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OB-GYN & Neonatology

- **Obstetric Management of Diabetes Mellitus**
- **Dietitian's Role in The Management Of Gestational Diabetes Mellitus**
- **Insulin Therapy in Pregnancy**
- **The Infant of a Diabetic Mother (IDM)**

CME ACTIVITIES

- 3rd Gynaecological & Early Pregnancy Ultrasound Workshop
  26 Mar 2011
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Obstetric Management of Diabetes Mellitus

- Pregnant women with diabetes have either pre-existing diabetes or gestational diabetes which develops during pregnancy but resolves after delivery.
- In pre-existing diabetes but not gestational diabetes, the fetus is at risk for congenital abnormalities, especially cardiac and neural tube defects. In both pre-existing and gestational diabetes, the fetus is at risk for macrosmia and the associated birth injuries as well as sudden intrauterine death which is often associated with poor glycaemic control. Women with pre-existing diabetes are especially prone to worsening of their diabetic retinopathy during pregnancy.
- There is good evidence to show that tight glucose control of diabetes in pregnancy results in outcomes similar to the non-diabetic population. At present the incidence of gestational diabetes at the Singapore General Hospital is about 12% which mirrors the prevalence of adult-onset diabetes in the non-pregnant population. Screening for gestational diabetes is performed using the 75g oral glucose tolerance test in women who are deemed to be at risk, such as those with a family history of diabetes.
- Good periconceptional glycaemic control is the key to reducing the risk of fetal anomalies in pre-existing diabetes. Diet and, if necessary, insulin therapy remain the cornerstones of diabetes control in pregnancy. There is interest in the use of oral hypoglycaemics such as metformin but these agents are not presently used routinely in pregnancy.
- Diabetes in pregnancy is ideally managed in the setting of a joint clinic, in which the patient is seen jointly by an endocrinologist and obstetrician. This allows optimum management of the diabetes as well as the pregnancy. **At the Singapore General Hospital, the Gestational Diabetes Joint Clinic is held every Wednesday afternoon in the Diabetes Centre** where one-stop facilities for retinal photography, dietician input and counselling by a nurse clinician are available.
- Home glucose monitoring is effective in pregnant women as they are usually well-motivated and able to use a glucometer without difficulty. At SGH, women are provided free glucometers during pregnancy and usually transmit their blood glucose profiles to the nurse clinician via email to facilitate closer surveillance.
- If insulin becomes necessary, a combination of intermediate-acting and short acting insulins are used. Up to 4 doses a day may be used to achieve better control of glucose levels as compared to the usual 2 daily doses which are frequently used in non-pregnant diabetics. The target level for glycated haemoglobin (HbA1C) is 6%.
- Vaginal delivery is the goal for women with diabetes in pregnancy. In the well-controlled diabetic, the usual management is to allow women to await spontaneous labour until their expected date of delivery (EDD). Women who achieve good control but require insulin therapy are usually advised induction of labour at 38 weeks. In poorly-controlled women on insulin, earlier delivery may be required though the concern with preterm delivery is the risk of respiratory distress syndrome which is more common in infants of diabetic mothers. Women who are poorly-controlled on diet therapy alone must progress to insulin therapy – early delivery is not a substitute for achieving good glycaemic control. Sudden intrauterine death is the basis for early delivery and this feared complication is believed to be related to wide fluctuations in maternal glucose (hyperglycaemia and hypoglycaemia) as would be expected to occur in the poorly-controlled diabetic.
- Delivery by caesarean section may be advocated in diabetic women with big babies (more than 4 kg at term). These babies are at risk of shoulder dystocia because they are often disproportionately large. These babies have larger abdominal measurements as compared to their heads due to excessive deposition of glycogen in the liver. This results from fetal hyperinsulinism in response to maternal hyperglycaemia. It is important to remember that the fetus is not diabetic and will utilise any additional glucose it receives by converting it into glycogen.
- After delivery, women who have pre-existing diabetes can often rapidly return to their pre-pregnancy treatment regimens. Women with gestational diabetes usually revert to their non-diabetic states but have a 30% risk of developing adult-onset diabetes in later life. Lifestyle modifications such as maintaining an ideal body mass index (BMI) and regular exercise are useful interventions in preventing this sequelae.
- The outlook for pregnancy in diabetic women is generally good as most women can achieve good outcomes and healthy babies if tight glucose control, close surveillance and, if necessary, timely intervention is carried out.

