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Gestational Diabetes Mellitus - A Perspective

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1. Introduction

The prevalence of diabetes is increasing globally and the total number of people with this condition is projected to rise from 171 million in 2000 to 366 million in 2030 (Wild et al, 2004). India is no exception, with projected rates of 79.4 million in 2030—a 151% increase from 31.7 million in 2000 (Wild et al, 2004). The increased prevalence is attributed to the aging population structure, urbanization, the obesity epidemic, and physical inactivity (Hunt & Schuller, 2007). While all these factors contribute to the epidemic of diabetes, intrauterine exposures are emerging as potential risk factors (Barker, 1995). The "fetal origin of adult disease" hypothesis proposes that gestational programming may critically influence adult health and disease (Barker, 1995). Gestational programming is a process whereby stimuli or stresses occurring at critical or sensitive periods of fetal development, permanently change structure, physiology, and metabolism, which predisposes individuals to disease in adult life (Lucas, 1991). If the stimulus happens to be glucose intolerance in pregnancy, it predisposes the offspring to an increased risk of developing glucose intolerance in the future. This vicious cycle is likely to influence and perpetuate the incidence and prevalence of glucose intolerance in any population (Seshiah et al., 2004). Therefore, preventive measures against type 2 diabetes should start during the intrauterine period and continue from early childhood throughout life (Tuomilehto, 2005). In this respect, detection of gestational diabetes mellitus (GDM), defined as carbohydrate intolerance of variable severity with onset or first recognition during the present pregnancy (Metzger, 1991), becomes an important public health issue. The etiopathogenesis of glucose intolerance that develops in women with GDM could be the result of their inability to increase insulin secretion enough to overcome insulin resistance that occurs even in non diabetic pregnancy (Kuhl et al., 1985). The present concept is that GDM represents, detection of chronic β cell dysfunction, rather than development of relative insulin deficiency as insulin resistance increases during pregnancy (Buchanan et al., 2007).

2. Implications

The usual recommendation of lifestyle modifications or drug intervention for prevention of diabetes is likely to delay or postpone the development of overt diabetes in persons diagnosed with abnormal glucose tolerance. These measures essentially target only the post primary prevention of diabetes whereas the aim should be primary prevention of diabetes by keeping the genetically or otherwise susceptible individuals normoglycemic, apart from preventing them from developing type 2 DM (Tuomilehto, 2005). In this context, women

with GDM become the ideal group for primary prevention of diabetes (Girling & Dornhorst, 2003), as women with GDM are at increased risk of developing diabetes predominantly type 2 DM as are their children (Dornhorst & Rossi, 1998). The diagnosis of GDM offers a unique opportunity in identifying individuals who will be benefited by early therapeutic intervention with diet and exercise, thus normalizing the weight to delay or even possibly prevent the onset of diabetes.

3. Prevalence

The epidemiology of GDM is subject to various factors such as the population to be screened, the screening methods, the gestational weeks for screening and the glycemic criteria for diagnosis. Screening recommendations range from inclusion of all pregnant women (universal) to the exclusion of all other women except those with very specific risk factors (selective): (e.g., age > 25 years, obesity: BMI > 30, ethnicity: Hispanic, Native American, Asian-American, African-American, family history: first degree relative, and previous GDM or large for gestational age infant) (Mazze, 2006). Different ethnic groups when exposed to the same environmental setting, experienced a widely variable risk. Among ethnic groups in South Asian countries, Indian women have the highest frequency of GDM (15%), followed by Chinese (13.9%), Vietnam-born (7.8%) and Australian-born (4.3%) (King, 1998).

For a given population and ethnicity, the risk of diabetes in pregnancy, mirrors that of the underlying frequency of type 2 DM in that population (King, 1998). Impaired Glucose Tolerance (IGT) is generally much more prevalent than diabetes in women of child bearing age (King, 1998). Among Indians, the prevalence of IGT in the age group of 20 to 29 years and 30 to 39 years was found to be 12.2% and 15.3% respectively. No gender difference was seen in the prevalence of IGT (Ramachandran et al., 2001). It was observed in a national survey performed in 2002, the frequency of the occurrence of GDM was 16.55% by the World Health Organization (WHO) criteria (Seshiah et al., 2004) which was closer to the prevalence of IGT in the child-bearing age group of women in India (Ramachandran et al., 2001). Parallel to the increased prevalence of IGT in the general population, the frequency of GDM had also increased. The prevalence of GDM was 2% in 1982 (Agarwal & Gupta, 1982) [IGT - 2% (Ramachandran et al., 1988)] which increased to 7.62% in 1991 (Narendra et al., 1991) [IGT – 8.2% (Ramachandran et al., 1992)], and doubled to 16.55% in 2002 (Seshiah et al., 2004) [IGT – 14.5% (Ramachandran et al., 2001)]. The prevalence data published (Seshiah et al., 2004) included pregnant women attending different health care providing centres spread in different parts of the country (Table – 1).

