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Clinical Review on Gestational Diabetes Mellitus

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ABSTRACT
Gestational diabetes mellitus (GDM), which is defined as glucose intolerance of various degree with onset of observation during pregnancy.The prevalence of GDM varies greatly over the world, from 1 to 28%, depending on population traits, screening procedures, and diagnostic standards. The primary hormone associated with elevated insulin resistance in GDM is human placental lactogen. Growth hormone, prolactin, corticotropin-releasing hormone, and progesterone are additional hormones linked to the onset of this condition. Various pathophysiological condition which leads to gestational diabetes mellitus are insulin resistance, inflammatory cytokines, C – reactive protein, Interlukin, tumor necrosis factor – alpha, letin, adipokines, resistin, visfatin, adiponectin. The ADA recommends nutrition counselling and a diet that adequately meets the needs of pregnancy while limiting carbohydrates to 35 to 40% of daily calories. Insulin used in gestational diabetes mellitus are rapid acting, short acting, intermediate acting and long acting insulin. Oral hypoglycemic agents include metformin and glyburide widely used in gestational diabetes mellitus.

KEYWORD : Gestational diabetes mellitus, insulin resistance, dietary fibre, metformin.

I. INTRODUCTION :

One of the most prevalent clinical consequences of pregnancy is gestational diabetes mellitus (GDM), which is defined as glucose intolerance of various degree with onset or first observation during pregnancy [1]. The majority of overweight or obese women already have a higher chance of having T2DM; this group of patients, particularly when pregnant later in life, have a higher risk of acquiring GDM. Additionally, there is a significant link between the rise in type 2 diabetes mellitus and the prevalence of GDM (T2DM) [2]. Up to 90% of pregnancies affected by diabetes can be attributed to GDM, which is the most important cause of diabetes during pregnancy . In the five to ten years following pregnancy, women with GDM had a 40–60% chance of acquiring diabetes mellitus [3]. The national and international guidelines' current diagnostic and management recommendations are mostly concentrated on short-term hazards during pregnancy and delivery[4]. GDM has been linked to poor pregnancy outcomes for both women and their offspring [5]. While good prenatal care and favourable lifestyle adjustments might help reduce the poor maternal outcomes in patients with GDM[6]. According to the American Diabetes Association (ADA),Gestational diabetes mellitus (GDM) is diabetes that was not immediately apparent before becoming pregnant and was discovered in the second or third trimester[7]. Medical nutrition therapy, along with weight management and exercise, is the first line of treatment for GDM [8]. There have been reports of a variety of dietary practices, such as low glycemic index (GI), caloric restriction, an increase or decrease in carbohydrates, and changes to the kind or amount of fat or protein[9]. Since postprandial glucose levels have a greater connection with foetal macrosomia than fasting plasma glucose levels, controlling postprandial glucose levels may be more crucial[10]. Insulin is the ready treatment for pregnant women with gestational diabetes who need medication[11]. The use of insulin is linked to both weight gain and hypoglycemia. Insulin may not be as advantageous as the use of safe and efficient oral medications.For pregnant women with gestational diabetes mellitus, oral metformin makes sense. It enhances insulin sensitivity without causing weight gain or hypoglycemia, most likely by activating AMP kinase[12]. Metformin therapy minimized the chance of developing diabetes by lowering body weight, improving other metabolic variables, and reducing blood sugar levels[13]. Currently, individuals with type 2 diabetes in the United States have access to five classes of oral medications, each of which improves glycemic control through a different mechanism of action[14]. Children born to GDM-affected mothers are more likely to experience macrosomia, newbornhypoglycemia, hyperbilirubinemia, neonatal respiratory distress syndrome, obesity in

International Journal of Pharmaceutical Research and Applications
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childhood, and adult-onset cardiovascular disease[15]. In addition to juvenile obesity, intrauterine exposure to gestational diabetes mellitus (GDM) or preexisting diabetes in the mother is linked to a higher risk for impaired glucose metabolism in the offspring[16].

