



Gestational Diabetes Mellitus – A Forerunner of DM

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The most important and wanted guest in human life is the foetus in uterus. Mother has to accept multiple adjustments, sacrifice and tolerance to stress and strain for the interest of her future. Pregnancy not only determines the immediate outcome of the foetus but also the future physiology and pathology of the mother and the children. Future evolution of diabetes in the mother and children are programmed during pregnancy and delay or avoidance of the process can be designed by effective management during and after pregnancy. Maternal hyperglycaemia impairs foetal beta-cell development leading to increased chances of obesity and diabetes, independent of genetic factors.¹ Indian woman has got eleven times increased risk of abnormal glucose tolerance compared to white Caucasians.² and there is doubling of incidence by last ten years. Children born in 1965 of GDM mothers were followed up for 35 years upto 2000 by Dabela D et al and more than 50% of them were found to develop diabetes during follow up period.³

Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance with onset or first recognition during pregnancy. The definition does encompass whether insulin with diet or diet alone was effective for glycaemic control or the glucose tolerance continues after pregnancy. It may so happen that diabetes was undetected before the pregnancy or developed during pregnancy as a chance.

Incidence rate of GDM is 3-5% during pregnancy, but in India the rate is higher. V Seshiah et al recently reported an incidence of 16.2% of GDM out of 1251 pregnant women diagnosed by 2 hours 75 gram post-glucose value \geq 140 mg/dl. The mean age of these women was 23 ± 4 years. Significant increase in the

prevalence of GDM was also correlated with number of gravida.⁴ Not only GDM, but any isolated abnormal blood glucose value is also foetotoxic. During normal pregnancy, fasting plasma glucose (FPG) is between 55-70 mg/dl and one hour post-prandial plasma glucose (PPPG) is below 120 mg/dl.⁵ Recently Loi Jovanovic accepts the goal of FPG as 50-65 mg/dl, PPPG 1 hr below 90 mg/dl and at the end of third trimester peak level below 110 mg% together with HbA_{1c} <5%. She recommends 1 hour PP value for optimizing treatment.⁶ Plasma glucose values above this level are detrimental. In normal pregnancy in the first trimester insulin requirement is less. But subsequently the increased metabolic need and insulin resistance (IR), produced by different hormones, stimulate beta-cell for more and more insulin liberation. In normal pregnancy the situation is compensated. But in type 2 diabetes mellitus (T₂DM) with already set in IR or in type 1 diabetes mellitus (T₁DM) with insulin deficiency, hyperglycaemia sets in.

The prevalence of GDM in USA varies from less than 10% to 14%⁷ with ethnic variation. Asian women are more vulnerable to white women despite their low BMI.⁸ The most of reported risk factors GDM are summarized in Table 1.⁹

In GDM, in majority glucose tolerance becomes normal immediately after delivery, but recurs in future pregnancy (30-50%) and develops glucose intolerance as either overt diabetes mellitus (DM) in 3 to 65% of cases or impaired glucose tolerance (IGT) as reported. Table 2 summarizes different reports.¹⁰

The above results are heterogenous because of variability in ethnic predisposition, duration of follow up and diagnostic criteria during GDM and future assessment.

Table 1 : Risk factors for GDM

Maternal Factors	Past Obstetric History	Pregnancy Factors	Family History	Protective Factors
Older age	Congenital malformations	Pregnancy hypertension	Diabetes	Young age
High parity	Still-birth	Multiple pregnancy	GDM in woman's mother	Alcohol use
Pre-pregnancy weight	Macrosomia	Increased iron stores		
Weight gain during pregnancy	Previous GDM			
BMI \geq 27				
Polycystic ovary syndrome				
Short stature				
Low birth weight				
α -thalassaemia trait				
High intake of saturated fat				
Features of IR				

Table 2 : Follow up studies in GDM

Reference	No of cases	Length of follow up (yrs.)	Abnormal GT		Control
			DM	IGT	
Mestman, USA	89	12 – 18	65%		
O Sullivan, USA	615	22 – 28	36%		5.5% DM
Dornhost et al, UK	56	6 – 12	39%	25%	
Ali & Alexis, Trinidad	60	3 – 7	62	17%	
Cataland et al, USA	103	7 weeks	3%	4%	
Damn et al, Denmark	241	2 – 11	3.7% T ₁ DM 13.7% T ₂ DM	17%	5.3% IGT
Coustan et al, USA	350	upto 10	7%	4%	

DIAGNOSTIC CRITERIA AND FOLLOW UP DIABETES

Incidence of future diabetes will vary according to the diagnostic criteria. Where higher blood glucose values and higher glucose load are taken as cut off value (other than WHO criteria), incidence of future diabetes will be higher because of higher metabolic derangement. Moreover studies with longer follow up in the groups with insulin treatment than diet controlled group shows higher incidence of future DM. Higher incidence of future DM has also been reported in cases of oral hypoglycaemic therapy during pregnancy.¹¹

