

METABOLIC COMPLICATIONS

Microangiopathy and pregnancy

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Abstract

Diabetic microangiopathy is a frequent complication of longstanding diabetes mellitus. Micro vascular lesions may have severe implications for both maternal and foetal health.

Patients with advanced underlying lesions are at increased risk of progression during pregnancy. Severe retinal lesions can progress during pregnancy and one year after delivery. Poor glycaemic control prior to conception and rapid improvement during pregnancy are other risk factors of progression. Treatment of lesions with high risk of progression and progressive blood glucose lowering in the preconception period can improve the prognosis. Diabetic nephropathy predisposes to preeclampsia, premature delivery, intrauterine growth retardation and perinatal mortality. Patients with elevated creatinine levels are at increased risk of permanent impairment of kidney function. These patients should be closely monitored and their blood pressure tightly controlled. Gastroparesis may be aggravated by pregnancy hyper emesis. Autonomic neuropathy may result in erratic maternal glucose control, foetus growth retardation and foetal loss.

Keywords: Diabetes mellitus, Pregnancy, Microangiopathy.

Introduction

The incidence of diabetes mellitus (DM) among women of childbearing age is increasing relentlessly. DM in pregnant women concerns, especially type 1 DM, but also type 2. The last one is driven by an epidemic obesity induced by environmental, nutritional, and lifestyle modifications.¹

As a consequence of environmental factors, DM in general

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is expected to be a common situation during pregnancy. DM can be known before conception, or diagnosed for the first time during pregnancy. In the latter situation it is called gestational DM (GDM). Pre-gestational DM affects 1% of all gestations but, it can reach 3.7% in some populations as in the Middle East due to high prevalence of type 2 diabetes among young women.² GDM occurs in approximately 4% of pregnancies, although the figures can rise to 18% in some populations.

DM chronic complications are numerous, but the most disturbing are vascular ones including micro and macro angiopathies. Those complications generally occur after many years of DM evolution. Microangiopathy affects the small vessels located everywhere, although the most bothersome lesions are those affecting the eyes (or retinopathy), kidneys (nephropathy) and the nerves (neuropathy). Some factors such as genetic background, systemic hypertension, dyslipidaemia and smoking may contribute to their apparition and/or aggravation. However, chronic hyperglycaemia, due to poor glycaemic control, is the main pathogenic factor in the occurrence and or aggravation of diabetic microangiopathy. Consequently, pregnant women with preexisting DM are more prone to microvascular complications. Those with type 1 DM are at the highest risk as improvement in DM care and advanced maternal age at conception lead to an increase in women with longstanding DM. Patients with type 2 DM are also at risk but to a lesser degree. In general, GDM does not put pregnant women at risk for microangiopathy. However, some patients can have unnoticed preexisting diabetes and are therefore at risk although this case seems to be rare.

On the pathogenic point, controversies exist regarding the role of pregnancy itself on the development and progression of diabetic microangiopathy. Actually many researchers think that the risk of developing maternal microvascular complications during pregnancy is linked to many factors such as DM duration, quality of glycaemic control, and degree of preexisting lesions. The present

article aims to discuss possible relations between pregnancy and diabetic microangiopathy, focusing especially on retinopathy and nephropathy as diabetic neuropathy is generally rare in pregnant women.

Diabetic Retinopathy

Diabetic retinopathy (DR) is the leading cause of blindness around the world. It is the most frequent complication of DM affecting nearly all people with type 1 DM and 60% of patients with type 2 DM after 20 years duration. DR evolves in several stages as evidenced in Table-1.

Macular oedema is the most serious complication because it leads to blindness. It can be seen at any stage of DR, but it is more frequent in the proliferative one.

Many studies reported that pregnancy affects adversely DR. The DCCT (Diabetes Control and Complications Trial) is one of the largest trials which evaluated pregnancy's impact on diabetic retinopathy in type 1 DM after an average follow up of 6.5 years. This study comparing 180 women who had 270 pregnancies to 500 non pregnant women demonstrated that pregnancy was associated with a high risk of retinopathy: Pregnant women had a 1.63-fold greater risk in the intensive group and a 2.48-fold greater risk in the conventional group.³ In another study, it was shown that DR progression in women with type 2 DM during pregnancy was observed in 14%.⁴ Other studies plead also for the development or progression of DR in 16 to 85%. This wide range may be explained by the baseline retinal status and DM control before and during pregnancy. Presence of severe retinal lesions at the beginning of pregnancy is an important predictive factor for progression. Chew et al in a prospective study showed that DR progression was observed in 10.3% in patients with no baseline DR, and in respectively 21%, 18.8% and 54.8% for patients with micro aneurysms only, mild non-proliferative DR, and severe non-proliferative DR.⁵ Diabetes duration is an important factor for progression as DR worsening is more frequent in longstanding DM. Poor glycaemic control prior to conception and rapid improvement during pregnancy are also important

Table-1: Classification of diabetic retinopathy.

