Diabetes mellitus in pregnancy

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INTRODUCTION

Diabetes mellitus in pregnancy could either be pregestational (pre-existing) or gestational. Gestational diabetes mellitus (GDM) is the most common cause of diabetes during pregnancy, accounting for up to 90 % of pregnancies complicated by diabetes.[1] Gestational diabetes mellitus is defined as "any degree of glucose intolerance with onset or first recognition during pregnancy. [2] Marked variation in GDM prevalence among different racial/ethnic groups has been documented, with higher prevalence among Native-American, Asian, African-American, and Hispanic populations than among non-Hispanic whites. The prevalence of gestational diabetes mellitus is increasing reflecting the global epidemic of obesity.[3] In Sri Lanka, the prevalence of GDM was shown to be 5.5% in a study carried out in Sri Jayawardena general hospital while in another study done at the North Colombo teaching hospital, Ragama the prevalence of GDM was shown to be 5.7% with the prevalence of both gestational and pregestational at 7.1%.[4 5]

PRE-GESTATIONAL DIABETES MELLITUS

Preconception care forms the cornerstone of a successful pregnancy outcome in women with diabetes preceding pregnancy. The aim of glycaemic management at this stage is to attain a HbA1c <6.1%, without troublesome hypoglycaemic symptoms. Screening for retinopathy by an ophthalmologist and assessment for nephropathy by estimating glomerular filtration rate (eGFR) and urinary protein excretion should be done prior to conception. The medications should be reviewed and modified to avoid teratogenic effects in the event of a pregnancy (eg: angiotensin inhibitors/ angiotensin receptor blockers/statins). Folic acid 5 mg should be commenced and continued throughout the first trimester, while 75mg of aspirin should be commenced at 12 weeks of gestation and continued until birth of the baby.

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Table 1 – GDM diagnostic threshold values from various organizations

	Plasma glucose concentration (mg/dl)				
Organization	OGTT glucose load	Fasting	1 hour	2 hour	3 hour
ADA*	100g	95	180	155	140
ACOG*	100g	105	190	165	145
NCE[8]	75g	100.8		140	
IADPSG[8]	75g	92	189	153	
DIPSI[8]	75g			140	

**Diagnosis of GDM made if two or more glucose values equal to or exceeding the threshold values. §Diagnosis of GDM if one or more glucose values equal to or exceeding the threshold values. OGTT: Oral Glucose Tolerance Test, ADA: American Diabetes Association, ACOG: American Council of Obstetricians and Gynecologists, NICE : National institute of clinical excellence, IADPSG: International Association of Diabetes and Pregnancy Groups DIPSI: Diabetes in pregnancy study group India*

SCREENING FOR GESTATIONAL DIABETES MELLITUS

There exists various guidelines for diagnosing GDM (Table 1). Urine glucose testing, fasting plasma glucose and postprandial plasma glucose have been shown to have low sensitivity as screening tests for GDM and therefore they are not recommended as screening tests for gestational diabetes mellitus[6].

In March 2010, the International Association of Diabetes and Pregnancy Study Group (IADPSG) issued a consensus guidelines to potentially attain a single approach for GDM diagnosis based on the results of the HAPO (The Hyperglycemia and Adverse Pregnancy Outcome) study which was a landmark multinational study whose objective was to clarify risks of adverse outcomes associated with degrees of maternal glucose intolerance less severe than overt diabetes mellitus. [7] While the HAPO study demonstrated a positive linear relationship between screening glucose values and adverse perinatal outcomes it showed that blood glucose values that were previously considered 'normal' were associated with adverse perinatal outcomes and that the relationship of maternal glucose to outcomes is a continuum. The cut offs for gestational diabetes mellitus was based on the level of maternal blood glucose above which key adverse outcomes (birth weight, C peptide levels and percent fetal body fat >90th percentile) achieved an odds ratio of 1.75 compared to mothers with average glucose levels. The recently published NICE guidelines have lowered the cut off value for FBS to 100.8mg/dl, from the previous 126mg/dl.[8] (Table 1) The DIPSI recommends a glucose challenge test with 75g of glucose taken any time of the day (no need for fast) with an abnormal 2 hour post glucose blood sugar level considered significant.[9]

Universal screening for GDM is practiced in Sri Lanka with the 75g OGTT performed at 24-28 weeks of pregnancy while screening for pregestational diabetes is advocated at the booking visit in women not known to have preexisting diabetes.

