WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.074
Volume 8, Issue 5, 88-103. Research Article ISSN 2277– 7105

PREGNANCY OUTCOMES IN WOMEN WITH STRICTLY CONTROLLED TYPE 1 DIABETES MELLITUS

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Article Received on
03 Feb. 2019,

Revised on 24 Feb. 2019,
Accepted on 18 March 2019

DOI: 10.20959/wjpr20195-14548

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ABSTRACT

Prenatal care, glucose regulation, and regular antenatal visits are the mainstays of the management of diabetic pregnant patients. We offer and inform the diabetic patients about these management protocols before planning the pregnancy. It is clear that these protocols could decrease all of the adverse outcomes of the pregnancy especially ketoacidosis, abortus, and congenital anomalies. According to our results even in the most favorable conditions, the patient would have a great risk for preterm delivery and cesarean section, the moderate risk for macrosomia, preeclampsia, and an undefined risk for antenatal death. These facts should be kept in mind for informing diabetic patients about pregnancy during prenatal counseling.

KEYWORDS: Pregnancy, Type 1 Diabetes Mellitus.

INTRODUCTION

Pregnancies with type 1 diabetes have been a challenge to multidisciplinary physicians. Among these women, the worst pregnancy outcome was often seen in the subgroup of women with severe diabetic nephropathy (DN). The prevalence rates of preeclampsia (PE) and preterm delivery were reported as 48% and 73% in Klemetti's study in the subgroup of DN, much higher compared with the 24% and 44% in the background T1DM population.[1]

The DN is defined by urine albumin excretion (UAE) > 300mg/24 h in most researches. However, microalbuminuria (which is defined by UAE in the range of 30e300mg/ 24 h) serves as an early indicator of DN risk. Several studies have involved the subgroup of microalbuminuria and showed that these women had a high incidence rate of adverse

pregnancy outcome as well. Ekbom et al. showed that the prevalence of PE was approximately 42% in pregnancies with microalbuminuria in early pregnancy.[2]

Pregnancy in women with type 1 Diabetes Mellitus (T1D) is associated with an increased risk of obstetrical and fetal complications like miscarriage, preeclampsia, macrosomia, congenital malformations, and even perinatal death.[3] Up to now, these complications have been attributed mainly to the effects of hyperglycemia. Therefore strict guidelines have been imposed for the care of diabetic women. These guidelines recommend an HbA1c < 53 mmol/mol before and during pregnancy in order to create advantageous conditions for implantation and fetal development.[4]

Although this approach has indeed resulted in an improved pregnancy outcome, the incidence of pregnancy complications in women with diabetes is still greater than in healthy women.[5] The question, therefore, arises whether other etiological factors are involved. In healthy pregnancies adaptations in immune responses take place in order to assure successful implantation and placental and fetal development.[6] The importance of these immunological adaptations is reinforced by the findings that many pregnancy complications are associated with aberrant immune responses.[7]

Recently we have shown that immunological adaptations to pregnancy are different in women with T1D than in healthy women.[8] Therefore, we hypothesized that aberrant immune responses in diabetic pregnancy might play a role in the unfavorable pregnancy outcomes of women with this disease. Here we review the current proof and views on the role of aberrant immunological adaptations in pregnancy complications and whether such aberrant adaptations could play a role in the pregnancy complications of T1D patients.[9]

Among pregnant women with preexisting diabetes, the worst pregnancy outcome occurs in the subgroup of women with diabetic nephropathy[10]. In the late 1990s, the prevalence of microalbuminuria and diabetic nephropathy among pregnant women with diabetes was 10% and 5%, respectively. The development of preeclampsia with severe hypertension and nephrotic proteinuria was common in these women and often led to early preterm delivery.[11] Outside of pregnancy, strict antihypertension treatment was proven to be effective in controlling hypertension and proteinuria. However, whether antihypertension treatment during pregnancy in women with diabetes and kidney involvement could improve pregnancy

outcome was not known. Preterm delivery, before 37 weeks, occurred in 40% of women with preexisting diabetes, whether or not they had kidney involvement.[12]

