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Gestational Diabetes Mellitus and Associated Impending Non-communicable Disease Epidemic: A Perspective for Actions

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Abstract: ***Diabetes Mellitus is emerging as an epidemic globally; the major causative factors involved are both environmental and genetic, affecting the intrauterine exposures to the fetus as well. If stimulus occurs to be glucose intolerance during pregnancy, gestational diabetes Mellitus (GDM) establishes. Hyperglycemia poses serious immediate adverse consequences for both mother and foetal development by permanently changing physiology and metabolism. The objective of this review was to identify the global key foetal complications, risk assessment and preventive solutions to avoid T2DM epidemics. Search was done through PubMed, Google Scholar and Aga Khan University, Karachi Campus Library resources. Literature indicated that gestational diabetes is strongly associated with higher birth weights, cesarean section of mother and risk of infant shoulder dystocia, Erb's palsy, clavicular fractures, fetal distress, and birth asphyxia resulting in 30-50 % of perinatal mortality. Respiratory distress syndrome (31%) of infants and cardiac septal hypertrophy was seen in 35-40 % of cases worldwide. GDM play a crucial role in increasing prevalence of diabetes, obesity and metabolic syndrome. Use of insulin therapy has decreased the incidence of foetal macrosomia however, the extent of any effect on maternal and neonatal health outcomes are uncertain. Policy makers need to work at ;1) to prevent the development of GDM per se, may implement appropriate guidelines such as ADA/WHO by which patients should be screened for risk factors for GDM at their initial visit and 2) to organize program for reducing the incidence of type 2 DM and non-communicable diseases***.

Keywords: Gestational Diabetes, Complications, Non-communicable diseases, Policy implementation

1. Introduction

Diabetes is the most common medical condition to complicate pregnancy, affecting 0.6%-15% of all pregnancies each year globally [1]. However the prevalence of Gestational Diabetes Mellitus (GDM) may range from 1 to 14%, depending on the population sample and diagnostic criteria. In Pakistan it is known to range between 8-14 % [2]. Almost 90% of all pregnancies are complicated by diabetes [3]. GDM detection is important because of its association with maternal and fetal complication. Undetected situation increases the mortality rate and cause permanent changes in the programming and development of the offspring and also leads to metabolic syndrome in both groups. The prevalence of GDM in USA indicated higher rates with women of Asian Origin [4] as compared to white women [5], [6]

Screening and Diagnosis: The finest way to screen GDM is not agreed upon at one level globally. In the past, a universal two step screening at 24-28 weeks of gestation with a 50-g oral glucose challenge test was recommended.

Women with a 1-hour glucose level >140 mg/dl were referred for a diagnostic oral glucose tolerance test (OGTT) and this test was able to identify about 80% of women with GDM [7]. Another screening tool, a one-step approach requires a diagnostic OGTT without prior screening with the 50-g, 1- hour glucose challenge test this may be cost effective in some high risk patients. However if a patient has a fasting plasma glucose level >126 mg / dl or a random plasma glucose level >200 mg/dl, further confirmation on subsequent day is required [8]. In a similar study, a selective screening approach is reported being developed in 1997 based on data collected from 3,131 pregnant women. The data was selected randomly from half of the women and categorized into three groups (low, intermediate, and high risk), a brief of study (table1), is based on a complex scoring system using weighted risk factors such as age, race and BMI before pregnancy. This selective screening approach resulted in a 34.6% reduction in the number of screening tests performed, without a decrease in the detection rate of GDM [9].

Table 1: Classification of Risk Assessment Criteria

High Risk One or more of the following criteria should be met	**Low Risk** All of the following criteria should be met
Marked obesity	Age <26 years
Personal history of GDM	Normal pre-pregnancy weight
Glucose intolerance or glycosuria	Not a member of an ethnic/racial group with a high prevalence of diabetes (e.g., Hispanic American, Native American, Asian American, African American, or Pacific Islander)
A strong family history of type 2 diabetes	No history of abnormal glucose tolerance
	No known diabetes in first – degree relatives
	No history of a poor obstetric outcome.
A women is considered intermediate risk if she does not fall into either the high-or-low risk category. An additional possible risk factor for GDM not mentioned in the list above is a history of polycystic ovary syndrome. However, other studies have not confirmed this finding [10].	

The American Diabetes Association (ADA) guidelines now recommends selective screening for GDM [11], by which patients should be screened for risk factors for GDM at their initial visit as given in flow diagram (fig.1), whether it is universal or selective, remains a controversial subject.