EPIDEMIOLOGY :

The prevalence of GDM varies greatly over the world, from 1 to 28%, depending on population traits, screening procedures, and diagnostic standards[17]. In 2013, 6 million pregnant women in India have hyperglycemia of some kind, with 90% having GDM[18].In 2017, GDM affected 14% of the world's population, with rates as low as 9% in Africa, 12.6% in North America, and 21% in Asia[15]. Globally, almost 1 in 6 pregnancies are impacted by the mother's failure to maintain normoglycemia, which leads to gestational diabetes mellitus due to a combination of insulin resistance and inadequate insulin production (GDM)[19]. According to the Malaysian National Health and Morbidity Survey (NHMS), the prevalence of overweight and obesity (BMI 25.0 kg/m2) among females under the age of 18 increased by 26.6% between 1996 and 2015[20]. Overall, 204 million women were afflicted by GDM in 2017, and by 2045, that number is expected to rise to 308 million, largely in developing nations[22].

ETIOLOGY :

The delayed or dysfunctional response of the beta cells to glycemic levels in the pancreas and the marked insulin resistance brought on by placental hormone release are thought to be the two causes of gestational diabetes[23]. The primary hormone associated with elevated insulin resistance in GDM is human placental lactogen. Growth hormone, prolactin, corticotropin-releasing hormone, and progesterone are additional hormones linked to the onset of this condition. These hormones help to promote insulin resistance and hyperglycemia during pregnancy[22].

RISK FACTORS OF GESTATION DIABETES MELLITUS :

There are various risk factors connected to the emergence of GDM. Obesity, advanced maternal age, prior GDM, significant family history of diabetes, belonging to an ethnic group with a high prevalence of T2DM, polycystic ovarian syndrome, and chronic glucosuria are the most frequent risk factors. Other risk factors for GDM include a history of having large babies (birth weight >4000 g), recurrent abortions, unexplained stillbirths, essential hypertension in the past, or pregnancy-related hypertension[23].

PATHOPHYSIOLOGY OF GESTATION DIABETES :

GDM is typically brought by ß - cell malfunction in the context of ongoing pregnancy insulin resistance[21]. Various pathophysiological condition which leads to gestational diabetes mellitus are ,

Insulin resistance [IR]

The placenta secretes more IR hormones during pregnancy, including progesterone, oestrogen, and human placental prolactin, which contributes to the rise in IR. Additionally, several adipocytokines (including adiponectin, leptin, etc.) produced by adipose tissue are also involved in IR[25].

Inflammatory cytokines

When pregnancies affected by GDM, there are elevated levels of pro-inflammatory markers including C-reactive protein (CRP), interleukin-6 (IL-6) and TNF-, as well as anti-inflammatory markers like IL-4 and IL-10, in the bloodstream[26].

C-Reactive protein [CRP]

Obesity and type 2 diabetes have both been linked to CRP. It is also widely known that obesity is linked to inflammation, which heightens the risk of developing insulin resistance. Increased first-trimester CRP levels are linked to an increased risk of GD.

Interleukin [IL]

A group of cells produce the inflammatory cytokine interleukin. There were around 38 different types of interleukins, numbered from IL-1 to IL-38. Interleukins such IL-1, IL-6, IL-8, and IL-10 were assumed to play a role in the emergence of GDM.IL-6 release during the early stages of diabetes can encourage insulin secretion, which causes hyperinsulinemia. When IL-6 levels rise to a certain point, it will prevent the release of insulin and harm islet cells, worsening the illness [27].

Tumor necrosis factor [TNF-α]

TNF-α reduces the efficiency of beta cells and insulin signalling, which may directly cause GDM. Additionally, due to oxidative stress and inflammatory alterations brought on by hyperglycemia, such as those seen in GDM, higher

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levels of TNF-α and IL-6 are present.Despite the fact that elevated circulating TNF- levels have been linked to insulin resistance in obesity, ageing, sepsis, muscle deterioration, and preeclamptic pregnancy, studies of a shift in levels during normal pregnancy and GDM have been scarce[28].

