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Gestational Diabetes Mellitus in Pregnant Women and Its Complication in Mother and Newborns – An Overview

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ABSTRACT

Gestational Diabetes Mellitus [GDM] is defined as the carbohydrate intolerance during pregnancy. In GDM glucose intolerance can be notified due to fetal development and other contributing factors, this may response to severe condition of hyperglycemia in pregnancy. Various maternal and prenatal adverse outcomes may resulted by GDM. The prevalence of GDM have a steep increase by year to year by the influence of contributing factors such as advancing age, life style modifications, changed diet pattern etc. The overall prevalence of GDM noted as 1-14% among population, also the epidemiological studies states that the occurrence of GDM varies on the basis of ethnic and racial composition. The pathophysiology of gestational diabetes is assumed by various factors but exact cause of is unknown. Gestational diabetes is influenced by hormones produced by placenta, progesterone, estrogen, human placental lactogen [HPL], human chronic somatotropin [HCS] etc. Women with Polycystic Ovarian Syndrome [PCOS] and family history of Type 2 diabetes mellitus are at high risk of having GDM. GDM on pregnancy period causes some important complications such as high cesarean sections, preeclampsia, post partum type 2 diabetes mellitus, urinary tract infection in both neonate and the mother, cardiovascular disease, hypertension and stroke in mother, also neonatal consequences such as congenital malformations, macrosomia, adiposity, hypoglycaemia, birth injuries and prenatal death. This overview describes all the complications of pregnant women and newborns due to GDM with the conclusion of treatment profile.

Keywords:Gestational Diabetes Mellitus, Oral Glucose Tolerance Test.

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INTRODUCTION

Gestational Diabetes Mellitus (GDM) is a condition that develops during the second trimester of pregnancy, the cause may be rise in the human placental lactogen and other hormones that contributes to insulin resistance. This may be continued during the postpartum period [1]. It becomes the commonest metabolic problem in pregnancy[2]. It also be known to any degree of glucose intolerance during pregnancy [3]. 1% -14% is the prevalence of GDM, reported in the different studies [3-5]. The pregnant women with GDM has many risk factors as well as new-borns are also involved in the risks such as caesarean and operative vaginal delivery, preeclampsia, pregnancy induced hypertension, macrosomia related complications, urinary tract infection[UTI] in mother also macrosomia, congenital malformations, shoulder dystocia, neonatal hypoglycaemia, respiratory distress syndrome and hyperbilirubinemia in newborns. Also in these women have the risk of developing Type 2 diabetes mellitus in later life and their children are at the higher risk of developing obesity and Type 2 diabetes mellitus early in life [6] ,condition in which decreased insulin secretion or insulin resistance develop in body resulting increased blood glucose level.

This review focused to cover a wide range of clinical issues related to GDM, including the prevalence, challenges of epidemiology, diagnostic criteria and screening, the pathophysiology of GDM, the treatment and prevention of GDM and the long and short term consequences of GDM for both mother and child. Importantly this article explain the complications of GDM in pregnant women and neonates, while GDM left undiagnosed and untreated during the period of pregnancy.

Prevalence of gestational diabetes mellitus by age and race

The prevalence of gestational diabetes mellitus increases by age [7]. Between ages 18 and 45 years, there has been a significant raise in the number of new cases. In certain population as well as race and ethnicity, the incidence of gestational diabetes mellitus has a direct correlation with the occurrence of Type 2 diabetes mellitus [8]. Furthermore, it was reported that by the year 2030, the prevalence of gestational diabetes mellitus trends worldwide will rise to a record level as a result of increment in diagnosis[9]. The high-risk groups for gestational diabetes mellitus are women with low socioeconomic status and uneducated[10]. It was found that the most significant link of gestational diabetes mellitus by demography is socioeconomic status, maternal age as well as ethnicity. Wang et.al[11] studies established that mothers with assisted reproduction technology (ART) treatment had a 28% chance of developing gestational diabetes mellitus compare to women with non-assisted reproduction technology treatment. ART is the *technology* used to achieve pregnancy in procedures such as fertility medication, in vitro *fertilization* and surrogacy. The

subfertility and particular ART procedures have potentially impacted in the increased of gestational diabetes.

Epidemiology

According to the estimation of International Diabetes Federation [IDF] in 2015, 16-27% is the prevalence of GDM has dramatically increased in the past 20 years among various ethnic groups and 16.2% of women with live births had some forms of hyperglycaemia in pregnancy(Figure 1) ,85%of which were due to gestational diabetes[12].

