Microvascular Complications and the Diabetic Pregnancy

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Current Diabetes Reports 2006, **6:**291–296
Current Science Inc. ISSN 1534-4827

Without strict glycemic control, diabetic pregnancies are frequently complicated by spontaneous abortion, stillbirth, or congenital malformation. Retrospective studies have been largely reassuring that pregnancy does not accelerate morbid outcomes in women with diabetic vascular disease. Improved outcomes of high-risk pregnancy in women with pregestational, type 1, or type 2 diabetes mellitus remain challenging, depending on a comprehensive and multidisciplinary team approach and extensive preconception counseling.

Introduction

Hyperglycemia, even when transient, is the primary cause of diabetic microvascular complications, likely via mechanisms mediated by oxidative stress [1] including retinopathy, nephropathy, and neuropathy [2]. Also, both hyperglycemia and insulin resistance have been linked to increased risk of coronary artery disease (CAD).

Although risks associated with pregnancy in diabetic women have fallen with new standards for glycemic control, especially the risk of fetal malformations in planned pregnancies [2], some studies suggest that microvascular complications [3] still worsen during diabetic pregnancy. This review focuses on microvascular complications (retinopathy, nephropathy, and neuropathy), and on CAD in diabetic pregnancy.

Diabetic Retinopathy

Diabetic retinopathy (DR) typically involves progression from nonproliferative microvascular abnormalities, with development of capillary microaneurysms, excessive vascular permeability, and the formation of vascular occlusions, to a phase of proliferative retinopathy, with neovascularization, fibrosis, and vitreous hemorrhage, leading ultimately to blindness [4]. After 20 years, nearly all patients who develop type 1 diabetes mellitus (DM) before age 30 will develop DR; 50% of these patients will have proliferative retinopathy. Thus, most pregnant women with type 1 diabetes have some degree of DR and many have proliferative retinopathy, which may not have come to clinical attention prior to conception.

The risk of progression from nonproliferative to proliferative DR is directly related to the current severity of retinopathy. The rates of development and progression of DR during pregnancy range from 16% to 85% [5–7]. Regular funduscopy, leading to prophylactic laser photocoagulation, can often prevent progression. This, in combination with other treatment modalities, including vitrectomy when indicated, has greatly improved clinical outcomes.

Pregnancy and diabetic retinopathy

The effect of pregnancy on the natural course of DR is a matter of controversy. Although some patients with type 1 DM experience rapid worsening of retinopathy during pregnancy [6,8–13], others do not [14–17]. In some cases, retinopathy during pregnancy progressed to proliferative disease that required photocoagulation [18,19,20••]. In some cohorts reported previously, pregnancy-associated changes regressed after delivery [19,20••,21].

Even if retinopathy progression is accelerated during pregnancy, it is unclear whether remote prognosis is worsening; some controlled studies have demonstrated no long-term effect [11,12], whereas others have demonstrated a deleterious effect [14], especially in the setting of other pregnancy complications. The DCCT (Diabetes Control and Complications Trial) study compared outcomes of 6.5 years after 270 pregnancies (180 women) with those in 500 women who did not conceive [8]. There was an increased risk (odds ratio 2.5–2.9) of transient retinopathy progression in both the conventional and intense treatment groups during pregnancy, although remote outcomes compared were not worsened, as had been suggested by Rosenn and Miodovnik [4].

Several large studies have focused on long-term outcomes following pregnancy. The EURODIAB PCS (Prospective Complications Study) followed 793 women

for 7.3 years, comparing outcomes in the 163 women with an incident pregnancy with those women who did not conceive [20••]. Pregnancy was not related to presence or severity of retinopathy at follow-up, which was, however, predicted by duration of diabetes and hemoglobin A_{1c}.

A larger retrospective study compared 776 nulliparous and 582 parous women with type 1 DM and found that the prevalence of retinopathy was lower in women who had two or more pregnancies (35%) compared with women who had only one pregnancy (45%) or no pregnancies (48%) [22]. Proliferative retinopathy was lower in parous women (8%) than in nulliparous women (16%). Although there may have been selection bias for favoring pregnancy in women with fewer diabetic complications, these differences persisted even after adjusting for glycemic control, suggesting that pregnancy is not a long-term risk factor for DR and its progression.

Hemachandra et al. [23] performed two nested, pair-matched, case-control studies within the EDIC (Epidemiology of Diabetes Complications) study. The first study found that the incidence of proliferative retinopathy among the 30 women with type 1 DM who had a pregnancy within the previous 2-year period was 25%, compared with 9.1% among the 30 nulliparous control subjects; however, the difference was not statistically significant. The second study found that the incidence of proliferative retinopathy among the 80 women who had a pregnancy during the previous 4-year follow-up period was 35%, similar to that among nulliparous women (36%). Taken together, all of these results suggest that although retinopathy may accelerate during and immediately following pregnancy, remote outcomes are unchanged.

