Review article

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Diabetes mellitus and pregnancy

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ABSTRACT

Diabetes mellitus is the most common medical complication of pregnancy and it carries a significant risk to the foetus and the mother. Congenital malformations and perinatal morbidity remain common compared with the offspring of non diabetic pregnancies. 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, healthy offspring. Gestational diabetes mellitus (GDM) which manifests for the first time during pregnancy is common and on the increase, its proper management will reduce the risk of neonatal macrosomia and hypoglycaemia. Post-partum evaluation of glucose tolerance and appropriate counselling in women with GDM may help decrease the high risk of subsequent type 2 diabetes in the long-term.

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.

INTRODUCTION

Diabetes mellitus is the most common medical complication of pregnancy. Gestational diabetes mellitus (GDM) represents approximately 90% of these cases and affects 2–5% of all pregnancies and varies in direct proportion to type 2 diabetes mellitus in the background population.[1] Pre-existing diabetes mellitus complicates 0.2% to 0.3% of pregnancies.[2] The importance of diabetes in pregnancy stems from the fact that it carries a significant risk to both the foetus and the mother. Despite major advances in clinical management, we are still facing a higher incidence of malformations and perinatal morbidity compared to the non-diabetic population.

Over the past 30 years, great strides have been made in improving the outcomes of women with type 1 diabetes who become pregnant. However, during the past decade, type 2 diabetes in pregnancy has emerged and is certain to become a prominent concern.[3] The St Vincent Declaration, which has been adopted by most European countries, calls for (an outcome in diabetic pregnancy approximating the non-diabetic women).[4] Unfortunately, pregnancy target has been achieved only in a few centres of excellence in Scandinavia and by the small intensive pre-conception control arm of the nine-year US Diabetes Control and Complications Trial.[5]

Normal Glucose Regulation during Pregnancy: Metabolic changes occur in normal pregnancy in response to the increase in nutrient needs of the foetus and the mother. There are two main changes which are seen during pregnancy, progressive insulin resistance that begins near mid-pregnancy and progresses through the third trimester to the level that approximates the insulin resistance seen in individuals with type 2 diabetes mellitus. The insulin resistance appears to result from a combination of increased maternal adiposity and the placental secretion of hormones (progesterone, cortisol, placental lactogen, prolactin and growth hormone). The fact that insulin resistance rapidly abates following delivery suggests that the major contributors to this state of resistance are placental hormones. The second change is the compensatory increase in insulin secretion by the pancreatic

beta-cells to overcome the insulin resistance of pregnancy. As a result, circulating glucose levels are kept within normal. If there is maternal defect in insulin secretion and in glucose utilisation, then GDM will occur as the diabetogenic hormones rise to their peak levels.

Risks to the Foetus & the Neonate (Table 1 & 2): If the mother has hyperglycaemia, the foetus will be exposed to either sustained hyperglycaemia or intermittent pulses of hyperglycaemia; both situations prematurely stimulate foetal insulin secretion. Foetal hyperinsulinaemia may cause increased foetal body fat (macrosomia) resulting in difficult delivery. It may also cause inhibition of pulmonary maturation of surfactant resulting in respiratory distress of the neonate.

The foetus may also have decreased potassium level caused by elevated insulin and glucose levels, and may therefore have cardiac arrhythmia. Foetal organogenesis is completed by seven weeks post-conception and there is an increased prevalence of congenital anomalies and spontaneous abortions in diabetic women with poor glycaemic control during this period.[6]

Table 1: Foetal complications in diabetic pregnancy
• Congenital anomalies: cardio-vascular, central nervous system, skeletal (sacral agenesis), and genito-urinary
• Excessive foetal growth (macrosomia)
• Foetal growth retardation (in diabetic pregnancy complicated by nephropathy)