Moreover, the incidence of future DM is increased with subsequent pregnancies after the index pregnancy than it remains single. Incidence of 30% is seen with the former group compared to 3% of the later.¹²

DEGREE OF GLYCAEMIA AND INSULIN STATUS

Impairment of beta-cell response induced by GDM as evidenced by higher FPG, need for insulin therapy and early onset of hyperglycaemia during GDM are strongly predictive of future DM. GDM population at Chicago developed DM in three-fourths of cases within six months whose FPG was > 130 mg/dl compared to 10% cases with FPG < 105 mg/dl.¹³ Women with GDM have reduced insulin to glucose ratio during 75 gm OGTT even in cases of IGT other than DM group, and is predictive of DM within 10 years.¹⁴

ETHNICITY AND GEOGRAPHICAL POSITION

Ethnicity is responsible for variations in cultural and lifestyle activity, determining the dietary and activity pattern, population of T₁DM and T₂DM contributing to the risk of both GDM and future DM. Post-GDM progression to DM is more rapid in ethnic groups with high prevalence of T₂DM and obesity, as seen in Pima Indians with 50% becoming diabetic by 5 years earlier than Caucasians at Denmark.¹⁵ This rate of progression is slower in white population but today it will be increased for all ethnic groups because of obesity and inactivity. Onset of DM is closer to pregnancy in ethnic groups with higher rate of T₁DM.

AGE

Age is the established determining factor for GDM and its future progression to DM. It occurs earlier in high ethnicity group. Age

at index pregnancy is not a risk for T₂DM but younger GDM is more predictive of T₁DM.¹⁶ But prolonged survival will reveal more cases of T₂DM.

EARLY GDM DIAGNOSIS

Diagnosis of GDM in the first half of pregnancy compared to later onset is associated with higher risk of future T₂DM. These groups show higher incidence of hypertension, greater dose of insulin to combat higher range of glycaemia, more perinatal death and neonatal hypoglycaemia. Diabetes is seen in 26.7% cases of early detection group than late detection group of 1.4%. Similarly IGT is seen in 40% cases of the former group than 5.56% of the later.¹⁷

DEGREE OF GLYCAEMIA IN EARLY POST-PARTUM

Immediately after the delivery, the higher degree of glycaemia is a strong indicator of future DM. Kjos et al studied in a 5 year follow up of 607 cases of GDM and stratified by quartiles the area under the glucose curve of 75 gm OGTT. 84% woman at higher quartiles developed DM compared to 12% of lowest quartile. Progression was 47% in high risk group but slower in low risk group. Woman, who remained normoglycaemic upto 12 years had lower insulin secretory response.¹⁵

Significant lower C-peptide / glucose value [(ng/ml : mg/ml) × 100] during pregnancy was shown to be independent predictor of future diabetes by F Pallardo et al. Lower insulin response to OGTT and lower first phase of insulin release are also predictive of abnormal glucose tolerance after pregnancy in this study.¹⁸

MACROSOMIA

Birth of large baby (weight > 4 kg) has been reported more in those women who developed diabetes subsequently. Congenital anomalies do not establish any statistically significant prediction.¹⁸

OBESITY DURING INDEX PREGNANCY

Obesity and insulin resistance are the predictors of both GDM and subsequent DM. Five years risk of DM was eight times higher in woman in the highest tertile for obesity and insulin response curve.¹⁹

MULTIPLE PREGNANCY BEFORE AND AFTER INDEX PREGNANCY

In different studies, 35.6% to 69% of recurrence of GDM has been noted. The main determining factors are infant birth weight of index pregnancy, maternal body weight (BMI > 30) before the subsequent pregnancies, GDM diagnosis before 24 weeks of pregnancy, higher insulin requirement and the interval between pregnancies < 24 months.^{9,22}

Persistent increase in body weight of 2 to 5 kg is noted after 1st pregnancy with significant central obesity. This is not intensified by further pregnancies. Diabetic risks like increasing age, obesity are though associated with increasing parity; development of DM is not well correlated in different studies. But multiple pregnancies with glucose intolerance definitely progressively worsen beta-cell failure, as beta-cell reserve is already compromised. Additional pregnancy is reported to increase three-fold annual incidence of DM following GDM.²⁰

Women who venture for additional pregnancy, risk ratio of T₂DM risk increases by 3.34. Increasing parity is also associated with higher incidence of progression of IGT to overt DM after GDM in Pima Indians.²¹

FAMILY HISTORY OF DM

With positive family history of DM, 35% cases after GDM developed DM compared to 22% cases of negative family history of DM in Australia.¹² In Chicago study DM within 5 years of GDM developed in those who had maternal history of DM.¹³ This establishes the maternal transmission of diabetes. GDM is also seen more in cases of history with GDM in mother or grandmother.

