MANIFESTATIONS OF CHRONIC DISEASE DURING PREGNANCY

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Any physiologic changes occur in pregnancy, beginning early in gestation. These changes allow the mother to tolerate the genetically incompatible fetoplacental unit, adapt her physiologic makeup to nourish and support its development, and prepare her for the hazards of delivery. As a consequence, these complex adaptations render her insulin-resistant, thrombophilic, relatively immunosuppressed, and hypervolemic. Healthy young women generally cope well with these physiologic changes, with pregnancy proceeding uneventfully to term. However, physiologic changes can interact with an inherited or acquired predisposition to disease to precipitate pregnancy complications. Furthermore, many of these complications of pregnancy have common antecedents with a variety of chronic diseases that usually manifest later in life. Pregnancy can unmask a woman’s potential for disease, thus providing a window to her long-term health outlook and presenting opportunities for primary prevention.

EVIDENCE ACQUISITION

We undertook a systematic review of chronic diseases relevant to pregnancy by searching the MEDLINE database for articles published between 1990 and 2005. Search terms included insulin resistance, preeclampsia, gestational diabetes, atherosclerosis, coronary artery disease, thrombophilia, autoimmune disease, cardiomyopathy, aneurysm, arteriovenous malformation, nephropathy, pregnancy, and pregnancy complications. This electronic search was supplemented by manual searches of reference lists and recent reviews. Methodological quality of the studies was assessed carefully, and only articles agreed on by both authors to contain relevant and sufficient data for...
interpretation were included in this review. Bibliographies and the Web sites of the International Society of Obstetric Medicine and International Society for the Study of Hypertension in Pregnancy were also reviewed.

**EVIDENCE SYNTHESIS**

**Physiologic Adaptations to Pregnancy**

Major physiologic changes occur in pregnancy (TABLE 1). Healthy women increase plasma volume by 50% by 32 to 34 weeks’ gestation. This increase in plasma volume, which is proportional to the size of the fetus, exceeds the increase in red blood cell mass, resulting in a physiologic anemia. In subsequent pregnancies, the increase is greater. This physiologic hypervolemia facilitates delivery of nutrients to the fetus, protects the mother from hypotension, and reduces the hazard of hemorrhage at delivery. The decrease in blood viscosity, resulting from a low hematocrit percentage, creates a lower resistance to blood flow. When this is coupled with the physiologic vasodilatation of pregnancy, a reduction in blood pressure occurs despite an increase in cardiac output. Reduced peripheral resistance may result from a relative refractoriness to the constrictor actions of angiotensin II. The mechanism is not fully established, but an effective vasodilating “buffer” system with nitric oxide, prostacyclin, and antioxidants may play a role. Interestingly, before delivery, part of the plasma volume shifts into the extravascular space, allowing “autotransfusion” to compensate for postpartum volume loss.

Pregnancy is also characterized by changes in the hemostatic and fibrinolytic systems, resulting in a hypercoagulable state. There are substantial increases in procoagulant factors such as factor VIII, von Willebrand factor, and fibrinogen. Endogenous anticoagulant systems are suppressed through a marked reduction in protein S. Fibri


<table>
<thead>
<tr>
<th>Table 1. Physiologic Changes During Pregnancy</th>
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<tr>
<td>Changes</td>
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<tr>
<td>Increase in plasma volume</td>
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<tr>
<td>Creation of a thrombophilic state</td>
</tr>
<tr>
<td>Increase in insulin resistance</td>
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<tr>
<td>Immunosuppression</td>
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women with glucose intolerance often occurs in pregnancy. In European women, glucose intolerance (gestational diabetes mellitus [GDM]) develops in 2% to 6% of pregnancies. In 90% of these women, nutritional counseling is sufficient, but in the remainder insulin is required to achieve normal glycemic levels. There are various diagnostic criteria for GDM, mainly based on fetal macrosomia, as well as ethnic differences in the incidence of GDM. The World Health Organization recommends that GDM be diagnosed following an oral glucose tolerance test (OGTT) using 75 g of glucose after overnight fasting. The internationally accepted values for the upper limits of normal for glucose in venous plasma following the 75-g OGTT are 5.3 mmol/L (96 mg/dL) for fasting, 10 mmol/L (180 mg/dL) at 1 hour, and 8.6 mmol/L (155 mg/dL) at 2 hours.