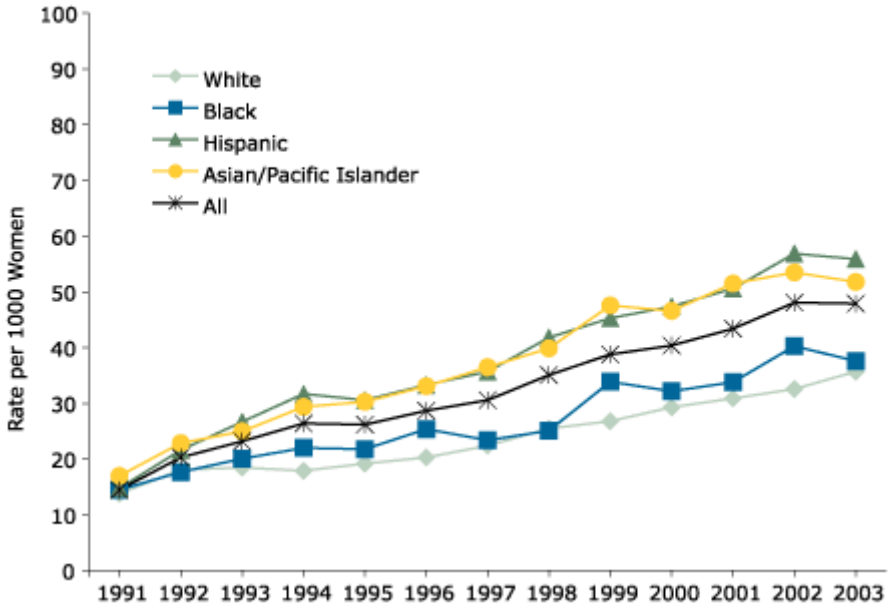

Figure 1: The epidemiological variation among different ethnic and racial groups

The epidemiology of GDM varies worldwide and even within a country's population, depending on the racial and ethical composition of the residents. In the United States the prevalence is higher amongst African American, Hispanic American, Native American, Pacific Islander, and South or East Asian women than in Caucasian women[13]. Furthermore the prevalence of GDM differs depending on the variety of screening strategies (universal or selective), diagnostic criteria and the prevalence of Type 2 DM in any specific country.

Yeyi Zhu *et.al* studies conducted on 2016 suggests that the prevalence was found to be Middle East and North Africa had the highest prevalence of GDM with a median estimate of 12.9 % (range 8.4–24.5 %), followed by Southeast Asia, Western Pacific, South and Central America, Africa, and North America and Caribbean (median prevalence 11.7, 11.7, 11.2, 8.9, and 7.0 %, respectively), whereas Europe had the lowest prevalence (median 5.8 %; range 1.8–22.3 %)[14](Figure 2).The report from the International Diabetes Federation estimated that worldwide 16% of live births in 2013 were complicated by hyperglycemia during pregnancy[15] and it is most

likely that the prevalence of GDM will increase due to the increase in risk factors like obesity and physical inactivity.

