Cardiovascular management in pregnancy

Effect of Maternal Cardiovascular Conditions and Risk Factors on Offspring Cardiovascular Disease

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Cardiovascular diseases (CVDs) constitute a particular challenge during pregnancy because physiological changes and fetal demands create an additional burden and fetal safety concerns limit treatment options. Other articles of this series review the physiological changes during pregnancy, the management of cardiovascular conditions most likely to endanger maternal and fetal health, and their long-term consequences for the cardiovascular health of the mother. This article focuses on their consequences in offspring.

Developmental programming resulting from in utero or early postnatal exposure to specific risk factors is increasingly recognized to determine CVD in later life. Clinically manifest cardiovascular conditions during pregnancy such as preeclampsia/eclampsia and gestational hypertension may not only affect maternal health and pregnancy outcome but also reduce fetal growth, which is associated with increased adult CVD. Furthermore, extensive evidence indicates that maternal cardiovascular risk factors (hypercholesterolemia, smoking, obesity, and diabetes mellitus) program endothelial dysfunction, insulin resistance (IR), hypertension, atherosclerosis, and type 2 diabetes mellitus in offspring. The mechanisms of developmental programming remain largely unknown, but specific factors affecting in utero programming have been identified and experimental models established in which causal relationships, mechanisms, and protective effects of maternal treatment can be explored. These findings suggest that interventions targeting in utero programming may reduce the susceptibility to CVD in offspring, a high priority given the increasing prevalence of obesity and dysmetabolic mothers and the concomitant increase in lifestyle risk in children. However, neither the cardiovascular consequences of many maternal risk factors nor the efficacy of maternal prevention and treatment is sufficiently supported by prospective double-blind studies.

The present review provides a critical evaluation of the associations between maternal cardiovascular conditions during pregnancy and offspring CVD, the role of low birth weight, and the evidence for developmental programming of CVD by other maternal cardiovascular risk factors. It then proposes an integrated view of in utero programming of CVD and its mechanisms based on emerging consensus and highlights priorities for future clinical and basic research. Finally, it discusses the promises and caveats of targeting developmental programming, that is, treating mothers to reduce CVD in offspring.

Cardiovascular conditions of particular clinical importance during pregnancy

Congenital heart disease and maternal cardiomyopathy

Maternal congenital heart disease requires particular attention during pregnancy and often leads to premature birth. The same is true for gestational cardiomyopathy, a rare condition with an enigmatic pathogenesis. As expected for any condition with a polygenic mode of inheritance, maternal congenital heart disease is associated with a high offspring recurrence risk, which varies depending on the type of cardiac defect.

However, family history contributes only a small percentage to the overall prevalence of congenital heart disease and a strong case can be made for an involvement of nongenetic factors. Establishing whether in utero programming by maternal cardiac disease contributes to the cardiac condition in offspring or their CVD risk in general is further complicated by confounding effects of maternal treatment, premature birth, and related neonatal care, in particular treatment with oxygen. In fact, in experimental animals without predisposing genetic defects, a combination of systemic maternal inflammation and neonatal hyperoxia was sufficient to alter cardiac structure and function and ultimately led to cardiac failure.

The most prominent argument for an involvement of fetal programming is that maternal heart conditions often impair fetal growth (see The Role of Altered Fetal Growth). Although to date there is little hard evidence that maternal heart conditions contribute to offspring CVD by developmental programming, epidemiology clearly indicates that cardiac pathologies in offspring may be programmed by maternal dysmetabolic conditions. For example, maternal diabetes mellitus is associated with fetal ventricular hypertrophy and less frequently with congenital heart disease.

Maternal obesity during early pregnancy is also linked to congenital heart defects, possibly as a result of increased inflammation.

Finally, both maternal diabetes mellitus and obesity are associated with complete atrioventricular canal defects.

