Review Article

Gestational Diabetes Mellitus
Salma Chowdhury¹, Tanvirul Hasan², Mir Moyeedul Islam³, Susmita Nargis⁴, ABM Moniruddin⁵

Abstract
Diabetes mellitus during pregnancy (i.e., Gestational Diabetes Mellitus or GDM) has definite impact on maternal & fetal health. A woman is diagnosed with gestational diabetes specially when glucose intolerance continues beyond 24-28 weeks of gestation GDM needs to be specially considered, because it may often remain undiagnosed leading to abortion, miscarriage, fetal obesity, intra-uterine growth retardation (IUGR), intra-uterine death (IUD) of fetus in addition to maternal morbidities & mortalities. Here we have reviewed in brief about the causes, pathophysiology, complications, risks, diagnosis, management, prevention etc. of GDM.

Keywords: Diabetes Mellitus, Dystocia, Gestation, Intra-uterine death, Obesity.

Date of received: 05.12.2017
Date of acceptance: 03.04.2018

Introduction
Gestational Diabetes Mellitus or GDM is a clinical problem where a woman specially and commonly without previously diagnosed diabetes mellitus present with high blood glucose level during pregnancy particularly in the third trimester. It is caused when insulin receptors malfunction or is insensitive or resistant destroyed. This GDM may occur owing to such pregnancy-related factors as the presence of HPL (human placental lactogen) interfering with receptors. This in turn causes excessively raised blood glucose levels. GDM commonly does have few minor symptoms and thus it needs to be diagnosed very often by screening of pregnant women. As with GDM, babies born to mothers with untreated diabetes are generally and typically at increased risk of problems such as being large babies for pregnancy duration with its attendant puerperal complications, hypoglycaemia, icterus etc. If left untreated or neglected and overlooked, it can also cause hyperglycaemic convulsions and stillbirths. GDM plus its attendant complications are preventable. Women with GDM who have adequate glycemic control can effectively nullify the risks and complications. The first recommended target for strategic management of GDM is essentially the “Food Plan”.

Women with mismanaged GDM are at increased risk of developing non-insulin dependent type 2 diabetes mellitus (NIDDM) or, very rarely, latent Autoimmune Diabetes Mellitus (DM) or Type 1 DM after pregnancy, as well as having a higher incidence of pregnancy related toxemias and Caesarean section. These children from GDM mothers are prone to developing childhood obesity plus type 2 DM later in life. However, most women are able to control their blood glucose levels with a modified diet plan along with the help of physical exercise. And some of them may need antidiabetic oral hypoglycaenic agents (OHA) or insulin.

Epidemiology
GDM may affect 3% to 10% of pregnancies, depending on the population, their food habit and life style.

Classification of GDM
Priscilla White had pioneered research on the effect of high blood glucose levels on pre-natal, perinatal and post-natal outcomes. The most commonly used White classification was proposed after his name. It is extensively used to evaluate and assess maternal and fetal risks.

1. Professor, Department of Obstructed & Gynaecology, Dhaka Medical College Hospital, Dhaka, Bangladesh.
2. Assistant Surgeon, Department of Surgery, Sher-e-Bangla Medical College, Barisal, Bangladesh.
3. Assistant Professor, Department of Pharmacology, Ad-din Sakina Medical College, Jessore, Bangladesh.
4. Assistant Professor, Department of Biochemistry, Ad-din Sakina Medical College, Jessore, Bangladesh.
5. Professor & Head, Department of Surgery, Khwaja Yunus Ali Medical College, Enayetpur, Sirajgonj, Bangladesh.

