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Review Article

Gestational diabetes mellitus — a forerunner of chronic disorders in mother and child

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Abstract

Gestational Diabetes Mellitus (GDM) can have serious immediate as well as long term consequences, both for the mother as well as the off-spring. It seems that women of south Asian origin are not only more likely to have GDM but also suffer more from the adverse consequences of the disorder. These consequences include the development of type 2 DM in women with a history of GDM and a higher risk of obesity and metabolic syndrome in the off-spring. Pakistani physicians should consider GDM seriously because the WHO states that rise in the prevalence of type 2 DM will mainly occur in developing countries such as ours. Since GDM can lead to development of type 2 DM, efforts should be made to prevent type 2 DM through lifestyle modification strategies in this high risk population. It is important that we develop some clear cut guidelines for prevention and treatment of GDM.

What is gestational diabetes mellitus?

The World Health Organization and the American Diabetes Association define GDM (GDM) as "Any degree of glucose intolerance with onset or first recognition during pregnancy."^{1,2} The term GDM is not used for type 1 or type 2 diabetes mellitus (DM) diagnosed before conception. In addition, this term is not dependent on the use of insulin during pregnancy or to the continuation of the diabetic state after the pregnancy is over.³

Adverse consequences of GDM:

GDM can have deleterious consequences for the mother as well as the off-spring. These consequences may be observed at the time of delivery, which will be referred as immediate consequences or they may appear later in life, which will be referred to as long-term consequences. Both will be reviewed.

Immediate adverse consequences of GDM for the mother:

Women with uncontrolled plasma glucose levels during pregnancy have immediate adverse consequences, in the form of obstetric complications, such as pre-eclampsia, preterm deliveries, still births, caesarian sections and insulin treatment.^{3,4} In Asian Indian women diagnosed with GDM up to 8.2% preterm deliveries have been reported.⁵ Moreover, in another Indian study one in six women who were diagnosed as having GDM continued to have diabetes even after the pregnancy was over.⁶ During pregnancy, such women develop changes in their fasting lipid level, blood pressure, large and small vessel function which causes hypertensive complications such as pregnancy induced hypertension and eclampsia.⁷ Metabolic syndrome is a condition which involves central obesity, plus any two of the following factors, raised triglyceride levels, reduced HDL cholesterol, raised blood pressure and raised fasting plasma glucose. During pregnancy there is development of insulin resistance causing a transient increase in lipid levels, in short a metabolic syndrome-like condition.⁷

Immediate adverse consequences of GDM for the offspring:

At birth, offspring of women with GDM are at an increased risk of developing congenital malformations, macrosomia, respiratory distress and hyperbilirubinaemia.³ Several studies have shown the association of GDM with congenital malformations such as cardiac defects, (especially patent ductus arteriosus), hypospadias, polydactyl and central nervous system defects.⁸ It has been reported that 20% -30% of births in women with GDM are complicated with macrosomia due to high values of amino-acids, glucose and lipid levels in the blood. Also increased insulin secretion in the pancreas of the foetus causes macrosomia.⁹ In a South Indian study, neonates of women with GDM were heavier with greater than average head, chest and abdominal measurements compared to neonates of women without GDM.¹⁰ This shows that the hyperglycemic state of the mother has an effect on the growth of the foetus since insulin release in the mother has growth hormone - like effect on the foetus in utero.

Long Term Consequences of GDM:

Long term consequences for the mother:

Women with a history of GDM are at a greater risk of developing various chronic diseases later in life such as Diabetes Mellitus (DM), metabolic syndrome and cardiovascular disease compared to women who did not develop GDM in a pregnancy. In a follow-up study in a Danish population, 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.^{11,12} 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. The authors found that the lowest rates were from studies that had the shortest follow-up period.¹³ Further more it was observed that the highest increase in the development of type 2 DM took place in the first five years after the index pregnancy and then increased slowly.¹³ However there was no comparison group in the above cited studies (women without GDM) which makes it difficult to ascertain whether the increase in DM incidence was due to having GDM in the past or related to a secular effect. In a better designed study which had a control group as well, subjects were followed for a period of 11 years, the cumulative incidence for type 2 DM and abnormal glucose tolerance was 13.8% and 42.2% respectively in women who had GDM and 0 and 2.8% respectively in women without GDM ($P < 0.05$).¹⁴ In an Indian retrospective study conducted 4.5±2 years after the index pregnancy, crude prevalence of type 2 DM was 52% in women with GDM as compared to the 4% observed in women without GDM.⁶ These studies indicate that the risk of developing type 2 DM is considerably higher in women diagnosed with GDM than in women who did not have GDM. Estimates of population attributable risk (PAR) for developing type 2 DM after GDM suggest that between 10-30% (PAR 0.10-0.30, CI 0.06-0.41) of the women who develop type 2 DM would have experienced GDM.¹⁵