Preeclampsia and eclampsia

Preeclampsia/eclampsia is the most frequent serious pregnancy complication; therefore, its effects on offspring have been intensely investigated. Together with proteinuria, maternal hypertension developing during pregnancy is one...
of the defining diagnostic criteria. Hypertension is also the best documented consequence in offspring. A recent meta-analysis of 18 studies with >45,000 subjects confirmed the result of many individual studies, that is, higher systolic and diastolic blood pressure (BP) levels and elevated body mass index (BMI) in children and adolescent offspring of preeclamptic mothers. Not surprisingly, individual studies found greater elevations of BP in offspring of mothers with early-onset eclampsia. In contrast, elevated plasma lipids were observed mainly at birth.7

Valuable insights into the mechanisms increasing CVD risk in offspring were obtained by comparing maternal preeclampsia with gestational hypertension. Given the complex origin of preeclampsia and eclampsia (which may involve poor placentation, hypoxic damage, increased systemic inflammation resulting from immune responses to paternal antigens in the placenta or fetus, endothelial damage, and altered vascular reactivity), the potential for adverse effects on offspring mediated by mechanisms other than maternal hypertension should be greater in preeclampsia than in gestational hypertension. Instead, large comparative studies such as the Avon Longitudinal Study of Parents and Children showed that both eclampsia and gestational hypertension are associated with increased systolic and diastolic BP in children, even after adjustment of the data for BMI. However, when the data were corrected for birth weight, the association between maternal hypertension and offspring BP was abolished for preeclampsia but was not significantly changed for gestational hypertension.8 Furthermore, the comparison provided no indication that offspring parameters other than BP, for example, plasma lipids or inflammation markers, are affected by maternal hypertension.9 Together, these findings suggest that eclampsia affects offspring BP mainly by programming mechanisms associated with impaired fetal growth, whereas gestational hypertension increases offspring BP by a different mechanism. Epigenetic programming of factors influencing BP is one candidate, but greater inherited susceptibility to hypertension cannot be ruled out. Further insights were provided by a study using births at high altitude to accentuate the influence of placental hypoxia during preeclampsia, which may increase the placental permeability of factors contributing to the pathogenic programming of the fetus.10 Under hypoxic conditions, pulmonary artery pressure was significantly increased and flow-mediated dilation was decreased in offspring of preeclamptic women compared with control subjects, indicating a permanent defect in the pulmonary circulation.

Maternal Hypertension

As discussed, gestational hypertension is associated with increased BP in offspring, even though it remains to be established whether this is due to fetal programming or inherited genetic factors shared by mother and offspring.5,5 It is therefore tempting to assume that maternal hypertension in general may also program offspring CVD. Unfortunately, most attention has focused on hypertension during pregnancy. Further epidemiological studies are required to establish whether chronic maternal hypertension independent of pregnancy enhances offspring BP. Studies in salt-sensitive animal models did not indicate a dramatic effect.11 In contrast, a recent study in a rat model combining genetic salt susceptibility and expression of human cholesterol ester transfer protein reported extensive spontaneous strokes in offspring exposed to mild dietary salt during pregnancy, weaning, and early adult age.12 This also suggests that maternal hypertension requires cofactors to become clinically relevant in offspring.

Conversely, extensive evidence indicates that hypertension in offspring is affected by developmental programming, not only by nutritional deficiencies impairing fetal growth but also by maternal hypercholesterolemia and obesity.

The Role of Altered Fetal Growth

Impaired Growth

Some of the studies cited above correlated cardiovascular predictors or manifestations in offspring with reduced birth weight of neonates rather than maternal cardiovascular conditions or quantitative measures thereof. In fact, the concept that the in utero environment influences adult diseases originates largely from the association between low birth weight and increased CVD first observed by Barker and colleagues.9 This prompted a large number of studies in cohorts of different ethnicities, socioeconomic conditions, and dietary habits, in particular in developing countries in which severe undernutrition and dysnutrition were prevalent. Most but not all of these studies confirmed the association of birth weight with adult hypertension and atherosclerosis-related conditions, whereas the association with type 2 diabetes mellitus remains more controversial.23–28 Low birth weight has gradually been replaced by low birth weight corrected for height or gestational age to exclude normally developed neonates whose low weight merely reflects a shorter gestation.29

The main weakness of the original Barker hypothesis is that birth weight is an outcome of pregnancy, not a maternal risk factor, much less a uniform one. Epidemiological studies of populations born during prolonged hunger periods established undernutrition as a cause of impaired intrauterine development,30 but many other, pathogenetically diverse causes of low birth weight have been identified, including mechanical obstructions of the uterine artery, maternal corticosteroid treatment, and severe protein deficiency.31–33 Some of these have been replicated in experimental models, but their interpretation is complicated by the fact that they do not consistently reduce weight in all offspring.34 Furthermore, birth weight is also affected by physiological variables such as the uterine implantation site and sibling competition for resources. All of this may have contributed to the discrepancies between epidemiological studies.