This prevalence was approximately four times higher compared with the background population[13] Strict glycemic control with appropriate diet and human insulin was the cornerstone of treatment to prevent preterm delivery in women with diabetes. However, strict glycemic control in women with type 1 diabetes was associated with a high risk of severe hypoglycemia.[14]

At present, fetal overgrowth is the most significant fetal complication. Approximately half of women with preexisting diabetes deliver infants that are large for gestational age (LGA).[15] Poor glycemic control is a well-known predisposing factor for LGA, but other factors predisposing to fetal overgrowth need to be considered and explored. At the Center for Pregnant Women with Diabetes in Copenhagen, we have a long tradition of clinical research that leads to optimized clinical care.[16] Each year, approximately 100 women with type 1 diabetes and 50 women with type 2 diabetes are followed during pregnancy. Our clinical care and research involve a fruitful collaboration in a team involving endocrine and obstetric expertise, including doctors, nurses, midwives, laboratory technicians, dietitians, and medical students. This overview covers the clinical research performed in Copenhagen over the past two decades in order to improve the pregnancy outcome in all women with preexisting diabetes and, in particular, women suffering from microalbuminuria and/or diabetic nephropathy.[17]

The prevalence of diabetes in pregnancy has been increasing worldwide.[18] The majority is gestational diabetes mellitus (GDM) with the remainder divided between pregestational type 1 diabetes and type 2 diabetes which is called pre-gestational diabetes mellitus (pre-GDM). Both pre-gestational type 1 diabetes and type 2 diabetes have a significantly greater risk than GDM.

Before the discovery of insulin, pregnancy in diabetic women was a catastrophic event. Nearly 60% of pregnant women were dying due to severe ketoacidosis and >90% of infants were stillborn or died in the first hours after birth.[19] Insulin therapy and multidisciplinary approach reduced the complications during the pregnancy and improved the pregnancy outcomes. Preconceptional care and controlled blood glucose levels during pregnancy are the key points for the management of pre-GDM.[20] In the preconceptional examination,

investigation of the vascular complications has great importance. The existence of vascular complications may predict the outcomes of the pregnancy. Patients without vascular complications and controlled glucose levels are good candidates for pregnancy.[21] Here we analyze the pregnancy outcomes of the pregnant patients with non-complicated T1DM with controlled blood glucose levels.

Background

Twenty years ago, the development of preeclampsia with severe hypertension and nephrotic proteinuria leading to early preterm delivery was frequently observed among women with type 1 diabetes complicated by diabetic nephropathy.[22] In nonpregnant subjects, antihypertension treatment with blockers of the renin-angiotensin system has for years been a well-established cornerstone in the treatment of diabetic nephropathy and microalbuminuria to control hypertension and proteinuria and thereby prevent the progression of the kidney disease.[23]

However, the possible benefit of antihypertension treatment during pregnancy was still a matter of debate. Although antihypertension treatment might prevent severe hypertensive complications in pregnant women without diabetes, it might also, in theory, impair fetal blood flow and fetal growth.[24] Therefore, in the late 1990s, our treatment strategy was only to initiate or intensify antihypertension treatment if blood pressure exceeded 140/95 mmHg in pregnant women with type 1 diabetes. Pathophysiological studies have shown that preeclampsia is often preceded by higher blood pressure[25], elevated urinary albumin excretion[26], endothelial dysfunction[27], impaired maximal vasodilatation of the arterial vessels[28], and increased levels of components of the renin-angiotensin system[29], markers of cardiac overload[30], and antiangiogenic factors in women with diabetes in early pregnancy. The majority of these factors can be modulated by antihypertension treatment.

To prevent the rise in blood pressure and urinary albumin excretion leading to preeclampsia, tight antihypertension treatment during pregnancy is, therefore, theoretically, beneficial in these women. In line with this, a case of a normotensive woman with type 1 diabetes and microalbuminuria touched my heart. She had been treated with antihypertension treatment for 8 years up to pregnancy without progression from microalbuminuria to diabetic nephropathy.[31]