Rosenn et al. [24] argue that several factors may contribute to the pathogenesis of DR, including 1) the role of glycemic control, "which is the cornerstone of management for pregnant women with DM, and has emerged as the single most important factor associated with improved maternal and neonatal outcome" [24]; 2) angiogenic growth factors that result in vessel proliferation in endothelial cell cultures in vitro [25]; and 3) hypertension, which has been consistently linked to the severity of retinopathy because it develops in 10% to 20% of pregnant women with DM and pregnancy-induced hypertension [26].

Intensive glycemic control is not only the cornerstone of management to improve neonatal outcome in pregnant women with DM [27], but also to limit retinopathy in the nonpregnant population [28–30]. Intensified glycemic control slows development and progression of several long-term microvascular complications, including retinopathy, nephropathy, and neuropathy [31–33]. Therefore, the institution of strict glycemic control during pregnancy may be expected to confer a benefit in terms of progression of retinopathy.

Paradoxically, however, rapid normalization of (previous uncontrolled) hyperglycemia can cause acute, albeit often transient, progression of retinopathy [34]. Similar results have been found in pregnancy [6].

In addition to institution of strict glycemic control, other changes occurring during pregnancy may affect retinopathy. It has been suggested that circulating and local factors may contribute to the progression of retinopathy. These factors include growth hormone [35], insulin-like growth factor-1 [36,37], and various other growth factors (eg, vascular endothelial growth factor) and other angiogenic factors isolated from the vitreous of patients with proliferative retinopathy that produce vessel proliferation in vitro [38,39]. The relevance of these findings to pregnancy is that the placenta also produces angiogenic factors that result in vessel proliferation in endothelial cell cultures in vitro [40]. The concentration of fibroblast growth factor-2, a potent mitogen and angiogenic factor that appears in normal maternal serum during pregnancy, is substantially elevated in pregnant women with DR compared to those without retinopathy [41•].

Progression of retinopathy during pregnancy has also been associated with the risk of fetal growth restriction [24], suggesting the possibility that worsening microvascular disease may be a manifestation of vascular changes during pregnancy that may affect not only the retina, but also other vascular beds such as the utero-placental unit [24].

Another concern related to pregnancy is that the abrupt hypertension during delivery may cause acute retinal hemorrhages in mothers with preproliferative changes. This concern has led some obstetricians to advocate cesarean delivery for these mothers. However, others argue that the vascular changes are predominantly postarteriolar and are unlikely to be affected by the Valsalva maneuver.

Whether use of insulin lispro during pregnancy increases the risk of progression of retinopathy is a subject of some debate. In a cohort of 14 women treated with insulin lispro during pregnancy, described by Kitzmiller et al. [40], three progressed from no background retinopathy to bilateral proliferative retinopathy, suggesting an association between lispro and progression of retinopathy. The authors questioned whether lispro might enhance the production or activity of local or systemic vasoproliferative factors during pregnancy, and pointed to the fact that lispro is a homologue of insulin-like growth factor-1. In contrast, several authors have studied larger cohorts of pregnant women with diabetes and have found no increased risk of retinopathy associated with the use of lispro during pregnancy [40]. Loukovaara et al. [41•] concluded that insulin lispro seems to improve glycemic control throughout pregnancy in women with type 1 diabetes better than regular insulin with no adverse impact on progression of DR.

In summary, retinopathy progression during pregnancy is related to the severity of any baseline retinopathy: women without baseline changes are at relatively low risk of progression, and women with proliferative retinopathy are at high risk. It is also clear that some women who show progression

of retinopathy during pregnancy will show regression within 1 or 2 years postpartum. However, it is not clear to what extent the irreversible component of progression observed during pregnancy is caused by pregnancy or simply reflects the natural history of a progressive disease. Also unclear is whether any changes attributable to pregnancy are caused primarily by the altered hormonal milieu of pregnancy, by the institution of strict glycemic control, by the occurrence of hypertensive complications of pregnancy, or by the hemodynamic stresses of pregnancy, labor, and delivery. Most important, however, it appears that pregnancy does not alter the long-term course of DR and does not affect the long-term prognosis of the disease.

Diabetic Nephropathy

Several factors have been implicated in the development and progression of diabetic nephropathy (DN), many of which may be affected by pregnancy. DN is defined by typical biopsy readings, progressive glomerular protein leak, and subsequent loss of glomerular filtration rate (GFR). Overt nephropathy is characterized by macroalbuminuria (> 300 mg/d), macroproteinuria (> 500 mg/d), and subsequent progressive decline in renal function leading to end-stage renal disease (ESRD). DN is the most common cause of ESRD in the United States, accounting for approximately 45% of new cases [24].