Studies in human twins with different birth weights should provide more definitive information on the impact of low birth weight on adult CVD because co-twin–control analysis allows the exclusion of the influence of all those factors that are shared by both twins. Smaller twin studies confirmed the association of birth weight with later CVD.37 In contrast, a larger recent Swedish study comparing the associations in homozygous and heterozygous twins found an association only in heterozygous twins, suggesting that in utero programming is dependent on genetic cofactors (which differ only between heterozygous twins).38,39
Clinically, the greatest disadvantage of focusing on birth weight is that it is too late to intervene when intrauterine growth retardation is detected at birth. In fact, low-birth-weight children who later gained weight at an accelerated rate showed increased coronary heart disease morbidity and mortality.46 Early detection may change this because it is now possible to raise birth weight in cases of severe early-onset intrauterine growth restriction, but the effect of such intervention on adult CVD remains to be seen.41

Excessive Growth
As pointed out, reduced fetal growth is associated with increased CVD in later life, whereas the causes of low birth weight are generally unrelated to maternal CVD. However, overnutrition rather than undernutrition poses the greater health risk in developed and many developing countries, and obesity and dysmetabolic conditions are increasingly prevalent in both mothers and children.42 Maternal obesity and gestational diabetes mellitus, in particular, are associated with excessive fetal growth, and macrosomia at birth is in turn associated with increased obesity and diabetic complications.43–45 Macrosomia may also enhance atherogenesis by increasing plasma lipids.46 Thus, it appears that both reduced and excessive fetal growth results in pathogenic programming, but the mechanisms involved may be quite different. As discussed later in the Maternal Obesity and Diabetes Mellitus section, both high and low maternal glucose levels increased the risk for type 2 diabetes mellitus,25 but the effect of gestational diabetes mellitus on offspring obesity cannot be explained by its effect on macrosomia at birth.43 Maternal obesity rather than glucose levels also correlated with macrosomia in another study on gestational diabetes mellitus.47 Mechanisms linking maternal obesity, macrosomia, and later obesity are therefore likely to play a key role in programming by excessive birth weight. Nevertheless, it is increasingly recognized that the focus of future investigations should be on specific pathogenic factors encountered by the fetus in utero rather than on fetal growth.

Other Maternal CVD Risk Factors
Maternal Hypercholesterolemia
Maternal hypercholesterolemia during pregnancy has long been considered a physiological event of little clinical relevance, to the point that cholesterol levels are not routinely determined in pregnant women in most countries. The first indication that it may be pathogenic was provided by the observation of increased fatty streak formation in the aortas of 6-month-old fetuses of mothers with temporary or chronic hypercholesterolemia.48 This indicated that the atherogenic process may begin much earlier than previously assumed but challenged the assumption that maternal cholesterol cannot cross the placental barrier. The placenta is clearly impermeable to cholesterol-carrying LDL particles, and term-born neonates of hypercholesterolemic mothers are normocholesterolemic in the absence of inherited forms of dyslipidemia. Nevertheless, high fetal cholesterol levels correlating with maternal levels in mid-pregnancy suggested that maternal-fetal cholesterol transport occurs at some stage of pregnancy. The placental cholesterol transport mechanisms have since been identified.49–52 The Fate of Early Lesions in Children (FELIC) study then showed that maternal hypercholesterolemia is associated with increased aortic atherosclerosis in normocholesterolemic children.51 This strongly suggested in utero programming by maternal hypercholesterolemia, but a contribution of inherited genes, for example, a prevalence of atherosclerosis-susceptible genes in children of hypercholesterolemic mothers, could not be ruled out. Conclusive evidence for atherogenic in utero programming was obtained in New Zealand White rabbits. In this model, diet-induced maternal hypercholesterolemia during pregnancy caused dose-dependent increases in fetal lesion formation and accelerated postnatal atherogenesis, whereas maternal treatment of hypercholesterolemic mothers with cholestyramine reduced it.54–56 Studies in murine models further supported this concept.57–59