The Infant of a Diabetic Mother (IDM)

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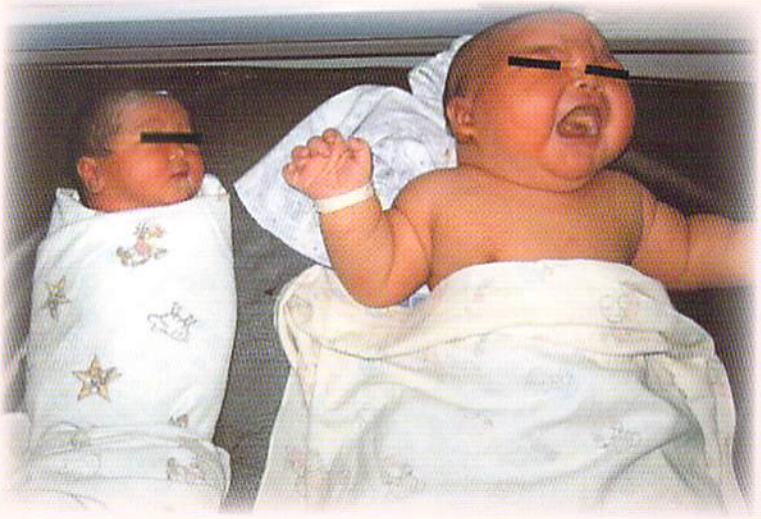

Almost 4% of pregnancies may be complicated by diabetes mellitus. [1] Diabetes in pregnancy is associated with an increased risk of complications in both mother and fetus. Perinatal outcome is related to the onset and duration of glucose intolerance, as well as to the severity of disease. In infants of mothers with gestational diabetes, complications are minimal. In contrast, teratogenicity occurs almost exclusively in babies of mothers with pre-gestational diabetes. Neonatal outcome of diabetic mothers depends not only on sugar control, but also on the presence of other obstetric complications like pre-eclampsia, which occurs more frequently in diabetic than in non-diabetic pregnancies.

Diabetes in pregnancy is associated with embryopathy (causing birth defects and spontaneous abortions) during the 6th to 7th week of gestation, and fetopathy (mainly macrosomia and hyperinsulinemia) during the second and third trimesters of pregnancy. Compared to the infant of a non-diabetic, the infant of a diabetic mother (IDM) is at higher risk of prematurity, congenital anomalies, perinatal asphyxia, respiratory distress syndrome and metabolic complications. Despite improved maternal insulin therapy as well as excellent prenatal and neonatal care, the IDM may have a perinatal mortality rate of up to 4.8%. Strict glycemic control during pregnancy is generally associated with lower perinatal mortality.

1) Macrosomia

Macrosomia, defined as a birth weight more than 90th percentile or >4000g, often occurs in IDMs where there was suboptimal glycemic control. The occurrence of macrosomia in IDM was almost four-fold that of infants of non-diabetic mothers. It occurs among all classes of diabetic pregnancies, except for those with vasculopathy where the fetus develops intrauterine growth restriction (IUGR) instead. IDMs with disproportionate macrosomia are more likely than those who are not macrosomic to have hyperbilirubinemia, hypoglycemia, acidosis, respiratory distress, shoulder dystocia and brachial plexus injury.

2) Premature delivery

Poor glycemic control and an associated high rate of urinary tract infections may contribute to premature labor. Maternal pre-eclampsia, which occurs more commonly in diabetic pregnancies, also contributes to premature delivery.[2]

3) Congenital malformations

IDMs are at significant risk for major congenital malformations. Pre-gestational diabetes was associated with an increased risk of multiple defects with a relative risk of 8.6 [3]. The relative risk for major malformations in infants of type 1 diabetics was 7.9 times that of healthy controls.[4] Congenital malformations account for about 50% of perinatal deaths in IDMs and the risk can be dramatically reduced through optimal glycemic control during pregnancy.

Common neonatal malformations in poorly controlled diabetics occur in the cardio-vascular, central nervous system,[3] genito-urinary, gastro-intestinal and skeleton. IDMs are at increased risk for hypertrophic cardiomyopathy where there is thickening of the inter-ventricular septum with reduction in the size of the ventricular chambers, potentially resulting in obstructed left ventricular outflow. Outflow obstruction occasionally is aggravated by anterior systolic motion of the mitral valve. Although infants may be asymptomatic, 5 – 10% have respiratory distress or signs of poor cardiac output or heart failure. CXR may show cardiomegaly. The hypertrophy is best detected by echocardiography; these changes occur in 30 to 50% of IDMs.