Table 2: Neonatal complications in diabetic pregnancy
• Traumatic delivery
• Pulmonary surfactant deficiency
• Hypoglycaemia
• Polycythaemia
• Hypocalcaemia
• Hypomagnesaemia
• Hyperbilirubinaemia

Because a woman may not even know she is pregnant at this time, it is imperative that pre-pregnancy counselling and planning occur in women of child-bearing age who have diabetes. It seems that post-prandial glucose levels are the most important determining factor on the subsequent risk of

neonatal macrosomia. Pregnancy in patients with diabetes is associated with a six-fold increase in perinatal mortality and a two-fold increase in the rate of major congenital malformations and an eight fold increase in preterm delivery compared to the general population.[7-9]

Table 3: Maternal complications in diabetic pregnancy

- Diabetic keto-acidosis
- Hypoglycaemia
- Visual deterioration/retinopathy
- Deterioration of nephropathy
- Vomiting (gastric neuropathy)
- Miscarriages
- Pre-eclampsia
- Polyhydramnios
- Premature delivery

There is also an increase in neonatal hypoglycaemia which may cause permanent neurologic damage, hyperbilirubinaemia, respiratory distress and stillbirth. The associated increase of congenital anomalies for the foetus and spontaneous abortion in women with poor glycaemic control appears to be related to maternal glycaemic control rather than to the mode of anti-diabetic therapy during early pregnancy.

The normalisation of maternal glucose before and throughout pregnancy can decrease pregnancy-related complications to those seen in non-diabetic pregnancies. Studies from many centres have shown that the higher the levels of glycosylated haemoglobin [HbA1c] in early pregnancy, the greater the incidence of anomalies and the higher the perinatal mortality. [7-9]

Risks to the mother (Table 3): Maternal diabetes complications are frequent in women with both type 1 and type 2 diabetes. Diabetic retinopathy and diabetic nephropathy may progress or start de novo during the pregnancy.

Pre-eclampsia occurs in both type 1 and type 2 diabetes mellitus and is high as it affects approximately 20% of cases. [10] Other complications including polyhydramnios and worsening of chronic hypertension are not uncommon.

Management of Pregnancy in Women with Pre-existing Diabetes: Pre-pregnancy planning (Table 4) is essential to achieve a

healthy baby and avoid maternal morbidity such as adverse pregnancy outcomes and progression of chronic diabetes complications. Ideally this is carried out by a team, which includes an obstetrician and a diabetologist for optimum care. Clinical trials of pre-conception care to achieve stringent blood glucose control in the pre-conception period and during the first trimester of pregnancy have demonstrated striking reductions in rates of malformation compared with infants of diabetic women who did not participate in pre-conception care.[11] Unfortunately, unplanned pregnancies occur in about two thirds of women with diabetes, precluding adequate pre-conception care and leading to persistent excess of malformations in their infants. To minimize the occurrence of these devastating malformations, standard care for all women with diabetes and of childbearing age should include. Counselling about the risk of malformations associated with unplanned pregnancies and poor metabolic control and the use of effective contraception at all times unless the patient is in good metabolic control and actively trying to conceive.

Table 4: Pre-pregnancy assessment

- Glycaemic control/appropriate medication
- Weight and diet
- Blood pressure/appropriate medication
- Review of diabetes complications: Retinopathy, nephropathy, autonomic neuropathy
- Coronary artery disease
- Smoking
- Rubella status
- Folic acid supplementation

Contraception for diabetic women: All forms of contraception carry some risk and every woman must be considered individually. The combined oral contraceptive pill is effective if taken reliably, however, the first generation, high dose oestrogen pills should be avoided as they may increase insulin requirement and increase the risk of vascular disease. The second and third generation pills have a much lower dose of oestrogen and can probably be used safely in the majority of women with diabetes. The progesterone-only pill is reliable if taken regularly but omission may be more likely to result in pregnancy than with the combined pill.

