Section 1   **Physiology of Normal Pregnancy**

Chapter

1 Maternal Hemodynamics in Health and Disease: A Paradigm Shift in the Causation of Placental Syndromes

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Summary

The belief that abnormal placentation causes preeclampsia (PE) and fetal growth restriction (FGR) has been championed for several decades – to the extent that they are collectively referred to as 'placental syndromes'. Although this may be true for the minority of early-onset disorders, consistent and emerging evidence suggests otherwise for the development of late-onset PE and FGR, which constitute the majority of cases. The inconsistencies with the placental origins hypothesis have been attributed to disease heterogeneity or explained as the maternal form of the disorders. These are neither adequate nor actual explanations of the causality of PE and FGR. It is increasingly clear that a stronger argument can be made for the role of the maternal cardiovascular system in the development of PE and FGR. While intrinsic placental dysfunction and the subsequent maladaptation of the maternal cardiovascular system is thought to lead to early-onset PE and FGR, late-onset disorders are more likely to be associated with acquired placental dysfunction as a result of the maternal cardiovascular system being unable to meet the excessive hemodynamic and metabolic demands of advancing pregnancy. Forming a better understanding of the precise etiology of so-called placental syndromes is critical for the development of accurate diagnostic aids, improved screening, better triage by disease severity and offering targeted preventative and therapeutic measures. This chapter, and other chapters in this volume, review the evidence that supports maternal cardiovascular involvement in the etiology of placental syndromes.

