STUDY OF DIABETIC PREGNANCY

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ABSTRACT

Diabetes mellitus is the most common medical complication of pregnancy and it carries a significant risk to the fetus and the mother. Congenital malformations and perinatal morbidity remain common compared with the offspring of non diabetic pregnancies.

Diabetes is a common metabolic complication of pregnancy and affected women fall into two subgroups:
women with pre-existing diabetes and those with gestational diabetes mellitus (GDM). When pregnancy is affected by diabetes, both mother and infant are at increased risk for multiple adverse outcomes. A multidisciplinary approach to care before, during, and after pregnancy is effective in reducing these risks. we herein summarize the evidence relating to pathophysiology and management of diabetes in pregnancy.
Diabetic mothers are at risk of progression of microvascular diabetic complications as well as early pregnancy loss, pre-eclampsia, polyhydramnios and premature labour. Glycaemic control before and during pregnancy is critical and the benefit may result in a viable and healthy offspring. Gestational diabetes mellitus (GDM) which manifests for the first time during pregnancy is common and on the increase, This article will briefly review the changes in the carbohydrate metabolism that characterise normal pregnancy and will focus on a practical approach to the care of patients with pre-existing diabetes as well as GDM.Therefore, this review is intended to serve as a practical guide for clinicians who are caring for women with diabetes and their infants. and choice of pharmacologic agents to treat hyperglycemia during pregnancy.

INTRODUCTION

More than 21 million births are affected by maternal diabetes globaly every year (1). In 2016 in the United States, pre-current (including type 1 or 2) and gestational diabetes mellitus (GDM) had a prevalence of 0.9% and 6.0%, respectively, amongst the women who delivered a live infant (2). Recently, efforts have redoubled to diagnose and to treat diabetes earlier in pregnancy (3). Diabetes during pregnancy has significant implications for the maternal-fetal dyad. Type 1 diabetes associated with a two- to five-fold increased risk of major complications including congenital anomaly, stillbirth, and neonatal death; and 50% of infants experience complications such as prematurity, large for gestational age (LGA), and the admission to a neonatal intensive care unit (4-6). Women with type 2 diabetes typically is less dramatic changes in glucose metabolism and are less prone to diabetic ketoacidosis (DKA) and caesarean delivery compared with those with type 1 diabetes (7,8).Although, studies are conflicting on whether their offspring have similar or lower rates of congenital malformations and stillbirth compared with those with type 1 diabetes (8). GDM is diabetes diagnosed in the second or third trimester of pregnancy in the absence of overt diabetes before gestation (9). Women with GDM have a 30% increased risk of cesarean delivery and a 50% increased risk of gestational hypertension. Their offspring have a 70% increased risk of prematurity and are 30% more likely to be LGA (10). GDM is strongly associated with future maternal type 2 diabetes (11); there is increasing evidence that exposure to all forms of diabetes in pregnancy confers a higher risk of childhood adiposity, insulin resistance, and detrimental neurodevelopmental outcomes (11 - 14).

The goal of this review is to provide an update on the pathophysiology and control of diabetes in pregnancy.

METHODS

The internet database was looked for English language studies and guidelines relating to diabetes in pregnancy. The following search terms were used alone and in combination: diabetes, pregnancy, gestational diabetes, GDM, prepregnancy, and preconception. Results were reviewed and selected for inclusion based on relevance to the topic. Additional articles were identified by manually searching reference lists of included articles.

PATHOPHYSIOLOGY

Normal Maternal Glucose Metabolism Although early pregnancy is a time of relative insulin sensitivity, this result decreases sharply in the second and early third trimester of pregnancy (15,16). This reduces insulin-dependent glucose uptake in tissues such as muscle and fat and serves as a maternal physiologic adaption to preserve carbohydrate for the rapidly growing fetus (17). In addition, impaired insulin mediated suppression of maternal lipolysis and fat oxidation provides fatty acids as an alternative energy source (18). This process is likely mediated by a number of factors including an increase in progesterone, estrogen, cortisol, and human placental growth hormone (19 - 21). Typically a two- to-three folds increase in insulin production is sufficient to meet this challenge, and studies confirm an increase in pancreatic fractional beta cell area in human pregnancy (22). It would appear that insulin secretion increases significantly by early pregnancy, even before increases in insulin resistance (23). In animal models, lactognic hormones seem to stimulate this process

through a direct effect on beta cells; however, it is uncertain if this is the case in humans (24, 25) GDM.

