a result of placental oxidative stress and inflammation is pivotal in the pathogenesis of MPS. Soluble fms-like tyrosine kinase-1 (sFlt-1), an antagonist of vascular endothelium-derived growth factor (VEGF) and placental growth factor (PGF), is upregulated in PE to increase systemic concentrations of sFlt-1 and lower circulating concentrations of the anti-inflammatory and vasodilatory VEGF and PGF-1. They, in turn, lead to an imbalance in circulating angiogenic factors [5]. One of the key elements involved in VEGF and sFlt-1 gene transcription is the transcription factor, hypoxia-inducible factor 1 alpha (HIF1α), which is stimulated by hypoxia and inflammation. Soluble endoglin (sEng) is up-regulated in PE, induces endothelial dysfunction and hypertension in vivo, and correlates with the severity of the clinical syndrome. In combination with sFlt-1, sEng augments vascular damage. Parallels again exist between PE and CVD, with higher sFlt-1 levels following acute MI, and higher levels correlate with increased morbidity [6]. Statins have anti-inflammatory effects and reduce the release of antiangiogenic factors including sFlt-1 in normal healthy term placentae. Further research into the use of statins as a potential modifying therapeutic agent in the prevention of PE is ongoing.

Research Spotlight
An imbalance of the angiogenic factors sFlt-1, VEGF and PGF-1 is implicated in the pathogenesis of both FGR and PE. Imbalances of these growth factors correlate with the myocardial damage post myocardial infarction.

Long-term vascular and metabolic changes
Epidemiological evidence for the increased risk of CVD in women with pregnancies complicated by PE and FGR is consistent, but there remains uncertainty as to the degree of adjustment for potential confounders; there is little direct evidence for this increased risk. Furthermore, there are minimal data on the underlying mechanisms for this apparent increase in risk of CVD. Women with a history of PE have persistent dyslipidemia, increased inflammation, higher concentrations of C-reactive protein, abnormal microvascular function, and vascular dilatation up to 30 years after the sentinel pregnancy. Features of metabolic dysregulation are not as apparent in women with a history of a delivery complicated by FGR. However, there remains an inverse relationship between delivery of a low-birth-weight infant and later life higher maternal systolic blood pressure, IR, dyslipidemia, and inflammatory markers, including CRP and IL-6. All are important predictors of vascular events outside of pregnancy. Moreover, mothers with small-for-gestation offspring at term exhibit disruption of both endothelial-dependent and endothelial-independent vascular function remote from the index pregnancy [7], even when controlled for maternal obesity and smoking. The variations in maternal metabolic and vascular phenotype, apparent in women with a history of MPS, may be directly responsible for the relationship with future CVD risk.

Long-term health strategies
Coronary heart disease (CHD) is the most common single cause of death among women in the Western world with...