Conventional Beliefs Regarding the Causation of Placental Syndromes

Human placentation is uniquely associated with physiological remodeling of the spiral arteries, where deep placentation involves almost complete transformation of maternal spiral arteries to produce a low-resistance uterine circulation. Defective deep placentation has been associated with the persistence of a high-resistance uterine circulation, subsequent impaired placental perfusion and the development of PE and FGR [1]. Impaired trophoblast development and hypoperfusion is thought to result in the subsequent development of FGR, whereas a placental biochemical 'stress' response mainly composed of antiangiogenic factors is thought to lead to the endothelial cell dysfunction characteristic of PE (Figure 1.1). PE and FGR complicate some 10–15% of all pregnancies and are collectively termed placental syndromes. As the placenta is essential for these diseases to occur, defective placentation is believed to be central in the pathogenesis of PE and FGR. Furthermore, the cure for PE is delivery of the placenta, supporting the crucial etiological
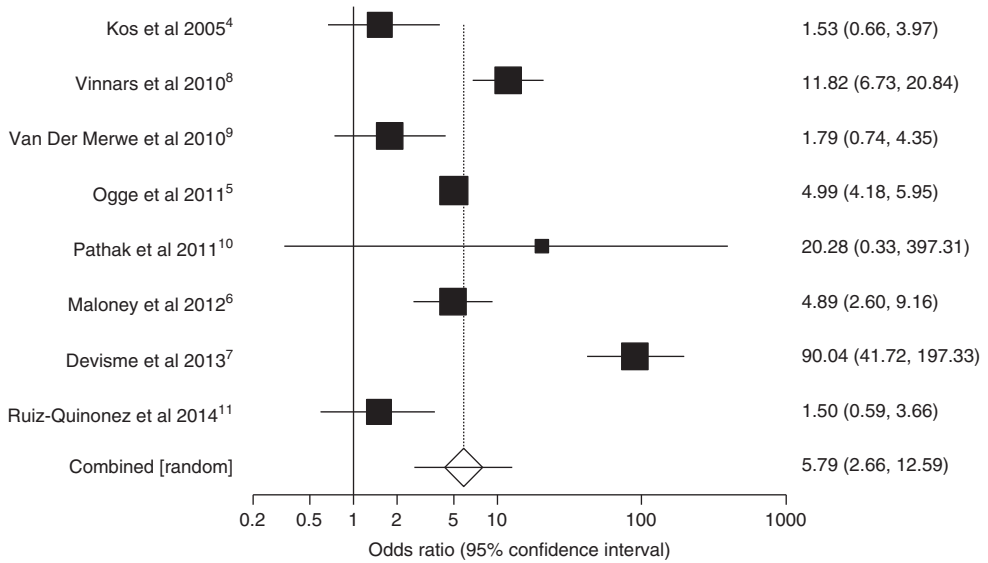
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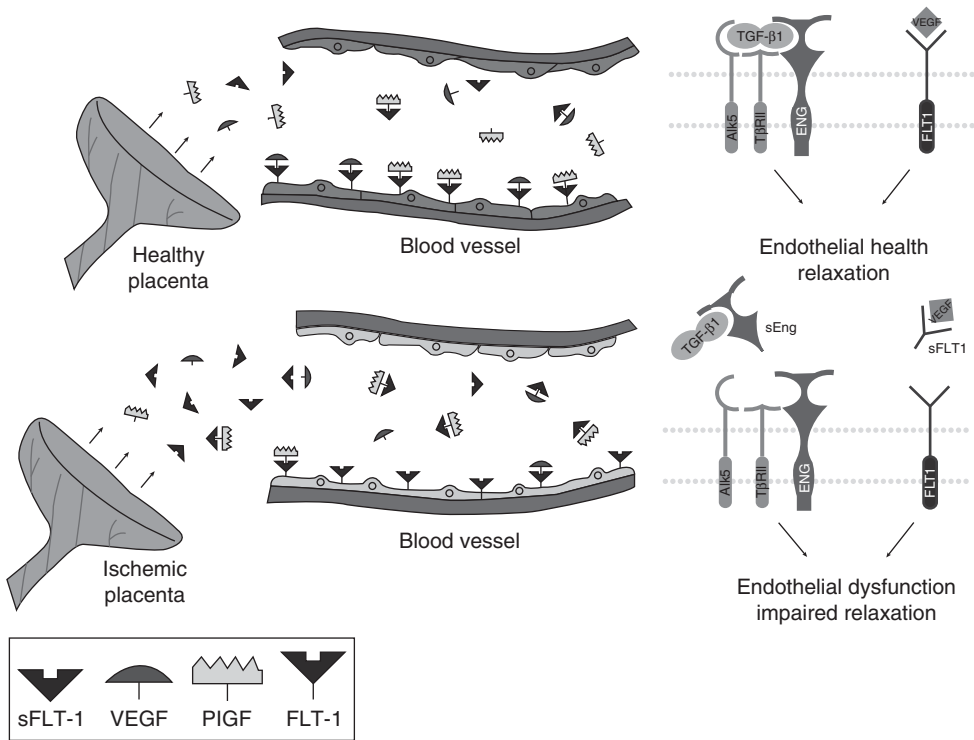
Figure 1.1 Healthy nonischemic placenta secretes normal (balanced) soluble fms-like tyrosine kinase (sFLT) leading to normal levels available for binding to fms-like tyrosine kinase 1 (FLT1) on endothelial cells systemically, leaving healthy and responsive endothelium. Ischemic placenta secretes increased sFLT, which binds circulating factors depleting their availability to FLT1 binding. The result is a dysfunctional endothelial cell leading to maternal systemic vasculopathy. (A black and white version of this figure will appear in some formats. For the color version, please refer to the plate section.)

role of the placenta in this disorder. The name 'placental syndrome' itself demonstrates the commonly accepted belief that the association between inadequate trophoblast invasion and the subsequent development of PE or FGR is causal in nature.

Placental Histology

A number of characteristic histological lesions of the placenta have been associated with the development of both PE and FGR – especially in early or preterm gestations [2]. A recent systematic review of large, well-conducted studies using objective diagnostic criteria demonstrated that preeclampsia was associated with a higher prevalence of both villous and vascular histological lesions of the placenta [3] (Figure 1.2). Importantly, the odds ratios for villous and vascular placental lesions in preeclampsia were consistently threefold lower in studies where the pathologist was blinded to the pregnancy diagnosis, demonstrating significant systematic operator bias in unblinded assessments. Furthermore, even though histological placental lesions are more prevalent in pathological pregnancies, the overall incidence is higher in normal pregnancies because the latter outnumber pathological pregnancies several-fold. This phenomenon is analogous to fetal aneuploidy, where the risk for trisomy may be higher in