A pathogenic programming effect of maternal hypercholesterolemia in humans was also indicated by a recent case-control study of children with or without congenital heart disease60 and by a report of greater cardiovascular mortality in children with heterogeneous familial hypercholesterolemia who inherited familial hypercholesterolemia from their mother and were therefore exposed to higher maternal cholesterol levels in utero than those who inherited familial hypercholesterolemia from their father.61 The results of a retrospective human study in an Italian cohort currently investigating the association between maternal cholesterol levels and severity of acute myocardial infarction in young adults may shed more light on the long-term effects of maternal hypercholesterolemia. However, the results of human studies using noninvasive measurements of surrogate parameters of CVD have to be taken with some caution. Apart from the confounding effects of genetic variability and lifestyle differences, in utero programming may vary considerably in different vessels and organs62 and may not be evident in the absence of atherogenic cofactors in offspring. Indeed, an elegant murine study comparing the effect of maternal hypercholesterolemia in heterozygous apolipoprotein E–deficient mice showed that atherogenic programming may be latent, that is, may remain hidden until additional atherogenic factors reveal its impact.63 In this study, genetically identical heterozygous progeny were generated by crossing apolipoprotein E–deficient mothers with wild-type fathers or vice versa. Differences in carotid atherogenesis between offspring exposed in utero to maternal hypercholesterolemia and controls born to wild-type mothers were detected only when an additional atherogenic stimulus was added (in this case, a carotid cuff).

Although the mechanisms responsible for placental cholesterol transport have been elucidated, it remains to be established whether atherogenic programming is the result of increased fetal cholesterol levels or is caused by maternal factors associated with hypercholesterolemia such as increased oxidative stress or inflammation. A pathogenic role of oxidative stress was established by the fact that maternal antioxidant treatment reduced atherosclerosis in offspring of hypercholesterolemic New Zealand White rabbits without affecting maternal cholesterol levels.54,55 Potential mechanisms by which fetal programming by maternal hypercholesterolemia may enhance atherogenesis in offspring have also been identified in various
models, including endothelial dysfunction, impaired vascular relaxation and increased BP, altered cholesterol synthesis, and altered arterial gene expression. Increased proinflammatory eicosanoids and activation of inflammatory pathways were seen in rabbit offspring and fetal primates. Finally, impaired glucose homeostasis in offspring of rats fed high-fat diets suggested that maternal hypercholesterolemia may also affect insulin resistance. Conversely, maternal immunization with oxidized lipoproteins, which protects rabbit and murine offspring against atherogenic programming, also delayed or decreased IR and type 2 diabetes mellitus in murine offspring. A greater activity of hepatic antioxidant enzymes was also noted in offspring of immunized mothers. The involvement of increased oxidative stress and inflammation suggests that fetal programming of CVD by maternal hypercholesterolemia may be linked to that by maternal obesity and (gestational) diabetes mellitus. This is also consistent with altered lipid profiles in human mothers with poorly controlled type 1 diabetes mellitus and in macrosomic offspring of obese mothers.

Experimentally, in utero programming by high-fat diets and maternal hypercholesterolemia is arguably better characterized than programming by any other risk factor, but the lack of large prospective studies demonstrating its effects on human CVD morbidity and mortality remains a critical issue.

### Maternal Smoking

Programming by maternal smoking is well documented in humans of all ages by both prospective and retrospective studies. Maternal smoking during pregnancy was linked to increased resistance in uterine, umbilical, and fetal middle cerebral arteries and with decreased flow and diameter of the ascending aorta. Maternal smoking was associated with increased intima-media thickness of the aorta in neonates and with increased intima-media thickness of carotid arteries in adults, even after adjustment for current risk factors. Maternal smoking during pregnancy also showed a striking association with offspring BMI. Although other CVD risk factors such as waist circumference, BP, hemoglobin A1c, and triglycerides were also increased in adult offspring of smokers, in contrast to BMI, these associations were abolished by adjustment for postnatal influences. In a prospective study, maternal smoking and BMI were associated with increased systolic BP in 5-year-old children. On the other hand, 3-year-old children of both former smokers and women who smoked in early pregnancy showed elevated systolic BP, whereas only early smoking during pregnancy was associated with increased BMI. The effects of maternal smoking on BP may therefore result from smoking-related epigenetic changes that are not limited to pregnancy, whereas the effects of smoking on BMI appear to be limited to pregnancy and therefore to reflect in utero programming.

Programming by maternal smoking may be due in part to increased oxidative stress, similar to programming by maternal hypercholesterolemia and obesity. Common mechanisms may also include immune programming. In fact, maternal smoking during pregnancy is associated with increased levels of immunoglobulins in cord blood, including IgM and IgA, and was reported to affect fetal immune responses to allergens.