Stage	Retinal Lesions
No retinopathy	Absent
Background retinopathy	Micro-aneurysms, Haemorrhages, Hard exudates
Pre-proliferative retinopathy	Soft exudates, Cotton wool spots, Intra-retinal micro-vascular abnormalities (IRMA), Venous abnormalities
Proliferative retinopathy	New vessels on the disc or elsewhere
Complicated retinopathy	Vitreous haemorrhage, Retinal detachments, Rubeosis iridis with neovascular glaucoma

Table-2: Monitoring of diabetic retinopathy during pregnancy.⁶

All diabetic women should have a dilated and comprehensive eye examination in the preconception period
Optimize glycaemic and blood pressure control. Blood glucose levels should be lowered slowly over a six month period before pregnancy in patients with severe non proliferative or proliferative DR
All diabetic women should have funduscopy in the first trimester with close follow-up throughout pregnancy and for one year postpartum.
Patients with no or minimal retinopathy should be evaluated in the first and third trimesters. Patients with mild retinopathy should be evaluated every trimester. Patients with moderate to severe DR should be evaluated monthly
Laser photocoagulation therapy is indicated in preconception and during pregnancy in patients with high-risk DR or clinically significant macular oedema
Assisted second-stage delivery or caesarean delivery should be considered in women with untreated severe DR as vaginal delivery has been associated with retinal and vitreous haemorrhage.

factors for DR progression. Actually, a sudden improvement in glycaemic control is responsible for retinal hypoxia. That one is secondary to a decrease in blood flow during tight glycaemic control. Systemic hypertension, nephropathy, hormonal inflation and changes in IGF1 (insulin growth factor 1) and other angiogenic factors may participate to DR worsening. DR that develops or progresses during pregnancy may progress during the first year after delivery, but it can also disappear spontaneously. This observation means that patients with early worsening of retinopathy may benefit from a strict metabolic control for the long term. In mild DR regression is complete in 50% and partial in 30%. In severe DR regression is complete in 17% and partial in 58%. Careful monitoring of DM during pregnancy is mandatory to improve vision outcome. Patients with high-risk lesions should be treated by laser photocoagulation therapy before or during pregnancy. Other actions to undertake are summarized in Table-2 as recommended by the American Diabetes Association (ADA).⁶

Diabetic Nephropathy

Diabetic nephropathy (DN) is a progressive disease which affects 20 to 40% of diabetic patients and is the leading cause of end-stage renal disease (ESRD). Micro albuminuria is the first manifestation of DN. Micro albuminuria is generally defined as repeated albumin excretion of 30 to 299 mg/24-h after exclusion of other causes of proteinuria such as urinary tract infections. DN is characterized by 24-h albumin urinary excretion over 300 mg, hypertension and progressive decline in glomerular filtration rate (GFR). Normal pregnancy is characterized by an increase in GFR by 50 to 100% and a slightly decrease in serum creatinine. Women with DN have an increase in protein excretion throughout gestation, with a peak

during the third trimester; furthermore creatinine clearance does not show the physiologic increase as in normal pregnancy. Albuminuria needs to be measured early, during the first trimester of pregnancy as proteinuria may physiologically increase later, after 20 weeks of gestation, overestimating protein excretion. Recent studies showed that prevalence of micro albuminuria and DN in pregnancy has decreased in these last years. The same thing is observed in non pregnant women probably as a consequence of a better control of DM and high blood pressure. Actually, micro albuminuria dropped from 11% to 3-5% and DN decreased from 5-15% to 2-3%.⁷

It is shown that pregnancy in patients with DN is associated with a dire prognosis for both the mother and the foetus. Maternal complications include an increased risk for preeclampsia, end-stage renal disease (ESRD) and preterm delivery. For the foetus the risks are: intra uterine growth retardation (IUGR), prematurity, and high perinatal mortality. Preexisting DN has also been associated with an increased risk of congenital malformations. But, this may be related to poor glycaemic control during the first weeks of pregnancy frequently observed in these patients. Although most studies are from patients with type 1 DM, the same results have been reported in patients with type 2 DM.⁸ In general, maternal and foetal outcomes are favourable in case of mild elevation in serum creatinine <1.4mg/dl, proteinuria <1 g/24 h, and normal blood pressure. In contrast, serum creatinine >2.0mg/dl, proteinuria in the nephrotic range >3 g/24 h and severe hypertension are associated with high complications' rate. Furthermore long term impairment of kidney function has been reported in women with elevated serum creatinine > 2.0mg/dl at the beginning of pregnancy. Preeclampsia is one of the most important complications of DN during pregnancy. It is characterized by high blood pressure, proteinuria, and peripheral oedema. Its incidence is closely related to the degree of renal impairment. It is shown that it increased from 12% in normal non-albuminuric women to 40% in patients with micro albuminuria.⁹ In overt DN, preeclampsia incidence ranges from 40 to 65%. The pathophysiology of preeclampsia in DN involves endothelial dysfunction, oxidative stress, impaired maximal vasodilatation, increased levels of renin angiotensin system components and anti-angiogenic factors. Caesarean section is required in nearly 70% of women with DN. Perinatal complications are enhanced in patients with DN. Preterm delivery occurs in 25%, intra uterine growth retardation in 15% and perinatal mortality in 5% [9]. Inhibition of renin angiotensin system (RAS), using either an angiotensin converting enzyme inhibitor

Table-3: Care of diabetic pregnant women with microalbuminuria and diabetic nephropathy.