Kos et al 2005[4]	1.53 (0.66, 3.97)
Vinnars et al 2010[8]	11.82 (6.73, 20.84)
Van Der Merwe et al 2010[9]	1.79 (0.74, 4.35)
Ogge et al 2011[5]	4.99 (4.18, 5.95)
Pathak et al 2011[10]	20.28 (0.33, 397.31)
Maloney et al 2012[6]	4.89 (2.60, 9.16)
Devisme et al 2013[7]	90.04 (41.72, 197.33)
Ruiz-Quinonez et al 2014[11]	1.50 (0.59, 3.66)
Combined [random]	5.79 (2.66, 12.59)

Odds ratio (95% confidence interval)

Figure 1.2 Forest plot, random-effects model of the odds ratio of villous lesions in the pregnancies complicated by preeclampsia and normotensive controls. The squares represent the studies included in the meta-analysis, arranged in time of publication order. In particular, the square boxes represent the effect estimates for each single study, and the horizontal line crossing the box shows the confidence interval, which is inversely proportionate to the reliability of the study. The diamante figure represents the summary effect and its width represents the degree of the heterogeneity. The vertical line intercepting 1 represents the line of no effect.

women ≥37yrs-old (point prevalence), but the majority of trisomic pregnancies occur in women <37yrs of age (population prevalence). Finally, the vast majority of FGR and PE pregnancies occur at term where these lesions occur far less frequently and are restricted to histology consistent with maternal under-perfusion of the placenta, such as perivillous fibrin deposition [4]. It therefore appears that the previously assumed characteristic placental lesions of PE and FGR are neither specific nor sensitive for the disorders – thereby questioning the validity of the histological basis for their placental etiology.

Birth Weight

An expected and anticipated consequence of poor placental development is impaired fetal growth, and, consistent with this, about 60% of early-onset PE cases before 34 weeks' gestation exhibit FGR. However, over 80% of PE cases occur at term and, using a large Scandinavian registry cohort, Rasmussen et al. demonstrated that there is a link between large for gestational age (LGA) birth and term preeclampsia, which is predominantly explained by maternal obesity [5]. The association of obesity and LGA birth with term preeclampsia is at odds with the universally accepted dictum that preeclampsia is a consequence of poor trophoblast development. The biochemical cascade responsible for preeclampsia is thought to occur as a consequence of a placental stress response – thought to be of placental origin in preterm preeclampsia. In the LGA form of term preeclampsia, maternal cardiac dysfunction and the inability to meet the metabolic demands of an enlarged fetoplacental unit may also result in placental stress. This hypothesis is supported by data showing that maternal cardiac dysfunction precedes preeclampsia,

significant maternal cardiac maladaptation in term pregnancy and worsening hemodynamic function in obese women compared to those of normal weight [6–8].

Uterine Artery Doppler

The physiological remodeling of the spiral arteries by the invading trophoblast is thought to result in a low-resistance uterine circulation. Defective placentation is associated with the development of PE and FGR as well as a persistence of the high-resistance uterine circulation. Increased uterine artery Doppler resistance indices have long been presumed to be the consequence of incomplete trophoblast invasion of maternal spiral arteries resulting in a high-resistance placental circulation and under-perfusion of the fetoplacental unit [1]. The largest individual patient data meta-analysis of first trimester uterine artery Doppler assessment demonstrates a sensitivity of 48% and a specificity of 92% for the detection of early-onset PE [9] (Figure 1.3). The finding that maternal ophthalmic artery Doppler and other peripheral waveform measures are equally effective as uterine artery assessment in screening for FGR and/or PE suggests that maternal uterine artery Doppler assessments may be reflecting maternal cardiovascular performance rather than be specific to trophoblast development [10].