Both an increase in insulin resistance and pancreatic β-cell insufficiency contribute to the development of GDM. The initiating factor is likely to be the increased peripheral insulin resistance of normal pregnancy, but in an attempt to overcome the increased insulin resistance, relative pancreatic β-cell insufficiency develops. Thus, the pathophysiology of GDM and type 2 diabetes is similar.

The prevalence of diabetes has more than doubled over a 10-year period, reflecting the increase in obesity in Western populations. This will affect the rate of gestational diabetes. Currently, there are no established cutoff values for an increased risk of developing type 2 diabetes following GDM. The best predictor for such conversion is postpartum impaired glucose tolerance. In a recent Danish study of women with diet-treated GDM, type 2 diabetes and impaired glucose tolerance were present in 39.9% (95% confidence interval [CI], 35.5%-44.3%) and 27% (95% CI, 23.1%-31.0%), respectively, 10 years after the index pregnancy. These women had fasting venous plasma values of more than 6.2 mmol/L (112 mg/dL) and 2-hour plasma glucose values of greater than 7.6 mmol/L (140 mg/dL).
The conversion of GDM to type 2 diabetes has been very variable, depending on diagnostic criteria, race/ethnicity, and, particularly, duration of surveillance (from 6 months to 28 years). Approximately 10% of patients have diabetes soon after delivery and the long-term (>10-year) risk is about 70%. A meta-analysis found that the cumulative incidence of type 2 diabetes is highest during the first 5 years after pregnancy. Thereafter, this rate declines, and 10 years after the pregnancy, the incidence curve reaches a plateau.

The American Diabetes Association recommends that an OGTT should be performed 6 to 8 weeks after pregnancy in cases in which GDM has occurred, then repeated every 3 years. If GDM is diagnosed early in pregnancy or has recurred in subsequent pregnancies or insulin treatment has been needed, an OGTT should be performed more frequently because the risk of type 2 diabetes is considered higher.

**Preeclampsia and Future Cardiovascular Disease**

A further consequence of the increased insulin resistance that occurs during late pregnancy can be development of preeclampsia. Preeclampsia is associated with increased insulin resistance and other features of the metabolic syndrome, including hypertension, lower serum high-density lipoprotein cholesterol concentrations, and higher plasma levels of triglycerides, uric acid, and insulin. Preeclampsia is also recognized as a state of sympathetic overactivity and proinflammatory changes, both related closely to insulin resistance. Thus, preeclampsia may be the first manifestation of the metabolic syndrome. Evidence of insulin resistance has been identified as long as 17 years after preeclamptic pregnancy; these women are more insulinemic during an OGTT and have higher serum testosterone levels than controls. More recently, Sattar et al have demonstrated elevated levels of the proinflammatory adhesion molecules and higher Hba1C levels compared with controls in women who had preeclampsia 15 to 25 years previously. A case-control study reported that nonpregnant women with a history of preeclampsia had higher systolic and diastolic blood pressure and increased plasma levels of von Willebrand factor, fibrinogen, cholesterol, triglycerides, and very low-density lipoprotein cholesterol than controls. Chambers et al demonstrated impaired vascular reactivity in women with a history of preeclampsia. This defect was more severe in women with recurrent preeclampsia compared with those with a single episode of preeclampsia. These women also had higher body mass index, waist-hip girth ratio, and ratio of total cholesterol to high-density lipoprotein cholesterol, all signs of the metabolic syndrome.