Correspondence: Salma Chowdhury, Professor, Department of Obstructed & Gynaecology, Dhaka Medical College Hospital, Dhaka, Bangladesh. Phone: +88 01712-978159, e-mail: salmac2411@gmail.com
It differentiates GDM (type A) from pregestational diabetes (i.e., diabetes that had been prior to conception). These two major groups are further subclassified in accordance to their possible risks and management strategies. The two subgroups of GDM under this classification system are: 1. Type A-1: Abnormal OGTT (oral glucose tolerance test), but normal blood glucose levels during fasting and two hours after food; (Diet modifications and lifestyle changes are sufficient to control these abnormal blood glucose levels. 2. Type A-2: Abnormal OGTT and abnormal glucose levels during fasting and/or after food; additional anti-diabetic therapies with insulin or other medications are thus needed.

DM that had been prior to conception is also subclassified into several subgroups in this system of White classification: 1. **Type-B**: Onset of DM at 20 years of age or older and duration of less than 10 years. 2. **Type-C**: Onset of DM at 10-19 years of age or duration of 10-19 years. 3. **Type-D**: Onset of DM before the age 10 years or duration more than 20 years. 4. **Type-E**: Overt DM with calcifications in pelvic vessels. 5. **Type-F**: DM with diabetic nephropathy. 6. **Type-R**: DM with diabetic proliferative retinopathy. 7. **Type-RF**: DM with diabetic retinopathy and diabetic nephropathy. 8. **Type-H**: DM with IHD (ischemic heart diseases). 9. **Type-T**: DM with past kidney transplant.

An early age of onset DM or longer-standing DM seems to be with higher risks. There are two other sets of criteria variably used to diagnose GDM, both based on blood sugar levels. Criteria to diagnose GDM, using the 100 gram GTT (Glucose Tolerance Test), in accordance to Carpenter and Coustan:

1. Fasting blood glucose 95 mg/dl. (2). 1 hour 180 mg/dl. (3). 2 hours 155 mg/dl. (4). 3 hour 140 mg/dl.

**Risk factors of GDM**

Classical risk factors for developing gestational diabetes are:

- Polycystic Ovary; a past record of DM or prediabetes,
- Impaired glucose tolerance, or impaired fasting glycaemia; a family history having a first-degree relative with type 2 diabetes; older maternal age (specially if over 35 years);
- Minority groups with increased risk factors include Afro-Americans, Afro-Caribbeans, Native Americans, Hispanics, Pacific Islanders and people originating from South Asia;
- Overweight, obesity or severe obesity augments the risk by a factor of 2.1, 3.6 and 8.6, respectively; a past pregnancy resulting in a child having a macrosomia [high birth weight: >90th centile or >4000 g (8 lbs 12.8 oz)]; past unfavorable obstetric history; other genetic risk factors (at least 10 genes where polymorphisms are associated with an augmented risk of GDM, most notably TCF7L2. Moreover, statistics reveals doubling risk of GDM in smokers. Some studies have looked at more controversial potential risk factors, such as short stature. Nearly 50% women with GDM have no detectable risk factor; thence it is better to screen all women. Typically, pregnant ladies with GDM present with no symptom of DM (requiring universal screening), but some may present with polydipsia, polyuria, tiredness, nausea and vomiting, cystitis, fungal infection and diminished vision.

**Pathophysiology of GDM**

The exact aetiology of GDM is not well known. The hallmark of GDM is increased resistance to insulin. Gestational hormones and other contributors are incriminated to interfere with insulin as it links its receptors. The interference probably occurs at the level of the cell signaling pathway behind the insulin receptor. Since insulin causes glucose entry into cells, insulin resistance prevents glucose entry, resulting in hyperglycaemia. Thus additional insulin is required to counteract this resistance; about 2 times more insulin is produced in GDM than in an otherwise normal gestation.