Uterine artery Doppler screening exhibits two characteristics – sensitivity for adverse outcome increases the later in pregnancy the test is performed, and the sensitivity for late-onset PE is poorer than for early-onset PE [9,11]. These features have conventionally been interpreted as lending support to the argument that early-onset PE is related to a dysfunctional placenta, while late-onset PE may have to be explained by a different etiology. An alternative explanation arises when one compares the similarities in test characteristics between uterine Doppler assessment and glucose tolerance tests in gestational diabetes – which is sensitive for early-onset gestational diabetes and shows improved performance the later in pregnancy it is performed [12]. Just as for pancreatic
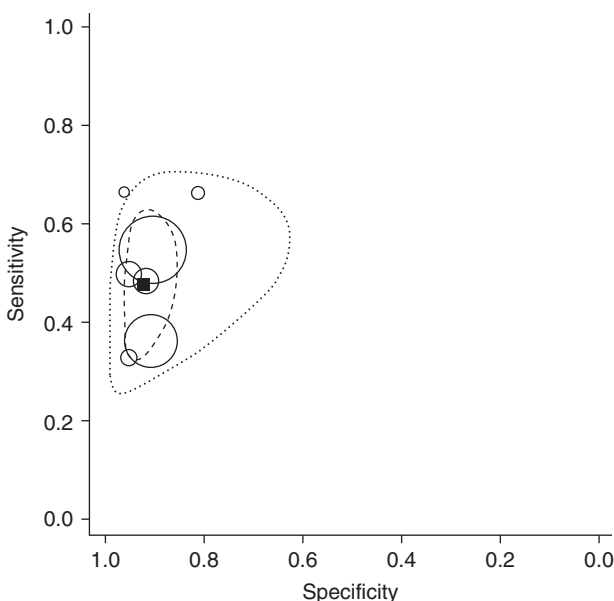
Figure 1.3 Summary estimates of accuracy of first-trimester uterine artery Doppler in the prediction of early-onset pre-eclampsia (a) and early fetal growth restriction (b) obtained with a bivariate model. Pooled sensitivity and specificity values were 0.48 (95% CI: 0.39–0.57) and 0.92 (95% CI: 0.89–0.95), respectively, for (a) and 0.39 (95% CI: 0.26–0.54) and 0.93 (95% CI: 0.91–0.95), respectively, for (b). Study estimate; summary point; 95% confidence region; 95% prediction region. Image reproduced by kind permission of Wiley.

function in gestational diabetes, early-onset PE may expose a pre-existing cardiovascular dysfunction, whereas late-onset PE may occur as a consequence of the maternal cardiovascular system's inability to deal with the excessive load of a term pregnancy. Corroborative evidence for this hypothesis is provided by MRI studies showing that early PE is associated with lower placental perfusion fractions compared to gestation-matched controls and late PE with larger placental perfusion fractions [13].

Placental Biomarkers

First trimester maternal serum levels of placental growth factor (PlGF) are reduced in pregnancies destined to develop preterm FGR and PE. In the studies with the best-reported screening performance, the sensitivity for early-onset PE using PlGF was around 60%, falling to approximately 15% for term PE for a fixed 5% false positive rate [14]. As with uterine artery Doppler assessment, these PlGF test performance characteristics were taken to support the placental origins hypothesis of early-onset PE, but allude to an alternative cause for late-onset PE. While PlGF is widely considered to be a pregnancy-specific hormone as it is produced by the trophoblast, it is also widely expressed in many extra-uterine tissues. PlGF has a significant role in cardiac adaptation to increased circulatory volume and resistance loads – where insufficient PlGF leads to impaired ventricular remodeling and cardiac maladaptation [15]. This is of particular relevance in PE, where low PlGF and high soluble fms-like tyrosine kinase-1 (sFlt-1) are characteristic of the PE phenotype. While low PlGF and high sFlt-1 have been considered to have an antiangiogenic adverse influence on the placenta, this combination of vascular factors also predisposes to increased systemic vascular resistance, abnormal ventricular remodeling and cardiac maladaptation – all hallmarks of PE. Just as for uterine artery Doppler and gestational diabetes, the pattern of PlGF screening performance for early and late PE may alternatively represent the difference between women with pre-existing cardiovascular dysfunction and those with acquired deficits due to the cardiovascular load of advanced pregnancy.