According to our antihypertensive strategy at that time, antihypertensive treatment was discontinued in early pregnancy. Shortly after, she developed hypertension and severe proteinuria and met the criteria for severe preeclampsia and had to be delivered preterm at 28 weeks. She gave birth to a girl born with cerebral bleeding. This case in combination with several similar cases with poor outcomes in women with preexisting microalbuminuria or diabetic nephropathy led us to investigate the prevalence of preeclampsia in relation to the occurrence of kidney involvement. In a cohort of 240 women, the prevalence of preeclampsia was 6% in women with normal urinary albumin excretion, 42% in women with microalbuminuria (30–300 mg/24 h), and 64% in women with diabetic nephropathy (albumin excretion. 300 mg/24 h) in early pregnancy.[32] Preeclampsia in women with microalbuminuria or diabetic nephropathy was often severe, with early development leading to preterm delivery before 34 weeks. In the year 2000, we changed our antihypertension strategy in women with microalbuminuria or diabetic nephropathy to initiate or increase antihypertension treatment if office blood pressure exceeded 140/90 mmHg or albumin excretion exceeded 2,000 mg/24 h. If the women already were on antihypertension treatment, this was changed to antihypertension agents well tolerated in pregnancy such as methyldopa, labetalol, or nifedipine.[33]

In a subsequent unselected cohort of 20 normotensive pregnant women with type 1 diabetes and microalbuminuria treated with this strategy, a significant reduction in early preterm delivery before 34 weeks was seen compared with the previous cohort where antihypertension treatment was given less rigorously.[34] However, the prevalence of preeclampsia and preterm delivery was still high. Therefore, in 2004, we decided to intensify the strategy by initiating or increasing antihypertensive treatment when blood pressure exceeded 135/85 mmHg or urinary albumin excretion exceeded 300 mg/24 h.[35] This strategy seemed to be associated with further improvement as fewer women with type 1 diabetes and microalbuminuria developed preeclampsia or delivered preterm. We have found a similar effect in women with type 2 diabetes complicated with microalbuminuria or diabetic nephropathy who were treated according to the same antihypertension strategy. Since 2004, this strategy for antihypertension treatment has been implemented for women with type 1 and type 2 diabetes complicated with microalbuminuria or diabetic nephropathy at our center. We now also use this strategy in women with preexisting diabetes and essential hypertension or pregnancy-induced hypertension, including preeclampsia.[36] Alongside optimized antihypertension therapy, the occurrence of preeclampsia has declined and the prevalence of

early preterm delivery before 34 weeks has declined from 10% (3) to 1% in an unselected cohort of 260 pregnant women with preexisting diabetes delivering at our center in the period 2012–2014.

The high prevalence of preterm delivery in the late 1990s (21) was tightly associated with HbA1c in the third trimester.[37] It is well known that maternal glucose freely passes through the placenta to the fetal circulation and maternal hyperglycemia thereby induces fetal hyperinsulinemia, fetal overgrowth, relative fetal hypoxia, and increased prevalence of fetal morbidity and mortality. This emphasizes the importance of strict glycemic control in pregnant women with diabetes. However, a high incidence of severe hypoglycemia with the women needing help from a third person was observed among women with type 1 diabetes.[38] In a prospective study including 108 women, 45% of women experienced at least one episode of severe hypoglycemia in pregnancy with the highest incidence between 8- and 16-weeks' gestation.[39] In a small cohort of pregnant women with type 2 diabetes who were treated with insulin, 17% experienced at least one episode of severe hypoglycemia during pregnancy.[40] A history of severe hypoglycemia the year preceding pregnancy[41], self-estimated impaired hypoglycemia awareness, and particularly the combination of these two factors were significant risk factors for severe hypoglycemia during pregnancy.[42] Pregnancy-induced nausea and vomiting have been proposed to be contributing factors for severe hypoglycemia in early pregnancy[43] due to fluctuations in food intake. However, a large prospective study evaluating the occurrence of nausea and vomiting among pregnant women with type 1 diabetes with or without episodes of severe hypoglycemia found that nausea and vomiting were not more prevalent in women with episodes of severe hypoglycemia. Therefore, nausea and vomiting are not major contributing factors for severe hypoglycemia in diabetic pregnancy.[44]

METHODS

The study was conducted on pregnant women with T1DM who were admitted to the hospital of al khark in Iraq between 2008 and March 2018.