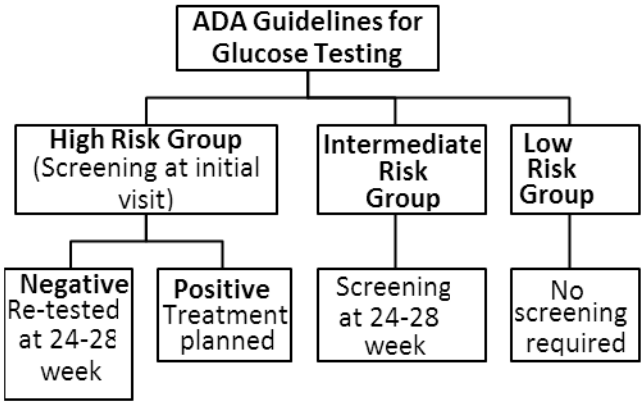

Figure1: Flow Diagram of Diagnostic Criteria as per ADA

Contradictory to the ADA recommendations described above, the United States Preventive Services Task Force concluded that there was insufficient evidence to recommend for or against screening and treatment of GDM significantly reduced important adverse maternal or fetal outcomes, including outcomes related to macrosomia. In addition, they had concerns about the potential harms and costs of screening, especially given the high false-positive rate (> 80%) of the 50-g glucose challenge test [12].

Diagnostic Criteria: OGTT is the most common method to diagnose GDM in the United States which is the 3-hours, 100-g OGTT. The diagnostic criteria for GDM, recommended by the ADA, describe, if two or more plasma glucose levels meet or exceed the following edge: fasting glucose concentration of 95 mg/dl, 1 hour glucose concentration of 180 mg/dl, 2 and 3 hours glucose concentration of 155 and 140 mg/dl respectively [12]. These values are lower than the thresholds recommended by the National Diabetes Data Group and are based on the Carpenter and Coustan modifications [13]. The ADA recommendations also include the use of a 2 -hour 75-g OGTT with the same glucose threshold as for fasting, 1-hour and 2- hour values [8]

The diagnostic criterion of World Health Organization (WHO) is based on a 2 hour 75-g OGTT, has been adapted in many countries outside of North America. Accordingly, GDM is diagnosed by WHO criteria if either the fasting glucose is > 126 mg/dl or the 2-hour glucose is 140 mg/dl.

2. Pathogenesis

Pregnancy is generally a diabetogenic condition typified by insulin resistance with a compensatory increase of B-cell response causing hyper-insulinemia. Insulin resistance generally starts in the second trimester and progresses throughout the gestational period. Placental release of hormones, like progesterone, cortisol, placental lactogen, prolactin, and growth hormone are main donor of insulin resistant state observed in pregnancy. The role of insulin resistance is likely to alter the maternal energy metabolism from carbohydrates to lipids, ensuring that the fetus has an adequate supply of glucose [14], [15]. A greater severity of insulin resistance in women with GDM has been observed compared to the insulin resistance observed in normal pregnancies. Normal pregnancies have also shown an impairment of the compensatory raise in insulin secretion, predominantly in first-phase of insulin secretion. This decrease in first phase insulin release may be a marker for weakening of B-cell function [16]. Increased resistance to the effects of insulin on glucose clearance and production in Latino women with GDM compared with normal pregnant women has been reported [17]. Further, the same study has observed that women with GDM had a 67% decline in their B-cell recompense compared with normal pregnant control subjects. Moreover, an evidence of islet cell autoimmunity (1.6-38%) has also been reported in a subset of women with GDM. The prevalence of other islet auto-antibodies which include insulin auto-antibodies and glutamic acid decarboxylase antibodies has also been found variable. These women may be at risk for developing an autoimmune form of diabetes later in life [16]-[18]. Further in 5% of all cases of GDM, mutation in glucokinase has also been reported [16].

GDM has serious adverse immediate consequences for the mother as well as for the off-spring with major financial implications. Furthermore, since GDM clearly leads to the development of type 2 DM in women later in life, it is important that GDM be considered as an early warning sign of type 2 DM occurrence. In the offspring this condition is associated with development of obesity and metabolic syndrome in childhood.

3. Complications

There are several fetal and maternal complications associated with GDM. Generally women with diabetes have a poor outcome compared with women without diabetes. The increased rates of congenital malformations, preeclampsia, premature delivery, perinatal mortality, and risk of delivering a macrosomic baby have been observed [15]. There is nearly a fourfold rise in perinatal mortality rate and twofold rise in congenital malformation rate in women with diabetes globally [19]. The risk of adverse outcome (malformation and perinatal mortality) is related to poor glycemic control in early pregnancy. Pre-pregnancy care is the only intervention that targets glycemic control at this critical early stage and has been associated with improvements in maternal and perinatal outcomes [20], [21]. The critical time period for optimal glycemic control is before 7 weeks' gestation during early organogenesis [22]. The association of pre-pregnancy care with reduced risk of major congenital malformation has been further confirmed by Meta-analysis [23].