Environmental and Genetic Risk Factors for Preeclampsia

PE and FGR have predisposing similar clinical risk factors such as increased maternal age, ethnic origin, increased body mass index, diabetes and other maternal co-morbidities. PE is also believed to result from a complex interplay between genetic components and environmental factors. Familial clustering has been observed and reported in PE, which is relatively more common among daughters and sisters of preeclamptic women, suggesting that the condition may be partly attributable to genetic susceptibility [16]. Furthermore, the prevalence of PE also differs between various ethnic groups [17]. Numerous susceptibility genes for PE have been reported in the literature; however, reports have been inconsistent and the function of the majority of the identified genetic loci remains unknown. The most recent meta-analysis of genetic variants reproducibly associated seven genetic variants with PE [18]. Several of the variants that were associated with PE were also identified risk factors for developing cardiovascular disease. For example, carriers of select lipoprotein lipase (*LPL*) alleles as well as *SERPINE1* rs1799889, rs268, *FV* rs6025 and *F2* rs1799963 variants are all associated with adverse lipid profiles and coronary disease. It is therefore evident that the PE shares both genetic and environmental risk factors with cardiovascular disease, which may contribute both to

the etiology of the disorder. The overlap in these predisposing environmental and genetic risk factors has been taken to imply that they have a deleterious impact on trophoblast development. However, it is important to acknowledge that these risk factors have long been associated with the development of cardiovascular disease in the nonpregnant population.

Maternal Cardiovascular Involvement in Preeclampsia

We have continued to observe that the placenta is a prerequisite and therefore crucial to the development of PE. There are inconsistencies in the placental origins hypothesis and the role of the maternal cardiovascular system deserves to be further evaluated to delineate whether cardiovascular derangement in PE is a secondary effect or the primary etiological factor. The concept that placental dysfunction is secondary to a maternal syndrome is not new when one considers the similarities between preeclampsia and gestational diabetes (Table 1.1). If we consider PE to be an analogous condition to gestational diabetes, where both conditions only develop in pregnancy and are cured by birth and passage of the placenta. In spite of these fundamental parallels between PE and gestational diabetes, the latter is not considered to be a placental disorder. In fact, it is well accepted that the glucose load and endocrine 'stress' of pregnancy results in the development of gestational diabetes when maternal pancreatic function is suboptimal. If similarities exist between so-called placental syndromes and gestational diabetes, then pregnancy will need to present a significant strain on the maternal cardiovascular system – as for pregnancy glucose levels and pancreatic function [19].

Maternal Cardiovascular Adaptation in Pregnancy

Maternal adaptation to pregnancy is expected to create optimal conditions for the growth and development of the unborn child without jeopardizing maternal health. Several studies have demonstrated progressive changes in cardiac geometry and ventricular function with advancing gestation. Pregnancy is associated with an increase in the intravascular compartment by about 1500ml, as well as an increase in the maternal heart rate. The combined effect of these two synergistic changes is to increase cardiac output – often misinterpreted as a maternal hyperdynamic state, but only because pregnancy metabolic demands are often significantly underestimated. In concert with the increase in cardiac output is a fall in systemic vascular resistance and redistribution of blood flow at a regional level [7]. By term, these profound changes in maternal hemodynamics result in an excessive increase in left ventricular mass by about 40%, adverse ventricular remodeling and even overt diastolic dysfunction in a small but significant proportion of apparently healthy women (Figure 1.4). To provide perspective, these cardiac changes are an order of magnitude greater than observed in elite athletes after several years of training and equate to changes seen in some pathological conditions in nonpregnant individuals.