Leptin

Preoptic area (POA), arcuate nucleus (ARC), lateral hypothalamus, ventromedial hypothalamus, and dorsomedial hypothalamus are all areas of the hypothalamus where leptin and leptin receptors are strongly expressed (DMH).Leptin has the potential to function as a metabolic switch that links the body's utrient situation to demanding metabolic processes. This is crucial during pregnancy because leptin not only regulates the mother's satiety and energy homeostasis.

The pathophysiology of GDM may be significantly affected by proinflammatoryleptin activities. Collectively, since hepatic insulin resistance and central leptin resistance are both caused by hypothalamic inflammation[29].

Adipokines

These are a collection of protein hormones and cytokines that are secreted by adipocytes, immune system cells, fibroblasts, and vascular cells and control the local and systemic activity of the organism by contributing to insulin sensitivity, appetite, glucose and lipid metabolism, immune response, and inflammation.The production of adipokines is dysregulated, which is a feature of obesity and disorders associated with obesity.

Adipokine profiles are directly correlated with excess body weight, the proportion of hormonally active adipose tissue, and the presence or absence of inflammation[30]. In a healthy pregnancy, adipokines increase insulin resistance; nevertheless, it is unclear how exactly adipokines contribute to the aetiology of GDM[31].

Resistin

In addition to monocytes and macrophages, adipocytes also express the hormone resistin.It is expressed in the human placenta during a healthy pregnancy, and pregnant women have much greater plasma resistin levels than healthy controls. It increases throughout the third trimester and might control the pregnancy's energy metabolism. Its levels have either been reported to be raised or lowered in GDM.Resistin is released more readily when there is a low concentration of insulin than when there is a high concentration of insulin[32].

Visfatin

Increased circulation amounts of visfatin, which activates the insulin receptor, have been observed in insulin-resistant conditions such as obesity and type 2 diabetes mellitus.Maternal serum adiponectin levels are decreased in gestational diabetes mellitus (GDM), although visfatin concentrations have been shown to either increase or decrease[33].

According to reports, visfatin mimics the activities of insulin by engaging the same receptor to activate the insulin signal transduction pathway. Visfatin levels in the body are acutely regulated by glucose and insulin and are higher in people with diabetes, obesity, and insulin resistance[34].

Adiponectin

Adiponectin is probably involved in the development of type 2 diabetes and insulin resistance[35]. Adiponectin is a protein generated from adipose tissue that fights inflammation and insulin resistance[36]. Through AMP-activated protein kinase, it increases the absorption of glucose in skeletal muscle and decreases the synthesis of glucose in the liver.

According to several studies, circulating adiponectin levels are lower in GDM patients compared to pregnant controls, regardless of prepregnancy body mass index (BMI) and insulin sensitivity.

In placental tissue, adiponectin mRNA expression is decreased in GDM-afflicted women.Low levels of adiponectin may make insulin resistance worse because of its impact on insulin sensitivity. Additionally, hyperinsulinaemia found in GDM may result in a considerable drop in plasma adiponectin since insulin has the ability to reduce plasma adiponectinconcentrations[37].

Other adipokines

Retinol binding protein :

Hepatocytes and adipocytes produce retinol binding protein-4, a protein that transports retinol through the blood. RBP-4 levels have been found to be higher in a number of metabolic disorders, including insulin resistance, polycystic ovarian syndrome, obesity, and cardiovascular disease. RBP-4 is also thought to increase the expression of gluconeogenesis-related enzymes in hepatocytes and disrupt insulin signalling pathways in skeletal muscle[38].

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CLINICAL FEATURES :

Due to the chronic nature of the condition, many people ignore the signs and symptoms of diabetes. Because the effects of hyperglycemia take time to appear, unlike many other diseases, many do not view this as a severe issue. People are unaware that damage can begin years before symptoms are visibly present. This is problematic because identifying early signs might aid in preventing vascular problems and quickly bringing the condition under control.

Type 2 diabetes is asymptomatic in its early stages, thus it's crucial that individuals are informed about its warning signals[42].