Insulin resistance is a common in second trimester, which in GDM increases to levels seen in a non-pregnant women with type 2 DM. Women with GDM have an insulin resistance that they cannot compensate for by synthesis in pancreatic -cells. Placental hormones and increased fat of pregnancy meddle insulin resistance here. Cortisol and progesterone are the principal agents, but placental lactogen, prolactin and estradiol have roles too. Other placental hormones, leptin, tumor necrosis factor (TNF) alpha, and resistin are involved in the decrease in insulin resistance during pregnancy, with tumor necrosis factor (TNF) alpha named as the most powerful independent factor of insulin sensitivity in pregnancy. It is unknown why some women are unable to integrate insulin demands and develop GDM; howbeit, several arguments have been put forth, like those in type 2 DM: autoimmune processes, genetic mutations, overweight and obesity, along with other dynamics.

**Complications of GDM**

The two principal risks GDM entailing the baby are growth anomalies and chemical imbalances following birth, which may need hospitalisation a neonatal ICU. Infants born to women with GDM are at risk of being both large for gestational age (macrosomic) if mismanaged GDM, and small for gestational age and intrauterine growth retardation or death even if managed GDM. Macrosomia complicates instrumental deliveries (e.g. forceps, ventouse and caesarean section) or complications during vaginal delivery (like shoulder dystocia). Macrosomia may occur in 12% of normal women as compared to 20% of women with GDM. Neonates born from women with hyperglycaemia are also at an augmented risk of having hypoglycaemia, icterus, erythrocytosis, hypocalcemia and, hypomagnesemia.

Untreated GDM also interferes with maturation, causing dysmature babies who are likely to develop respiratory distress owing to inadequate lung development and maturation and impaired surfactant production. Unlike pre-gestational DM, GDM has not been clearly shown to be an independent risk factor for birth complications. Defects commonly start sometime during the first trimester, whereas GDM gradually starts and is least marked during the first and early second trimester. Owing to compounding and conflicting studies, it is not clearly understood whether ladies with GDM have an increased risk of preeclampsia (PET).
Screening for GDM
A variable number of screening, assessing, diagnostic and evaluative tests have been proposed to detect hyperglycaemia. In one method, an schematic way is where a probable result on a screening test is followed by confirmatory diagnostic test. Alternately, a more defined diagnostic test can be undertaken at the first antenatal visit for a lady with an increased-risk of GDM (as in those with polycystic ovary or acanthosis nigricans). Non-challenging blood glucose tests involve measuring blood glucose in blood samples without giving glucose solutions to the woman. Blood glucose levels are estimated when fasting, 2 hours after a meal, or simply at any random time. In contrast, challenging tests involve drinking a glucose solutions and estimating blood glucose level after that; in DM, they approach a high levels. Artificial flavours may be added to the glucose solution if a woman dislikes simple glucose solution; A women may nauseate during the test, and more so with higher blood glucose levels.

Management
A lady with GDM should be taught to use a kit with a glucose meter and to maintain a diary. The aim of treatment is to remove the risks of GDM for mother and baby. Studies has shown that treating hyperglydaemia correctly results in less fetal complications (like macrosomia) and increased maternal well-being. Unfortunately, therapy of GDM is also accompanied by more babies hospitalised to neonatal wards and more inductions of labour, with no proven decrease in cesarean section rates or perinatal complications. These observations are current and controversial. A repeated Oral Glucose Tolerance Test (OGTT) should be performed out 6 weeks after delivery, to ascertain where the GDM has gone off. Thereafter, regular screening for type 2 DM is suggested. Administration of insulin is indicated, if diet control or Glycemic Index (G.I.) diet, exercise, and oral medications are ineffective to control GDM. The intra-uterine macrosomia can be diagnosed by ultrasonography. Ladies who are being treated with insulin or with a history of stillbirths or with blood pressure are managed like women with overt DM.44