This phenomenal increase in the prevalence of GDM prompted the authors to initiate a project on 'Diabetes In Pregnancy Awareness and Prevention (DIPAP)', funded by the World Diabetes Foundation and supported by the government of Tamil Nadu, India. To have a community based prevalence data under the DIPAP project, the author's group screened a total of 4151, 3960 and 3945 pregnant women in the urban, semi urban and rural areas of Tamil Nadu, respectively (Seshiah et al., 2008a). This was the largest prospective study (N=12,056) other than Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study. GDM diagnosis was based on the WHO criterion of 2-h plasma glucose (PG) ≥ 7.8 mmol/L with 75g oral glucose. WHO recommendation serves both as one step screening and diagnostic procedure, and is easy to perform besides being economical (Seshiah et al., 2004, 2005). WHO criterion of 2-h PG ≥ 7.8 mmol/L identifying a large number of cases may have a greater potential for prevention (Schmidt et al., 2001). In addition, a study performed by

	Centre	Number of pregnant women screened	Prevalence Rate
Dr. Balaji et al	North Chennai, Tamil Nadu	891	16.2%
Dr. Anjalakshi et al	South Chennai, Tamil Nadu	1002	15%
Dr. K. P. Paulose	Trivandrum, Kerala	750	15%
Dr. Mary John	Ludhiana, Punjab	220	17.5%
Dr. Prasanna Kumar	Bangalore, Karnataka	49	12%
Dr. Shyam Mukundan	Alwaye, Kerala	200	21%
Dr. Aruyerchelvan	Erode, Tamil Nadu	562	18.8%
	TOTAL	3674	16.55%

Table 1. Prevalence of GDM in different parts of India – 2002

Crowther et al found that treatment of GDM diagnosed by WHO criterion reduces serious perinatal morbidity and may also improve the women's health-related quality of life (Crowther at al., 2005). Similarly a long term outcome study conducted by Franks et al documented that when maternal 2-h PG was ≥ 7.8 mmol/L, the cumulative risk of offspring developing type 2 DM was 30% at the age 24 yrs (Franks et al., 2006). Both these short term and long term outcome studies validate the WHO criterion and hence the authors chose this criterion for the DIPAP project. In this project GDM was detected in 739 (17.8%) women in urban, 548 (13.8%) in semi urban and 392(9.9%) in rural areas. In this community based study, the overall prevalence of GDM was 13.9% (Seshiah et al., 2008a). The prevalence of GDM had increased from 16.55% to 17.8% in the urban areas in two years (Seshiah et al., 2004, 2008a). There is a definite divide between the rural and urban areas in the prevalence of GDM. The possible cause for the low prevalence in the rural settings may be due to the less mechanized, agriculture based lifestyle. In this population the risk factors for the development of GDM were: age ≥ 25 years, BMI ≥ 25 and family history of diabetes (Figure 1).

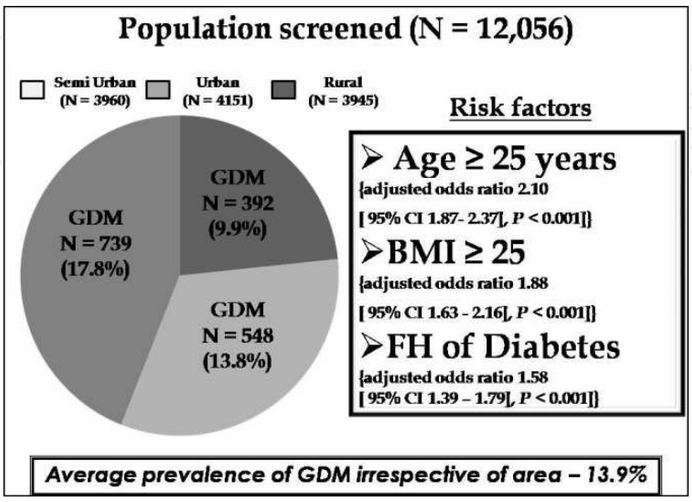

Fig. 1. Risk factors for the development of GDM

3.1 Geographical variations in the prevalence of GDM

Prevalence varies between 1% to 16% depending on the geographical variation and ethnicity and from one region to another in the same country (Yogev et al., 2003). The prevalence of GDM corresponds to the prevalence of IGT within a given population (King, 1998). The prevalence of GDM in India was 16.55% in the urban area and the frequency varied from 12% to 21% in different parts of the country (Seshiah et al., 2004) (Table 1). A low prevalence of GDM was observed in Kashmir (Zargar et al., 2004) (northern tip of India) 4.4% and a high prevalence of 16.55% in the southern part of India (Seshiah et al., 2004). The prevalence of GDM in other developing countries also showed regional variations. In Mexico, the prevalence of GDM varied from 4.3% to 11% when screening was done in different parts of the country (Forsbach et al., 1998). The rate of abnormal screening test results ranged from 8.0% to 20.7% for different regions of Poland (Wojcikowski et al, 2002). Among Pan Arab countries, Saudi Arabia (12.5%) and Bahrain (13.5%) had the highest prevalence of GDM (Al Mahroos et al, 2005; Ardawi et al, 2000). The frequency of GDM in Argentina was between 2% and 12% depending upon the population studied and geographical variations (Liliana et al, 2003).

4. Rationale for universal screening

Selective screening based on risk factors scored poorly in predicting GDM (Shamsuddin et al, 2001). If selective screening is employed, it is likely that 27% of GDM women will go undetected (Shamsuddin et al, 2001). GDM diagnosis is overlooked in about 1/3rd of the women, where selective rather than Universal screening is performed (Cosson et al., 2004a). Further selective screening recommended by American Diabetes Association (ADA) may be applicable for women belonging to the ethnic group with low prevalence of GDM. Risk factor screening does not take into account the inevitable difficulties in implementation, including the potential for substantial under-diagnosis of GDM (Simmons et al., 2009). Among ethnic groups in South Asian countries, Indian women have the highest frequency of GDM necessitating Universal Screening (Beischer et al., 1991). The recognition of glucose intolerance during pregnancy is more relevant as Indian women have 11 fold increased risk of developing GDM compared to Caucasians (Dornhorst et al., 1992).