Thus, preeclampsia, characterized by widespread endothelial damage and dysfunction, insulin resistance, coagulation activation, and increased systemic inflammatory response, shares many risk factors and pathophysiologic processes with cardiovascular disease. It is not surprising that epidemiologic studies show an increased risk of cardiovascular disease in later life in women with a history of preeclampsia. The risk is greatest when preeclampsia and preterm delivery are combined, where preeclampsia is more severe.

A large, retrospective discharge data analysis of all 129,290 singleton first births in Scotland between 1981 and 1985, with 15 to 19 years of maternal follow-up, found a significant association between preeclampsia and maternal risk of hospital admission for ischemic heart disease or death (adjusted hazard ratio, 2.0; 95% CI, 1.5–2.5). Preeclampsia has also been shown to be a risk factor for stroke in later life. Thus, pregnancy can reveal preexisting risk factors for vascular disease and can exaggerate responses similar to the metabolic syndrome. These women are appropriate candidates for careful screening of cardiovascular disease risk factors and for possible interventions, including diet and lifestyle modification (Table 2).

**Pregnancy and Thrombophilia**

Pregnancy is essentially a thrombophilic state. The risk of venous thrombosis is increased by 7- to 10-fold and is highest after delivery. This risk is about 3-fold higher than that associated with combined oral contraceptives. Venous thrombosis in pregnancy is often the first manifestation of hereditary thrombophilia. Such thrombophilia is present in at least 15% of Western populations and underlies about 50% of episodes of venous thromboembolism in pregnancy. Heritable thrombophilia and the procoagulant physiologic changes of pregnancy appear to interact. For example, on systematic review and meta-analysis, factor V Leiden heterozygotes have an odds ratio of thrombosis in pregnancy of 8.32 (95% CI, 5.44–12.70; P < .001), increasing to an odds ratio of 34.4 (95% CI, 9.86–120.0; P < .001) for homozygotes. In absolute terms, this is modest, translating to a risk of venous thromboembolism of about 1% for factor V Leiden heterozygotes and 3% to 4% for homozygotes. With age, the penetrance of hereditary thrombophilia increases. Hereditary or acquired thrombophilia is also associated with pregnancy complications such as severe preeclampsia and recurrent pregnancy loss, disorders in which the hemostatic system is important in the pathophysiology.

**Autoimmune Diseases and Pregnancy**

Successful pregnancy depends on the ability of the maternal immune system to tolerate a genetically incompatible fetoplacental unit. One of the important adaptations leading to this immunotolerance is the shift, at implantation, of helper T-cell 1 (Th1) dominance to Th2 dominance. Since successful pregnancy is a Th2-dominant immune state, it is not surprising that women with a Th1-dominant immune state, such as rheumatoid arthritis, thyroiditis, or multiple sclerosis, improve during preg-
nancy, while patients with T2-dependent immune diseases, such as systemic lupus erythematosus, fare worse during pregnancy.54,58

Interestingly, 3 autoimmune diseases—rheumatoid arthritis, multiple sclerosis, and thyroiditis—that are reported to ameliorate or stabilize during pregnancy in the majority of women are more likely to relapse during the following year after delivery.54,55 The postpartum period can be regarded as a time of ongoing heightened inflammatory activity.60 Among women with rheumatoid arthritis, its onset occurs in 9.7% to 28.3% after pregnancy; the postpartum state confers a 5-fold relative risk of new-onset rheumatoid arthritis compared with any other time.61,62 The risk is highest after the first pregnancy.63 Activation of disease between 1 and 3 postpartum months may be due to an increase in cytotoxic immunity; thereafter, activation is related to humoral immunity.64

Multiple sclerosis is known to ameliorate during the last trimester of pregnancy.55,65 In a recent large study, the mean (SD) relapse rate in late pregnancy was 0.2 (0.1) relapse per woman per year compared with the prepregnancy year, when it was 0.7 (0.9). After delivery, the relapse rate was higher than before pregnancy.66 Importantly, the decrease in the relapse rate during pregnancy was more marked than any drug-mediated therapeutic effect reported to date.