- Unexplained weight loss
- Frequent fatigue
- Irritability
- Repeated infection especially in the
  - Genital area
  - Urinary tract
  - Skin
  - Oral cavity
  - Delayed wound healing
- Dry mouth
- Burning , pain , numbness on feet
- Itching
- Decreased vision
- Reactive hypoglycaemia

DIAGNOSIS :

A fasting plasma glucose test can be used to identify GDM (FPG)>126 mg/dl concentration on two distinct occasionsor a blood glucose level of >200 mg/dl at randomat two different times. HbA1c must be detected during pregnancies, but is frequently normal in GDMespecially during the first trimester [40]. Insulin resistance rises throughout the second trimester and glucose levels rise in women who are unable to make enough insulin to adopt this resistance, screening for GDM is typically done at 24-28 weeks of gestation .

<u>2015 Criteria from the American Diabetes Association (ADA) :</u>

The ADA has two ways for diagnosing GDM in women who don't already have diabetes:

"One Step" Procedure: Performing an OGTT in the morning following an overnight fast of less than eight hours, 75g OGTT with fasting plasma glucose (PG) measurements at 24-28 weeks in women without previous diabetes, and diagnosing GDM if PG readings equal or exceed:

- Fasting serum glucose of 92mg/dl (5.1mmol/l)
- 1-hour serum glucose of 180mg/dl (10.0mmol/l)
- 2-hour serum glucose of 153mg/dl (8.5mmol/l)

The "Two Step" Procedure entails doing a 50 gramme glucose challenge test regardless of the last meal at 24-28 weeks in women who do not have diabetes as long as the PG at one hour after the load is less than 140 mg/dl (7.8 mmol/l) before moving on to a 100 gramme glucose OGTT. Step two is carried out while the patient is fasting. When two or more PG levels equal or exceed:

- Fasting serum glucose of 95 mg/dl or 105 mg/dl (5.5/5.8 mmol/l)
- 1-hour serum glucose of 180 mg/dl or 190 mg/dl (10.0 / 10.6 mmol/l)
- 2-hour serum glucose of 155 mg/dl or 165mg/dl (8.6 / 9.2 mmol/l)
- 3-hour serum glucose of 140 mg/dl or 145 mg/dl (7.8 /8.0 mmol/l)[41].

MANAGEMENT OF GESTATIONAL DIABETES MELLITUS :

Glycemic control is the core of GDM management. Lifestyle measures, such as regular exercise and medical nutrition therapy, are the first line of treatment for GDM. To ensure that the glycemic targets are met, patients must periodically check their blood glucose levels at home. With these measurements, medical therapy should be started if the glycemic targets are not met[25].

Diet

The ADA recommends nutrition counselling (preferably with a registered dietitian) and a diet that adequately meets the needs of pregnancy while limiting carbohydrates to 35 to 40% of daily calories. Caloric restriction should be used with caution because two studies have found a link between elevated maternal serum ketone levels and lower psychomotor development and IQ at three to nine years of age in the offspring of diabetic mothers[43].

Dietary fibre and glycemic index of foods

Dietary fibre consumption has been positively linked to GDM. Consumption of dietary fibre, especially that found in cereal and fruit, was inversely and highly correlated with the risk of developing type 2 diabetes. Each 10 g/d increase in total fibre intake was linked to a 26% reduction in risk; each 5 g/d increase in the fibre in cereal and fruit was linked to 23% and 26% reductions in the risk of developing type 2 diabetes, respectively. Increased dietary fibre consumption reduces hunger, which in turn lowers overall energy

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consumption. Additionally, it postpones gastric emptying and reduces glucose absorption, which results in reduced glucose absorption, glucose homeostasis, and a slower rise in insulin levels.

Exercise

Due to concerns about the foetus and mother, physical activity during pregnancy was discouraged, but studies have shown that it has no negative impact on pregnant women who engage in mild to moderate physical activity. Daily stair climbing was linked to a 49%-78% lower chance of developing GDM as compared to not stair climbing[44].

There is a lot of proof that regular exercise improves glucose management in persons with type 2 diabetes through increasing insulin sensitivity, promoting weight loss, and other benefits. It has been investigated in a number of small studies if regular exercise is also advantageous in the treatment of GDM. This small quantity of exercise reduced fasting glucose levels, glucose responses to a glucose challenge, and the HbA1c level.