Compared to selective screening, Universal screening for GDM detects more cases and improves maternal and offspring prognosis (Cosson, 2004b). Thus Universal screening appears to be the most reliable and desired method for the detection of GDM (Shamsuddin et al., 2001). For universal screening the test should be simple and cost effective. The two step procedure of screening with 50g Glucose challenge test (GCT) and then diagnosing GDM based on 75g OGTT is not feasible in a country like India, because the pregnant women may have to visit the antenatal clinic twice and at least 3 to 5 blood samples have to be drawn, which they resent. The scenario is likely to be the same in most of the developing countries.

5. Diagnosis of GDM

5.1 A single step procedure to diagnose GDM

All the diagnostic criteria require women to be in fasting, but most of the time pregnant women do not come in the fasting state because of commutation and belief not to fast for long hours. Attending the first prenatal visit in the fasting state is impractical in many settings (Metzger et al., 2010). The dropout rate is very high when a pregnant woman is asked to come again for the glucose tolerance test (Seshiah et al., 2004; Magee et al., 2001).

For the successful implementation of universal screening, a test has to be casual and reliable. A procedure that does not impose any restriction would be ideal for universal screening. The test performed should be able to diagnose GDM, as they walk into the prenatal clinic or clinical laboratory irrespective of their last meal timings. Hence the authors undertook a study to evaluate, whether a 2-h 75g oral glucose test performed in a non-fasting state, irrespective of last meal timing, is as efficacious as 2-h 75g oral glucose test done in the fasting state recommended by WHO in detecting GDM (Anjalakshi et al., 2009). A total of 862 consecutive pregnant women were subjected to 75g oral glucose test irrespective of time of the last meal. Venous samples were collected at 2-h after oral glucose administration. They were advised to follow a diet containing atleast 150g carbohydrate daily and usual activity for atleast 3 days and come to the prenatal clinic after an overnight fasting of 10-12 h. At the second visit 800 of them responded and underwent 2-h 75g oral glucose test in the fasting state recommended by WHO. The observation in this study was, all women diagnosed as GDM (N=87) by 75g glucose test irrespective of the last meal timings also satisfied the diagnostic criteria of 75-g oral glucose test performed in the fasting state recommended by WHO. It was also found that there was no statistically significant difference ($P > 0.05$) between the PG levels of the 75g glucose test in fasting and non fasting state, irrespective of last meal timing, performed in the GDM and in NGT pregnant women.
The rationale behind this study outcome is that, a normal glucose tolerant woman would be able to maintain euglycemia despite glucose challenge due to adequate insulin response, whereas in a woman with GDM who has impaired insulin secretion (Kuhl, 1991), her glycemic level increases with a meal and with glucose challenge, the glycemic excursion is expected to exaggerate. This cascading effect is advantageous as this would not result in false positive diagnosis of GDM. Performing this test procedure in the non-fasting state, irrespective of last meal timing, is prudent as glucose concentrations during the glucose tolerance are affected little by the time since the last meal (Gough et al., 1970).
Pettitt et al. observed that WHO criteria based on the glucose concentration 2-h after 75g oral glucose administered to non-fasting women correctly identified subjects with GDM (Pettitt et al., 1994). The non-fasting 2-h post 75g glucose concentration strongly predicts adverse outcome for the mother and her offspring (Pettitt et al., 1991). Philips et al also observed that plasma glucose value with a glucose challenge test was unaffected by the time after a meal or time of the day in Normal Glucose Tolerant non pregnant subjects (Philips et al., 2009). Thus, this single test procedure performed irrespective of the last meal timing is rational and a patient friendly approach, which causes least disturbance in her routine activities. This procedure is a modified version of WHO criteria in that, only 2-h PG is taken into consideration for the diagnosis of GDM and is being followed by the Diabetes In Pregnancy Study Group India (DIPSI) (Seshiah et al., 2009)

5.2 Comparison of WHO and IADPSG criteria

All the diagnostic criteria, except the existing diagnostic criterion of WHO 2-h plasma glucose (PG) ≥ 7.8 mmol/L with 75g oral glucose load (King, 1998), are country specific or recommended by various associations. Recently, based on the HAPO study, the International Association of Diabetes and Pregnancy Study Groups (IADPSG) consensus panel recommended that GDM can be diagnosed, if any one value of fasting plasma glucose (FPG), 1-h and 2-h PG concentrations meet or exceed 5.1 mmol/L, 10.0 mmol/L and 8.5 mmol/L respectively, with 75g oral glucose tolerance test (OGTT) (Metzger et al., 2010).
India one of the most populous countries in the world was not part of the HAPO study. Hence the authors group undertook a prospective, collaborative study to ascertain whether