An abnormality that is unique to IDMs is the small left colon syndrome which may result in a transient inability to pass meconium but resolves spontaneously. The majority of cases of caudal regression syndrome occur in IDMs. The caudal regression syndrome (also known as sacral agenesis) consists of a spectrum of structural defects of the caudal region, including incomplete sacral development and, to a lesser degree, lumbar vertebrae. Spinal cord disruption results in neurologic impairment, leading to bowel/ urinary incontinence and a paucity of movement in the lower limbs with severely limited growth and deformities.

4) Perinatal asphyxia

IDMs are at increased risk for intrauterine or perinatal asphyxia, fetal heart rate abnormalities during labor, low Apgar scores and intrauterine death. Maternal vascular disease, manifested by diabetic nephropathy, may contribute to the development of fetal hypoxia and subsequent perinatal asphyxia.

5) Respiratory distress syndrome (RDS)

The mechanism for RDS may be a delayed maturation of surfactant synthesis caused by hyper-insulinemia, possibly by interfering with the action of glucocorticoids in inducing fetal lung maturation by.[5] In contrast, fetal lung maturation may occur early in diabetic pregnancies complicated by vasculopathy. Other causes of respiratory distress in IDMs include pneumonia, hypertrophic cardiomyopathy and transient tachypnea of the newborn.

6) Metabolic complications

The most frequent metabolic complications are hypoglycemia, hypo-calcemia and hypo-magnesemia. The onset of hypoglycemia typically occurs within the first few hours after birth. Risk of hypoglycemia is worsened in the premature or "small for gestational age" (SGA) baby who has low glycogen stores and hyper-insulinemia, decreasing the ability to mobilize hepatic glycogen.[6] Therefore IDMs require close blood glucose monitoring and, where required, supplementation in the form of parenteral glucose infusions.

7) Other short-term complications of IDMs

Polycythemia may lead to hyperviscosity syndrome, where there is vascular sludging, ischemia and infarction of vital organs. The end result may be a vascular stroke. Hyperbilirubinemia is thought to be secondary to increased hemolysis. The excess hemolysis may result from glycosylation of erythrocyte membranes.

8) Long-term Metabolic Risks

IDMs have an increased risk of developing diabetes themselves, and this is in part genetically determined. The lifelong risk of type 1 diabetes is about 6% in offspring. Development of type 2 diabetes is influenced by genetic susceptibility. The lifetime risk for a first-degree relative of a patient with type 2 diabetes is 5-10 times higher.[7]

Intrauterine exposure to hyperglycemia and hyper-insulinemia may affect the development of adipose tissue and pancreatic beta cells, leading to future obesity and altered glucose metabolism. Macrosomia at birth resolved by 1 year, but obesity recurred in childhood, resulting in a greater body mass index in offspring of diabetic mothers than controls between 14 and 17 years old. [8] Impaired glucose tolerance occurred in 36% of offspring of diabetic mothers.

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Insulin Therapy in Pregnancy

Importance of Glycaemic Control in Pregnancies Complicated by Diabetes

Diabetes is the most common medical condition complicating pregnancy. It is associated with an increased rate of congenital malformations and an increased incidence of adverse outcomes for both mother (including spontaneous abortion, polyhydramnios, preterm birth, and cesarean delivery) and infant (including macrosomia, perinatal mortality, neonatal hypoglycemia and hyperbilirubinemia).

Whether the pregnancy is classified as pregestational diabetes (occurring in women who have been diagnosed with type 1 or type 2 diabetes prior to pregnancy) or as gestational diabetes (GDM, occurring when a non-diabetic women develops diabetes only during pregnancy), the goal of treatment is to maintain maternal blood glucose levels as near to normal as possible throughout the pregnancy.

Dietary therapy and insulin form the mainstay of treatment for hyperglycemia during pregnancy. Once glycemic goals cannot be attained by dietary therapy, insulin should be initiated to achieve normal glucose concentrations. Insulin is the pharmacologic therapy that has most consistently been shown to reduce fetal morbidities when added to dietary therapy.

Can We Use Oral Antidiabetic Agents in Pregnancy?