Postpartum thyroiditis occurs in 11% to 17% of women 1 to 3 months after delivery.67 There is infiltration of the thyroid with lymphocytes, and a small goiter may be present.68 The presence of antinuclear antibodies, a family history of autoimmune thyroid disease, and insulin-dependent diabetes increase risk.69 The disease often starts with signs of thyrotoxicosis before progressing to hypothyroidism.70 Antithyroid antibodies are found in 80% to 85% of patients.71 Although this condition is subclinical in more than 60% of women, in about 23% it progresses to permanent hypothyroidism within 3 to 5 years and recurs in subsequent pregnancies in 15%.72 Similar amelioration of disease can be observed with Grave disease, with activation of this disease occurring within 4 to 6 postpartum months.67

Neonatal lupus (in the absence of apparent maternal disease), characterized by hematologic abnormalities such as leukopenia, anemia, and thrombocytopenia, a reversible skin rash, hepatosplenomegaly, and, in some cases, irreversible congenital heart block (associated with maternal anti-Ro antibodies) can signify future development of autoimmune disease in the mother.73 Within 10 years of the birth of a child

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Table 2. Physiologic Adaptations During Pregnancy and Practical Recommendations After Pregnancy Complications for Next Pregnancy and Later in Life6,7,19,34,38-54

<table>
<thead>
<tr>
<th>Physiological Adaptations</th>
<th>Hypervolemia</th>
<th>Hypercoagulation</th>
<th>Insulin Resistance</th>
<th>Immunosuppression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathologic changes</td>
<td>Massive proteinuria</td>
<td>Deep venous thrombosis, pulmonary embolism, recurrent miscarriage, early onset preeclampsia, (&lt;32 weeks), severe IUGR</td>
<td>Gestational DM</td>
<td>Preeclampsia</td>
</tr>
<tr>
<td>Assess after pregnancy</td>
<td>Diagnostic confirmation: Nephropathy: renal function and biopsy (rarely during pregnancy), PCMP: cardiac function (ultrasound) and endomyocardial biopsy if diagnostic problems</td>
<td>Investigate for hereditary (antithrombin and protein C/S deficiencies, factor V Leiden, prothrombin G20210A) and acquired (lupus anticoagulant, antiphospholipid antibodies) thrombophilia</td>
<td>OGTT 6-8 weeks postpartum</td>
<td>Blood pressure/urinary albumin, BMI control; investigate for components of MBS</td>
</tr>
<tr>
<td>Advise next pregnancy</td>
<td>Nephropathy: increased risk of superimposed preeclampsia, PCMP: pregnancy should be avoided, Arterial aneurysm/AVM: if successfully treated, not contraindicated</td>
<td>Thromboprophylaxis with LMWH or UFH, depending on thrombotic condition and clinical manifestation</td>
<td>If obese: weight loss, exercise, pharmacologic treatment (for type 2 DM, hypertension)</td>
<td>Amelioration of helper T-cell 1–dominant autoimmune disease (MS, rheumatoid arthritis, thyroiditis) but relapse after pregnancy</td>
</tr>
<tr>
<td>Advise later in life</td>
<td>Nephropathy: risk of hypertension, renal failure, PCMP: chronic heart failure, Arterial aneurysm/AVM: if aneurysm successfully operated, normal life</td>
<td>Risk of deep venous thrombosis, pulmonary embolism: appropriate thromboprophylaxis</td>
<td>Risk of type 2 DM after gestational DM, stroke, CAD, Thorough follow-up to diagnose and treat components of MBS, avoid β-blockers and thiazide diuretics if at high risk for MBS</td>
<td>Risk of chronic autoimmune disease (MS, rheumatoid arthritis)</td>
</tr>
</tbody>
</table>