the present practice of diagnosing GDM by the guidelines recommended by Diabetes In Pregnancy Study Group India (DIPSI) (Seshiah et al., 2009) based on WHO criterion of 2-h PG ≥ 7.8 mmol/L can still be followed in India or adopt IADPSG recommendations. A total of 1,463 consecutive pregnant women with no previous history of GDM/pre GDM underwent a 75g OGTT and fasting, 1-h and 2-h PG were measured. Using the DIPSI criterion, 196 (13.4%) women were diagnosed as GDM. By applying IADPSG recommendation the cumulative prevalence of GDM was 14.6% (n=214). There was no significant difference (P > 0.05) in the discordant pair of diagnosing GDM by the two criteria which in turn implies, that the disagreement in diagnosing GDM by both criteria was not significant (P = 0.21, by Mc Nemar test). The difference in the diagnostic capability between IADPSG and DIPSI was 1.2% which was not significant (P>0.02) (Seshiah et al., 2011). IADPSG recommendation necessarily requires estimation of PG in three blood samples after administrating 75g oral glucose load. Pregnant women despise this procedure, as venous blood is drawn three times and they feel too much of blood is drained. Whereas, DIPSI criterion requires one blood sample drawn at 2-h following a 75g glucose load for estimating the PG. The cost involved in performing IADPSG recommended procedure is high, as this procedure requires three blood tests compared to one blood test of DIPSI. The cost will escalate further, if IADPSG diagnostic procedure is performed in each trimester in high risk population in whom GDM manifests in all trimesters of pregnancy (Seshiah et al., 2007). Among women with normal OGTT results in the first visit when tested in the subsequent visits, 28% of them were detected to have GDM (Seshiah et al., 2007). Hence, DIPSI procedure based on WHO criterion is feasible, sustainable, cost-effective and best buy to diagnose GDM in any country and particularly in less resource nations. IADPSG recommendations are suitable in clinical settings where financial and technical supports are available. The performance of both IADPSG and WHO criteria are similar as per GRADE ratings.

5.3 Inadequacy of fasting plasma glucose to diagnose GDM

The IADPSG criteria suggests FPG ≥ 5.1 mmol/L but ≤ 7.0 mmol/L to diagnose GDM in the first prenatal visit (Metzger et al., 2010) whereas the authors observed in their study that by applying this criterion of FPG ≥ 5. 1 mmol/L, only 24% (3.2% of the total population) of those diagnosed as GDM using WHO criterion 2-h PG ≥ 7.8 mmol/L would have been classified as GDM (Balaji et al., 2011a). Further, FPG of 5.1 mmol/L was not able to diagnose GDM in comparison to 2-h PG ≥ 7.8 mmol/L (Table 2). This is due to the ethnicity of Asian Indians who have high insulin resistance (IR) and as a consequence, their postprandial plasma glucose is higher compared to Caucasians (Mohan et al., 2007; Snehalatha et al., 2009). Asian and South Asian ethnicity are both independently associated with increased IR in late pregnancy (Retnakaran et al., 2006). Siddhartha Das et al documented an increased IR during pregnancy in Asian Indian Women and IR escalates further in GDM (Das et al., 2010). These studies provide evidence that FPG may not be an appropriate option to diagnose GDM in Asian Indian women. Further, in all GDM, the FPG values do not reflect the postprandial hyperglycemia (Valensi et al., 2009), which is the hallmark of GDM (Weiss et al., 2000). In addition, there is a paucity of data regarding the reproducibility of the FPG test (Sacks et al., 2010). Hence, administering 75g oral glucose load and measuring 2-h PG serves as a one-step definitive procedure to diagnose GDM in less serviced regions. Perucchini et al also suggest one-step diagnostic procedure, though their observation was based on different ethnic population (Perucchini et al., 1999).

FPG (mmol/L)	Test positive	2- h PG value		Macrosomia	
		Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
5.0	3.9	29.1 (22.9-36.1)	89.4 (87.6-91.0)	21.2 (12.5-33.3)	87.2 (85.0-89.2)
5.1	3.2	24.0 (18.3-30.7)	93.0 (91.4-94.3)	15.2 (7.9-26.6)	90.2 (88.2-91.9)
5.5	1.8	13.8 (9.4-19.6)	97.4 (96.3-98.2)	6.1 (2.0-15.6)	95.6 (94.1-96.7)
6.1	0.9	7.1 (4.1-11.9)	99.2 (98.5-99.6)	1.5 (0.1-9.3)	98.2 (97.1-98.9)
6.6	0.6	4.6 (2.3-8.8)	99.8 (99.4-100.0)	0.0 (0.0-6.9)	99.3 (98.6-99.7)
2- h PG 7.8	13.4			13.6 (6.8-24.8)	86.3 (84.0-88.3)

Table 2. Performance of FPG test for the predictor of gestational diabetes and macrosomia