Injectable progestogens/implants are suitable for some patients. Intra-uterine contraceptive devices have the advantage of the lack of detrimental metabolic effect and the need for compliance; however, its failure rate is high. Other methods of contraception such as mechanical contraception can also be used in diabetic patients. Emergency contraception is safe for diabetic women and should be prescribed if needed.

Optimise glycaemic control: In preparation for pregnancy, oral hypoglycaemic agents should be discontinued and insulin started if needed, statins and ACE-inhibitors should also be discontinued. Hypertension should be controlled with safer drugs like Methyldopa, Nifedipine or Labetalol. Diabetic complications should be assessed and treated. Regular self-monitoring should be encouraged to optimise control. Folic Acid should be started at least four weeks pre-conception. Glycaemic control should be optimised with the aim of pre-prandial blood glucose < 5.5 mmol/l (<95mg/dl) and HbA1c < 7%.

Diabetes ante-natal care: this should be provided in a special clinic and the team caring for pregnant women should ideally include a Diabetes Nurse Specialist, Dietician, Diabetologist and an Obstetrician. The aim of ante-natal care is to maintain tight glycaemic control and to monitor the mother for diabetes complications. Tighter glycaemic control has an impact on maternal and foetal complications, therefore, excellent glycaemic control should be continued throughout pregnancy, fasting blood glucose should be kept < 5.5 mmol/l (<95mg/dl), post-prandial glucose < 7.8 mmol/l (<140 mg/dl) and HbA1c <7%. Tighter glycaemic control may lead to an increase in episodes of severe hypoglycaemia and worsening of hypoglycaemia unawareness. The patient should be aware of subtle signs of hypoglycaemia, and the patient's family should be taught the proper treatment of severe hypoglycaemia (i.e. Glucagon).

Glucose monitoring: Home blood glucose monitoring is an essential part of maintaining euglycaemic state and its goal is to detect glucose concentration to allow fine-tuning of insulin adjustment. Pre-prandial glucose level < 5.5 mmol/l (<95mg/dl), and post-prandial level glucose <7.8 mmol/l (<140mg/dl). Post-prandial glucose levels have been shown to

correlate more with macrosomia than do fasting levels. Diabetes in early pregnancy studies found that third trimester post-prandial glucose levels were the strongest predictors of percentile birth weight.[12]

Dietary advice: The goal of diet in pregnancy is to provide adequate nutrition for the mother and the foetus, provide sufficient calories for appropriate maternal weight gain, maintain normal glycaemia and avoid ketosis. Eating three small to moderate size meals and three snacks per day is appropriate. Monitoring with a pre-breakfast ketone measurement is recommended for patients who are on a hypo-caloric or carbohydrate restricted diet.

Insulin therapy: Insulin regimes should be individualised but in type 1 patients multiple injection/ basal bolus regime of human insulin is preferable and in type 2, twice-daily injections may be appropriate. The aim is to achieve blood glucose as near normal as possible without excessive risk of hypoglycaemia.

Hypoglycaemia: hypoglycaemia is common in pregnancy, particularly in the first trimester. Education of patients and their families in the recognition and management of hypoglycaemia is vital. A Glucagon kit should be provided early in pregnancy.

Ketoacidosis: Ketoacidosis is a preventable condition but potentially lethal to the foetus at any stage of pregnancy. Women should be instructed to test their urine for ketones if their blood glucose readings are high or if they feel unwell.

Retinopathy: Diabetic retinopathy may accelerate during pregnancy.[13] Fundoscopy is necessary before conception and once in each trimester of pregnancy for all women with diabetes.

Nephropathy: [13] Baseline assessment of renal function by serum creatinine and some measure of urinary protein excretion (urine albumin/creatinine ratio or 24-hour albumin excretion) should be undertaken before conception. Women with microalbuminuria may experience transient worsening during pregnancy; however, those with established nephropathy with overt proteinuria are at increased risk of pre-eclampsia and intra-uterine growth retardation and premature delivery.