Apart from GDM, pregnancy can also be complicated by pre-existing or pre-gestational diabetes mellitus (PGDM). Women with DM are at increased risk for pre-eclampsia [24] and Caesarian delivery [25] while their infants tend to experience higher rates of macrosomia [26] and shoulder

dystocia [27]. PGDM occurrence is diagnosed before pregnancy. Pregnant women with pre-gestational type 1 and type 2 diabetes are more likely to have cesarean deliveries, macrosomic infants, fetal congenital malformations, and preterm deliveries [28].

The impact of hyperglycemia on adverse maternal and neonatal health outcomes is undoubtedly continuous. Although insulin therapy decreases the incidence of fetal macrosomia for those women with more severe grades of hyperglycemia, the extent of any effect on maternal and other neonatal health outcomes is uncertain [29]. Although both pre-gestational and gestational diabetes are strongly associated with higher birth weights, in the presence of vascular disease associated with diabetes, birth weight may be restricted [30].

3.1 Gestational Diabetes Associated Risk to the Mother

The immediate dangers to the mother with GDM are in the form of obstetric complications, such as pre-eclampsia, preterm deliveries, still births and caesarian sections [31], [32]. In Asian Indian women diagnosed with GDM reported to have 8.2% preterm deliveries [33]. There have also been reports of increased occurrence of cesarean section (30%), preeclampsia (20-30%), and polyhydramnios (20%) which can result in preterm labor [34]. Moreover, there are reports which show one in six GDM diagnosed Indian women who have persistent diabetes after the pregnancy was over [35]. During pregnancy, such women developed changes in their fasting lipid level, blood pressure, large and small vessel function which caused hypertensive complications such as pregnancy induced hypertension and pr-eclampsia. Further, during pregnancy there was development of insulin resistance causing a transient increase in lipid levels, representing a metabolic Syndrome like condition involving central obesity, plus any two of the following factors, raised triglyceride levels, reduced HDL cholesterol, raised blood pressure and raised fasting plasma glucose [36].

Periodic GDM pregnancies and the considerable risk (50 %) of developing Type 2 DM in 5-10 years is the long-term threat to the mother which are associated with GDM. In a Danish population study, 39.9% women with a mild form of GDM (treated by diet alone) had developed type 2 DM in 9.8 years after the index pregnancy [37, 38]. In another review, 2.6-70% women with GDM progressed to type 2 DM, when women were followed up from 6 weeks post-partum to 28 years post-partum and the lowest rates were found from studies that had the shortest follow-up period [39]. In another study involving a control group (without GDM), subjects were followed for a period of 11 years, the cumulative incidence for type 2 DM and abnormal glucose tolerance in women who had GDM was 13.8% and 42.2% respectively. It was 0 and 2.8% ($P<0.05$) respectively in women without GDM [40]. In an Indian retrospective study, crude prevalence of type 2 DM was 52% in women with GDM as compared to the 4% observed in women without GDM, conducted 4.5±2 years after the index pregnancy [35]. The development rate for type 2 DM in women with GDM indicated wide variation and discrepancies. The role of ethnicity in the increase of type 2 DM in women with GDM remained controversial. In a UK study, 35% of the Indo-Asians had persistent glucose intolerance 3 months postpartum compared with 7% of Caucasians and 5% of the Afro-Caribbean subjects [39]. the effect of ethnicity became insignificant when the analyses were adjusted for duration of post-partum follow-up in a systematic review of several studies indicating that the data was not consistent on the role of ethnicity in development of type 2 DM in women with GDM [40].

Women with a history of GDM are at a greater risk of developing various chronic diseases later in life, other than diabetes, such as metabolic syndrome and cardiovascular disease compared to women who did not develop GDM. Data collected on parous women in a cross sectional analysis showed that women with prior GDM were more likely to have the metabolic syndrome compared to women who did not have GDM (86.6% vs. 73.5%; p=0.001). They also had a higher prevalence of CVD (15.5 vs. 12.4%, OR 1.85, 95% CI, 1.21- 2.82) that occurred at a younger age and was independent of metabolic syndrome and type 2 DM [3] Furthermore, the vascular changes if develop during GDM lead to vascular diseases in women during later years of life [31]. Overall at global level hemorrhage, hypertensive disorder, obstructed labor and infection /sepsis are among the leading causes of maternal mortality, all linked to High blood pressure and hyperglycemia, directly or indirectly as leading risk factors of death by chronic condition in women.