### Maternal Obesity and Diabetes Mellitus

The evidence for developmental programming by maternal obesity and diabetes mellitus is reviewed together because of their pathogenetic links, in particular the frequent occurrence of the metabolic syndrome in obese mothers and the presumed progression of IR to type 2 diabetes mellitus. Although maternal obesity is clearly associated with increased BP in offspring, the evidence for developmental programming of hypertensive and metabolic effects rests largely on experimental models, and studies often focused on, or were complicated by, other maternal risk factors. Developmental programming by maternal diabetes mellitus also remains controversial. Several epidemiological studies reported an association of maternal diabetes mellitus with reduced birth weight and thus presumably with increased CVD risk in offspring. This was consistent with the observation that increased fetal glucocorticoid exposure resulted in lower birth weight and offspring hypertension in an experimental model. Although a detrimental effect of maternal diabetes mellitus on fetal development was not challenged, early on, alternative mechanisms were proposed that could account for this. For example, genetically determined IR could cause both insulin-mediated effects on fetal growth and IR in adult life. Later studies indicating a high prevalence of type 2 diabetes mellitus in adult offspring of women with gestational diabetes mellitus or type 1 diabetes mellitus also were consistent with either in utero programming or differences in inherited genetic background. However, a comparison of siblings born before and after their mother developed diabetes mellitus indicated greater BMI and diabetes mellitus in those who were exposed to diabetic conditions. Although siblings were not genetically uniform, this approach clearly reduced the impact of confounding genetic influences and strengthened the case for developmental programming.

The idea that programming is attributable to low birth weight is also weakened by the fact that maternal diabetes mellitus may also be associated with macrosomia and that gestational diabetes mellitus usually results in normal or macrosomic offspring. A study in Pima Indians showed a U-shaped relationship between maternal glucose concentrations and birth weight. The low-weight offspring later gained less weight and developed relatively greater IR than the heavy offspring who had also gained more body weight, but both groups were insulin resistant. These and other data suggest that increased IR in offspring is associated with both low and high birth weights and that later-life weight gain is an important cofactor. In contrast, a meta-analysis found little evidence for a role of low birth weight but indicated high birth weight and early postnatal weight gain as risk factors for type 1 diabetes mellitus. Evidence for an association between maternal diabetes mellitus and offspring BP, lipids, or C-reactive protein was also weak. Finally, another recent study reported that maternal diabetes mellitus increased offspring BMI by in utero mechanisms that are independent of maternal BMI and suggested that offspring adiposity may be responsible for the higher BP.

In view of the many potential interactions, it is important to remember that maternal obesity, dysmetabolic conditions, and diabetes mellitus seldom constitute pathogenetically uniform entities. Obesity may be accompanied by the metabolic...
syndrome and varying degrees of hypertension, IR, and dyslipidemia. Chronic or gestational diabetes mellitus varies in the degree of hyperinsulinemia and hyperglycemia and may be accompanied by hypercholesterolemia. Not all of these parameters may ultimately be confirmed to influence fetal programming. Future studies of these maternal conditions would therefore be well advised to correlate offspring outcomes with basic maternal risk factors, for example, body weight, BP, cholesterol, glucose, and insulin levels. Another important consideration is the possibility that the effects of maternal diet, obesity, or diabetes mellitus on cardiovascular outcomes may be mediated by earlier development of obesity in the offspring rather than being directly programmed.45,91

Developmental Programming of CVD: An Overview

Maternal Causes of Fetal Programming

The concept of developmental programming of CVD presented below is based on several notions. The first is the more general version of the Barker hypothesis that adult disease is influenced by the in utero environment. This central tenet has been strengthened by the recognition that fetal programming can occur by mechanisms independent of impaired intrauterine growth and by the identification of specific maternal factors affecting programming in humans and experimental models. The second is that programming does not necessarily end with birth but may continue some time beyond. During this period, maternal influences may still be exerted through lactation, but programming is increasingly influenced by postnatal factors and the maturation of the cellular immune system. The importance of the perinatal period for immune programming is well documented.92 The rate of postnatal growth also determines later CVD.40 This prompted the hypothesis that adult CVD is the result of a mismatch between the conditions encountered in utero, to which the fetus has adapted by programming compensatory mechanisms (predictive adaptive response), and the actual conditions later encountered.17,93 Independently of whether such a mismatch is required for or enhances the effects of programming, we can safely assume that developmental programming is increasingly influenced by postnatal factors affecting programming in humans and experimental models.