Abbreviations: AVM, arteriovenous malformation; BMI, body mass index; CAD, coronary artery disease; DM, diabetes mellitus; IUGR, intrauterine growth retardation; LMWH, low-molecular-weight heparin; MBS, metabolic syndrome; MS, multiple sclerosis; OGTT, oral glucose tolerance test; PCMP, peripartum cardiomyopathy; UFH, unfractionated heparin.
with congenital heart block, 60% of mothers without identifiable disease in the index pregnancy develop an autoimmune disease, usually Sjögren syndrome.7 This is not directly related to pregnancy. It relates to the presence of anti-Ro antibodies, which in pregnancy are associated with risk of neonatal lupus and congenital heart block and in adults with Sjögren syndrome.73,74

Recently, other mechanisms for the onset of autoimmune diseases after delivery have been proposed. These include the transfer of fetal cells or DNA to the maternal circulation (a phenomenon called microchimerism), which could explain the temporal association of pregnancy and autoimmune diseases.75

Pregnancy and Hypervolemia

The increase in plasma volume is accompanied by an increase in both renal blood flow and the glomerular filtration rate.76 The renin-angiotensin system is activated but, despite high levels of angiotensin II, a state of high volume/low resistance is created because of induction of vasodilatory agents such as prostacyclin and nitric oxide.77 Pregnancy can unmask a subclinical glomerulopathy.77 The first sign is proteinuria, which develops early and can mimic preeclampsia.78 The proteinuria is often massive and hypertension is relatively mild.77 After pregnancy, proteinuria improves but does not disappear. Hyperfiltration could play an important role and could itself induce a glomerular lesion.77 The differential diagnosis between glomerulopathy and severe preeclampsia is difficult, and renal biopsy may be required. Most nephrologists restrict antepartum kidney biopsy to cases of rapidly progressive deterioration of renal function or of intense nephrotic syndrome occurring prior to 32 weeks’ gestation.78,79

Hypervolemia and high pulse pressure can also reveal previously subclinical arterial aneurysms or arteriovenous malformations.41,42 More than 50% of 40-year-old women in whom an arterial aneurysm ruptures sustain the rupture during pregnancy.79 These aneurysms develop typically in cerebral, splenic, or renal arteries.80 The risk of rupture is highest when hypervolemia is maximal, in the third trimester.41,42,79

Hypervolemia and cardiac hyperkinesia can induce a dilated cardiomyopathy, namely peripartum cardiomyopathy. This develops during the last month of pregnancy or within 6 months of delivery. It occurs in 1 in 1300 to 15 000 deliveries. Important risk factors are multiparity and age.80 The etiology remains unclear, although genetic, immunogenetic, and viral etiologies have been proposed.80-83

Intrahepatic Cholestasis of Pregnancy and Cholelithiasis

Intrahepatic cholestasis of pregnancy (ICP) is a cholestatic disorder that complicates 0.5% to 1.8% of otherwise normal pregnancies.84-86 It causes no risk to the mother but is associated with increased risk of preterm delivery and fetal loss.89,90 Familial clustering and uneven geographical distribution indicate a genetic basis and in 10% to 16% of mothers with ICP, the disorder appears dominantly inherited.85,86

The prevalence of cholelithiasis is known to be higher in patients with ICP than in the general population.87 In a recent study, the prevalence of cholelithiasis was 22% in patients with ICP compared with 4.8% to 15.3% in the general population.89 Of interest is the finding that 55% of patients had relatives who had diagnoses of cholelithiasis or had undergone cholecystectomy. This finding was supported by the identification of MDR3 mutations in patients with cholesterol lithiasis89 and pregnancy.89 However, a recent molecular genetic analysis suggests that MDR3 is not implicated in Finnish ICP families with dominant inheritance.85 Although the genetic basis for the connections between ICP and gallstones remains to be resolved, women with a history of ICP are at greater risk of developing gallstones later in life.85

Pregnancy and Opportunities for Primary Prevention

The difference between disease unmasked by pregnancy and disease caused by pregnancy is often difficult to discern. This reflects interactions between the physiologic changes of pregnancy and an underlying phenotypic susceptibility to a particular disease (Table 3). In this review, the phenotypic susceptibility to disease revealed by pregnancy is highlighted. Practical recommendations based on information given by pregnancy history are summarized in Table 2.