3.2 Gestational Diabetes Associated Risks to the Infant

Congenital malformation risk in infants from mothers with GDM increases slightly but mostly associated with undiagnosed type 2 DM among GDM, indicating that congenital malformation are related with maternal blood glucose level, gestational age at diagnosis and maternal obesity. The patterns of congenital malformation are same as for preexisting diabetes.

Macrosomia to the fetus in women with GDM is about 20-30% and is a major risk [41]. The theory of excessive fetal insulin due to increased transport of maternal energy to the conceptus has been hypothesized among many theories which have been produced over the years to elucidate the macrosomia associated with diabetes in pregnancy [42]. Diabetes in pregnancy is associated with increased delivery of glucose and amino acids to the fetus via the maternal circulation [43]. These fuels motivate increased production of fetal insulin which promotes somatic growth. Other maternal substrates such as free fatty acids and triglycerides add to the growing supply of fetal substrate and further support excessive growth. This situation also falls under the goal of management of pregnancies risk factor. Some mothers who appear to have optimal metabolic control still give birth to macrosomic infants [44]. Furthermore, macrosomia is not limited to the diabetic population; in fact, approximately 25% of macrosomic infants are born to mothers without GDM. It has recently been shown that women may have glucose level within target range yet there is superfluous shunting of glucose to the fetus as confirmed by increased amniotic fluid insulin levels which are thought to be best predictor of macrosomia and decisions about

treatment therapy in the mother are based on this evidence of fetal hyper insulinemia [45] In search of the effects of intrauterine contact on adiposity and blood pressure at three years of age (n=1238) adiposity assessed by skin fold measures was found to be higher in offspring of women with GDM compared to offspring of women without GDM [12].

The frequency of neonatal complications varies from 12-28% with aggressive management of GDM and the commencement of screening [46]. Macrosomia increased the danger of requiring a cesarean section of mother and place the infant at risk of shoulder dystocia. It is reported in a randomized trial that insulin therapy in women with GDM can decrease the rate of fetal macrosomia in those women whose maternal glucoses are at target levels on diet alone but whose fetuses showed excessive growth [47]. Shoulder dystocia can result in Erb's palsy, clavicular fractures, fetal distress, low APGAR scores, and even birth asphyxia while unrecognized [48]. Shoulder dystocia occurs nearly 50% of the time when a 4500 gram infant is delivered vaginally [49]. Preterm labor can result due to polyhydramnios from the fetus because of ultra-filtrating glucose through the kidneys. In mothers who have poor glycemic control, respiratory distress syndrome may occur in up to 31% of infants while cardiac septal hypertrophy may be seen in 35- 40 % [46]. There is also an increased risk of fetal mortality due to fetal acidemia and hypoxia with extremely poor glucose control. Common metabolic abnormalities in the infant of a GDM mother, consist of neonatal hypoglycemia, is common in women in suboptimal glycemic control because the infant may continue to produce excessive insulin for up to 24 hours after birth before the normal feedback loop starts operating. An estimated fetal weight of >4500 grams carries much higher risk of shoulder dystocia and an elective cesarean section is usually recommended [46]. Women with good dating criteria, a favorable cervix, and an estimated fetal weight <4000 grams are often electively induced at 38- 39 weeks in an attempt to decrease macrosomic births [50].

4. Long Term Consequences for the Risk of NCDs in the Offspring

The long-term squeals of GDM for offspring are debatable. Reports of an increased risk of adolescent obesity and Type 2 diabetes are compelling. It is reported that fetal islet hyperplasia occurs in-utero with maternal hyperglycemia resulting in an increased risk of developing Type 2 diabetes in teenage years or as a young adult [51]. In Pima Indians, the incidence of childhood Type 2 DM at 10-14 years in the offspring of GDM mother is higher of non-diabetic mothers and 5-fold higher than that of pre-diabetic mothers who develop Type 2 DM after pregnancy has been reported [52]. Elevated amniotic fluid insulin levels (due to fetal hyper-insulinemia as a result of maternal hyperglycemia) predicted teenage obesity in one study, independent of fetal weight, and one-third of these offspring had impaired glucose tolerance by 17 years of age [53]. This situation creates massive likelihood for the incidence of Type 2DM on these children with impaired glucose tolerance especially those females become mothers themselves in future, disseminating the cycle.