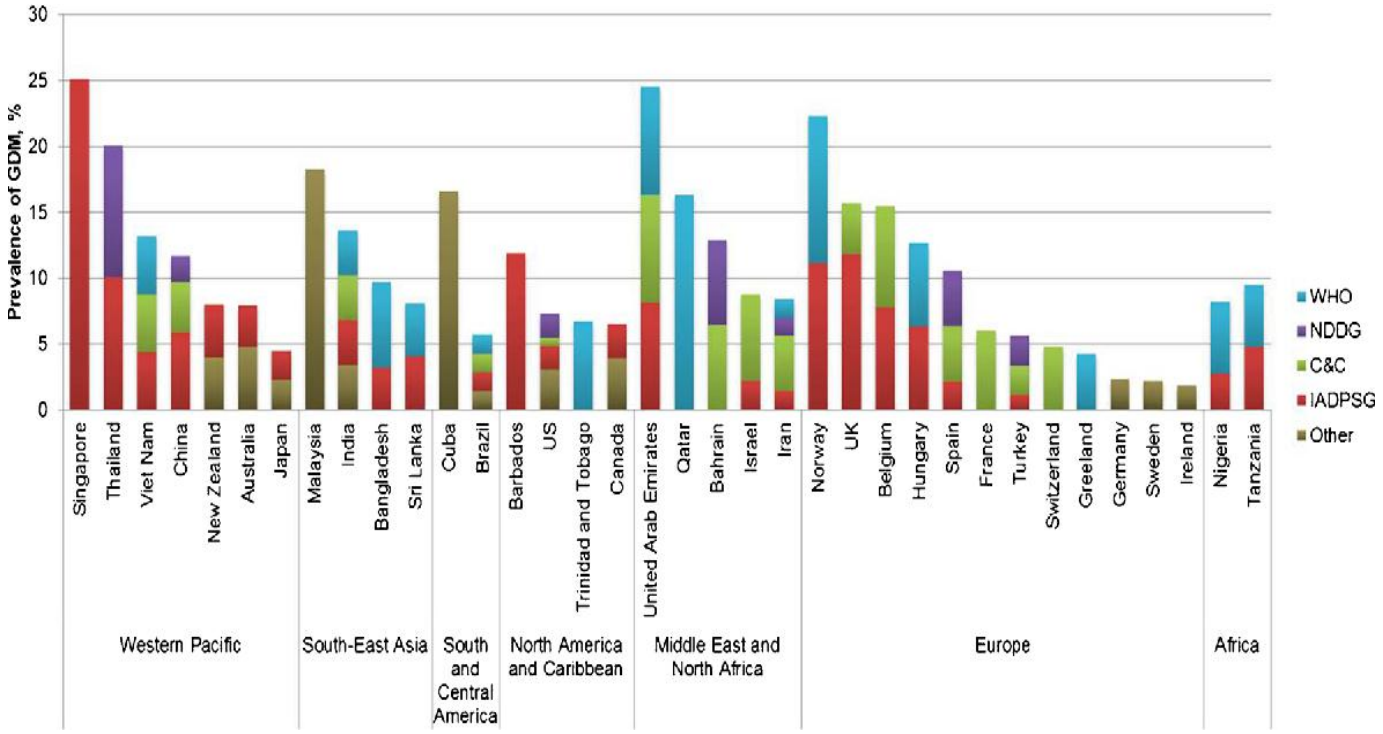

Figure 2: The prevalence of GDM among world According to different diagnostic criteria

Mohan Bairwa *et.al* studies reported that the India have a high prevalence of GDM about 8.7%, which was reported in the 21st International Epidemiological Association World Congress Epidemiology 2017 on August 22[16]. According to Balaji Bhavadharini *et.al* studied the overall prevalence of GDM in Tamil Nadu during 2016 was observed on the basis of WHO 1999 criteria about 14.6% [17](Figure 3).