Cardiovascular Maladaptation in Preeclampsia

At the time of PE diagnosis, there is evidence of abnormal ventricular geometry, impaired myocardial relaxation and diastolic dysfunction, and these findings are mirrored – to a slightly lesser extent – in FGR [20, 21]. Mild-moderate left ventricular diastolic

Table 1.1 Hypertension in pregnancy and gestational diabetes: disease similarities and apparent differences

	Gestational diabetes (GDM)	Pregnancy hypertension
Epidemiology		
Predisposing factors	Same as for type 2 diabetes	Same as for cardiac disease
Onset of disorder	Mid to late pregnancy	Mid to late pregnancy
Effect of parity	More common in primips	More common in primips
Recurrence risk	Increased risk if previously affected pregnancy	Increased risk if previously affected pregnancy
Fetal and placental effects		
Placental histology	Some histological lesions seen more often in GDM	Some histological lesions seen more often in pregnancy hypertension
Specificity of histology	None of the placental histological lesions are specific for the disorder	None of the placental histological lesions are specific for the disorder
Temporal nature of lesions	Seen more frequently in early-onset and/or severe disorder	Seen more frequently in early-onset and/or severe disorder
Placental function	Increased maternal-to-fetal transplacental glucose transfer	Impaired maternal perfusion of the uteroplacental bed
Fetus	Increased fetal glucose levels lead to macrosomia	Impaired placental function leads to impaired fetal growth
Screening/diagnostic tests		
Mechanism of screening	GTT gauges pancreatic reserve	Uterine Doppler, PlGF and BP are all measures of cardiac function
Performance of screening	Better for early-onset GDM	Better for early-onset PE
Timing of screening test	Improved sensitivity the later in pregnancy it is performed	Improved sensitivity the later in pregnancy it is performed
Diagnostic test	Supra-normal glucose levels in both pregnant and non-pregnant	High BP in both pregnant and nonpregnant population
Management		
Cure for disorder	Birth	Birth
Treatment/amelioration	Insulin – treats the biological deficit	Antihypertensive medications – treats a sign of the disorder
Long-term maternal health	50% develop type 2 diabetes by 10 years postpartum	20% develop chronic hypertension by 10 years postpartum

Table 1.1 (cont.)

	Gestational diabetes (GDM)	Pregnancy hypertension
Biology		
Maternal adaptation	Insulin requirements increase two- to three-fold in pregnancy	Cardiac output increases by about 50% in pregnancy
Early-onset phenotypes	Present with normal or lower insulin levels compared to non-pregnancy	Present with normal or higher cardiac outputs compared to non-pregnancy
Late-onset phenotypes	Present with supra-normal (high) insulin levels compared to non-pregnancy	Present with supra-normal (high) cardiac output compared to non-pregnancy
Aetiology	Inability of maternal pancreas to deal with the glucose load of pregnancy	Impaired trophoblast invasion or maternal cardiac maladaptation?
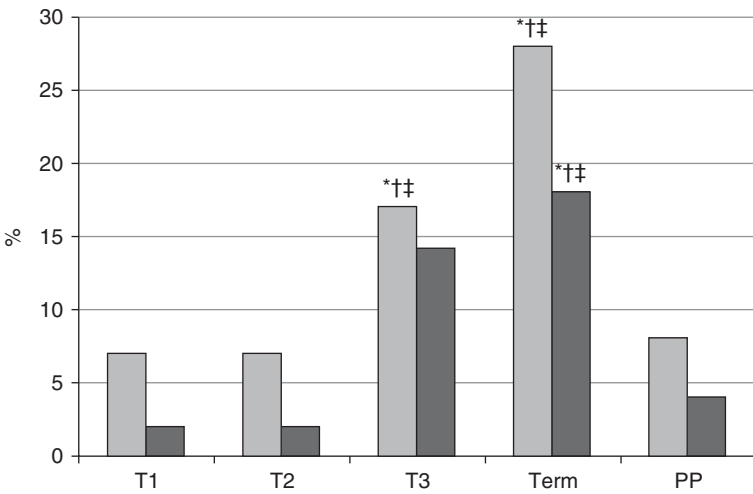
Figure 1.4 Summary of significant left-sided cardiac findings in pregnancy presented in a dichotomized analysis with indices rated as normal or dysfunctional. Myocardial diastolic dysfunction (white columns) was diagnosed with average early to late strain rate ratio of<1 and chamber diastolic dysfunction (black columns) according to the American Society of Echocardiography diagnostic algorithms. 1st indicates first trimester; 2nd, second trimester; 3rd, third trimester; NP, nonpregnant control; PP, 1-year postpartum; and Term, term of pregnancy. *$P<0.05$ v nonpregnant control; †$P<0.05$ v T1; ‡$Pv0.05$ v T2.