The Role of the Placenta

Fetal programming may result from direct effects of maternal risk factors on the fetus or may be secondary to pathogenic effects on the placenta. As shown in greater detail in Figure 2, the exchange between the maternal and fetal circulation takes place in the placental villi, either via placental permeability for small molecules or via active transport mechanisms. Both of these may be affected by maternal risk factors. For example, placental permeability is greatly increased by maternal diabetes mellitus, but it is unknown whether this is due to endothelial damage or effects on proteins regulating aqueous exchange under physiological conditions. More important, little is known about the permeability of many potential risk factors (eg, short-chain fatty acids, oxidation products, antigens, and cytokines) under such pathological conditions, whereas the effects of maternal CVD on endothelial cell functions have been studied in cells cultured from the umbilical vein.94,95 Similarly, active transport mechanisms for maternal cholesterol have been identified, but little is known about their function under different conditions. There are good reasons to believe that they are regulated differently in different stages of pregnancy, by fetal demand, and by high maternal cholesterol levels,46–52 but the effects of other maternal risk factors on active transport mechanisms are unknown. These caveats for placental permeability and transport should also be kept in mind when comparing plasma concentrations in cord blood with those in later life.

In addition to affecting placental permeability and transport mechanism, maternal factors may alter mRNA and protein expression or activities of transcription products in the syncytiotrophoblast or endothelial cells of the fetal circulation, some of which may in turn affect the mother or fetus.96 For example, the human placenta has been shown to be an active contributor to fetal oxidative stress.97 Finally, altered placental function may result from pathological changes elsewhere in the placenta, for example, in decidual arteries. Insufficient vascular adaptation at the utero-placental interface, poor placentation,
or mechanical obstructions may lead to placental hypoxia. Maternal CVD may affect placental blood supply via hemodynamic effects, altered vasoactive factors, or activation of the coagulation system. Other causes unrelated to maternal CVD such as immune responses to paternal antigens may also lead to placental hypoxia, inflammation, and endothelial damage.

### Effects of Developmental Programming on Later CVD

As a result of maternal or placental pathogenic factors reaching the fetus, in utero programming occurs. To date, very little is known about the nature of such epigenetic programming. Proposed mechanisms include intrauterine growth retardation, selective underdevelopment of organs or tissues, and persistent differences in cellular composition, all of which may account for later phenotypic differences. For example, a reduction in nephrons caused by intrauterine growth retardation has been postulated to cause compensatory hyperfiltration, progressive nephron damage, hypertension, and ultimately renal failure (Brenner hypothesis). Other lifelong consequences of tissue immaturity are well known in very premature newborns. Classic epigenetic changes such as DNA methylation and

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Figure 1. Current concept of developmental programming. Maternal causes of fetal programming include clinically relevant cardiovascular conditions during pregnancy, other cardiovascular disease (CVD) risk factors such as chronic or gestational dysmetabolic conditions, and maternal factors unrelated to CVD that may influence offspring CVD by impairing fetal growth (left). To date, only a limited number of specific factors have been proven to affect in utero programming (right). Cardiovascular manifestations during pregnancy may program the fetus via hypoxia, hypertension, or altered fetal growth. Complex metabolic conditions in mothers may also influence programming via several specific factors. For example, the programming effects of maternal hypercholesterolemia may be attributable to hypercholesterolemia itself, increased oxidative stress, and inflammation. Similarly, obesity and the metabolic syndrome may affect programming via hyperinsulinemia, hypercholesterolemia or dyslipidemia, increased oxidative stress, and increased inflammation. Maternal diabetes mellitus may act via hyperinsulinemia or hyperglycemia, as well as by altered fetal growth (macrosomia). Impaired fetal growth or specific factors such as corticosteroids are thought to be responsible for programming by many non-CVD causes. Maternal genetic susceptibility may enhance the causes of fetal programming or affect placental function, whereas maternal adaptive immunity may result in protective immune programming or may protect against pathogenic programming by maternal factors such as oxidative stress. Fetal programming may result from direct effects of maternal factors on the fetus or may be secondary to pathogenic effects on the placenta (see Figure 2 for details). Developmental programming is not limited to in utero programming but continues after birth. In addition to maternal environmental factors, programming may be influenced by the genetic susceptibility of the fetus and by maternal treatment. In later childhood and adult age, the programmed mechanisms (gray box on the right) determine offspring CVD, together with genetic susceptibility, lifestyle risk factors, and treatment. Note that the evidence for a protective effect of maternal immunity and treatments before or during pregnancy to date rests almost exclusively on experimental models.
histone acetylation leading to irreversible changes in the transcriptional machinery are currently considered the most likely mechanism and are the focus of large-scale investigation, not just for their role in developmental programming. The number of established epigenetic changes potentially relevant to CVD is also rapidly increasing. However, the sheer number of epigenetic differences (even between newborn homozygous twins), the difficulty of establishing the contribution of specific epigenetic changes to offspring disease, and our current inability to target individual modifications are formidable obstacles on the way to translational use of such observations.