Lifestyle
Advising prior to conception (for example, about preventive folic acid supplements) and multidisciplinary management are of significance to ensure better outcomes. Most ladies can manage their GDM with dietary measures and exercise. Self-monitoring is found quite valuable in most cases. Some ladies will need antidiabetic therapies, most commonly insulin. The prescribed diet must provide adequate calories for pregnancy, ideally 2,000-2,500 kcal with the omission of simple staches. The principal aim of dietary management is to omit high spikes in blood sugar levels. This can be ensured by dividing carbohydrate intake over meals and snacks throughout the day, and giving slow-release carbohydrates-known as the ‘G.I. Diet’. As insulin resistance is highest in mornings, breakfast carbohydrates have to be limited more. Intaking more fiber in diets with whole grains or fruit and vegetables, one can also limit the risk of GDM. Moderately intense regular physical exercise is suggested, though there is no unanimous consensus on the type of physical exercise programs for GDM. Self-monitoring can be implemented using a ‘handheld capillary glucose dosage system’. Compliance with these systems can be variable and inadequate. Target ranges suggested by the ‘Australasian Diabetes in Pregnancy Society’ are as described: fasting capillary blood glucose levels <5.5 mmol/L, 1 hour postprandial capillary blood glucose levels <8.0 mmol/L, 2 hour postprandial blood glucose levels <6.7 mmol/L. Regular blood samples can be estimated to determine HbA1C levels, which give an idea of glucose levels over a prolonged period of time. Researchers suggest a possible advantage of breast-feeding is there to reduce the risk of diabetes and its related risks for both mother and baby.

Medication for GDM
On failing to control hyperglycaemia by exercise, dietary measures and life style modification, or if there is such complications as excessive fetal weight gain, administration of insulin would be essential. This is most desirably rapid-acting soluble insulin administered just before food to prevent post-prandial hyperglycaemia. Utmost caution must be be there to prevent insulin-induced hypoglucaemia. Thus insulin therapy should be followed correctly; more injections may result in better glycaemic control but that needs more tasks. However there is no consensus of getting very big benefits. There are some oral hypoglycaemic agents that are proven as safe in pregnancy, or at least, are less harmful to the growing fetus than inadequately controlled GDM. Oral metformin is definitely superior to oral glybu ride. Oral metformin and parenteral insulin in together may be superior to insulin alone. Oral metformin therapy for polycystic ovarian syndrome during pregnancy has been found to decrease blood levels in GDM. About 50% of women did not have adequate glycaemic control with metformin alone and they were given supplemental insulin therapy. When compared to those treated with only insulin, they needed less insulin, and they had less weight gain. With having no long-term studies on children of ladies treated with the drug, here remains a probability of long-term complications from metformin therapy. Babies born to women treated with metformin have been found to gain less visceral fat, making them less prone to insulin resistance in their later life.

Prevention of GDM
Frankly speaking, stoppage of smoking might decrease the risk of GDM amongst smokers. Physical exercise alone has no proven effect for primary prevention of GDM in randomized controlled trials. It may be proved effective for tertiary prevention in women who had already developed GDM.

Prognosis
GDM generally resolves once the baby is born. Based on multiple studies, the chance of developing GDM in a second pregnancy, if one had GDM in first pregnancy, is around 55%, ranging between 30% to 83%, depending on genetic and ethnic backgrounds. A second pregnancy within 1 year of the immediate past pregnancy has a higher rate of relapse. Women diagnosed with GDM have an augmented risk of developing DM in future. The risk is highest in ladies who needed insulin treatment and who had antibodies associated with diabetes (such as antibodies against glutamate decarboxylase, islet cells and/or insulinoma antigen-2),
ladies with more than two past pregnancies, and ladies who were obese (in order of importance). Ladies who used insulin to manage GDM have a 50% risk of developing DM by the next five years. Depending on the demographic samples studied, the assessment criteria and the length of follow-up, the risks can vary profoundly. The risks appear to be highest in the first 5 years, reaching a plateau there after. Children of ladies with GDM have an augmented risk for childhood and adult obesity and an augmented risk of glucose intolerance and type 2 DM later in life. This risk is linked to higher values of maternal glucose. It is now not clear how much genetic and environmental variables each contribute to this risk, and if treatment of GDM can influence this outcome.

References