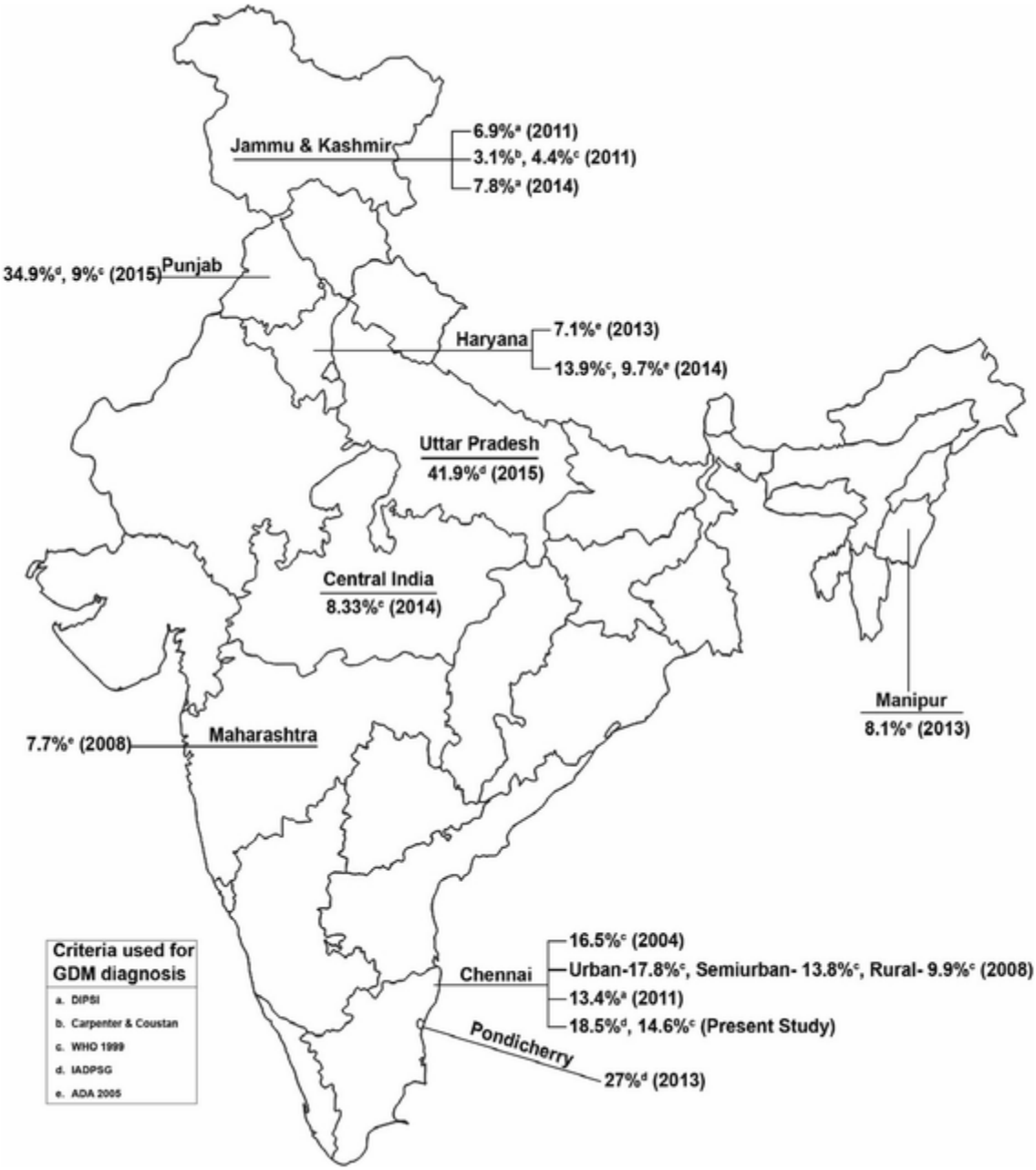

Figure 3: The Prevalance of GDM among Indian population

Pathophysiology

Pathophysiology of GDM has been postulated and well recognized in the Third International workshop-conference on GDM in Chicago, Illinois, on 8 November 1990. Until then it was not known how the GDM developing in pregnanancy[18]. The exact cause of this is unknown and may be due to genetic factors, as well as the hormones produced by the placenta, progesterone, estrogen, human placental lactogen (HPL), and human chorionic somatotropin (HCS) (Figure 4).

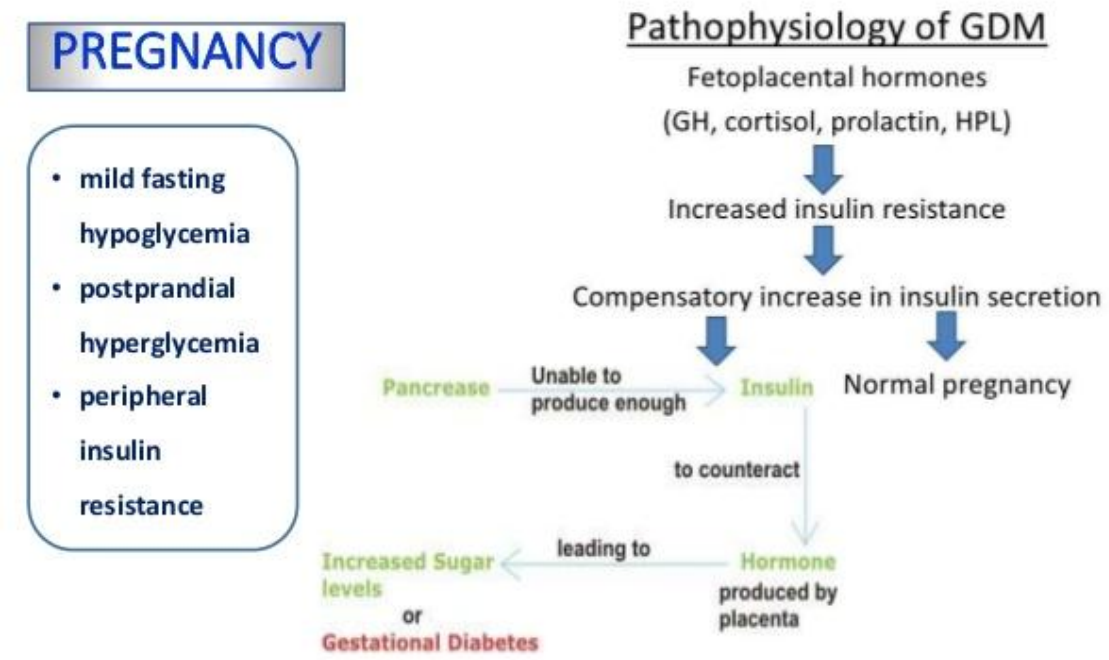

Figure 4: Flow chart showing the pathophysiology of GDM

Even though, insulin production is increased, its effect is diminished, which is indicative of insulin resistance with hyperinsulinemia and poor insulin response. The insufficient insulin produced by the mother allows glucose to circulate in the blood stream and be passed on to the foetus[19].Decreased maternal pregravid insulin sensitivity (insulin resistance) coupled with an inadequate insulin response are the pathophysiological mechanisms underlying the development of GDM. Insulin regulated carbohydrate, lipid and protein metabolism are affected and increases nutrient availability to the foetus, possibly resulted with fetal overgrowth and overweight[20].

Risk factors for gestational diabetes mellitus

According to Nora.*et.al* study, the GDM was influenced by advancing age, BMI (>30), BP>140/90, previous history of induced labour, abortion and large size baby. And no significance with socio-economic status, previous history of hypertension and family history of hypertension[21].Fong a et.al studied data have shown that the incidence of gestational diabetes mellitus has increased lately[22]. The increasing maternal age at delivery and the environment women live also contribute significantly. Women who live in urban areas are more likely than women living in rural environment to have gestational diabetes mellitus [23-25]. Furthermore, the quality and access to health care services before and during first time pregnancy helps to reduce the chances of gestational diabetes mellitus. The lack of continuation of health care services after child birth may contribute to the chances of gestational diabetes mellitus reoccurrence as well as being diagnosed with Type 2 diabetes in the future [26].