PATHOPHYSIOLOGY OF GDM

Normal pregnancy is associated with a number of changes in glucose metabolism. Data from the gold standard of assessment of insulin action, the euglycaemic glucose clamp demonstrates that insulin action reduces as pregnancy progresses due to the insulin resistance created by certain hormones. Human placental lactogen and placental production of tumour necrosis alpha (TNF-alpha) appear to play a key role in the development of insulin resistance. Pregnancy as an insulin resistant state may reveal even the smallest pre existing defects in insulin secretion or insulin sensitivity and as a consequence, relative β-cell failure. The pathophysiological changes of GDM are similar to those observed in type 2 diabetes mellitus, which is also characterized by peripheral insulin resistance accompanied by an insulin secretory defect. At the same time there are changes in fasting glucose likely reflecting an increased uptake of glucose by the fetoplacental unit, with average fasting capillary glucose readings low as 56mg/dl, found in healthy, lean, normal glucose tolerant women in the third trimester of pregnancy.[10]

ADVERSE EFFECTS OF DIABETES MELLITUS ON PREGNANCY

The adverse consequences of gestational diabetes mellitus has been known for some time but was clearly delineated by the HAPO study. Macrosomia, neonatal hypoglycaemia, caesarean section, shoulder dystocia, preeclampsia, preterm delivery, hyperbilirubinuria and admission to the neonatal intensive care unit was shown to be associated with maternal hyperglycaemia.

Major maternal morbidity and mortality is more common in women with pregestational diabetes mellitus than in women with GDM.[11]

MANAGEMENT OF DIABETES MELLITUS IN PREGNANCY

Benefits of treating gestational diabetes mellitus has been demonstrated. The Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS), found reduced perinatal morbidity and mortality when standard contemporary treatment of gestational diabetes mellitus was compared with no intervention, while more recently the maternal fetal medicine network (MFMU) study confirmed that treatment of GDM is beneficial in reducing macrosomia and large for gestational age babies. [12] [13]

Dietary intake is fundamental to optimal pregnancy outcomes because nutritional quality and quantity have an important impact on the overall growth and development of the fetus. Medical nutrition therapy (MNT) is the cornerstone of managing gestational diabetes. MNT has been defined as a 'carbohydrate controlled meal plan that promotes adequate nutrition with appropriate weight gain, normoglycemia, and the absence of ketosis.' According to the ADA recommendations, carbohydrate intake should be approximately 40 % of total calorie intake and should be selected from foods with low glycaemic index values.[14] In pregnant women of normal body weight (BMI between 18–22.9 kg/m^2), the recommendation is to consume 30–32 kcal/kg body weight, especially during the second half of pregnancy.[15] All women should receive nutritional advice, preferably from an appropriately skilled dietitian. Advice on individualized plan for weight gain and caloric needs and determining protein, fat, and micronutrient needs should also be provided.

It is also imperative to note that only 20% of subjects in the ACHOIS trial and 8% of Maternal fetal Medicine Units Network subjects required insulin, implying that lifestyle modification and dietary intervention will be effective in 80–90% of women with GDM.

Compared to diet alone, exercise with dietary modifications has been found to lead to improved glycaemic control. [16] The proposed mechanism for such an improvement in glycaemic control is heightened sensitivity of peripheral tissues to insulin. Unfortunately, researchers have not been able to suggest an evidence based intervention with guidelines for frequency, intensity, time and type of physical activity (FITT principle for exercise prescription) that would achieve good glycaemic control in women with GDM. Based on the available evidence on the benefits of exercise in managing GDM, ADA recommends moderate exercise programs for women without medical or obstetrical complications.[17]

Pharmacological intervention in the management of GDM is usually employed when the woman fails to meet established goals with conventional therapy of diet and exercise. It is also indicated when elevated fasting glucose levels occur while on conventional therapy, because dietary modification alone has limited effect on fasting levels. NICE recommends immediate treatment with insulin, with or without metformin, as well as MNT, to women with gestational diabetes who have a fasting plasma glucose level of 126mg/dl or above at diagnosis while in those with a FBS between 100.8-126 mg/dl at diagnosis, addition of pharmacological agents to MNT is advocated when FBS remains above 126mg/dl following a two week trial with MNT alone. [8]

