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A Brief Review on Gestational Diabetes Mellitus

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Abstract: *Gestational Diabetes Mellitus(GDM) or impaired glucose tolerance is the most common complication of pregnancy. It is first diagnosed during pregnancy, affects ~14 % of pregnant women (135,000 women) per year in the US. It has many harmful implications for the woman, and foetus. The understanding of risk factors, pathophysiological factors and biomarkers helps in identifying the women at risk of developing GDM.Initial management includes blood glucose monitoring, Medical Nutritional Therapy (MNT) and exercise. Even if the glucose levels remain above target levels, then pharmacological therapy with insulin and metformin has to be started. This review mainlyfocuses on the epidemiology,etiopathogenesis,risk factors,clinical manifestations,screening, diagnostic criteria, treatment as well as role of pharmacist inthe management of GDM.*

Keywords*: Gestational Diabetes Mellitus, Medical Nutritional Therapy, Hypertension (HTN).*

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I. Introduction

GDM or impaired glucose tolerance,originally identified by O`Sullivan and Mahan in 1964 is a transient condition that usually develops during late second trimester and disappears instantly after delivery[1, 2].The definition of GDM also includes the undiagnosed cases of T2DM in early pregnancy andtrue GDM that develops later[3].It is a serious pregnancy complication affecting approximately 14 % of all pregnancies or 1, 35,000 women per year in the US[4].The prevalence of GDM is increasing risk of developing short and longterm complications for both mother and foetus[5].Hence the diagnosis of GDM is necessary to identify the pregnant women at risk of perinatal morbidity,long term obesity and glucose intolerance in offspring[6].

II. Epidemiology

The exact prevalence of GDM remains unknown,however some studies revealed that the incidence of GDM has doubled over the past 6-8 years and is increasing in parallel with advanced maternal age and obesity[3, 7].As per the International Association of Diabetes and Pregnancy Study Groups (IADPSG's), International Diabetes Federation (IDF) estimated that 18 million births were affected worldwide by GDM in 2017[8].The prevalence of women born in Asian countries range from 3%-21.2%, however in 3/4th of the African &Asian communitiesand in2/3rd of the pacific populations> 50% of GDM cases remains undiagnosed[9,10]. It was found that Asian women are at higher risk than the United States Caucasian or Australian descent as per many studies[9]. The prevalence was found high in Zuni Indian women (14.3%); Chinese women,Indian-born women in Melbourne,Australia(13.9% and 15% respectively) and Asian women in Illawara,Australia(11.9%) and the relative risk was higher in black [1.81,95%,confidence interval(CI)] and Hispanic(2.45,95% CI) women than in white women.A recent study revealed that Asian women are likely to have GDM than White woman (31.7 % and 14%, respectively,P = 0.002),without considering their low BMI[11]. Dietary interventions with life style modifications has shown to reduce the prevalence of GDM[12].

III. Etiopathogenesis

The major etiological factor of GDM i.e. Insulin resistance appears mainly due to increased maternal adiposity and placental derived hormones due to their insulin- desensitizing effects[6].Adiposity is associated with increased free fatty acids and hepatic glucose production leading to severe insulin resistance.Even though during gestation about 200 -250% increase in insulin secretion is seen inorder to maintain normal glycaemic levels , hormones released by placenta plays a major contributing factor in disturbing the maternal physiology to achieve insulin resistance[7]. Placental hormones such as Progesterone, cortisol, prolactin, Human Placental Lactogen (hPL),Human placental growth hormone(hPGH) and Human chorionic gonadotropin (hCG) releasing hormone are implicated in the insulin resistance of pregnancy[3]. hPL is found to be the major implicating factor of peripheral insulin resistance in humans as it risesup to 30 fold and make insulin release from β – cells of pancreas during gestation. Another hormone namely hPGH raises 6 to 8 fold and replaces pituitary growth

hormone in maternal circulation by nearly 20 weeks of gestation causing overexpression of itself leading to severe peripheral insulin resistance[7].Hyperlipidaemia is another factor showing detrimental effects by expression of cytokines and resulting in insulin resistance[14].Not only insulin resistance but also β – cell dysfunction are usually seen in GDM, thus both β – cell impairment and tissue resistance are important components of the pathophysiology of GDM. . In pregnancy conditions the hallmark of normal glucose regulation is the plasticity of β cell function in the face of progressive insulin resistance[6]. The actual cause of pancreatic β cell dysfunction in GDM is unknown, but three categories are identified.These include autoimmune, genetic abnormalities in insulin secretion and chronic insulin resistance. In GDM, insulin resistance exists in two forms;(a)late pregnancy leading to physiological insulin resistance and (b)pre-pregnancy chronic insulin resistance with exacerbations by the physiological changes.Monogenicforms of diabetes i.e. Maturity Onset Diabetes of the Young(MODY;autosomal dominant inheritance) and mitochondrial diabetes (maternal inheritance) accounts for about <5% cases of GDM[13].Neurohormonal networks contribute to GDM by influencing adiposity & glucose utilization.Important regulators of neurohormonal networks are adipokines, cell signalling proteins that are secreting primarilyby adipose tissue.These include leptin and adiponectin. Leptin, a protein hormone produced by placenta related to the bulk of fat stores shows elevated during pregnancy leading to placental insulin resistance contributing to hyperleptinemia, a condition that facilitate amino acid transport across the placenta leading to foetal macrosomia.Adiponectin is an adipocytokine polypeptide that has anti-inflammatory properties and insulin sensitizing actions.The role of adiponectin in GDM is not clear.Evidence suggests that it impairs insulin sensitizing andamino acid transport across placenta,limiting the growth of foetus and it is associated with maternal glucose intolerance and foetal macrosomia[8].