- Short term effect of physical activity :

In healthy pregnant women, 30 minutes of treadmill exercise lowers blood glucose and insulin levels. Women who are susceptible to GDM Following an oral glucose tolerance test, 20 minutes of moderate-intensity cycling decreased blood glucose excursions and insulin levels one to two hours after glucose administration.

- Long term effect of physical activity :

The longer-term benefits of physical exercise are more varied since they could have a direct impact on glucose metabolism or they could have an impact on pregnancy outcomes, where glucose metabolism is a factor.

- Societal interventions :

The association between neighbourhood walkability and factors associated with GDM was recently discussed in a single research. In general, increased neighbourhood walkability was linked to lower pre-pregnancy BMI and higher levels of physical activity.

Insulin therapy in GDM

When dietary measures alone are unable to meet treatment goals, insulin is then needed. To manage post-prandialhyperglycemia, fast-acting insulin is given during the meal, and if there is fasting hyperglycemia, basal insulin is given after bedtime. In the third trimester of pregnancy, the required insulin dosage typically rises gradually. Insulin needs may decrease as the pregnancy nears its conclusion. This could be a precursor to placental insufficiency[45].

Type of insulin used during pregnancy :

- Rapid acting insulin :

Commonly used rapid-acting insulin analogues include glulisine, aspart, and insulin lispro. Within 15 minutes or less of administration, they start to work. Maximum activity lasts between three and six hours, with peak concentrations occurring between 30 and 80 minutes thereafter.

- Short acting insulin :

Regular human insulin has a maximum duration of action of five to twelve hours, with an onset of action between 30 and 60 minutes and a time to peak concentration of 90 to 120 minutes.

- Intermediate –acting insulin :

Unbiased protamine is a longer-acting version of conventional human insulin, hagedorn insulin, also known as isophane insulin, has an onset of action of 60 to 120 minutes and a time to peak action of 240 to 480 minutes. Action may last up to 16 to 18 hours at its longest.

- Long acting insulin :

This analogue of insulin, known as insulin detemir, begins to work 60 to 120 minutes after delivery and continues to work for 18 to 20 hours. There is no action's zenith.The analogue of insulin known as insulin glargine takes effect 60 to 120 minutes after delivery and remains active for 24 hours. There is no action's zenith.

Rapid-acting or short-acting insulin is combined with intermediate-acting insulin in pre-mixed insulin offers a quicker onset of effect, a later peak, and a longer duration of activity[46].

Non insulin antihyperglycemic agent therapy.

Despite being the gold standard for managing GDM, insulin is costly, intrusive, requires daily injections, and patient compliance is frequently poor. Oral hypoglycemic medications, on the other hand, are less expensive, less invasive, and more acceptable. They may also improve patient compliance and produce results that are comparable to those of insulin during pregnancy.

Since IR and comparatively reduced insulin secretion are features of GDM, a therapy with non-insulin antihyperglycemic drugs may be of potential relevance. Congenital abnormalities and foetal hypoglycemia are the main worries associated with using non-insulin

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antihyperglycemic medications during pregnancy. The majority of the information on the safety of non-insulin antihyperglycemic medications during pregnancy centres on glyburide and metformin. Metformin and glyburide have been used throughout pregnancy for years without any known negative effects on the foetus in Europe and South Africa. Except for glyburide, the majority of oral antihyperglycemic medications penetrate the placenta and induce foetal hyperinsulinism.

Metformin

The other oral hypoglycemic medication being evaluated as an alternative to insulin for the treatment of people with GDM is metformin. Given that it has no risk of maternal hypoglycemia or weight gain, metformin may be a more sensible choice for GDM patients than insulin. Since metformin is a category B medicine, there is no indication that it is hazardous to animals or teratogenic to humans or foetuses. However, studies have demonstrated that metformin crosses the placenta without any problems.Metformin is administered at a starting dose of 500 mg, and the dosage can be gradually increased up to 2500 mg, depending on how well it is tolerated and the level of maternal blood sugar. Insulin should be started if diabetic control is not obtained.