A longitudinal cohort study compared the development of metabolic syndrome in four groups of children 6-11 years old; these were large for gestational age offspring and appropriate for gestational age offspring of mothers with GDM, with similar offspring of control mothers. The observation of the study showed that large for gestational age offspring of GDM mothers represent a higher prevalence of developing the metabolic syndrome (50%), compared to offspring of the other 3 groups. It has also estimated in the same study that 5-7 year old children of mothers with GDM have increased prevalence of obesity and metabolic syndrome, especially when they are heavier at birth [54]. Further the large for gestational age offspring of the same study were at an increased risk of developing insulin resistance. The odds ratio of developing diabetes in children of mothers with gestational diabetes was 7.46 (CI 4.85 - 11.50) compared with development of diabetes in children of mothers without GDM [54]. Further, observations in a small cohort of children (average age 9 years) of a low risk Caucasian population, showed that offspring of mothers with GDM were at an increased risk of developing glucose intolerance [55]. Similar observations have been reported in a multi-ethnic population, the odds of having type 2 DM was 5.7 (CI 2.4-13.4) after exposure to maternal GDM in utero [56].

There are some likely biological mechanisms through which GDM increases the risk of an offspring to have obesity or DM. In the early phase of intrauterine development of the fetus in women with GDM, there is increased vulnerability of having a defect in organogenesis and physiologic function development when exposed to increased levels of metabolic substrates, such as amino acids, glucose and fatty acids, Moreover IUGR in a female fetus can also result in women having GDM as adults [34], [57].

5. Solution

Diabetic pregnancy was associated with high maternal and fetal mortality before the discovery of insulin. The perinatal mortality was 50% before and has reduced to 2-5% at the present time after the discovery of insulin. Further, we support the previous suggestions that after fetal lung maturity confirmation by amniocentesis, an earlier delivery should be considered in women with GDM who require insulin or glyburide or those who are not taking insulin but have suboptimal glycemic control, and should undergo fetal surveillance at 32 weeks gestation [34]. Similarly an ultrasound for growth to look for head to body disproportion and evidence at 28-32 weeks would influence treatment [47]. Ultrasonography can often envisage the risk of fetal macrosomia by measuring the abdominal circumference of the fetus at 29-33 weeks.

Applications of careful regulation of maternal glycaemia giving benefits to fetus have been accepted but the question of intrauterine deaths and congenital malformations is quiet there. It is suggested that chronic intrauterine hypoxia leading to acidemia is the most likely cause of still birth. In the past, the congenital anomalies were responsible for 10 % of all perinatal deaths. At present, they account for 30-50 %

of perinatal mortality. Currently it's thought that derangement in maternal glycaemia possibly in association with genetic susceptibility and epigenetic changes contributes to abnormal embryogenesis.

There is a need to work at two levels in this high risk population in low income countries such as Pakistan, with increasing trend of diabetes and other chronic diseases, such as in Pakistan other low income countries. One is to prevent the development of GDM and the other is to organize program for reducing the incidence of type 2 DM. In agreement with a prospective cohort study reported from Karachi showing that increased BMI, increased body fat percentage, decreased physical activity levels and diet are autonomous adjustable interpreters of GDM [2]. Therefore it is suggested that prevention programs and health care system along with the resources such as directing for improved physical activity levels, reducing weight and improving diet in women of reproductive age may be helpful to overcome the consequences of GDM.

Further high BMI values and post-partum impaired glucose tolerance of women are strong clinical indicators for type 2 DM in women with GDM. Postpartum screening of women with GDM should assess cholesterol and lipoprotein levels, plasma glucose and BMI measurements in women to establish a rigorous lifestyle plan, which should include diet and physical activity to prevent development of GDM in subsequent pregnancies, as well as type 2 DM and metabolic syndrome later in life. Awareness of the women with regard to the threat of type 2 DM after GDM should be increased. We reemphasis the previously suggested ways of several studies [49] that better maternal education of women with a history of GDM should be introduced. The best time for motivating and educating women is during pregnancy so that they carry it further during the postpartum period to delay development of diabetes and recurrent GDM.

For implementing these suggestions the role of health professionals is of tremendous importance. They have a responsibility towards the society to ensure better health and reduction in diseases related events in individuals at higher risk. At present, there are no standard guidelines for prevention and treatment of GDM in Pakistan. There is an immense need for developing them to address this important health area.

6. Conclusion

GDM can have serious immediate as well as long term implications for the health of the mother as well as the offspring. Diabetes situation is different in terms of the scale, type of problem and health care system dealing with problem. In Pakistan the prevalence rate of type 2 DM has been projected to rise in the future. Preventive strategies as life style modifications such a healthy diet, losing weight, quit smoking and healthy physical activity will reduce the rate of obesity and hypertension which in turn will go a long way in decreasing the rising incidence of Type 2 Diabetes Mellitus.

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