Screening of gestational diabetes mellitus

The screening of GDM is done by accessing the clinical risk factors or by the 50gm glucose challenge test [OGTT] (Figure 5). The followings are some important criteria used[2]

1. WHO guidelines proposed in 2010 as International Association of Diabetes and Pregnancy Study Groups[IADPSG] Criteria

   Screening with 75-g Oral Glucose Tolerance Test (OGTT)

   - Fasting Blood Glucose (FBS) ->5.1mmol/L(>91.4 mg/dl)
   - 1-h glucose threshold – >10mmol/L (>180mg/dl)
   - 2-h glucose threshold – >8.6mmol/L (>154mg/dl)
   - 3-h glucose threshold - nil

2. American Diabetes Association criteria [ADA] in 2014

   Screening with 50-g Oral Glucose Tolerance Test (OGTT)

   - Fasting Blood Glucose (FBS) ->5.3mmol/L(>95.4 mg/dl)
   - 1-h glucose threshold – >10mmol/L (>180mg/dl)
   - 2-h glucose threshold – >8.6mmol/L (>154mg/dl)
   - 3-h glucose threshold - >7.8 mmol//L (>140mg/dl)

3. European Association for Study of Diabetes criteria in 1991

   Screening with 75-g Oral Glucose Tolerance Test (OGTT)

   - Fasting Blood Glucose (FBS) ->5.5mmol/L(>99.4 mg/dl)
   - 1-h glucose threshold – nil
   - 2-h glucose threshold – nil
   - 3-h glucose threshold - >9.0 mmol//L (>162mg/dl)

4. National Diabetes Data Group [NDDS] criteria in 2013

   Screening with 50-g Oral Glucose Tolerance Test (OGTT)

   - Fasting Blood Glucose (FBS) ->5.8mmol/L(>104 mg/dl)
   - 1-h glucose threshold – >10.5mmol/L (>189.1mg/dl)
   - 2-h glucose threshold – >9.2mmol/L (>165.4mg/dl)
   - 3-h glucose threshold - >8 mmol//L (>144.1mg/dl)

5. Diabetes in Pregnancy Study group in India [DIPSI] in 2009

   Screening with 75-g Oral Glucose Tolerance Test (OGTT)