Mogensen et al. [42] described several distinct clinical and subclinical stages of the disease. Initially, renal hypertrophy and microscopic lesions appear in genetically susceptible individuals within a few years of the onset of diabetes. These lesions are characterized by scattered sclerosis of glomeruli that can be demonstrated on renal biopsy even in the absence of clinical findings. Within 5 to 10 years, minute amounts of albumin (30–300 mg per 24 hours) and other anionic proteins appear in the urine, constituting the phase of incipient nephropathy, often associated with development of hypertension as well. Within a few years, overt nephropathy develops (> 300 mg of albumin per 24 hours) characterized by progressive, widespread glomerular sclerosis, resulting in excretion of progressively larger amounts of protein and then loss of GFR and progressive anemia.

The incidence of DN is related to the duration of diabetes and to glycemic control: approximately 15% of people with type 1 DM have nephropathy within 15 years, 30% within 20 years, and 40% within 30 years from onset [43]. Once nephropathy is established, renal function continues to deteriorate progressively, with the GFR declining at an average rate of 10 mL/min each year. Progression to ESRD occurs in at least 75% of patients within the following 10 years [44], although this can be slowed by tight blood pressure control and blockage of the renin-angiotensin system.

Although angiotensin-converting enzyme (ACE) inhibitor therapy is standard for nephroprotection, both ACE inhibitors and angiotensin receptor blockers can lead to fetopathy and fatal neonatal acute renal failure when used later in pregnancy [45–47].

Pregnancy and diabetic nephropathy

Several factors associated with pregnancy could, hypothetically, increase the risk of nephropathy, including renal hyperfiltration and hypertensive complications of pregnancy. Gestational glomerular hyperfiltration with GFR increments of 40% to 60% are due to balanced afferent and efferent arteriolar vasodilation; thus, they do not lead to glomerular hypertension or progressive loss of renal function. Whether this benign physiology applies in kidneys already exhibiting didactic damage is uncertain. Hypertension and preeclampsia affect 15% to 20% of all women with diabetes, and an even greater proportion of those with nephropathy; effects in nephropathy progression are uncertain. Tight blood pressure control during pregnancy will improve maternal and fetal outcomes without exacerbating fetal growth restriction, assessing whether the choice of antihypertensive agents used in gravidas with DN should differ from those used in women with chronic hypertension [48], and determining whether use of newer markers related to the pathophysiology of preeclampsia may allow early and accurate differentiation of superimposed preeclampsia from worsened hypertension and proteinuria due to DN alone.

Several studies have attempted to follow women with DN during and after pregnancy to assess outcomes. These pregnancies often lead to marked increases in proteinuria, to nephritic levels, which usually resolve following delivery, often returning to prepregnancy levels.

Miodovnik et al. [49] retrospectively studied 182 women with type 1 diabetes, of whom 46 had overt DN. These patients were followed for a period of 3 to 16 years (median, 9.1 years) after delivery. Of the 136 women without nephropathy at the time of pregnancy, only 13 (10%) eventually developed nephropathy later in life, within a mean of 10.1 years following the pregnancy. Proteinuria appearing during pregnancy and poor glycemic control during pregnancy, but not parity, was significantly associated with the subsequent development of nephropathy. Of the 46 women who had overt nephropathy prior to pregnancy, 12 (26%) progressed to ESRD after a median period of 6 years, but again this was not associated with parity. Using life-table analysis, the investigators found that in this parous population, the overall risk of developing nephropathy was 44% after 27 years of diabetes, and the risk of progressing to ESRD was 30% after 10 years of overt DN.

In a large cross-sectional study [23], 776 nulliparous and 582 parous women with type 1 DN were examined and found that glycemic control was better in parous women; also, that age- and duration-adjusted prevalence of microalbuminuria were similar in parous and nulliparous women, but macroalbuminuria was lower in parous women (6% vs 10%, $P < 0.0001$). Ultimately, equivalent levels of

microalbuminuria and background retinopathy in parous and nulliparous women suggest that pregnancy may not exacerbate these early complications.

In the EURODIAB PCS [20], results showed that hemoglobin A_{1c} was a significant risk factor for progression to microalbuminuria, but age, duration of diabetes, systolic blood pressure, or giving birth were not; also, that giving birth was not significantly related to the incidence of neuropathy. This is in accordance with the findings of the DCCT, which showed that having a first or another pregnancy is not a risk factor for long-term progression of microvascular complication.