Pregnancy may lead to permanent worsening of renal function in more than 40% of those with serum creatinine of 250 umol/l or greater or creatinine clearance < 50ml/minute and therefore it should serve as a contraindication to pregnancy. However, at that level of impaired renal function fertility is reduced and pregnancy is rare. ACE-inhibitors for treatment of microalbuminuria should be discontinued in women who are attempting to become pregnant.

Hypertension: Hypertension is a frequent concomitant of diabetes. Patients with type 1 diabetes frequently develop hypertension in association with diabetic nephropathy, as manifested by the presence of overt proteinuria. Patients with type 2 diabetes more commonly have hypertension as a concomitant disease. In addition, pregnancy induced hypertension is a potential problem for women with diabetes. Hypertension contributes to worsening of diabetic nephropathy and retinopathy in pregnancy. ACE-inhibitors, beta-blockers and diuretics should be avoided in women contemplating pregnancy if they are being used for hypertension. Methyl-Dopa or Labetalol may be substituted.

Neuropathy: Compartment syndromes such as carpal tunnel syndrome may be exacerbated by pregnancy and should be treated symptomatically with splints. Autonomic neuropathy particularly manifested by gastroparesis, hypoglycaemia unawareness, or orthostatic hypertension may complicate the management of diabetes in pregnancy. These complications should be identified, appropriately evaluated and treated before conception.

Cardiovascular disease: Untreated coronary artery disease is associated with a high mortality rate during pregnancy and women with significant coronary artery disease should be advised against pregnancy.

Foetal monitoring: The major risks for the foetus of a diabetic woman are congenital malformations, intra-uterine death, usually after 30 weeks and macrosomia, which may result in significant problems in labour for both mother and baby. Ante-natal foetal surveillance must be planned so that each risk is addressed efficiently and in a timely manner. Ultrasound scanning must be available for assessing gestational age, examining for congenital abnormali-

ties and monitoring foetal growth and liquor volume. All diabetic patients should be counselled about the possibility of a neural tube defect and offered serum alpha-fetoprotein blood test between 15 and 19 weeks gestation. A detailed ultrasound scan at between 20 and 22 weeks for careful assessment of foetal anatomy is mandatory. The risk of intra-uterine foetal death is increased by a factor of approximately three times, mostly confined to the third trimester. Although strict control of maternal blood glucose levels will reduce this risk, but not as low as that of the general population. Ultrasound assessment should be carried out at each visit from 26 weeks. The programme of surveillance must be modified if there are additional recognised risk factors, such as hypertension or renal disease. This may mean more frequent ultrasound assessment in addition to umbilical artery Doppler measurement and cardio-tocography. Unlike in the non-diabetic, it is excessive foetal growth rather than retarded growth that may be associated with the greatest risk. Increasingly large abdominal circumference in relation to the bi-parietal diameter can be easily monitored by serial ultrasound scans and these two parameters should be measured and documented at each visit, in association with assessment of liquor volume.

Timing of delivery: Uncomplicated case with no evidence of foetal compromise, spontaneous delivery at term is standard practice. When there are maternal complications of diabetes, complications of pregnancy, previous stillbirth or evidence of abnormal foetal growth, each case must be considered in its own merit with timely delivery in hospital. Delivery by elective Caesarean section should be considered if the ultrasound estimated foetal weight is > 4kg. A previous Caesarean section in a diabetic woman will usually be managed by a repeat Caesarean section. In the absence of these or other obstetric contra-indications a spontaneous vaginal delivery should be possible, with induction of labour as required. If delivery is indicated before 36 weeks then administration of a steroid to the mother for 48 hours prior to delivery should be undertaken. Steroids will upset glycaemic control and should only be given on an inpatient basis with careful monitoring of the glucose level and appropriate alteration of the insulin regime.