POST-GDM OBESITY

47% woman of GDM with subsequent weight gain develops DM on 16 years follow up in comparison to 28% of women who were non-obese or had lost weight after GDM.²⁰

Increased risk of T₂DM with a rate ratio of 1.95 is seen with each 4.5 kg weight gain during follow up.¹⁷ Post-pregnancy weight gain may be related to increasing age, as average increase in body weight in woman from 18 years to 50 years of age is 11 kg (0.35 kg/year).

DIET

High dietary fat (>40%) after GDM is definite risk for future development of DM. Restriction of dietary fat (<30%) is advocated, which also avoids cardiovascular risk factors.

PHYSICAL ACTIVITY

Regular physical activity and avoidance of sedentary habit are definitely beneficial by improving whole body insulin sensitivity, and the incidence of T₂DM is reduced by 30-50%.

PRETERM DELIVERY

Preterm delivery is not necessarily due to iatrogenic intervention but more frequently seen in women with T₁DM more so with poor metabolic control. Its predictive role for future DM is statistically proved (odd ratio 3.6, 95% confidence interval 1.1-11.6).²³

IMMUNOLOGICAL MARKERS

GAD65 antibody, islet cell antibody and insulin autoantibody are the predictive markers for developing T₁DM in non-pregnant state and during GDM. The most sensitive is GAD65 and all the positive GDM cases developed T₁DM within 4-11 years.²⁴ Islet cell antibody positive cases developed T₁DM in 75% cases within 3-52 months.²⁵

Hardu et al reported more history of T₂DM in the maternal-grandmaternal line than paternal-grandpaternal line establishing history of diabetes in the mother as a risk for GDM. Studies on genetic predisposition hypothesise that GDM has got heterogenous genotypic and phenotypic features and the risk of GDM is related to interaction between obesity and insulin receptor candidate genes. The later and IGF₂ alleles interact to produce risk of GDM also. These genes are also diabetogenic for T₂DM.¹⁷

FEATURES OF INSULIN RESISTANCE

Together with obesity and hyperglycaemia, hypertension, dyslipidaemia, acanthosis nigricans, PCOS, gout, coronary and peripheral artery disease etc. are the markers of IR and predictive of future T₂DM. GDM women presenting with this abnormalities are expected to develop DM more in frequency than women without these features.

Woman with PCOS after GDM has got stronger inclination for developing IR than woman with normal ovary and past GDM.²⁷ PCOS is a prediabetic state with chances of IGT as 31-35%, T₂DM of 7.5-10% and conversion of IGT to T₂DM is 10 times higher.²⁷

PREVENTION

Development of DM or IGT after GDM is determined by some modifiable factors and some unmodifiable factors as discussed, scope of intervention is only with the later group.

Nonmodifiable risk factors for development of DM from GDM are ethnicity, age, family history and features of IR. There is very little scope to target this. But targeting the modifiable risk factors like multiple pregnancy obesity or weight gain during or after GDM, dietary indiscretion, sedentary habit, hyperlipidaemia, hypertension and smoking is an achievable goal. The procedure which can be achieved are regular follow up and biochemical monitoring, regulation of diet, exercise, smoking, hypertension, lipid abnormality, avoidance of further pregnancy, and hormone replacement therapy in menopausal age group, all being supplemented by patient education and public awareness. Education programme delivered during pregnancy should also include the risk of recurrent GDM and future DM, hypertension and dyslipidaemia and thereby the need for regular follow up. They should also know that frequently diabetes develops without any symptoms and should also know the symptoms for self referral.

For ethnic groups with a high prevalence of DM, blood sugar estimation immediately after delivery, after 2 months and every year thereafter should be followed. Risk of developing DM is highest between 6 months to 5 years but becomes a plateau after ten years. High risk group particularly with high FPG during or after delivery should be monitored more frequently.

Till now as for diabetes prevention lifestyle modification is best. In those cases where this is not efficiently possible, therapeutic intervention may be done with metformin as documented by Diabetes Prevention Programme in USA or thiazolidinediones particularly in cases with PCOS and post GDM development of IGT cases.

TRIPOD study has established that there is 56% decrease in T₂DM after GDM with the use of troglitazone.²⁸ Improving insulin sensitivity by metformin and reduction of risk T₂DM has also been observed by Dornhorst et al.²⁹ As troglitazone has been rejected, trials with newer thiazolidinediones are awaited. Immunomodulatory treatment of GAD positive woman with GDM is another option for prevention of T₁DM.

One of the important causes of DM developing after GDM is discontinuity of care as neglected by young woman after delivery. Current American Diabetes Association guidelines recommend blood sugar estimation after child-birth, after 6-8 weeks and every 3 years thereafter.³⁰ Woman with high risk factors require more frequent testing.

CONCLUSION

The incidence of diabetes mellitus in future will reach unexpected level in our country. GDM is one of the fore-runners of diabetes. Keeping aside the non-modifiable factors there are many modifiable factors which if targeted before, during and after GDM will impart good result. Proper detection and management of GDM and preventive measures thereafter are the affordable goals.

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