Oral antidiabetic agents (OADs) are generally not recommended during pregnancy. Before conception, OADs should be stopped and insulin started and titrated to achieve acceptable glucose control. Women who become pregnant while taking OADs should start insulin as soon as possible.

Among the sulphonylureas, only glibenclamide (a second generation sulphonylurea) has been demonstrated to have minimal transfer across the placenta and has not been associated with excess neonatal hypoglycemia or congenital anomalies. Controlled trials are lacking to determine the safety of glibenclamide use in pregnancy. Concerns remain regarding the inadequacy of glucose control with glibenclamide in pregnancy and potential long-term effects of glibenclamide on fetal beta-cell hypertrophy and function.

Metformin does cross the placenta. Some observational studies have reported good outcomes with metformin use in women with pregestational diabetes. Results from a large Australian study suggests that second and third trimester metformin treatment of GDM appears to be safe and effective. There is also some data in polycystic ovary syndrome that suggest metformin may be useful to prevent early pregnancy loss and GDM. However, more clinical studies are needed to firmly establish the safety and efficacy of metformin therapy in pregnant women with diabetes.

The use of all other OADs (including thiazolidinediones, metglitinides, acarbose, and dipeptidyl peptidase-4 inhibitors) are not recommended in pregnancy due to the paucity of safety data.

Which Type of Insulin is Safe in Pregnancy?

To achieve normoglycemia during pregnancy, insulin therapy should be individualized and intensification of treatment usually requires the use of basal and prandial insulin for optimal glucose control. Most guidelines recommend the use of human insulin which is the least immunogenic, thus minimizing the transplacental transport of insulin antibodies.

Prandial Insulin

Human regular insulin has been used extensively to control postprandial hyperglycemia. Compared to human regular insulin, insulin lispro and aspart (rapid-acting insulin analogues) both improve postprandial glucose excursions and may be associated with decreased risk of delayed postprandial hypoglycemia. Both lispro and aspart have been investigated in pregnancy, demonstrating clinical efficacy, minimal transplacental transfer, and no evidence of teratogenicity. Neonatal outcomes are similar to those of women treated with human regular insulin.

Early reports raised concerns that lispro may exacerbate diabetic retinopathy during pregnancy due to its greater affinity with the IGF-I receptor. However, subsequent reports showed that the incidence for progression of retinopathy is no different with lispro than with human insulin. Both lispro and aspart are assigned the pregnancy category "B" rating, indicating that adequate clinical studies in pregnancy have not revealed increased risk to the fetus. As for insulin glulisine (another rapid-acting insulin analog), there are no available reports documenting its use in pregnancy.

Basal Insulin

For basal insulin requirements, only NPH insulin is currently recommended. There are increasing observational studies demonstrating the apparent safety of insulin glargine (a long-acting insulin analog) in pregnancy. Compared to NPH insulin, similar fetal outcomes in terms of congenital malformations have been shown when glargine is used in pregnancy. However, no randomized controlled trial is available to confirm the safety and efficacy of glargine in pregnancy. Concerns remain regarding the mitogenic risks of glargine since it has a six-fold increase in IGF-I activity over human insulin. Up to now, glargine is assigned a pregnancy category "C" rating, indicating the lack of adequate and well-controlled studies in pregnant women.

Insulin detemir, another long-acting insulin analog, is not recommended for use in pregnancy as no clinical studies have been performed. A multinational study on the safety and efficacy of detemir for the treatment of pregnant type 1 diabetic women is almost complete.

Conclusion

- Maintaining normal glucose concentrations is crucial in a pregnant woman with diabetes to reduce both maternal and fetal complications.
- Dietary therapy and insulin form the mainstay of treatment for hyperglycemia.
- Oral antidiabetic agents are generally not recommended during pregnancy.
- Human insulin (NPH and regular insulin) is still the recommended choice when insulin therapy is needed.
- Insulin lispro and aspart have been shown to be safe and may be used to control postprandial hyperglycemia.
- Long-acting insulin analogs are generally not recommended as safety in pregnancy has yet to be demonstrated in clinical studies.