Management of labour and delivery:

1. Glucose control during labour. It is necessary to administer IV insulin and Dextrose to prevent 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 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 delivery and insulin dose should be reduced to around the pre-pregnancy level. Breastfeeding also reduces insulin requirements and appropriate reduction should therefore be made once feeding is 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 whil the patient is in hospital.

Gestational diabetes mellitus:
GDM is defined as a glucose intolerance that begins or is first detected during pregnancy. Differences in screening programmes and diagnostic criteria make it difficult to compare frequencies of GDM among various populations. Nevertheless, ethnicity has been proven to be an independent risk factor for GDM, which varies in prevalence in direct proportion to the prevalence of Type 2 diabetes in a given population or ethnic group.
The prevalence may range from 1

Table 5: Maternal risk factors for gestational diabetes

- Obesity
- Diabetes in first-degree relative
- Previous infant with macrosomia
- Previous diagnosis of GDM
- Age more than 35 years
- Polycystic ovary syndrome
- Multiparity
- Member of high risk population (e.g. Asian or African descent)

- 14% of all pregnancies, depending on the population sample, with 2 - 5% being the most common rate.[1] GDM develops when a woman is unable to secrete sufficient insulin to compensate for the increased insulin resistance during pregnancy. The foetus responds to hyperglycaemia by secreting large quantities of insulin. The result is increasing adiposity and the accrual of visceral fat. Women who develop GDM are at increased risk for type 2 diabetes mellitus.[14] The screening and diagnostic methods for GDM remain controversial, especially the threshold values for the diagnosis. [15]

Table 6: Perinatal complications of gestational diabetes mellitus

- Death: still birth and neonatal death
- Shoulder dystocia
- Bone fracture
- Nerve palsy
- Neonatal hypoglycemia

Data from the Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) study, correlating blood glucose levels with outcomes will hopefully lead to common agreement on the value for the diagnosis in future.[16] Screening methods for GDM vary from presence of maternal risk factors (table 5) to biochemical screening with 50gm OGTT (1hr blood glucose > 7.8 mmol/l (>140 mg/dl); screening based on maternal risk factors is more cost effective.[15]

Several European centres support a glucose load of 75 gm for diagnosis performed between weeks 24 and 28 of gestation as recommended by the World Health Organization and the Diabetes Pregnancy Study Group of the European Association for the Study of Diabetes.[17]

Management of GDM: Treatment of GDM can substantially reduce perinatal morbidity (table 6) from 4% to 1%.[18, 19] Women diagnosed with GDM should receive dietary advice and calorie intake should be reduced if overweight.

Such measures will achieve metabolic control in the majority of women. They should monitor their own blood glucose levels and, if the pre-prandial glucose levels are consistently above 5.5mmol/l (95 mg/dl), insulin should be commenced with the aim of keeping

pre-prandial blood glucose below 5.5 mmol/l (95 mg/dl), and two hour post-prandial below 7.8 mmol/l (140 mg/dl).

There is limited data on the safety and efficacy of Glibenclamide or Metformin in GDM. [20, 21, 22] A 75g oral Glucose Tolerance Test should be performed 6 weeks or more after delivery and the results interpreted by revised WHO criteria. (Table 7) Women with a history of GDM should be screened for GDM during any future pregnancy. They should be advised to make life style changes to reduce their risk of subsequent type 2 diabetes mellitus.[14] For further reading, readers are advised to refer to the Report of the Expert Committee on the diagnosis and classification of Diabetes Mellitus. [23]

Table 7: Reclassification of glucose tolerance status post-partum75-g oral glucose tolerance test

	Fasting Plasma Glucose	2-hour OGTT
Normal	6.1mmol/l [<110mg/dl]	< 7.8mmol/l [140mg/dl]
Impaired	5.6-6.9mmol/l [100-125mg/ dl] Impaired fasting glucose	7.8-11mmol/l [140-199mg/dl] Impaired glucose tolerance
Diabetes	>7mmol/l [126mg/dl]	> 11.1mmol/l [200mg/dl]

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