IV. Risk Factors[3,13,16]

The understanding of various risk factors is an important factor as it helps in identifying the women at risk of developing GDM, so as to provide adequate management of the condition. Different risk factors linked with GDM are:

Obesity with BMI > 30kg/m^2
Previous history of macrosomic baby ≥ 4.5 kgor > 9 lb.
Previous history of GDM
Family history of diabetes (1stdegree family member with diabetes or a sister with GDM)
Ethnic background(African – American; Latino, Native American;Asian – American, Pacific Islander)
Age ≥ 40 years
PolyCystic Ovarian Syndrome (PCOS)
Lack of physical activity
Medications: Corticosteroids, Antipsychotics
Previous history of cardiovascular disease like Hypertension (HTN)
Signs of insulin resistance such as **acanthosis nigricans**
HbA1c ≥ 5.7% and previous impaired glucose tolerance (IGT) or impaired fasting glycaemia
HDL – C < 0.90 mmol/L and /or TG > 2.82mmol/L
Glycosuria
Previous adverse pregnancy outcomes such as polyhydramnios, or large foetus in present pregnancy
Increased maternal weight
Essential HTN or gestational HTN and multiple pregnancies
High parity
Short stature
α – Thalassemia trait

Low risk factors such as age < 25 years, low risk ethnicity, no diabetes in first-degree relatives, normal pre-pregnancy weight and pregnancy weight gain, no personal history of abnormal glucose levels and no prior poor obstetrical outcomes are also observed to play a role in GDM.

V. Complications[15, 17,18]

GDM has detrimental effects in mother,unborn foetus and infant.However control of blood glucose has shown to reduce these complications.The maternal clinical outcome associated with GDM includesincreased risk of caesarean delivery, preterm delivery, intrauterine growth restriction, abortion, pre-eclampsia, recurrent GDM in subsequent pregnancies, Type 2 diabetes, cardiovascular disease, uterine atony, and post-partum haemorrhage.The foetal clinical outcome associated with GDM includesmacrosomia/large for gestational age, hypoglycaemia, shoulder dystocia, neonatal hypoglycaemia, increased admission to Neonatal Intensive Care Unit (NICU), hyperbilirubinaemia, neonatal death, still birth, bone fracture, nerve palsy, jaundice requiring phototherapy, type 2 diabetes, infant respiratory death syndrome, congenital malformation and obesity.

VI. Clinical Manifestations[12, 19]

GDM patients usually remain asymptomatic, however the classic triad of symptoms such as polyphagia, polydipsia and polyuria are common and are not diagnosed without screening tests.But the patients may manifest with past history of complications of diabetes such as chronic hypertension, renal disease and obesity.

VII. Screening & Diagnostic Criteria

O'Sullivan in 1960's proposed a diagnostic criteria for the interpretation of Oral Glucose Tolerance Tests(OGTT's) during pregnancy where pregnant women undergo 3 hour,100-gms OGTT with glucose values exceeding 2 standard deviations above the mean which were now accepted to modern methods for measuring blood glucose as per the modern definition of GDM[6]. TheAmerican Diabetes Association's (ADA's) criteria for diagnosing GDM is also based on O'Sullivan where Glucose cut point ≥ 140mg/dL(7.8mmol/L) is considered as threshold for GDM diagnosis[12]. The first test for GDM must be done during first visit after conceiving whereas the second is recommended during 24-28 weeks of pregnancy.At least four weeks gap should be present between the two tests. Single step testing using 75gms oral glucose and measuring the blood glucose levels with plasma standardized glucometer after 2 hours irrespective of the last mealis done. Blood glucose level ≥ 140 mg/dL is taken as cut off for diagnosis of GDM[18].

VIII. Management Of Gdm

The management of GDM aims at normal maternal glycaemia where initial management is by Medical Nutritional Therapy(MNT),daily exercise and by adjusted doses of insulin [19].

Blood glucose monitoring[2]:The measurement of blood glucose should be done 4 times a day i.e. fasting blood glucose (after waking up) and one or two hours post meal (after first bite of meal).The glycaemictargets for women with GDM are as follows:

For Fasting blood glucoselevels ≤5 – 5.3mmol/L or 90-95 mg/dL

For one hour post meal ≤ 7.8mmol/l or 140 mg/dL

For two hour post meal ≤ 6.7mmol/l or 120 mg/dL

Exercise:Most ideal type of exercise is unknown, but physical exercise to walk fast after the main meals for 30 minutes/day for 2 weeks is recommended[12]. Brisk walkingor arm exercises at least for 10 minutes while seated in the chair helps to reduce raised post prandial glucose levels[2].