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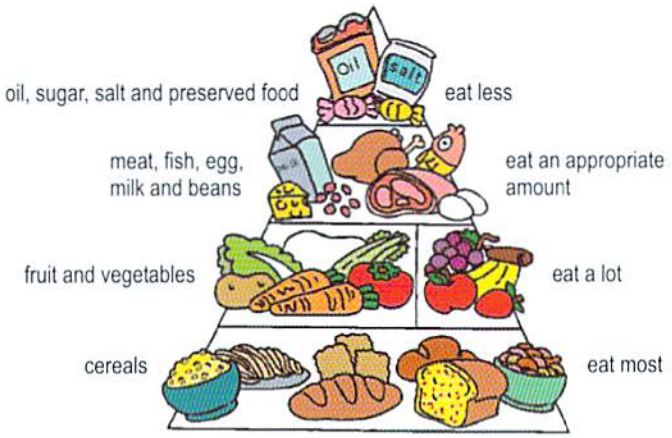
Dietitian's Role in The Management of Gestational Diabetes Mellitus

Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance that begins or is first recognized during pregnancy. Prevalence of GDM in Singapore has been reported to be 8.6% of pregnancies. The treatment for women with gestational diabetes includes dietary advice by a qualified dietitian, blood glucose monitoring and insulin therapy which has shown to reduce the rate of serious perinatal complications, without increasing the rate of cesarean delivery. It has also been shown that infants born to mothers receiving intensive therapy were significantly less likely to be large for gestational age. Infants who are large for gestational age are at a higher risk of impaired glucose tolerance or diabetes in later life, and girls have an increased risk of gestational diabetes. These women also have an increased risk of preeclampsia.



In women with GDM, medical nutrition therapy (MNT) is the primary intervention for managing blood glucose. The American Diabetes Association (ADA) recommends all women with GDM should receive nutrition counselling by a dietitian when possible. MNT should be individualized, based on maternal weight and height, physical activity level, and lifestyle. The goal of nutrition therapy is to provide adequate nutrients and energy for optimal gestational weight gain, normalize blood glucose level and avoid urinary ketones. This is achieved by a healthy balanced diet and appropriate carbohydrate intake. A dietitian will closely monitor blood glucose levels, appetite and weight, based on which care plans are adjusted to achieve the best outcome for the pregnancy. If nutrition therapy alone does not achieve near-normal glycemia in a short period of time (1 or 2 weeks), insulin therapy should be considered.

During pregnancy, the mother experiences many necessary changes to her body to carry the child to term. Therefore, to meet the nutritional demands of maternal and fetal growth, additional nutrients are necessary. The recommended dietary allowances for a pregnant woman includes additional 200-285 kilocalories per day, additional 9 gram protein per day, adequate folate, calcium and iron intake. It is important to recognize that this increased requirement for calories is modest. Hence, a policy of "eating for two" is to be discouraged.

Here are some general dietary guidelines :

A pregnant woman is recommended to aim for three meals a day and two to three snacks a day. Eat a variety of foods, distributing calories and carbohydrates evenly throughout the day.

Basic Nutritional Advice for GDM Patients

- Regular meal timing and even distribution of complex carbohydrate foods may help to stabilize blood glucose levels.
- Additional protein is needed during pregnancy for fetal growth.
- Avoid sweet foods and beverages that contain simple sugars such as soft drinks, fruit juice and most desserts. Most of these foods can quickly elevate blood glucose levels. Use artificial sweetener if you need a sweet fix.
- Limit fat intake. Fat delays carbohydrate absorption which may cause blood glucose level to remain high for longer time. Excessive fat intake may also result in undesirable weight gain.
- Include high fiber foods, such as fresh fruits and vegetables, whole grain breads and cereals, beans and legumes. These foods are absorbed more slowly than simple carbohydrates which increase your blood glucose level more gradually.
- Include adequate folate, calcium and iron intake.
- Limit caffeine and alcohol intake.
- Regular physical activity can improve blood glucose control. Consult the doctor for the duration and intensity of exercise.

Sample Snack Options for Women with Diabetes in Pregnancy

- 1 slice of wholemeal bread
- 3 pieces of wholemeal cream cracker
- 1 medium orange/apple/pear
- 15 grapes
- 1 small banana
- 1 slice papaya
- 1 glass low fat milk
- 4 Tbsp low fat milk powder (30g)
- 1 small tub plain yogurt (220 gram)

Nutrition tip : Eating carbohydrates in combination with protein and/or fat may help to keep patients feel fuller and satisfied.

In conclusion, MNT is the cornerstone of treatment for gestational diabetes. Women should be encouraged not to regard the diabetic diet as a restrictive or regimented diet designed only for someone with gestational diabetes. Instead, it is actually a balanced, nutritious diet which should be the goal for all pregnant women.