Frequently, the insulin secretory response is inadequate and hyperglycemia Develops is leading to a diagnosis of GDM in women without pre-existing diabetes. There are limited evidences from physiologic studies in such women suggests that subtle abnormalities of insulin secretion precede pregnancy and persist after parturition. In one study of high-risk women with GDM, independent predictors of a postpartum abnormality of glucose tolerance were hyperglycemia before 22 weeks' gestation and a low first-phase insulin response during an intravenous glucose tolerance test (26). The first-phase insulin response to intravenous glucose represents an early burst of insulin release and is followed gradually by increasing phase of insulin secretion over several hours (27). This first-phase response plays a significant role in maintaining glucose homeostasis in healthy individuals and is lost in the early stages of diabetes (28). The insulin resistance degree in the third trimester of pregnancy is not an important predictor of abnormal glucose tolerance within 6 months after GDM. This su*ggests a chronic beta cell defect exacerbated by pregnancy (29,30). Pre-existing Diabetes. Women with preexisting diabetes face similar changes in insulin resistance. The ability of the beta cell to compensate is more profoundly impaired in type 2 diabetes and negligible in type 1 diabetes.

Although the clinical impact may be insignificant, a pregnancy-induced increase in C-peptide (suggesting improved beta cell function) has even been observed in women with established type 1 diabetes and undetectable C-peptide levels at baseline (31, 32).

EARLY PREGNANCY HYPERGLYCEMIA AND FETAL EFFECTS:

Maternal hyperglycemia both periconceptually and during the first trimester

of pregnancy can result in major birth defects and pregnancy loss (33).Whereas these outcomes typically affect pregnancies with pre-existing diabetes on women with GDM risk of malformations increases with maternal fasting glucose, body mass index (BMI), and earlier gestational age at diagnosis (34). Most commonly these malformations affect the cardiac or central nervous system and include transposition of the great arteries, septal defects, neural tube defects, and caudal regression syndrome d the latter of which is almost universally associated with diabetes in pregnancy (35).Oxidative stress has suggested to play a role in the development of such complications, but further studies of mechanism are needed (36,37). Although maternal hyperglycemia in the second and third trimester is typically associated with excessive the fetal growth, women with pre-existing diabetes may have impaired fetal growth through two mechanisms. Maternal microvascular disease confers a significant risk of intrauterine growth restriction, whereas hyperglycemia in the first trimester may impair placental development and subsequent fetal growth through poorly understood mechanisms (38,39).

FETAL OVER NUTRITION:

Maternal glucose is transferred to the fetus across the placenta down the concentration gradient determined by both maternal and fetal glucose levels. Therefore; maternal hyperglycemia promotes fetal hyperglycemia

and stimulates fetal insulin secretion (40). This process constitutes the "hyperglycemia-hyperinsulinemia hypothesis" or the "Pedersen hypothesis"(41). Taking this process a step further, fetal glucose use increases with fetal hyperinsulinemia, lowering fetal glucose and increasing the transplacental glucose gradient and rate of glucose transfer. This is described as the "fetoplacental glucose steal phenomenon" and once established, is believed to favor a high glucose flux with stimulation of fetal triacylglycerol formation and deposition of excess fetal adipose tissue even when maternal blood glucose is normal (40). The Pedersen hypothesis was developed in an era when most cases of hyperglycemia in pregnancy were due to type 1 diabetes. However, during the past 50 years, increases in maternal obesity have been changed this landscape, and the metabolic milieu to which the developing fetus is exposed is undoubtedly different in obesity (with or without type 2 diabetes) (42). For example, maternal triglyceride levels are 40% to 50% higher in mothers with obesity and GDM compared with normal-weight mothers during pregnancy. Placental lipases