In contrast, many functional consequences of fetal programming have been identified that may enhance CVD in later life (Figure 1). These include impaired endothelial function, vascular reactivity and increased BP, altered mRNA and protein expression of genes relevant to growth, proliferation and circadian rhythm, altered activities of antioxidant enzymes, altered cholesterol synthesis, altered glucose and insulin metabolism, changes in mediators and regulators of inflammation such as cytokines and eicosanoids, and increased atherogenesis. It therefore seems that in utero programming is not limited to a small number of genes or transcriptional products but involves extensive systemic changes.

Programming is not limited to gestation but may continue for some time after birth. From a mechanistic point, this may mean that not all fetal programming needs to affect CVD. For example, it is conceivable that in utero programming causes macrosomia and that macrosomia and later obesity then enhance CVD by conventional mechanisms. It is also important to remember that not all in utero programming is pathogenic. Fetal B and T cells can also be programmed in utero, even though they are still immature and become capable of cognate responses only after birth. In experimental models, maternal immunization with oxidized lipoproteins before pregnancy programs specific B cell–dependent IgM and IgG immune responses in offspring and reduces the susceptibility of their offspring to atherosclerosis, IR, and type 2 diabetes mellitus. Whether this is due to...
fetal protection against maternal oxidative stress by maternal antibodies induced by the immunization or results from enhanced protective immune responses in offspring remains to be determined. Consistent evidence from other fields supports the notion of fetal immune programming but in view of the complex role of the immune system in atherogenesis and diabetes mellitus, further exploration of immune programming is indicated.

**Therapeutic Potential of Developmental Programming**

From a translational perspective, the most important aspect of developmental programming is clearly the possibility of achieving long-lasting benefits in offspring by brief interventions in mothers. That this is feasible has been shown with cholesterol-lowering drugs, antioxidants, or dietary restriction in experimental models of maternal hypercholesterolemia and obesity. Interventions before pregnancy are obviously preferable to avoid adverse effects of dietary restrictions or drugs administered during pregnancy. The benefits of reducing maternal risk factors seem self-evident, given the experimental evidence for pathogenic effects. Furthermore, in theory, treatment is not limited to preventing pathogenic programming but also may aim at inducing beneficial programming, for example, of protective immune responses.

Unfortunately, in the absence of evidence from large prospective, double-blind trials, almost none of the causes of developmental programming are recognized as risk factors of offspring CVD. Neither maternal screening nor treatment for the purpose of preventing pathogenic programming is covered by current guidelines or justified under the standards of evidence-based medicine. Ironically, the only exception is low birth weight, which is listed as a risk factor of CVD by the World Health Organization but is also least correctable. Prospective studies may eventually establish maternal risk factors for some offspring diseases, but even the extraordinarily large and expensive National Children’s Study was designed to follow up offspring only until 20 years of age and may therefore establish associations only with surrogate parameters of CVD rather than with clinical manifestations or outcomes. Prospective studies of the effects of maternal treatment effect will also take decades.