Prandial insulin and basal insulins are the two main regimens used during pregnancy. Studies have shown that short acting insulin analogues (lispro and aspart) are more effective than regular human insulin in achieving target glucose values and minimizing the risk of macrosomia.[18] [19] Because the insulin analogues have shorter durations of action and more rapid onsets of action than regular insulin, they are associated with improved postprandial glycaemic control and less postprandial hypoglycaemia. Due to limited data on the use of basal analogues in pregnancy, NICE recommends neutral protamine

hagedorn (NPH) as the first choice for long acting insulin during pregnancy.[20] The type of regimen and number of injections per day are determined based on the individual's needs and lifestyle. A basal bolus insulin regimen (three bolus doses of short acting insulin just prior to meals with NPH insulin at night) or a split mixed dosage regimen (combination of short acting and intermediate acting insulin- Eg: Mixtard insulin twice daily) is used in pregnancy, though the former regimen achieves better glycaemic control.[21] Pump therapy (Continuous subcutaneous insulin infusion- CSII) more closely mimics physiological insulin secretion with evidence of less severe hypoglycaemia. CSII should be considered when adequate blood glucose control is not obtained by multiple daily injections of insulin without significant disabling hypoglycaemia. However, benefits of CSII on glycaemic control during pregnancy have not been realized, with a Cochrane review suggesting a potential increase in infant birth weight associated with CSII.[22] The potential of a closed loop therapy, linking real time continuous glucose monitoring with insulin dose adjustments to improve management of diabetes during pregnancy is under investigation.

Metformin and glibenclanide are the two oral hypoglycaemics that can be used in pregnancy. Metformin can be used as an alternative or adjunct to insulin therapy. Metformin was shown to be similar to insulin with regard to glycaemic control and neonatal outcome.[23] Glibenclamide is comparable to insulin in terms of birth outcome and glycaemic control and is a suitable alternative to metformin.[24] NICE recommends glibenclamide for women with gestational diabetes in whom blood glucose targets are not achieved with metformin but who decline insulin therapy or who cannot tolerate metformin. There is limited evidence with regard to which oral hypoglycaemic should be selected. Failure of glibenclamide was shown to be higher in women with higher initial fasting glucose values above 115mg/dl.[25] Similarly for metformin, women who required supplemental insulin had higher BMI in early pregnancy and higher baseline glucose levels.[26]

Daily self monitoring of blood glucose (fasting, premeal, postmeal and bedtime at night), appears to be superior to intermittent monitoring of plasma glucose as the hypoglycaemic regimen could be tailored accordingly. Consensus was reached at the fourth International workshop conference on GDM on target capillary glucose values concentrations. Blood sugar <95 mg/dl in the fasting state, <140 mg/dl at 1 hour, and <120 mg/dl 2 hours after starting the meal should be the treatment targets.[27] In women on insulin or glibenclamide, the blood sugar should not be allowed to drop below 72mg/dl.[8] Urine glucose monitoring is not useful though urine ketone monitoring can be used in patients who are restricting calories to detect insufficient caloric or carbohydrate intake.[28]

Although there is consensus about postprandial glucose levels being more important than preprandial levels since the former correlates better with adverse neonatal events such as fetal malformations, macrosomia, hypoglycaemia, and shoulder dystocia, it has been debated as to whether glucose should be measured one or two hours after a meal.[29] Continuous blood glucose monitoring using the continuous glucose monitoring system has recently shown that glucose peaks occur about 70 ± 13 minutes after a meal in non diabetic pregnant women and after about 90 minutes in diabetic women.

Women with diabetes should have contact with the joint diabetes and antenatal clinic for assessment of blood glucose control every 1–2 weeks throughout pregnancy.

TREATMENT ADJUSTMENT ACCORDING TO THE FETAL BIOMETRIC PARAMETERS AND ANTENATAL FETAL SURVEILLANCE

Despite optimum glycemic control there is a potential increase in the risk of fetal macrosomia in women with GDM.[30] In contrast, some fetuses may be at risk of growth restriction due to excessively tight maternal glucose control .[31] A correlation has been reported between ultrasound (USS) fetal abdominal circumference (AC) (AC>75th percentile) and high amniotic fluid insulin levels in a recent study [30]. There have been four randomized controlled studies looking at the use of USS fetal AC as a guide to adjust the blood sugar levels. [32 33 34 35]. Bonomo et al randomised 229 women to conventional treatment of GDM (glucose targets <90 mg/dl (5.0 mmol/l) fasting and <120 mg/dl (6.7 mmol/l) 2-hour post-prandial), or modified treatment targets based on abdominal circumference on fetal ultrasound done two weekly as below. [35]

- AC≥ 75th percentile: fasting< 80 mg/dl(4.4 mmol/l) and post-prandial <100 mg/dl (5.5 mmol/l)
- AC< 75th percentile: fasting< 100 mg/dl(5.5 mmol/l) and post-prandial <140 mg/dl (7.8 mmol/l)

They have reported a significant reduction in the percentage of LGA infants (7.9 vs. 17.9%), SGA infants (6.0 vs. 9.0%), and macrosomia (3.3 vs. 11%) with this modified treatment. [35] USS fetal biometry may allow more pragmatic treatment targets in some low risk patients, whilst tighter control may be suggested for other patients at high risk of adverse perinatal outcomes.