   - Fasting Blood Glucose (FBS) - nil
   - 1-h glucose threshold – nil

- 2-h glucose threshold – >7.8mmol/L (>140mg/dl)
- 3-h glucose threshold - nil

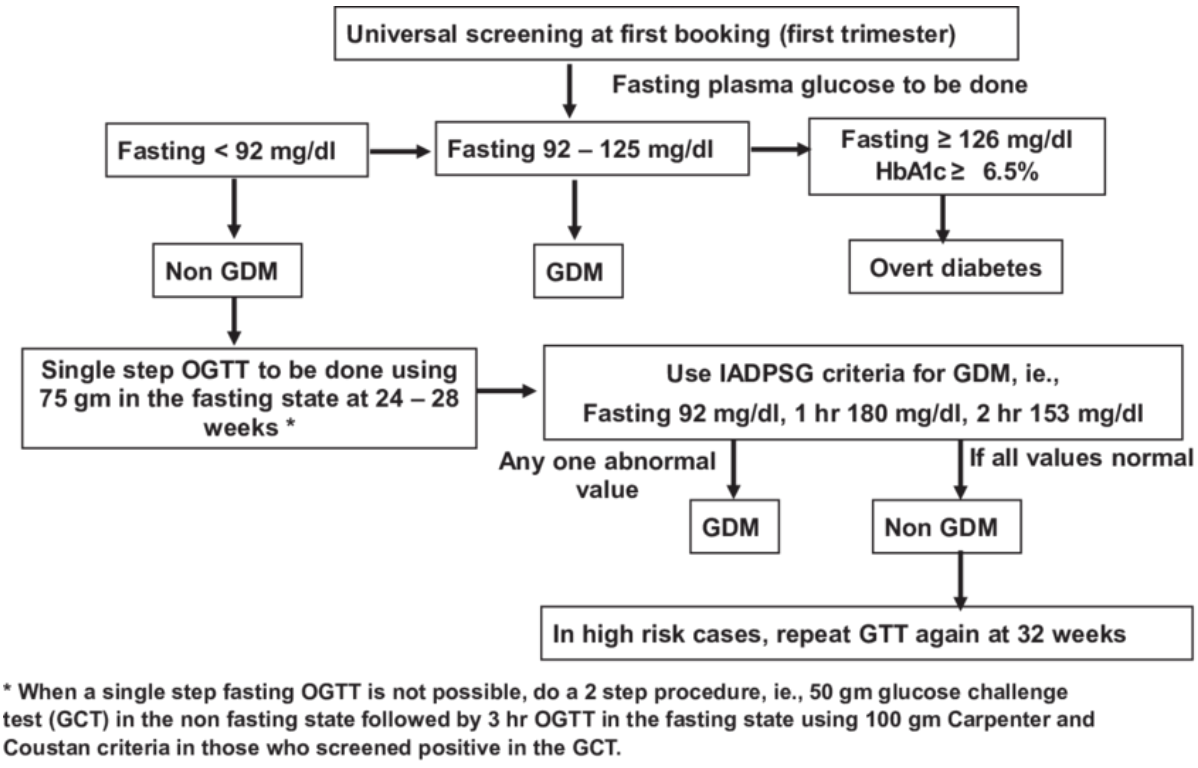

Figure 5: Flow chart showing the brief explanation of screening of GDM

MAJOR COMPLICATIONS IN MOTHER ASSOCIATED WITH GESTATIONAL DIABETES MELLITUS

Gestational diabetes mellitus is associated with adverse outcome not only for the mother, but also for the child, whether as a foetus, a neonate, a child or an adult (table 1). Maternal consequences include increased rate of operative and cesarean delivery, hypertensive disorders during pregnancy and future risk for type 2 diabetes mellitus as well as other aspects of the metabolic syndrome, such as obesity, cardiovascular morbidities and recurrent GDM**,** which was explained briefly as follows:

1. Hypertensive disorder during pregnancy

During pregnancy, GDM women had more risk on hypertensive disorders than others without GDM[27 28] .In the pathogenesis of the hypertensive disorders during pregnancy insulin resistance plays an important role it may be lead to pregnancy induced hypertension [PIH] or pre eclampsia[29]. The metabolic abnormalities linked to the insulin resistance syndrome are also observed in women with PIH. These include glucose intolerance, hyperinsulinemia, hyperlipidemia and high level of plasminogen activator inhibitor 1.liptin and tumour necrosis factor - ∝[30].One of the main cause of

PIH is insulin resistance by Homeostatic Model Assessment (HOMA) during gestation in first trimester[31 32] . Other causes are polycystic ovarian syndrome and obesity [33].The overall risk of PIH in the pregnant women is 17% in the GDM population[34].

2. Caesarean section and instrumental deliveries

According to the current National Institute for Health and Clinical Excellence (NICE) guidelines induction (or elective caesarean section) should only be considered before 40+6 weeks for women with gestational diabetes if there are maternal or fetal complications [29]. Diabetes should not in itself be considered a contraindication to attempting vaginal birth after a previous caesarean section [35]. Significant increase in the risk for operative delivery is independent to the degree of glucose intolerance and maternal weight [36]. If fetal weight is high, it is considered to be one of the main reasons for caesarean section in the patient who are suffered from GDM. It is because of avoiding other complications[37]. The other reasons considered or assumed that are risk of preeclampsia and bacterial infections[38].The risk increased not for the caesarean deliveries, but similarly and independently increased for operative deliveries[38].

3. Postpartum type 2 diabetes mellitus

The women suffered from GDM in their pregnancy had a increased risk of developing type 2 diabetes mellitus in the future. The risk of developing these can be depends upon the co-existing risk factors. Some of them are treatable, while others are not [38]. It can be diagnosed shortly after delivery or after some weeks, months and years after delivery[39 40]. In a 28 year follow up of the original cohort from Osullivan's work[4o]. It also determined that OGTT cutoff's for GDM, nearly half of the women with GDM had type 2 DM late in life.

4. Macrosomia related complications

If the birth weight above 4000-4500gm, regardless of the gestational age is absolutely defined as macrosomia, large of gestational age (LGA) is defined as the birth above the 90% for a given gestational age, based on sex adjusted growth curves increased fetal birth weight, macrosomia, LGA are predisposed features of maternal hyperglycaemia[42]. By the macrosomia, maternal complications experienced such as increased risk of operative and caesarean deliveries, post prandial haemorage, birth trauma and shoulder dystocia leads to maternal morbidity[43-45]

5. Urinary Tract Infection[UTI]

Gestational diabetes mellitus will suppress the immunity during pregnancy period and it will leads to the attack of acute cystitis to acute pyelonephritis and renal abscess. In addition to the anatomical and physiological changes seen in the renal tract during pregnancy, UTI is the most

commonly observed maternal infection[46]. By Majeda R Al-Bash *et.al* studied on 2016 have shown that the prevalence of UTI in GDM is 6.7%[46].

6. Cardiovascular events and stroke

Burlina et.al [47] studies suggested that GDM will have significant impact on endothelial function and structure, triggering the first step towards the development of atherosclerosis. Carotid artery intima-media thickness (CIMT) is a subclinical measure of early atherosclerosis that strongly predicts heart disease and stroke. Due to PIH and dyslipidemia these events are occurred among in women in their later life.

MAJOR COMPLICATIONS IN FOETUS ASSOCIATED WITH GESTATIONAL DIABETES MELLITUS

Untreated, moderate or severe gestational diabetes mellitus (GDM) increases the risk of fetal and neonatal complications, and the risk of congenital malformations is slightly increased in infants of mothers with GDM compared to the general population[38]. Maternal obesity increases the risk of gestational diabetes and is an independent risk factor for perinatal complication.