Pregnant women with uncomplicated T1DM who were treated by insulin therapy were included in the study. The patients had regular antenatal visits at obstetrics and endocrinology polyclinics. The fasting blood glucose levels were <100 mg/dL and the 1st-hour post-meal blood glucose levels of the patients were <180 mg/dL. The patients with uncontrolled blood glucose levels and HbA1c >7% were excluded from the study. Retinopathy, nephropathy, and

neuropathy were accepted as exclusion criteria. The patients with chronic illness except diabetes mellitus were also accepted as exclusion criteria. The demographic characteristics, perinatal mortality, congenital anomalies, preterm delivery, route of delivery, cesarean indications, cord pH, Apgar scores, neonatal results, and maternal results of the patients were analyzed.

At the end of the study, the Statistical Package for Social Sciences (SPSS) 16.0 program (SPSS Inc, Chicago, USA) was used to assess the data. Number, percentage, average, and standard deviation were used from the descriptive statistics for information describing the pregnant women with T1DM.

RESULTS

30 pregnant patients with uncomplicated T1DM with controlled blood glucose levels were analyzed. The mean maternal age of the patients was 32,9 years. The fasting blood glucose levels of the patients were between 59 mg/dL and 95 mg/dL. The 1st-hour post-meal blood glucose levels were between 129 mg/dL a 170 mg/dL. Two patients had perinatal death. An unexplained death after 27 weeks of gestation occurred in one patient. The blood glucose levels of the patient were between normal ranges. Patient and patient's family denied the autopsy. The other patient had perinatal death at 24 weeks of gestation during delivery. The type of delivery was induced abortion due to the hypoplastic left ventricle.

Twenty (54%) out of 37 patients had a preterm delivery (<37 weeks of gestation). Eighteen (48.6%) patients had delivery between 32 and 37 weeks of gestation. Two (5.4%) patients were delivered before 32 weeks of gestation.

The type of delivery was induced vaginal delivery in 9 (24.3%) patients and cesarean section in 27 (72.9%) patients. The most common indication for cesarean section was repeated cesarean section.

DISCUSSION

T1D is associated with an increased incidence of pregnancy complications (Evers et al., 2004), even when, as outlined in the introduction, glycemia is strictly controlled. This should not be interpreted as a suggestion that glycemic control is not of pivotal importance for a healthy pregnancy during T1D. The importance of adequate glycemic control has convincingly been demonstrated by pre-conceptional improvement of glycemic control or

continuous glucose monitoring for prevention of congenital malformations and macrosomia.[45] However, although congenital malformations and macrosomia can be directly related to hyperglycemia, strong evidence for a sole influence of hyperglycemia on recurrent miscarriage, pre-eclampsia, IUGR, and preterm birth is largely lacking. As described above, these complications are also influenced by immunological disturbances during pregnancy. Therefore, in a recent series of experiments, we tested the hypothesis that immunological adaptations to pregnancy are disturbed in women and rats with T1D. To this end, we studied peripheral immunological changes during pregnancy in women with T1D and rats with T1D, i.e. diabetic prone BB rats.[46] We showed many peripheral disturbances in the immunological adaptations in both pregnant women and pregnant rats with T1D. The most important differences were found in Th cells, NK cells, and monocytes. We observed an increased Th1/Th2 ratio in pregnant women with T1D versus healthy control women.[47] NK cells showed an increased cytotoxic potential in pregnant T1D women.[48] Our results were in line with a study from Burke et al, who also found in T1D pregnancies a shift towards a Th1 immune response as well as changes in peripheral NK cells.[49] Moreover, we observed increased numbers of intermediate monocytes, which also showed increased MHC-II expression.[50] In T1D pregnant rats, as compared to non-diabetic pregnant rats, we found similar results, i.e. an increased percentage of NK cells and intermediate monocytes and an increased Th1/Th2 ratio.[51] Therefore, the immune response in pregnant individuals with T1D may be interpreted as a Th1 type immune response with a general activation of the innate immune response. Immune responses with these characteristics are also observed in non-diabetic women with pregnancy complications like preeclampsia. In future studies, it would be important to directly compare (local and peripheral) immune responses during T1D pregnancy and preeclamptic pregnancy, since to the best of our knowledge such studies have never been performed.