The question of whether to consider the prevention or treatment of mothers is particularly challenging, not only because of the increasing prevalence of risk factors and the extraordinarily long time required to establish risk factors and treatment effects but also because treatment would be intended mainly to benefit offspring, not the patient herself. On the other hand, the dilemma may not be as insurmountable as it appears. Most of the risk factors of fetal programming identified to date are also established conventional risk factors of CVD and are routinely treated under existing guidelines before pregnancy. The only major concern about the continuation of dietary or pharmaceutical treatment during pregnancy should be its safety for the fetus, in particular that of cholesterol-lowering drugs. Similarly, conditions that endanger the life of the mother or fetus are routinely treated under current guidelines. In both cases, interventions are carried out for the benefit of the mother and fetus, not to reduce offspring CVD, but offspring may benefit nevertheless. Studies investigating the effect on offspring CVD of maternal treatment before pregnancy, safe interventions during normal pregnancy, and treatment of manifest CVD during pregnancy should therefore not pose significant ethical problems and do not have to wait until risk factors of fetal programming and treatment effects are formally established. In fact, treatment of mild gestational diabetes mellitus was recently reported to reduce macrosomia.

Although the number of human studies is rapidly increasing, several obstacles remain to be overcome. The need to focus

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**Table. Key Unresolved Questions and Promising Areas of Future Clinical or Basic Research**

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<tr>
<td>Which of the basic parameters increased by CVD during pregnancy or maternal dysmetabolic conditions are actually responsible for developmental programming?</td>
<td>Epidemiological associations between risk factors of developmental programming and offspring CVD</td>
</tr>
<tr>
<td>Can pathogenic programming by specific risk factors be prevented?</td>
<td>Demonstration of causality in experimental models of specific risk factors</td>
</tr>
<tr>
<td>How effective is conventional prevention or treatment before pregnancy?</td>
<td>Dietary and drug interventions in experimental models</td>
</tr>
<tr>
<td>How effective are safe dietary interventions during pregnancy?</td>
<td>Prospective studies on offspring of mothers treated under existing guidelines before or during pregnancy</td>
</tr>
<tr>
<td>How safe are current cholesterol-lowering, anti-inflammatory, or antioxidant drugs during pregnancy?</td>
<td>Clinical trials</td>
</tr>
<tr>
<td>What is the relative contribution of developmental programming to offspring CVD compared with genetic susceptibility and postnatal risk factors?</td>
<td>Critical review of case reports</td>
</tr>
<tr>
<td>What fetal cells/tissues/organisms are programmed?</td>
<td>Epidemiology</td>
</tr>
<tr>
<td>What epigenetic mechanisms affect CVD mechanisms or manifestations in offspring?</td>
<td>Clinical trials</td>
</tr>
<tr>
<td>Does maternal immunomodulation influence developmental programming in humans?</td>
<td>Epidemiology focusing on specific maternal risk factors and postnatal lifestyle</td>
</tr>
<tr>
<td></td>
<td>Animal studies</td>
</tr>
<tr>
<td></td>
<td>Identification of epigenetic changes in tissues of humans and experimental animals</td>
</tr>
<tr>
<td></td>
<td>Association studies in humans</td>
</tr>
<tr>
<td></td>
<td>Studies testing causality of specific mechanisms in experimental models</td>
</tr>
<tr>
<td></td>
<td>Initially, retrospective studies only</td>
</tr>
</tbody>
</table>

CVD indicates cardiovascular disease.
more on individual maternal risk factors than on diagnostic categories has already been discussed, but it is complicated by the physiological variability of many parameters during pregnancy. For example, maternal cholesterol increases mainly in the third trimester, but its pathogenic effects on the fetus are likely to be greater during midpregnancy, when fetal cholesterol levels are highest and the fetus’ vulnerability to programming may be greater. To allow comparison between studies, it would be highly desirable to standardize time points at which maternal parameters are assessed, taking into consideration the realities of clinical practice. Advances of noninvasive or minimally invasive diagnostic techniques make it possible to determine some predictors of later CVD at a very young age and thus to facilitate shorter prospective studies, but we cannot simply assume that surrogate measures of CVD are necessarily good indicators of fetal programming because programming effects may remain latent in the absence of cofactors. Retrospective studies are much faster and often provide better characterization of outcomes, but they have to rely on medical records with inconsistent time points of determinations and often lack key parameters that are not routinely determined during pregnancy.

Conclusions
It is now widely accepted that developmental programming influences later CVD. The increasing prevalence of maternal obesity and dysmetabolic conditions, combined with increasing lifestyle risks in children, highlights the need for action, but substantial further work is needed to conclusively identify the maternal risk factors of fetal programming, to elucidate the programming mechanisms, and to establish the safety and cardiovascular benefits to offspring of maternal interventions. The Table lists key unresolved questions and promising areas of future clinical or basic research.

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References


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