Congenital malformations

Mainly there are two types of GDM 1) Diabetes strictly related to pregnancy with no increased risk of congenital malformations and 2)diabetes diagnosed during pregnancy but pre-existing before pregnancy with similar risk of congenital malformations of that pre existing diabetes[38]. If the GDM is undiagnosed and remain untreated there is an increased risk of congenital malformations such as neural tube defect, respiratory system disorders lead to respiratory distress syndrome, CVS defect leads to immature heart, also not well developed organs such as mainly liver and kidney etc. Maternal diabetes has toxic effects on the development of the embryo and significantly increased risk of congenital malformations in humans. pregnant women with foetus with diabetic embryopathy may have chronic or unrecognized hyperglycaemia and elevated level of glycosylated haemoglobin [47]. The pre-existing diabetes can be reported the patterns of congenital malformations are being similar to the reported ones[38]. So impact of GDM is highly in neonates with congenital anomalies.

Birth weight and adiposity

Adiposity is otherwise called as obesity or overweight in which the excess fat deposition under skin. Large gestational age (LGA) is defined by the birth above 90% for the given gestational age, which will leads to the macrosomia in newborns. Maternal blood glucose levels, increased birth weight and neonatal adiposity, condition in which fat deposition under the skin had positive

correlation between them. This is due to hyperinsulinism secondary to the maternal hyperglycaemia[48]. The complication of increased adiposity and macrosomia in later life are obesity, CVS events like atherosclerosis, hyperlipidemia, dyslipidemia, hypertension , earlier sexual maturation etc. Maternal overweight and obesity is the other risk factor for macrosomia. The diagnosed and treated GDM reduce the incidence of macrosomia.

Perinatal death

S L Wood *et.al*, studies suggested that the prenatal mortality rate was increased in the prediabetic pregnancies and the rate increased steadily until the time of diagnosis of diabetes[49]. Maternal obesity is often associated with type2 diabetes or GDM is an additional risk factor for perinatal death[50 51]. This is due to the congenital abnormalities, respiratory distress with prematurity and intrauterine hypoxia (Figure 6). Stillbirth is caused by maternal, foetal and placental conditions including placental insuffiency[52].

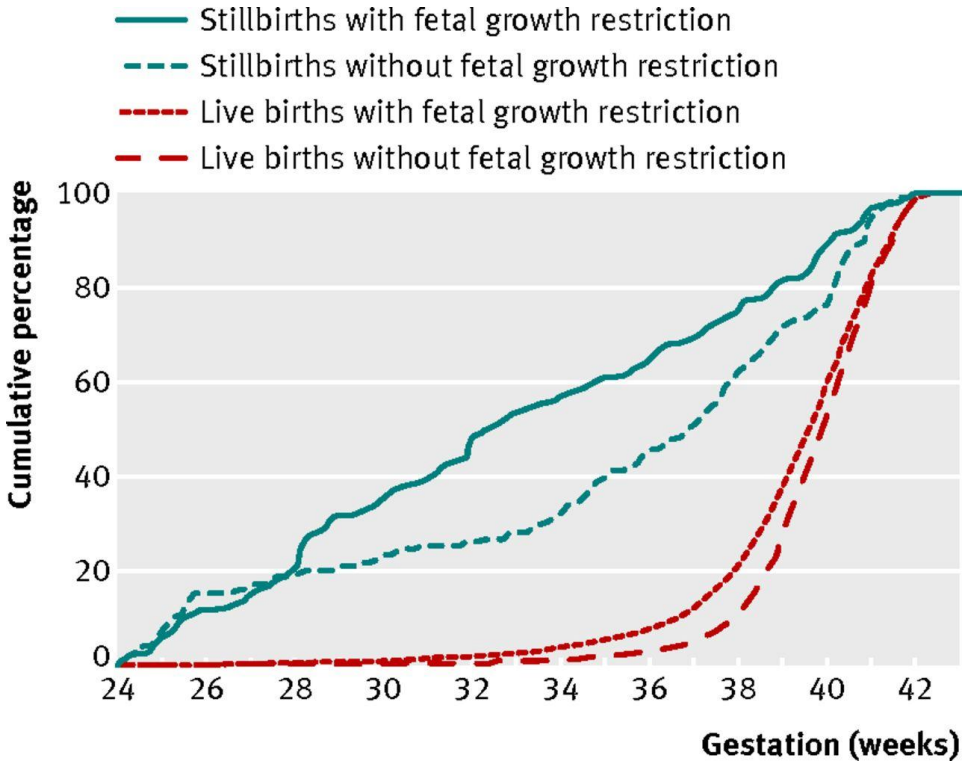

Figure 6: Perinatal death and live birth outcomes on fetal on pregnancy with GDM

Birth injuries

The untreated and undiagnosed GDM will causes birth injuries and bronchial plexus injuries. This is mainly associated with macrosomia[38]. These are due to fetal congenital abnormalities, fetal aneuploidy, placental abnormalities, placental insufficiency, fetal infection, polyhydramnios, and premature rupture of membranes, preterm birth and maternal gestational diabetes mellitus [51]

Neonatal hypoglycaemia

Hypoglycaemia is common in foetus due to hyperinsulinemia. The blood glucose level is less than 30mg/dl in first 24 hrs of life and 40mg/dl in later. After delivery, these is persist and causes hypoglycaemia[38]. The incidence of hypoglycaemia requiring intravenous therapy is low (5%). Dextrose infusion is commonly used for neonates as slow continues administration with proper blood glucose monitoring, dose of 4-8mg/kg/min upto max 20-30mg/kg/min. The impact of hypoglycaemia is cyanosis (blue colouring), apnea (stopping breathing), hypothermia (low body temperature), poor body tone, poor feeding, lethargy, seizures etc

TREATMENT OF GESTATIONAL DIABETES MELLITUS

Non Pharmacological Treatment

Accordingly, the primary intervention recommended to women diagnosed with GDM is dietary counseling in combination with physical activity and self-monitoring of blood glucose[53 54].