After pregnancy, women who have had gestational diabetes or preeclampsia should ideally be observed closely because of their increased risk of developing metabolic syndrome and/or vascular disease. The actual risk associated with GDM is unclear due to differences in definitions for GDM. Still, an important aspect for the development of treatment strategies to pre-

Table 3. Diseases Revealed or Caused by Pregnancy

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<th>Phenotype After Pregnancy</th>
<th>Time to Disease Expression</th>
</tr>
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<tbody>
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<td>Preeclampsia</td>
<td>Coronary artery disease</td>
<td>&gt;20 y</td>
</tr>
<tr>
<td>Deep venous thrombosis</td>
<td>Hereditary thrombophilia</td>
<td>At any time of increased thrombotic risk</td>
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<tr>
<td>Quiescent autoimmune disease</td>
<td>Rheumatoid arthritis</td>
<td>&lt;1 y</td>
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<tr>
<td>Intrahepatic cholestasis of pregnancy</td>
<td>Gallstones</td>
<td>Years</td>
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vent type 2 diabetes will be identification of women with limited β-cell reserve at an early stage because pregnancy can worsen insulin resistance and increase the risk for conversion to type 2 diabetes.30 A nonpharmacological approach to intervention with diet and an increase in aerobic exercise should be attempted,49-51 with monitoring of plasma glucose and blood pressure levels (Table 2). If hypertension develops, clinicians should avoid prescribing β-blockers and diuretics because of their diabetogenic effect.52

Sattar and Greer33 have proposed a model in which cardiovascular risk changes throughout life. This risk peaks during pregnancy because of metabolic and vascular changes. Women who develop preeclampsia may make greater excursions into metabolic disturbance during each pregnancy and return to an increased baseline level of risk of future metabolic and vascular disease compared with women with normal pregnancies.33 As shown earlier, these women run a greater risk of developing the metabolic syndrome and cardiovascular diseases; therefore, consideration should be given to primary prevention after pregnancy, having established their increased risk. How best to intervene is uncertain. Weight reduction where appropriate is clearly of value, along with dietary advice and increased exercise.49,92

Continuing follow-up should identify any additional risk factors, and opportunities for primary pharmacologic interventions may include statins in selected patients.53-55 Interestingly, the risk of cardiovascular disease attributed to the metabolic syndrome appears to be especially high in women, and it is estimated that half of cardiovascular events in women are related to the metabolic syndrome.88 This could account for the relatively high risk of small-vessel coronary artery disease and impaired endothelial function in women compared with men. This could also explain the relatively high prevalence of heart failure after myocardial infarction, despite angiographic evidence of only minor changes,37 and lower success rates after coronary artery angioplasty and bypass graft surgery than in men, who have more epicardial vessel disease.88

Pregnancy complications often precipitate the identification of hereditary thrombophilia. Although thrombophilia is attributed to the risk of venous thrombosis and pregnancy complications, it may also contribute to development of arterial disease in relation to the progression of atherosclerosis.89 Hormone replacement therapy with estrogen is known to increase the risk of venous thrombosis (by 2- to 3-fold), which becomes relevant with aging and presence of thrombophilia.4 Thus, knowledge of thrombophilia, identified during pregnancy, can lead to better preventive measures during at-risk situations such as surgery, long-distance travel, contraception and hormone therapy use, and subsequent pregnancy.

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