dysfunction is seen in approximately half of women with early-onset PE, with 20% of women having biventricular systolic dysfunction. This impairment in cardiac function is likely to be related to increase in cardiac afterload (high systemic vascular resistance) and abnormal left ventricular remodeling/hypertrophy. The abnormal pattern of remodeling observed in PE is similar to that observed in nonpregnant individuals with essential

hypertension and is consistent with an impairment that is afterload-induced. The extent and severity of these findings explain the significant cardiovascular morbidity associated with PE and raise the possibility that these changes may be used for the early identification of abnormal maternal cardiovascular and volume adaptation leading to the development of PE. However, cardiovascular adaptations in pregnancy require both volume and resistance load to be raised significantly and for a prolonged period. Similarly to glucose tolerance testing, a conventional echo assessment prior to or in early pregnancy is unlikely to detect limited reserve capacity of the maternal cardiovascular system.

Postpartum Cardiovascular Legacy

The numerous parallels between placental syndromes and gestational diabetes also extend into the postpartum period. Women whose pregnancies were complicated by gestational diabetes have a 50% risk of developing diabetes in the subsequent decade. Similarly, women whose pregnancies were complicated with PE or FGR are predisposed to increased postpartum cardiovascular morbidity and mortality, including chronic hypertension, myocardial infarction, heart failure, stroke and death [22]. Detailed longitudinal follow-up with echocardiography in apparently healthy women after pregnancies complicated by placental syndromes has demonstrated persistent remodeling and left ventricular dysfunction up to two years or more postpartum [23]. A more recent epidemiological study of hypertension rates demonstrated that the peak incidence of hypertension was in the first decade after birth and that the effect of pregnancy is to increase a woman's age-related hypertension risk as if she were two decades older [24] (Figure 1.5). Other population studies have suggested that the association of PE with adverse cardiovascular outcome postpartum may be due largely to shared prepregnancy risk factors rather than reflecting a direct influence of PE. Irrespective of whether the cardiovascular morbidity preceded the pregnancy or occurred as a consequence of the cardiovascular maladaptation in pregnancy, these findings undermine the placental origins hypothesis for PE and stress the importance of continuing to monitor the cardiovascular health of these women.