A. Dietary therapy of GDM

A healthy diet is important for every woman. Eating the correct and right amount of diet were the best way to normalize the sugar level in blood. The first line management of women with gestational diabetes mellitus consists of medical nutrition therapy .The aim of medical nutritional therapy are to provide adequate nutrition for the mother and foetus, provide sufficient calories for appropriate maternal weight gain, maintain normoglycemia, and avoid ketosis.

B. Physical therapy of GDM

Physical activity can be helpful in lowering blood glucose levels and reducing stress. It also increases the insulin sensitivity. In addition, regular exercise help in the management of back pain, muscle-cramps, swelling, disturbances in sleep and constipation. Physical activity prepares the body for delivery, improve the insulin sensitivity, and improve the glucose uptake and glycogen synthesis.

1. Pharmacological Management

If these measures are insufficient in terms of achieving optimal glycemic control subcutaneous insulin therapy is the therapy of choice as insulin does not cross the placenta and is therefore considered harmless to the foetus. However insulin is relatively expensive and difficult to administer. Insulin is the hormone which regulates the level of glucose in the body. It requires education to ensure a safe administration and it is associated with an increased risk of hypoglycemia and weight gain. The use of safe and effective oral agents may therefore offer advantages over insulin but has not yet been formally approved for GDM therapy in all countries[55].

A large randomized controlled trial was performed by Rowan et al[56] in which 751 women with GDM at 20 to 33 wk of gestation were assigned to open treatment with metformin or insulin if lifestyle intervention had failed to achieve glycemic control. Three hundred and sixty three women were assigned to metformin. 92.6% continued to receive Metformin until delivery and 46.3% in the Metformin group received supplemental insulin. Metformin is the commonest oral hypoglycemic agent belongs to the class of biguanides, which will helps to cells for the uptake of glucose in case of glucose resistant The guidelines concluded that metformin, alone or with supplemental insulin, was not associated with increased perinatal complications as compared with insulin.

Thus the treatment with Metformin was considered safe and effective and moreover, the women preferred metformin to insulin treatment. Further follow-up data are however necessary to establish long-term safety. Another randomized controlled trial included 404 women between 11 and 33 wk of gestation with singleton pregnancies and GDM that required treatment and assigned them to either glyburide or insulin. All the women received dietary advice and eight women in the glyburide group required additional insulin therapy. Glyburide is belongs to sulphonyl ureas class of drug in which it stimulates the pancreatic cells to secrete insulin. There were no significant differences between the glyburide and insulin groups regarding macrosomia, neonatal hypoglycemia, lung complications or foetal abnormalities and it was concluded that glyburide is a clinically effective alternative to insulin therapy[57]. Other studies show that both metformin and sulfonylurea have been increasingly and safely used in the treatment of GDM [58]. However, both glyburide and metformin cross the placenta and given the growing evidence of epigenetic foetal programming in utero, administration of drugs potentially affecting foetal metabolism is of major concern and as long term follow-up data on both mother and offspring are lacking oral antihyperglycemic agents should be used with caution[58].

Prevention of GDM

The best method of prevention is for mothers to practice healthy behaviours such as physical activity and healthy diet to help avoid or improve the onset of diabetes mellitus [59]. Also good counselling about follow up and care plan for both mother and newborns is effective. If mother suffers from pre-existing diabetes or recurrent GDM, use birth control pills until your blood glucose level becomes normal. Probiotics are live micro-organisms that, when administered in adequate amounts, may confer a health benefit to the host. Probiotics may improve insulin resistance by changing the microbiota of the gut. Myo-inositol is a polyol that occurs naturally in

the diet, is present in certain fruit, vegetables, beans, nuts, seeds and grains and is thought to mimic the action of insulin[60]

CONCLUSION

In the worldwide the prevalence of GDM become increased day by day and also the complications such as obese overweight would affect the next generation as a basis of many problems such as CVS, CNS etc occurred on early adolescence in fetal and postpartum type 2 diabetes, CVS disorders, stroke etc in maternal. This article had an overview in concept of gestational diabetes mellitus in terms of prevalence, epidemiology, pathophysiology, screening, complication and treatment etc. The GDM can be best prevented by healthy diet and improved physical activity. This the best way to prevent complications on both mother and newborns.

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