Determine urinary albumin excretion and estimate GFR early and throughout pregnancy
Optimize glycaemic control
Optimize antihypertensive treatment to reach blood pressure and urinary albumin excretion targets (<135/85 mm Hg and <300 mg/24h respectively)
Use antihypertensive drugs well tolerated during pregnancy: methyldopa, beta-blockers such as labetalol and long-acting calcium antagonists such as nifedipine and diltiazem
Use of low dose aspirin from 12 weeks of gestation to 1 week before delivery
Strict obstetric monitoring

or an angiotensin receptor blocker, can slow DN progression. Those medications considered as cornerstones in DN in general are contraindicated in pregnancy as they were associated to congenital malformations and neonatal renal failure. However, treatment with renin angiotensin inhibitors combined with strict glycaemic control initiated at least 6 months before pregnancy in women with DN may have a remnant benefic effect throughout pregnancy despite stopping these agents before conception. Care of women with DN, especially stringent antihypertensive treatment when blood pressure exceeds 135/85 mm Hg or urinary albumin excretion superior to 300 mg/24h, may dramatically improve the prognosis of this condition. In patients with micro albuminuria, it was shown that this strategy decreased preeclampsia rate from 20% to 0%, whereas preterm delivery rate decreased from 40% to 20%. In patients with DN, intensive antihypertensive treatment decreased the severity of preeclampsia too.¹⁰ As renin angiotensin inhibitors are contraindicated, other antihypertensive agents which are well tolerated during pregnancy should be used. These include, methyldopa, beta-blockers (such as Labetalol: the selected beta-adrenergic blocker) and long-acting calcium antagonists or calcium channel blockers such as Nifedipine and Diltiazem. Some women need a combination of antihypertensive agents to control blood pressure and urinary albumin excretion. Low-dose aspirin treatment is recommended in women with microalbuminuria or DN to reduce the risk of preeclampsia. Aspirin should be started from 12 weeks of gestational age after the organogenesis phase and stopped one week before delivery to reduce the risk of bleeding. Standards of care for diabetic pregnant women with nephropathy are delineated in Table-3.

Diabetic Neuropathy

Diabetic neuropathy is a heterogeneous disease involving both peripheral and autonomic nerves function. Usually symmetric distal polyneuropathy is the most common form

of neuropathy. Its manifestations are pain and loss of sensitivity in both legs. Diabetic neuropathy predisposes to foot lesions such as ulcerations. There are limited data on whether pregnancy worsens or not symptoms of neuropathy. Manifestations of autonomic neuropathy include cardiovascular, digestive and urinary signs. Other organs may also be involved. The most relevant manifestations of autonomic neuropathy during pregnancy are hypoglycaemia unawareness and gastroparesis. Hypoglycaemia unawareness is associated with very high risk of severe hypoglycaemia with implementation of intensive insulin regimen and tightening of glycaemic goals during pregnancy. These patients should be educated and their blood glucose levels closely followed to reduce the risk of severe hypoglycaemias. Gastroparesis is characterized by delayed gastric emptying. Its manifestations are vomiting, nausea and sensation of postprandial fullness. Pregnancy hyperemesis may exacerbate nausea and vomiting. Scintigraphy is the gold standard for gastroparesis diagnosis. This procedure is contraindicated during pregnancy. However, presence of retained food 12 hours after ingestion during endoscopic procedure is a high suspicion for gastroparesis. Severe gastroparesis is rare during pregnancy. However, when present, it is associated with high maternal and foetal complications. It can result in irregular nutrients absorption and inadequate nutrition. Erratic glucose control may result, leading to both severe hypoglycaemia and ketoacidosis. Foetus complications include growth retardation, foetal loss and prematurity.¹¹ Patients with gastroparesis may benefit from treatment with prokinetic agents such as Metoclopramide. Erythromycin may be helpful too. Severe cases may require total parenteral nutrition. For some authors, severe gastroparesis is a relative contraindication for pregnancy.

Conclusion

The number of women with pre-gestational diabetes will increase relentlessly in the forthcoming years as a consequence of an increasing prevalence of diabetes mellitus in the whole world. Pregnant women with preexisting diabetes are at increased risk for micro vascular lesions. The last ones are linked to the degree of underlying lesions and to rapid improvement of glycaemic control. Therefore, preconception care is fundamental to minimize worsening of micro vascular complications during pregnancy. For this, glycaemic control should be smoothly improved over a period of six months in the preconception period. In addition, diabetic women should

be thoroughly assessed before, during and in the post partum period. Those with advanced retinal lesions, large amount of proteinuria, elevated creatinine levels, and severe neuropathy should be stabilized with appropriate treatments before pregnancy will be allowed. Then after delivery they should be regularly followed and monitored.

Declaration of Interest: The authors declare there is no conflict of interest that would prejudice the impartiality of this scientific work.

Funding: This research did not receive any specific grant from any funding agency in the public, commercial or profit sector.

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