Late-onset Uteroplacental Dysfunction and FGR

As with PE, late-onset FGR is considered to have a different etiological basis from the early-onset versions of the disorders. FGR near term is considered to have a different phenotype that suffers from absence of distinct placental pathology and lack of an effective screening test, as well as similar risk factors, cardiovascular disease changes and postnatal cardiovascular morbidity as PE [2,3,11,25]. These findings raise the possibility that late-onset FGR may not be a primary placental problem, but results from acquired uteroplacental dysfunction as a consequence of maternal cardiovascular maladaptation near term. In support of this hypothesis, a recent population-based epidemiological study demonstrated a 2% increase in risk of term small-for-gestational-age (SGA) for every 1 mm Hg increase in maternal blood pressure within the normotensive range [26]. Although the authors suggested that maternal prehypertension may be a response to impaired placental function, consideration should be given to the possibility that the placenta is a perfusion-dependent organ and that impaired cardiovascular function may cause placental dysfunction, rather than the other way round. Previous work has demonstrated maternal ventricular remodeling and diastolic function as well as significantly poorer placental perfusion in normotensive FGR pregnancies [21]. This evidence suggests that term FGR
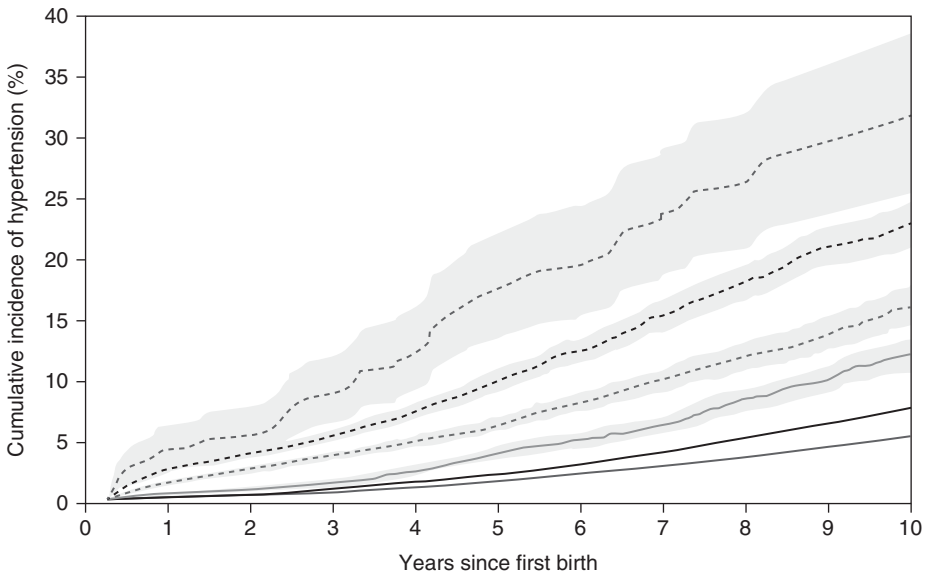
Figure 1.5 Ten-year cumulative incidences of hypertension by years since first pregnancy in women with and without a hypertensive disorder of pregnancy, by age at first delivery, Denmark, 1995-2012. Follow-up began in 1995 or 3 months postpartum, whichever came later; for women with a second pregnancy, follow-up ended at 20 weeks' gestation in the second pregnancy. Unbroken lines: women with no hypertensive disorder of pregnancy in their first pregnancy. Broken lines: women with a hypertensive disorder of pregnancy in their first pregnancy. Gray bands: 95% confidence intervals. Age at delivery: 20-29 years, blue; 30-39 years, green; 40-49 years, red. (A black and white version of this figure will appear in some formats. For the color version, please refer to the plate section.)

may well occur as a consequence of secondary placental dysfunction caused by impaired maternal cardiovascular function. This implies that both impaired maternal perfusion of the placenta (an extrinsic defect) and impaired placental development (an intrinsic defect) may lead to FGR.

Conclusions

A critical evaluation of maternal cardiovascular physiology reveals that there are profound changes in cardiac and hemodynamic performance in human pregnancy. The magnitude of these changes and maternal cardiovascular adaptation to pregnancy has previously been significantly underestimated. The consequences of these physiological findings only become apparent when considering the biological consequences of maternal cardiac maladaptation to increasing demands of advancing pregnancy. Placental dysfunction is fundamental to the pathophysiology of pregnancy complications such as PE and FGR, but, to date, the placenta has been considered in isolation without regard to the fact that its functioning is dependent on adequate maternal perfusion [27]. There is now incontrovertible evidence that failure of the maternal cardiovascular system to adapt to pregnancy is the primary mechanism leading to secondary placental dysfunction and so-called placental syndromes.

Key Points

- The placental origins theory seems aligned to the minority of cases of preeclampsia and/or FGR with early onset in pregnancy
- Placental dysfunction in late pregnancy may lead to the rapid development of preeclampsia and/or FGR without clear evidence of impaired or defective placentation
- The placental origins theory does not recognize that as an organ of perfusion, placental function may be dependent on maternal cardiovascular function (and related placental perfusion)
- Late-onset preeclampsia and/or FGR have epidemiological, biochemical, biophysical and clinical features which are in keeping maternal cardiovascular dysfunction leading to impaired placental function

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