can hydrolyze maternal triglycerides to free fatty acids for fetal-placental availability, and there is increasing evidence that these are also important substrates for fetal fat accretion and overgrowth (43). Excessive fetal growth may be expressed as macrosomia or LGA. Macrosomia is typically defined as an absolute birth weight of greater than 4000 to 4500 g, whereas LGA refers to a birth weight greater than 90th percentile for gestational age. Affected infants are at risk for asphyxia, perinatal death, shoulder dystocia with or without birth injury, respiratory distress, and hypoglycemia. Additional metabolic complications that may be present at birth and arise from maternal hyperglycemia include hypocalcemia, hypomagnesemia, polycythemia, and hyperbilirubinemia.

LONG-TERM OFFSPRING OUTCOMES:

It is difficult to separate the role of fetal exposure to maternal hyperglycemia from factors such as maternal obesity and environmental exposures. However, offspring of mothers with pre-existing diabetes or GDM are heavier at birth and at every age with an increased risk of type 2 diabetes compared with those born to mothers without diabetes (38). Epigenetic variation established in utero may explain the link between the uterine milieu and later disease susceptibility (44). Although a number of offspring methylation variants appear to be independently associated with GDM and type 2 diabetes, these observations have not led to the development of biomarkers to predict which children are most at risk of metabolic disease (45). Another emerging concern is the potentially negative effect of maternal diabetes on offspring cognitive development, but reports have been conflicting and causal pathways are unclear (46). Type 1 diabetes risk is increased in offspring with maternal or paternal diabetes of any type, and appears even higher with paternal diabetes (47).

TYPE 1 DIABETES

Women with type 1 diabetes have an increased risk of hypoglycemia in the first trimester and, like all women, have altered counter regulatory response in pregnancy that may decrease hypoglycemia awareness. Educate patients and family members about the prevention, recognition, and treatment of hypoglycemia is important before, during, and after pregnancy to help to prevent and manage the risks of hypoglycemia. Insulin resistance drops rapidly with delivery of the placenta. Women become very insulin sensitive immediately after delivery and may initially require much less

insulin than in the prepartum period. Pregnancy is a ketogenic state, and women with type 1 diabetes, and to a lesser extent those with type 2 diabetes, are at risk for diabetic ketoacidosis at lower blood glucose levels than in the nonpregnant state. Women with preexisting diabetes, especially type 1 diabetes, need ketone strips at home and education on diabetic ketoacidosis prevention 13). The role of continuous glucose monitoring in pregnancies impacted by diabetes is still being studied. In one RCT, continuous glucose monitoring use in pregnancies complicated by type 1 diabetes showed improved neonatal outcomes and a slight reduction in A1C, but interestingly no difference in severe hypoglycemic events compared with control subjects (48).and detection. In addition, rapid implementation of tight glycemic control in the setting of retinopathy is associated with worsening of retinopathy (

TYPE 2 DIABETES

Type 2 diabetes is often associated with obesity. Recommended weight gain during pregnancy for overweight women is 15–25 lb and for obese women is 10–20 lb (49). Glycemic control is often easier to achieve in women with type 2 diabetes than in those with type 1 diabetes but can require much higher doses of the insulin, sometimes necessitating concentrated insulin formulations. As in type 1 diabetes, insulin requirements drop dramatically after delivery. The risk of associated hypertension and other comorbidities may be as high or higher with type 2 diabetes as with type 1 diabetes, even if diabetes is better controlled and of shorter in apparent duration, with pregnancy loss appearing to be more prevalent in the third trimester in women with type 2 diabetes compared with the first trimester in women with type 1 diabetes (50, 51).

PLACENTAL WEIGHT

Placental measurements have been used as indicators of its growth and function. Epidemiological studies have shown associations between placental measurements and perinatal and later life outcomes (52). Placental weight , for instance, relates to the risk of stillbirth, 5-minute Apgar score lower than ,neonatal seizures, and ventilation for more than 3 minutes after birth. Placental measurements are also associated with the adult diseases, namely hypertension, diabetes, coronary heart disease, stroke, and colorectal cancer. Studies on the developmental origins of health and disease postulate that placental measurements signal fetal and placental adaptations to environmental insults (53).