5.4 The validation of WHO criterion (DIPSI criterion) based on the fetal outcome

The authors investigated whether the diagnosis of GDM by WHO criterion is rational based on the fetal outcome (N = 1463). Macrosomia was the end point of this study as this is the most common morbidity of GDM (Jovanovic, 2001). They observed that there was no statistically significant difference in the mean birth weight of neonates born to women in the normal glucose tolerance (NGT) and with intervention in GDM groups (P=0.705) (Balaji et al., 2011b). This was due to the medical nutrition therapy (MNT) and/or insulin in maintaining FPG ~ 5.0 mmol/L and 2-h post meal ~ 6.7 mmol/L in GDM women. Intervention helped in maintaining the pregnancy outcome in GDM women equivalent to that of NGT women. Gayle et al also observed that diagnosis of GDM with OGTT 2-h PG ≥ 7.8 mmol/L and treatment in a combined diabetes antenatal clinic is worthwhile with a decreased macrosomia rate and fewer emergency cesarean sections (Gayle et al., 2010). The distribution of birth weight of neonates born to GDM and NGT women were similar (Figure 2) in the study conducted by the authors, indicating that the intervention given to pregnant women with 2-h PG ≥ 7.8 mmol/L had a significant effect in obtaining neonatal birth weight appropriate for gestational age. The level of association between macrosomia and GDM status after controlling the factors: maternal age, gestational age, family history of diabetes and BMI was elucidated. It was found that, the GDM status (2-h PG ≥ 7.8 mmol/L) of the pregnant women after intervention was not associated with macrosomia (adjusted OR = 0.752; 95% CI (0.406-1.390); P=0.363). There are publications confirming that treatment of GDM women as defined by WHO criterion was associated with a reduced risk of pregnancy outcome (Crowther et al., 2005; Gayle et al., 2010). In pregnancy, the decision to perform a placebo controlled trial requires clinical equipoise (Gifford et al., 2001). Hence, in this study, the authors did not have a control group of untreated pregnant women with 2-h PG ≥ 7.8 mmol/L, as there are evidences confirming that the treatment of GDM women as defined by WHO criterion was associated with a reduced risk of pregnancy outcome (Crowther et al., 2005; Gayle et al., 2010). The policy of not treating women with 2-h PG ≥ 7.8 mmol/L amounts to deliberately exposing the pregnant mothers to unphysiological glycemic level despite our extensive knowledge of the benefits of treatment of mild hyperglycemia during pregnancy (Seshiah et al., 2008a; Landon et al., 2009; Bevier et al.,

1999; Negrato et al., 2008). Wahi et al observed in their prospective study, the advantage of adhering to a cut-off level of 2-h PG ≥ 7.8 mmol/L in diagnosis and management of GDM for a significantly positive effect on pregnancy outcomes (Wahi et al., 2011). Fetal exposure to high maternal glucose (1-h PG > 7.2 mmol/L with 50g GCT) in the absence of preexisting diabetes/GDM may contribute to the development of overweight/obesity in the offspring, independent of maternal pre-pregnancy BMI (Deierlein et al., 2011). All these studies validate WHO/DIPSI criterion for the diagnosis of GDM

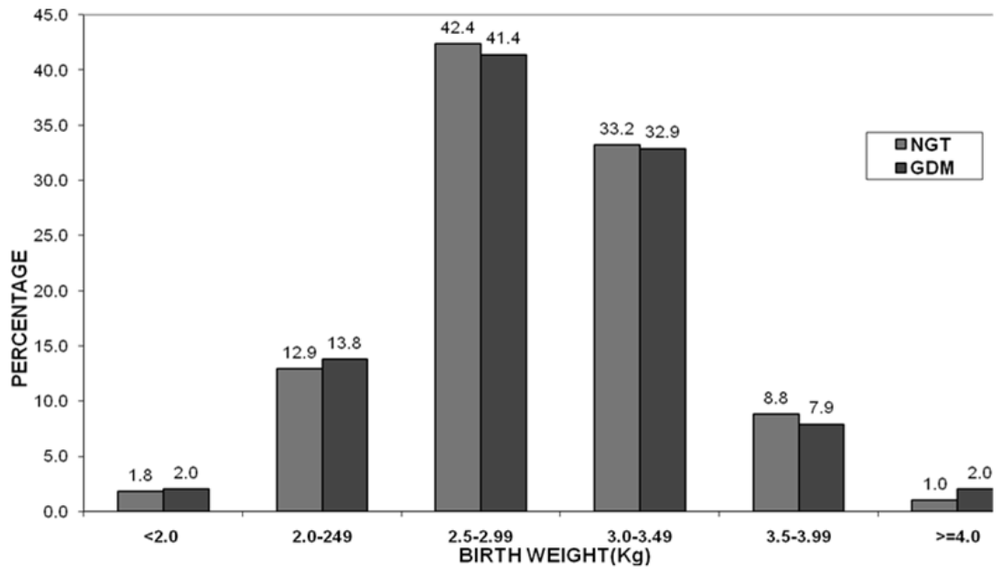

Fig. 2. Neonate Birth weight distribution of women with NGT and GDM

6. Gestational weeks for screening

The current recommendation is to perform screening test between 24 - 28 weeks of gestation, though there are reports that claim, about 40% to 66% of women with GDM can be detected early during pregnancy (Super et al., 1991; Nahum et al., 2002). Nahum et al also suggest that the ideal period to screen for GDM is around 16 weeks of gestation and even earlier in high-risk groups with a history of fetal wastage (Nahum et al., 2002). This is due to the embryological development of fetal β cells. Each islet cell functions as an endocrine organ and differentiates between 10^{th} and 12^{th} weeks of gestation. They recognize and respond to maternal glycemia before 15 weeks of gestation, suggesting that metabolic perturbations are underway before diagnosis and that earlier screening and intervention may be warranted (Tisi et al., 2011). The study performed by the present authors group in the DIPAP project revealed that, 16.3% had glucose intolerance within 16 weeks, 22.4% between 17 - 23 weeks and remaining 61.3% more than 24 weeks of gestation (Seshiah et., 2007). If a pregnant woman has an A1c level > 6%, she is more likely to be an overt diabetic (Balaji et al., 2007). These studies stress the need for screening for GDM during the early weeks of gestation. If the test is normal in the first visit, the test has to be repeated in the subsequent visits. GDM diagnosis may not be missed by screening around 24 -28 weeks of gestation, but a substantial number of pregnant women who develop GDM in the earlier weeks of