In diabetes-prone BB rats, we studied the local immune response in the placental bed, and also here we observed immunological disturbances. There was an increased number of NK cells and type 1 macrophage in the mesometrial triangle in the uterus (i.e. the placental bed) of T1D pregnant rats as compared to healthy control rats. This was associated with decreased trophoblast invasion and suboptimal spiral artery remodeling in the T1D rats. Burke et al. studied NK cells in the decidua basalis of NOD mice (also a model for T1D) and found decreased numbers of NK cells early in pregnancy.

Differences between our study and the study of Burke may be the timing of pregnancy (day 18 in our study vs days 6–8 in the Burke study) or the location of the NK cells (Mesometrial triangle vs decidua basalis). Further studies are needed to determine whether similar changes take place in the placental bed of T1D pregnant women. The immunological changes observed in T1D women and rats are similar to the immunological changes observed in women with pregnancy complications like recurrent miscarriage, preeclampsia, IUGR, and preterm birth and are in line with our hypothesis that the pregnancy complications in T1D women may result from aberrant adaptions of the maternal immune response to pregnancy.[52]

Besides the fact that the immune response of women with T1D is altered due to the autoimmunity, women with T1D also suffer from chronic vascular inflammation, which might also affect placentation and the mother's vascular response to inflammation or inflammatory factors, resulting in pregnancy complications like preeclampsia.[53]

T1DM has got many risks during pregnancy. Specific risks of diabetes include fetal anomalies, preeclampsia, macrosomia, intrauterine fetal demise, neonatal hypoglycemia, and neonatal hyperbilirubinemia, among others.[54]

The frequency of hypertension in pregnancy and preeclampsia in diabetic women is 2–4 times more frequent than in the non-diabetic population. In our study, the frequency of preeclampsia was 16.9%, which is more frequent than reported 12% in other studies.[5] It has been reported that preeclampsia developed in 19.1% of patients without vasculopathy and 49.1% of diabetic patients with vasculopathy.[56] Our preeclampsia cases were not with chronic hypertension. In cases, with chronic hypertension, the preeclampsia ratio would be much higher. It is clear that preeclampsia is more common in T1DM patients than in general population, normotensive, and in non-vasculopathic diabetic patients. The incidence of premature labor during the study period was 54%. It is much more frequent than reported before.[57]

Women with T1DM have higher rates of cesarean section in general. Its frequency has been reported between 60% and 78%. The cesarean ratio was 72% in our cases. Even in the most favorable conditions, a pregnant patient with T1DM is likely to deliver by cesarean section. Macrosomia is one of the leading causes of the high rate of cesarean section. Nine (24%) out of 37 patients were macrosomic in our study. This ratio is lower than reported before. The

macrosomia ratio was 54% in the nation-vasculopathy group. The most common indication of cesarean section was repeated cesarean section.[58]

Four infants had positive criteria for neonatal asphyxia. Three out of four infants were premature, and the remaining one was delivered by cesarean section due to fetal distress. All infants had predisposing factors for neonatal asphyxia. Antenatal death with unknown cause occurred in one patient. One patient had a congenital anomaly.

The coincidence of diabetes mellitus and pregnancy predisposes the mother and fetus to a lot of serious risks. Preconceptional care and prenatal follow up has great importance. Vasculopathy is the main factor for predicting the pregnancy outcome. It is necessary to plan the pregnancy in a period of optimum metabolic compensation of DM.[59]

In our study, we have included the non-complicated diabetic patients with optimum prenatal and antenatal care. Macrosomia, preterm delivery, preeclampsia, and cesarean delivery were significantly higher than in the general population. One antenatal death at the third trimester occurred without any apparent cause.

Prenatal care, glucose regulation, and regular antenatal visits are the mainstays of the management of diabetic pregnant patients. We offer and inform the diabetic patients about these management protocols before planning the pregnancy. It is clear that these protocols could decrease all of the adverse outcomes of the pregnancy especially ketoacidosis, abortus, and congenital anomalies. According to our results even in the most favorable conditions, the patient would have a great risk for preterm delivery and cesarean section, the moderate risk for macrosomia, preeclampsia, and an undefined risk for antenatal death. These facts should be kept in mind for informing diabetic patients about pregnancy during prenatal counseling.

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