Medical nutritional therapy(MNT):As soon as GDM diagnosis is made, such pregnant women has to get medical nutritional therapy which primarily involves a carbohydrate controlled balanced meal plan that promotes optimal nutrition for maternal and foetal health and adequate energy for appropriate weight gain[18]. It includes limiting the calories and nutrients as a normalization strategy. The quality and quantity of MNT has shown an important role in the development of embryos[12].MNT has shown to maintain desired glycaemic levels in about 80-90% of GDM cases[2].

Pharmacological interventions:

If the glycaemic goals are not achieved with MNT and exercise, then pharmacological therapy with antihyperglycaemics must be initiated[2].

Table 1: Treatment of GDM

S.No.	Drug Name	Dose	Frequency
1.	Insulin	Initial dose: 0.2 units/kg Maximum dose: 20 units/kg	OD / BD
2.	Glibenclamide	Initial dose : 2.5 mg Maximum dose: 20 mg	BD
3.	Metformin	Initial dose: 500 mg Maximum dose: 2500 mg	OD / BD

Insulin therapy:The standard therapy for women diagnosed with GDM requiring drug treatment is insulin and it can be started at any time during pregnancy to manage GDM[18, 20].Human insulin is the commercially available least immunogenic preparation,but rapid acting insulin analogues include lispro and aspart have been investigated in pregnancy[13].The dose and dosage regimen is based on the severity of hyperglycaemia; initially 0.2 units/kg Neutral protamine hagedorn(NPH) – insulin for women having fasting hyperglycaemia is given; whereas only prandial insulin is given for other woman who has to control elevated post-meal blood glucose[3]. It was found that when insulin and glibenclamide used in combination, it has lower the dose of insulin compared with insulin monotherapy[21]. Dose**:** For non-obese women**:**0.8 U/Kg bed time or both before breakfast and at bed time.For obese women and overweight**:**0.9-1.0u/kg. Available doses: 4, 6, 8 units SC;Max dose: 20units/day[18].

Non-insulin anti hyperglycaemic agent therapy:In patients whose glycaemic control is not achieved with MNT and exercise, they are advised to take glibenclamide as a suitable alternate to insulin therapy.Oral hypoglycaemic agents such as glibenclamide and metformin are preferred over insulin therapy as they are less expensive, less invasive and enhance patient compliance whereas insulin is more expensive, more invasive, involve daily injections and less patient compliance[2].

Glibenclamide:Starting dose of 2.5mg must be initiated in the morning, if response is not seen dose must be increased to 5mg in the morning,then add in the evening time when advisable.If response is not observed then 5mg should be added in to the morning and then to the evening doses upto a total dose of 20mg. Antihyperglyaemic agents cross the placenta and stimulate foetal hyperinsulinism, except glibenclamide[2].

Metformin:If MNT fails metformin can be started at 20 weeks of gestation with 500mg dose once daily taken with food and increase to a maximum dose of 2500mg/day given in divided doses with meals[2,8]. Side effects such as hypoglycaemia and weight gain are less compared with insulin therapy[18].

IX. Role Of Pharmacist

Pharmacist is an important member of the health care team and plays animportant role in the management of GDM with his/her knowledge of pharmacotherapy and experiences in management of medication. Pharmacist along with health care providers is able to provide appropriate services at each stage of pregnancy and follow-up[22]. Clinical pharmacist involvement in medication therapy management has shown to improve patient's glycaemic levels, maintain weight and blood pressure goals[23].

Life style modifications[18]:Apart from medication, it is very important to make necessary life style modifications for better health outcome.

- Have Carbohydrate foods(wheat, ragi, rice etc.) spread as four to fivesmall meals and 2-3 snacks each day instead oftaking three large meals.
- The aim should be 2-3 carbohydrate serves(1 serve =approx.15gms) at each major meal and 1-2 carbohydrate serves at each snack.
- Saturated fat (sources-palm oil,red meat etc.) intake should be less than 10 % of total calories and dietary cholesterol should be less than 300mg/dl.In obese and overweight patients a lower-fat diet overall can help slow the rate of weight gain.
- Prefer low fat dairy products in place of whole milk.
- Avoid fried foods
- Choose fresh fruits,salads,baked and steamed food items instead of high fat snacks such as cakes,biscuits,chocolates and pastries
- Prefer fibre and protein rich food in meals and additionally 23gms/day of protein is required during pregnancy to allow for foetal growth.
- Nearly three servings of protein foods(milk, egg, fish, chicken, pulses, nuts etc.) are needed to meet the increased biological demand.
- High fibre foods especially soluble fibre(flax seed, oat, legumes etc.) may help control blood sugar by delaying gastric emptying, retarding the entry of glucose into the blood stream and by lessening the postprandial rise in blood sugar.

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