Glyburide (glibenclamide)

Glyburide treatment for GDM has more clinical experience. Glyburide was considerably less likely than insulin to cause hypoglycemia episodes, achieve targeted glucose levels, or have a positive pregnancy outcome.If the diagnosis is obtained prior to 25 weeks of pregnancy and in obese patients. Pregnant women are advised to begin taking 2.5 mg of glyburide in the morning. Increase glyburide to 5 mg in the morning, then add 5 mg in the evening as needed if glycemic control is not attained.

The morning and evening doses should each contain 5 mg, for a total of 20 mg, if the desired level of glycemic control is still not attained[24].

Preventive measures of GDM

For the prevention and treatment of GDM, lifestyle treatments, like as dietary changes and exercise, are effective and first-line preventive measures. Additionally, it can slow the progression of high-risk people to GDM. All pregnant women are urged to maintain healthy eating and lifestyle choices.To prevent and manage GDM, exercise is a non-invasive therapy approach.

PATIENT EDUCATION :

It is crucial to inform women with GDM (as well as their spouses) about the condition and how to manage it.Understanding of the following by the patient is necessary for compliance with the treatment plan,

- Dietary and physical activity suggestions
- monitoring one's own blood sugar
- Adjusting insulin dosages and self-administration of insulin
- Diagnosis and management of hypoglycemia (patient and family members)
- Incorporate safe physical activity (such as arm exercises or brisk walking).
- the creation of stress-reduction and denial-coping strategies[47].

Complication in GDM

Short-term risk :

Specifically related to foetal macrosomia and polyhydramnios, women with GDM are more likely to require obstetric interventions such as IOL, caesarean sections, and problems during birth such as perineal lacerations and uterine rupture.

Anomalies in glucose metabolism disrupt trophoblast invasion, impairing placentation and raising the risk of preeclampsia, which is consistent with the link between diabetes and microvascular illness.

Long term risk :

Pre-IADPSG diagnostic criteria place women at higher risk of developing GDM in subsequent pregnancies; recurrence rates have been observed to range from 30% to 84%.Type 2 diabetes is 10 times more likely to strike women with a history of GDM, usually within the first 5 years after GDM.

Additionally, studies show that women with past GDM had a 26% higher risk of hypertension and a 43% higher risk of myocardial infarction or stroke. International organisations, like the American Heart Association, have recently recognised the relevance of GDM as a risk factor for type 2 diabetes and cardiovascular disease[38].

II. CONCLUSION

Pregnancy-onset or first-observed glucose intolerance of varying degrees is known as gestational diabetes mellitus (GDM).The majority of overweight or obese women already have a higher chance of having T2DM.The delayed or dysfunctional response of the beta cells to glycemic levels in the pancreas and the marked insulin resistance brought on by placental hormone release

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are thought to be the two causes of gestational diabetes.There are various risk factors connected to the emergence of GDM. Obesity, advanced maternal age, prior GDM, significant family history of diabetes.TNF-α reduces the efficiency of beta cells and insulin signalling, which may directly cause GDM.Detecting GDM (FPG) >126 mg/dl concentration on two separate occasions or a blood glucose level of >200 mg/dl at random on two separate occasions can both be done using a fasting plasma glucose test.The cornerstone of GDM management is glycemic control. The primary line of treatment for GDM is lifestyle changes, such as frequent exercise and medical nutrition therapy.Consumption of dietary fibre has a favourable relationship with GDM. Consumption of dietary fibre was inversely and significantly connected with the risk of type 2 diabetes, especially that present in cereal and fruit.This modest amount of exercise decreased the HbA1c level, glucose responses to a glucose challenge, and fasting glucose levels.Insulin is thus required when dietary changes alone are inadequate to achieve treatment objectives., a non-insulin antihyperglycemic medication therapy may have some value.Glyburide and metformin are the main focus of knowledge on the safety of non-insulin antihyperglycemic drugs during pregnancy.

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