Reported progression rate for type 2 DM in women with GDM indicate wide variation and inconsistencies. There is controversy about the role of ethnicity in the development of type 2 DM in women with GDM. In a recent study in the UK 35% of the Indo-Asians had persistent glucose tolerance 3 months post partum compared with 7% of Caucasians and 5% of the Afro-Caribbean subjects.¹⁶ Whereas in a systematic review of several studies the effect of ethnicity became insignificant when the analyses were adjusted for duration of post-partum follow-up indicating that the data is not consistent on the role of ethnicity in development of type 2 DM in women with GDM.¹³ Women with GDM are also at a greater risk of developing metabolic syndrome and coronary vascular disease later in life. A cross sectional analysis of data collected on parous women who had participated in the GENNID (genetics of non-insulin dependent diabetes) study 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.¹⁷ Furthermore, the vascular changes which develop during GDM lead to vascular diseases in women during later years of life.³

Long term consequences in the offspring:

Most studies done on offspring of GDM mothers have assessed the association of birth weight and in utero exposure to a diabetic environment with obesity and metabolic syndrome in childhood. In an investigation of the effects of intrauterine exposure 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.¹⁸ In a comparison of offspring (average age 5.0 years) of mothers with GDM, with those of diabetic fathers (ODF) and offspring of parents who did not have diabetes (controls) in India, the BMI of offspring of mothers with GDM was significantly higher than that of the other two groups.¹⁹ In another investigation a positive dose response relationship was observed between degrees of maternal hyperglycemia during pregnancy adjusted for birth weight, maternal weight gain, age, parity, ethnicity and obesity in children (n=9349) at 5-7 years of age.²⁰

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. It was observed that large for gestational age offspring of GDM mothers showed a higher prevalence of developing the metabolic syndrome (50%), compared to offspring of the other 3 groups.²¹ Likewise, observations in a small cohort of children (average age 9 years), of a low risk Caucasian population (n=89), showed that offspring of mothers with GDM were at an increased risk of developing glucose intolerance.²² Similar observations were made in another study in which large for gestational age offspring of women with GDM were at an increased risk of developing insulin resistance at 6-11 years of age. Furthermore, the odds ratio of developing diabetes in children of mothers with Gestational diabetes compared with development of diabetes in children of mothers without Gestational diabetes was 7.46 (CI 4.85 -11.50).²¹ Similarly, in a multi-ethnic population, the odds of having type 2 DM after exposure to maternal GDM in utero was 5.7 (CI 2.4-13.4).²³

There are several plausible 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 foetus 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.^{24,25} It has been estimated 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.²¹ Moreover IUGR in a female fetus can also result in women having GDM as adults.²⁴

Why is it an important health problem for Pakistan?

The World Health Organization estimates that the number of people with diabetes mellitus (DM) will increase from 150 million to 333 million by the year 2025. Furthermore, this increase in the prevalence of DM will mainly occur in the 45 -64 years age population, belonging to the developing regions of the world.²⁶

The prevalence of type 2 DM in Pakistan has been estimated to be 10% -14% in various regions of the country.^{27,28} Moreover even the younger population (18 years age) is getting afflicted with type 2 DM.²⁹ With increasing prevalence of obesity in children and adolescents of the country, there is an increased risk of rise in the prevalence of type 2 DM.³⁰

GDM is a common condition affecting 0.6%-15% of all pregnancies each year, Globally.³¹ In Pakistan, a study conducted in Karachi observed 8% prevalence of GDM.³²

GDM has serious adverse immediate consequences for the mother as well as the offspring 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.

Solution:

There is a need to work at two levels in this high risk population. One is to prevent the development of GDM per se and the other is to organize programmes for reducing the incidence of type 2 DM in this high risk group. In our prospective cohort work (n=612) conducted in Karachi, increased BMI (OR 1.09 (1.01-1.17)/increased body fat percentage (OR 1.07(1.03-1.13), decreased physical activity levels (OR 0.89 (0.79-0.99) and diet (OR 0.75 (0.60-0.95) were independent modifiable predictors of GDM.³² Therefore it is suggested that prevention programmes should target improving physical activity levels, reducing weight and improving diet of Pakistani women of reproductive age.

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 includes 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. It has been suggested in several studies 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.³³

For implementing these solutions the role of health professionals cannot be ignored. They have a responsibility towards the society to ensure better health. At present, there are no standard guidelines for prevention and treatment of GDM in Pakistan. There is a dire need for developing them to address this important health area.

In summary, GDM can have serious immediate as well as long term implications for the health of the mother as well as the off-spring. In Pakistan the prevalence rate of type 2 DM has been projected to rise in the future. Preventive strategies as life style modifications including a healthy diet and physical activity, will reduce the rate of obesity which in turn will go a long way in curbing the rising incidence of Type 2 Diabetes Mellitus.

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