pregnancy are likely to have delayed diagnosis and may not receive appropriate medical care. Further, early screening for glucose intolerance and care could avoid some diabetes related complications in women with gestational diabetes (Bartha et al., 2003). To substantiate the above observation the present author's group screened 207 pregnant women attending their referral centre for diabetes and pregnancy with a 75g OGTT (Seshiah et al., 2006). Among them, 87 (42.03%) were diagnosed with GDM. Women in whom GDM was detected between 0 - 23 weeks of gestation were classified as Group 1 [54 (62.7%)] and beyond 24 weeks of gestation as Group 2 [33 (37.93%)]. All of them were treated and followed till confinement. There was no statistically significant difference ($P < 0.05$) between the birth weight of the neonates born to Normal Glucose Tolerance (NGT) women (3.28 ± 0.50 kg) and GDM women in group 1 (3.13 ± 0.55 kg). In group 2, the neonatal birth weight was 3.42 ± 0.58 kg which is the upper limit of the normal range in Indian new born babies. In India, the normal birth weight varies between 2.5 to 3.5 kg (Paul et al., 2002). The observation of this study was that, by early detection of glucose intolerance during pregnancy and by giving adequate care to the antenatal women, a good fetal outcome can be achieved similar to that of NGT pregnant women (Seshiah et al., 2006, 2008b).

7. Management

The goal in the management is to avoid both low birth weight and macrosomic babies, as they are prone to develop diabetes in their adolescent and adult life (Jovanovic, 1998). In India, both under nutrition and over nutrition exists during pregnancy. There are two reported studies in India that relates size at birth to future risk of type 2 DM. In Mysore, low birth weight did not increase the risk of diabetes but babies who were short and fat at birth (higher BMI) were at increased risk (Fall et al., 1998). Fall et al speculate that the rise in type 2 DM in Indian urban populations would have been triggered by mild obesity in mothers, leading to glucose intolerance during pregnancy, macrosomic changes in the fetus and insulin deficiency in adult life (Fall et al., 1998). Yet another study attributes high prevalence of type 2 DM and IGT in Indian people linked to poor fetal growth (Yajnik et al., 1995) which is at variant to Fall *et al* observation (Fall et al., 1998).

7.1 Medical Nutrition Therapy (MNT)

The meal pattern should provide adequate calories and nutrients to meet the needs of pregnancy metabolism. The meal plan advised has to be simple and easy to practice. The MNT recommended is based on their routine diet habit and glycemic excursions that occur with the meal. In a normal person, the peaking of the plasma glucose is high after breakfast (due to 'Dawn phenomenon') than after lunch and dinner, and the insulin secretion also matches the glycemic excursions that occur with these three meals (Polonsky et al., 1988). Since GDM mothers have deficiency in first phase insulin secretion, the quantity of food at one time should also be less, to overcome this insulin deficiency, particularly after breakfast. To avoid the post prandial plasma glucose peaking with breakfast, the authors guide their women with GDM to distribute calorie consumption especially the breakfast into two portions 'Split Breakfast'. This implies splitting the usual breakfast into two halves and consuming these portions with a two-hour gap in between. By this, the undue peak in plasma glucose levels after ingestion of the total quantity of breakfast at one time is avoided.

7.2 Insulin therapy

7.2.1 Human insulin

The policy followed in India is to advise human insulin in women with GDM who failed to achieve FPG of ≤ 5.0 mmol/L and 2-h post meal plasma glucose level of ≤ 6.7 mmol/L with MNT. The aim is to maintain post meal peak plasma glucose level of ≤ 6.7 mmol/L. This time point is suggested as the diagnosis of GDM is made with 2-h PG and it is easy to remember the same timing. A number of studies have established the benefits of maintaining the plasma glucose at this level (Franks et al., 2006; de Sereday et al., 2003; Ben-Haroush et al., 2004). However whichever time is targeted for monitoring glycemic control and adjusting the insulin dose, the blood tests have to be done at the same time at each visit. GDM women usually have high post breakfast plasma glucose level compared to post lunch and post dinner. The period between breakfast and lunch are often problematical because of the physiological tendency to hyperglycemia at this time and may necessitate substantial increases in the morning dose of short acting insulin, together with careful adjustment of meal timing and snacks to avoid pre-lunch hypoglycemia (Langer et al., 2000).

7.2.2 Insulin analogues

Due to the pharmacokinetic action of human regular insulin, a considerable segment of pregnant women with GDM, fail to achieve optimum glycemic control, mostly the post prandial plasma glucose. In them, the best option is to administer ultra short acting analogues, insulin lispro (Humalog) or insulin aspart (Novo rapid). These analogues improve the post prandial glucose control in pregnant women with type 1, type 2 DM and GDM, and are also safe and effective (Hermansen et al., 2002; Jovanovic et al., 1999).

The authors group conducted an open label trial using a large independent cohort of GDM patients to evaluate the efficacy, safety and foetal outcome for Biphasic Insulin aspart (BIAsp 30) compared with biphasic human insulin (BHI 30) in the management of GDM (Balaji et al., 2010). GDM women (N = 323) who remained unable to maintain a FPG ≤ 5.0 mmol/L and 2-h PG ≤ 6.7 mmol/L with MNT were randomly allocated in a 1:1 ratio to receive either BIAsp 30 (Group A) or BHI 30 (Group B). There was no statistical significance in the levels of glycaemic control achieved by the groups by labour onset. However, the mean total insulin dose administered by the last visit was significantly lower for Group A [19.83±15.75 U compared with 26.34±23.15 U for Group B (p=0.006)], implying that those receiving BHI 30 required a higher dose to achieve a similar degree of glycaemic control. The frequency of macrosomia was 6.3% in Group A and 6.9% in Group B. Although the proportion of macrosomia was numerically higher for Group B than Group A, the difference was not statistically significant (p=0.819). It was found that BIAsp 30 was non-inferior to BHI 30 and was well tolerated during pregnancy. Yet in another study, the authors observed that pregnant women found BIAsp convenient as this preparation allows flexibility in the meal time insulin dosing and did not disturb their routine life pattern. Most importantly, BIAsp was found to be safe during pregnancy (Balaji et al., 2010).