Fetal ultrasound assessment is frequently used to estimate the fetal weight and wellbeing and to assist safe prolongation of pregnancy and time the date of delivery. However, there is no uniform policy of frequency of USS examinations. Therefore, the frequency of USS examinations should be based on clinical indications. There is a paucity of high level evidence on the optimum gestational age for delivery in gestational diabetes. Different management strategies have been adopted for pregestational or pre-existing diabetes. Rasmussen et al noted that deaths in normally formed infants occurred when there was clinical evidence of fetal macrosomia, polyhydramnios or poor metabolic control. Consequently, uncomplicated GDM pregnancies could go up to 40

Probability of shoulder dystocia by birth weight in diabetic and non-diabetic pregnancies[37]		
Birth weight (g)	Diabetic pregnancy	Non-diabetic pregnancy
<4000	0.022	0.007
4000-4499	0.139	0.067
≥4500	0.525	0.145

completed weeks of gestation.[36]

The potential risk of shoulder dystocia is one of the major concerns in vaginal delivery in women with gestational diabetes. Although increasing fetal weight is positively associated with the risk of shoulder dystocia, as many cases occur in instances where birth weight is less than 4000 g. Rouse et al reported the probability of shoulder dystocia by birth weight in diabetic and non-diabetic pregnancies[37]. Royal College of Obstetricians and Gynaecologists has recommended to offer an elective Cesarean delivery in case of estimated fetal weight >4500g in diabetic mothers.

DIABETIC KETOACIDOSIS

In pregnancy, diabetic ketoacidosis (DKA) can occur at a relatively lower blood glucose level due to physiological changes that accompany pregnancy. Emesis and the tendency for early lipolysis following relatively short episodes of fasting ('accelerated starvation of pregnancy'), result in ketonuria being found in a significant number of healthy pregnant women. Therefore, for a diagnosis of DKA in pregnancy, ketonaemia or academia (pH < 7.3 or serum bicarbonate < 15mmol/L) should be demonstrated. DKA is associated with poor uteroplacental blood flow and fetal acidosis, which is reflected on cardiotocography. As fetal acidosis reverses with satisfactory treatment of DKA, emergency delivery should not be planned in the presence of an abnormal CTG in this setting. DKA is a medical emergency and should be managed in intensive care setting. The management is similar to that of a non-pregnant adult with DKA.

INTRAPARTUM MANAGEMENT

The insulin requirement during the latent phase remains at a stable level though it may increase during the active phase. Maternal hyperglycaemia during labour increases the risk of fetal hyperinsulinaemia and thus hypoglycaemia and fetal acidaemia. Therefore maternal blood sugar surveillance should be continued during labour with hourly monitoring of blood sugar, in women who have been on insulin or oral hypoglycaemics during pregnancy.

Women should have their normal diet and continue their insulin regimen until active labour begins. Women on long acting basal insulin should continue this, while short acting and intermediate acting insulin should be discontinued at the time of active labour. The aim is to maintain blood glucose between 70 and 126 mg/dl during labor irrespective of whether the women has type 1 or type 2 diabetes or GDM.[8] A maternal blood glucose value of more than 180 mg/dl has been conclusively proven to be associated with high risk of neonatal hypoglycemia. [38] The protocols for use of insulin during pregnancy are mostly based on studies in type 1 diabetes mellitus patients.

During labour, normoglycemia is mostly achieved with rapid acting insulin when indicated, so as to prevent hypoglycemia in the neonate. Blood glucose should be monitored hourly and an insulin infusion regimen commenced when two consecutive blood sugar readings are above 126 mg/dl, with insulin adjusted according to an insulin infusion scale. Intravenous dextrose and insulin infusion should be considered for women with type 1 diabetes from the onset of established labour. The infusion scale should consider both the insulin requirement in late pregnancy and the blood glucose level. (Table 2)

A syringe pump is set up with 50 U of soluble insulin in 50 ml of normal saline, while a 5% dextrose solution containing 20 mmol/L of potassium chloride is commenced at 100ml per hour. If two consecutive blood sugar readings are above 162 mg/dl, the infusion rate should be shifted one column to the right and if two consecutive readings are below 72 mg/dl , the infusion rate should be shifted one column to the left. Following delivery the infusion should be reduced to the lowest scale and blood sugar monitored hourly until the woman resumes her normal meals.