An increased placental weight has been reported in the pregnancies complicated with gestational diabetes (GDM). Making studies on foetal (F) and placental weight (P) and foetal length in 143 consecutive normal (N) and 132 gestational diabetes GDM pregnancies in relation to type of treatment and to the number of maternal variables. A significant difference was observed between normal and gestational diabetes pregnancies for maternal age, pre-pregnancy weight and body mass index BMI. Foetal weight became significantly higher in the gestational diabetes group. Significantly higher placental weights and significantly lower F/P weight ratios were found in GDM pregnancies.In gestational diabetes pregnancies a significantly negative correlation was found between the OGTT response and weights of foetus and placentae at delivery, suggesting that both foetal and placental growth are affected by maternal insulin resistance (54).

PLACENTAL COTYLODENS

Egan et al., (2020) referred to the Placentas from diabetic pregnants and non-diabetics were compared by means of photographic planimetry. The material was investigated in fresh state and gained from three well-defined areas within the cotyledon, central, intermediate and lateral regions. Length and area of the villi in each areas were calculated (55).

1. The non-diabetic one showed a consistent organization of the cotyledon, with increasing in the villous length towards the periphery. The surface areas increases with increasing of the length.

2. In placentas of diabetic mothers, this organization was disrupted. The villi were of even length throughout the cotyledon. The average length of a villus in the diabetic group didn`t differ from the average length in the controlled group.

UMBILICAL CORD ROTATION

The umbilical cord forms the only connection between the placenta and developing fetus. It is surrounded by the amnion, and contains a pair of umbilical arteries and an umbilical vein supported by loose connective tissue.

For gestational diabetes structural changes in the umbilical cord of full term fetuses from cases of gestational diabetes. The studies showed that all these were insulin-dependent and their blood glucose level was well controlled. Light microscopy showed rupture and erosion in the endothelial lining of umbilical arteries resulting in increasing permeability and haemorrhages. The umbilical vein was excessively be dilated. The smooth muscle in the walls of these vessels showed a

disruption and degeneration in the fibres. 'Wharton's jelly' showed alteration in the pattern of distribution of the fibres with large empty spaces amongst them. It is suggested that gestational diabetes has a deleterious effect on the umbilical vessels and the connective tissue component of 'Wharton's jelly'.

MANAGEMENT OF LABOUR AND DELIVERY

1. Glucose control during labour: It is necessary to administer an IV insulin and Dextrose to prevent the ketoacidosis and to maintain the blood glucose as near normal as possible. The insulin requirements after delivery should return to about the pre-pregnancy level. Labour and delivery of women with diabetes should be undertaken in the units where there is neonatal care.

2. Neonatal problems: This would include hypoglycaemia, polycythaemia,respiratory distress syndrome, jaundice, hypocalcaemia and hypomagnesemia. Routine blood glucose monitoring of the baby should be performed for the first 12 hours.

3. Post-natal care: Insulin requirements fall dramatically at the time of the delivery and insulin dose should be reduced to an around the pre-pregnancy level. Breastfeeding also reduces insulin requirements and appropriate reduction should therefore be made once feeding has been established. It is usually possible to stop insulin in women with GDM and in women with type 2 diabetes mellitus who do not intend to breastfeed. Contraception should be discussed while the patient is in hospital.

CONCLUSION AND RECOMENDATION

Diabetes in pregnancy poses a unique set of challenges for both the mother and her developing baby. Women with pre-existing diabetes can benefit from targeted prepregnancy care with optimization of glycemic control and assessment and treatment of co-morbidities.

During pregnancy, women with pre-existing diabetes and GDM benefit from a multidisciplinary approach to care with the aim of minimizing maternal complications and ensuring normal fetal development and growth.

GDM confers a high risk of future type 2 diabetes and affected women should receive appropriate counseling and long-term follow-up.

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