7.3 Oral hypoglycemic agents

7.3.1 Glibenclamide

Glibenclamide (Glyburide) may be an alternative safe therapy for many GDM women who are hesitant to take insulin. This drug decreases the insulin resistance and improves insulin secretion, the pathogenic factors in the causation of hyperglycemia in GDM (Groop et al.,

1991; Rossetti et al., 1990). Another advantage is that, the human placental transfer of glibenclamide is negligible. Maternally administered glibenclamide in pharmacologic doses, and even doses greatly exceeding therapeutic levels, may not reach the fetus (Elliott et al., 1991). The landmark study of Langer et al concluded that glyburide was as effective as insulin in maintaining the desired glycemic levels and resulted in a comparable outcome (Langer et al., 2000). The author's group undertook a prospective study comparing insulin and glibenclamide in GDM. In this study, both Glibenclamide and insulin treatment achieved equally good glycemic control and the perinatal outcome was not different (Anjalakshi et al., 2007). The observation of this study was that the mean dose of glibenclamide required at term was 1.45 ± 0.57 mg/day and mean insulin requirement at term was 21.7 ± 13.55 units/day to achieve the same glycemic level (Anjalakshi et al., 2007). It is noteworthy that Glibenclamide is very much economical and cost effective compared to insulin, which is not only expensive but also inconvenient as it has to be taken parenterally. Yet an another observation was that in Indian population, the dose of glibenclamide required is very much less compared to the other published studies (Langer et al., 2005).

7.3.2 Metformin

Women with polycystic ovary syndrome (PCOS) are advised metformin to induce ovulation. The drug is not withdrawn if a woman conceives while on metformin therapy and the maximum dose prescribed in the author's clinical practice is 1500 mg. If the plasma glucose is not under control with metformin, insulin is always added. No adverse pregnancy outcome with metformin therapy was observed. A preliminary study showed that metformin was safe in pregnant, glucose intolerant women either as an adjunct to insulin treatment or even as a monotherapy (Ramachandran et al., 2005). A prospective study found no adverse influence on the pregnancy outcome in PCOS women treated throughout pregnancy with Metformin (Glueck et al., 2004).

Metformin in gestational diabetes (MiG) trial found that in women with gestational diabetes mellitus, metformin (alone or with supplemental insulin) was not associated with increased perinatal complications as compared with insulin (Rowan et al., 2008).

8. Monitoring glycemic control

The success of the treatment for a woman with GDM depends on the glycemic control maintained with meal plan or pharmacological intervention. To know the effectiveness of treatment, monitoring of glycemic control is essential.

- Once diagnosis is made, medical nutritional therapy (MNT) is advised initially for two weeks. If MNT fails to achieve control i.e., FPG ≥ 5.0 mmol/L and/or 2-h PG ≥ 6.7 mmol/L, insulin may be initiated.
- Once target blood glucose is achieved, woman with GDM till the 28th week of gestation require laboratory monitoring of both fasting and 2-h post breakfast once a month and at other time of the day as the clinician decides.
- After the 28th week of gestation, the laboratory monitoring should be more frequent atleast once in 2 weeks, if need be more frequently.
- After 32 weeks of gestation, laboratory monitoring should be done once a week till delivery
- In high risk pregnancies, frequency of monitoring may be intensified with self monitoring of blood glucose (SMBG).

- Continuous glucose monitoring devices are available but these equipments need special training and are expensive. These devices may be useful in high risk pregnancies to know the glycemic fluctuations and to plan proper insulin dosage.

8.1 Glycosylated haemoglobin – A1c levels

If the glucose intolerance is detected in the early pregnancy, A1c level will be helpful to differentiate between a pre gestational diabetic and GDM. If A1c level is more than 6% (Balaji et al., 2007), the chances are that she may be a pre GDM or GDM, in whom the glucose intolerance was detected in the early weeks of pregnancy; all the more validating that the screening needs to be performed in the early weeks of gestation. The estimation of A1c may help in distinguishing a pre GDM from an early onset GDM, but not essential, as this differentiation is of no consequence in clinical practice, as the treatment approach is going to be the same (Seshiah et al., 2007). Further, A1c is not estimated in the community health centres, barring a few tertiary care hospitals due to the difficulty in standardization, inadequate technical support and the cost.

8.2 Measuring other parameters

The blood pressure has to be monitored during every visit. Examination of the fundus and estimation of microalbuminuria, every trimester is recommended.

8.3 Ultrasound fetal measurement

The management of gestational diabetes, based on the foetal growth by ultrasonogram demands that the fetus at risk must first manifest overgrowth before treatment decisions are made. Further, the cost of performing a number of ultrasonograms to monitor the foetal growth and recommending therapy has to be kept in mind. Until there is evidence to absolutely prove that ignoring maternal hyperglycemia when the fetal growth patterns appear normal on the ultrasonogram, it is prudent to achieve and maintain normoglycemia in every pregnancy complicated by gestational diabetes.