The infusion regimen can be adopted for women undergoing a caesarean section too, which should be performed in the morning hours.

Table 2- Insulin infusion regimen for women during active labour [39]

Current total daliy insulin dose	Up to 40 units/day	41-60 units/day	61-90 units/day	> 91 units/day
Capillary Glucose (mg/Dl)	Infusion rate (units / hr)	Infusion rate (units / hr)	Infusion rate (units / hr)	Infusion rate (units / hr)
0-54	0	0	0	0
55-125	1.0	1.5	2.0	2.0
126-160	1.5	2.0	3.0	4.0
161-195	2.0	3.0	4.0	5.0
196-270	3.0	4.0	5.0	6.0
>270	Exclude diabetic ketoacidosis	Exclude diabetic ketoacidosis	Exclude diabetic ketoacidosis	Exclude diabetic ketoacidosis

POST PARTUM MANAGEMENT

Immediately following delivery, insulin resistance falls dramatically. In addition to this, blood glucose falls as glucose passes into breast milk.

Breast feeding should be commenced immediately following delivery in order to reduce the risk of neonatal hypoglycaemia. Women with type 1 diabetes will need a reduction of their insulin requirements by about 30% while women with type 2 diabetes could continue metformin or glibenclamide with advise on frequent snacks to reduce the risk of hypoglycaemia. Women with GDM should have their antenatal hypoglycaemic regimen withheld while blood glucose should be monitored premeal and postmeal with advise on frequent snacks.

At six weeks postpartum the woman should be reviewed with blood sugar level. The NICE recommends a FBS at six weeks while some studies have shown that this would miss a significant number of women with diabetes, compared to the oral glucose tolerance test.[40] Advise on continuing breastfeeding should be reiterated at this point as the benefits of exclusive breastfeeding for at least 3 to 4 months has been demonstrated by a reduction in childhood obesity compared to women with GDM who did not breast feed exclusively for this period.[41]

INFANT OF A DIABETIC MOTHER

Congenital anomalies are a complications of pregestational diabetes mellitus as the fetuses are exposed to hyperglycaemia during the critical period of organogenesis. A linear relationship between HbA1c and malformation rates have been reported, with the optimal HbA1c set at below 6.1% with avoidance of troublesome hypoglycaemic symptoms. Unfortumately most anomalies occur before pregnancy is recognized, highlighting the need for optimal glycemic control at the preconception stage. The anomalies predominantly affect the cardiac, skeletal, central nervous and gastrointestinal systems.

Macrosomia, defined as a birthweight above 90th centile commonly complicates diabetic pregnancies. This is a result of fetal hyperinsulinaemia and is associated with increased risk of shoulder dystocia, obstructed labour, instrumental delivery, birth injuries and caesarean section.

Although less common than macrosomia, fetal growth restriction could occur as a consequence of placental insufficiency especially in women with pregestational diabetes with microvascular complications.

Respiratory complications that are commonly seen among neonates of diabetic women are due to inadequate pulmonary fluid absorption caused by lack of labour induced stress hormonal surge, as elective deliveries are performed to reduce the risk of late intrauterine death.

Other adverse fetal/neonatal effects include intrauterine death, polycythaemia, jaundice, hypocalcaemia, hypoglycaemia and hypertrophic cardiomyopathy.

LONG TERM EFFECTS OF GDM

The largest public health impact of GDM is it's role on future diabetes in the mother and obesity and diabetes in the offspring. It was found that 17–63% of women diagnosed with GDM will develop type 2 diabetes mellitus within 5 to16 years after delivery.[42] The cumulative incidence of type 2 diabetes is highest in the first five years after pregnancy and then it decreases, reaching a plateau at ten years postpartum. Though there have been studies showing a beneficial result of metformin and thiazolidinediones in preventing diabetes mellitus, further studies are needed to study this area more extensively.[43] [44] An annual HbA1c test should be performed in women who have a negative postnatal test for diabetes at 6 weeks .[8]

Though life style modifications in the form of nutritional adjustments and regular exercise have shown some promising results in preventing gestational diabetes mellitus, recently published systematic reviews and meta analyses do not show evidence of a lower risk of GDM with enhanced physical activity in pregnancy.[45] [46]

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