Taken together, most of the studies on DN during pregnancy suggest that pregnancy is not associated with development of nephropathy or with accelerated progression of pre-existing nephropathy. Although the incidences of worsened hypertension, superimposed preeclampsia, preterm birth, and intrauterine growth restriction are all high, live births are the norm and renal functional loss is seldom accelerated in women whose baseline serum creatinine is less than 1.4 mg/dL [50]. This similarity in satisfactory outcomes has recently been supported by a report comparing outcomes in women with DN, nondiabetic renal primary renal disease, and renal allograft recipients, all with well-preserved renal function; in these women, hypertension was the best predictor of adverse outcomes during pregnancy [51]. By contrast, several series of women with more severe renal insufficiency have demonstrated that approximately 30% to 40% will suffer irreversible acceleration of renal insufficiency during pregnancy, with many of these women progressing rapidly to ESRD [52–54]; further elevations of baseline serum creatinine (> 2.5 or 2.8 mg/dL) or uncontrolled hypertension each predict poorer renal and pregnancy outcomes [54].

Diabetic Neuropathy

Diabetic neuropathy may be focal or diffuse, and affect sensory, motor, or autonomic neuropathy. Approximately 50% of patients with diabetes have some form of neuropathy, with or without symptoms [19], with increasing prevalence, along with extended duration of diabetes, age, and poor glycemic control.

Pregnancy and diabetic neuropathy

Pregnancy effects in neuropathy have been studied less than other microvascular complications. There may be a short-term increase in the incidence of polyneuropathy due to pregnancy [21], but without long-term increases in its incidence or progression.

Chaturvedi et al. [21], in a cross-sectional study comparing 776 nulliparous and 582 parous women with type 1 DM, found that autonomic neuropathy was significantly less prevalent in parous than in nulliparous women. However, the parous women might have been lower risk at baseline. In a subsequent prospective study, these same authors found no increase in the incidence of diabetic neuropathy following pregnancy in the EURODIAB prospective cohort [20••]. The presence of gastroparesis is particularly relevant to pregnancy in that, with the hyperemesis of pregnancy, it could exacerbate nausea and vomiting, leading to irregular absorption of nutrients, inadequate nutrition, and aberrant glucose control. Rosenn et al. [24] observed exacerbations of autonomic neuropathy in association with hypertension in pregnancy. By contrast, some have noticed transient improvement in symptoms during pregnancy. Overall, it seems that pregnancy does not alter the natural course of diabetic autonomic neuropathy [25].

Coronary artery disease

CAD prevalence is extremely high (> 50%) in patients with diabetes, especially type 2, compared with the general population (~ 2% to 4%) [17]. Effects have been linked to hyperglycemia and especially to insulin resistance and "metabolic syndrome" [16].

Pregnancy and coronary artery disease

Despite the increased risk, diabetic pregnant women are relatively young and unlikely to suffer advanced CAD or myocardial infarction (MI) [45,55]. There have been 20 cases reported between 1953 and 1998 of mothers with diabetes who suffered an MI or ischemic cardiac event before, during, or shortly after pregnancy [38]. Among the 13 women whose event occurred during pregnancy or in the puerperium, seven mothers and seven infants died. Of the seven women whose myocardial event occurred prior to pregnancy, all of the mothers and infants survived. The difference in outcome between women who had an MI prior to pregnancy, and those who had an MI during pregnancy or the puerperium, may reflect the grave consequences of having an MI during pregnancy, but might also reflect a selection bias, in that this group of women with prior MI may have had minimal or no residual cardiac dysfunction after an MI and might represent the group that was less emphatically discouraged from conceiving or from carrying on with a pregnancy.

Historically, women with prior heart disease have been at considerable risk of maternal death during pregnancy. Prior to 1980, the overall maternal mortality rate was 70% (7 out of 10 women); whereas among cases reported after 1980, the mortality rate has dropped to 0 (0 out of 10) [38]. This may reflect improved care, heightened awareness of the risks associated with these pregnancies, better counseling for women with diabetic CAD, or reporting bias of unexpectedly successful outcomes despite pre-existing CAD.

Conclusions

Many women with diabetes develop complications, which may have a tremendous impact on their quality of life and their ultimate prognosis. Because type 1 diabetes

often begins at a very early age, it is quite common for women in their childbearing age to be affected by these complications. As described in this review, diabetic vascular complications and pregnancy may significantly affect each other, but it is not always easy to predict the course of either and to counsel these patients accordingly. Nevertheless, it appears that only in rare occasions or with more advanced disease should women with diabetes be advised against pregnancy, and that in most situations, with careful and knowledgeable management, starting prior to conception, a favorable outcome can be expected both for the mother and her infant.

In summary, even though perinatal mortality of infants born to mothers with DM has decreased remarkably and now approaches that of the general population, these infants still face a multitude of potential complications, both in utero and postnatally, many of which are related to poor maternal glycemic control. Thus, the key to an improved pregnancy outcome lies in preconceptional counseling and specialized prenatal and postnatal care, as well as a commitment on the part of the mother to adhere to a regimen of meticulous glycemic control.

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