9. Target glycemic level

Increased birth weight of neonates occurred even when the mother's glucose tolerance was less than the glycemic criteria recommended by WHO (2-h PG > 7.8 mmol/L) for diagnosis of GDM. Increasing carbohydrate intolerance in women without overt GDM was associated with graded increase in the incidence of macrosomia (Sermer et al., 1998). The author's group documented that the occurrence of macrosomia was continuum as the FPG increased > 5.0 mmol/L (Seshiah et al., 2008c) and the 2-h PG > 6.7 mmol/L (Balaji et al., 2006). Thus maintenance of mean plasma glucose level ~ 5.8 to 6.1 mmol/L is desirable for a good fetal outcome (Langer et al., 1989). This is possible if FPG and peak postprandial glucose levels are maintained ~ 5.0 mmol/L (4.4-5.0 mmol/L) and ~ 6.7 mmol/L (6.1 – 6.7 mmol/L, respectively)

10. Prevention of type 2 dm

The screening for glucose intolerance during pregnancy is not done routinely and probably the undiagnosed glucose intolerance that has been occurring in the past has resulted in the

increased prevalence of diabetes in India. This is likely to be true as GDM has a far reaching consequence in predisposing their offsprings to glucose intolerance. This observation was substantiated and documented in Pima Indians (Dabelea et al., 2000). The children born in 1965 to women with GDM were followed up till 2000. By the time they reached 35 years, more than half of the group had diabetes (Dabelea et al., 2000). Hence as a policy to identify GDM and its consequences on the infant, a 75 g OGTT has been recommended to all women in the population during the third trimester of pregnancy (Dabelea et al., 2000). Now it is obvious that taking care of women with GDM is the first step in the primary prevention of diabetes.

The important aspect of diabetes and pregnancy is that, the intrauterine millieu interieur, whether one of nutritional deprivation or one of nutritional plenty, results in changes in fetal pancreatic development and peripheral response to insulin that may lead to adult-onset GDM and type 2 DM (Savona-Ventura & Chircop, 2003). Thus, the timely action taken now in screening all pregnant women for glucose intolerance, achieving euglycemia in them and ensuring adequate nutrition may prevent in all probability, the vicious cycle of transmitting glucose intolerance from one generation to another (Aerts, 2004). GDM offers an important opportunity for the development, testing and implementation of clinical strategies for diabetes prevention (Buchanan et al., 2007).

'No single period in human development provides a greater potential than pregnancy for a long range pay off via relatively short range period of enlightened metabolic manipulation' - Norbert Frienkel.

11. Summary

- GDM women are at increased risk of future diabetes as are their children and following generations.
- Prevalence of GDM varies from one region to another region in the same country.
- Compared with selective screening, Universal screening for GDM detects more cases and improves maternal and offspring prognosis.
- Asian women are ethnically more prone to develop glucose intolerance compared to other ethnic groups.
- GDM based on 2-h 75g OGTT defined by WHO predicts adverse pregnancy outcome and warrants treatment.
- A 2-h 75g post plasma glucose ≥ 7.8 mmol/L serves both as screening and diagnostic criteria which is a technically simple economical and evidence based one step procedure.
- IADPSG recommendations are suitable in clinical settings where technical and financial supports are available.
- Early screening for glucose intolerance and care could avoid some diabetes related complications in women with gestational diabetes
- Women with NGT in the first visit are advised to undergo glucose tolerance test in the subsequent trimesters.
- The meal pattern advised has to be simple, and easy to understand and follow.
- The goal is to maintain mean plasma glucose of 5.8 to 6.1 mmol/L
- Occurrence of macrosomia was continuum as the FPG increased from 5.0 mmol/L and 2-h PG increased from 6.7 mmol/L.

- At least one point testing in the third trimester of measuring haemoglobin, blood pressure and plasma glucose in pregnant women will go a long way in achieving safe maternal and fetal outcome.
- Taking care of women with gestational diabetes is envisaged as the first step in the primary prevention of diabetes.

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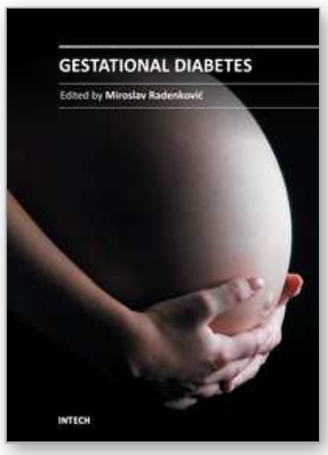

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Gestational diabetes mellitus is defined as hyperglycemia with onset or first recognition during pregnancy. The incidence of gestational diabetes is still increasing and this pathological condition has strong association with adverse pregnancy outcomes. Since gestational diabetes can have long-term pathological consequences for both mother and the child, it is important that it is promptly recognized and adequately managed. Treatment of gestational diabetes is aimed to maintain euglycemia and it should involve regular glucose monitoring, dietary modifications, life style changes, appropriate physical activity, and when necessary, pharmacotherapy. Adequate glycemic control throughout the pregnancy can notably reduce the occurrence of specific adverse perinatal and maternal outcomes. In a long-term prospect, in order to prevent development of diabetes later in life, as well to avoid associated complications, an adequate education on lifestyle modifications should start in pregnancy and continue postpartum.

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