UPDATE ARTICLE

Targeting Glycemic Level in Gestational Diabetes Mellitus to that of Normal Pregnancy would result in a better Maternal-Fetal Outcome

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Abstract

Women with a history of Gestational Diabetes Mellitus (GDM) are at increased risk of future diabetes and related Non-Communicable Diseases (NCD) as are their offspring. "Transgenerational transmission occurs". Independent of genetic risk, offspring of hyperglycaemic pregnancies are at increased risk of early onset type 2 diabetes mellitus (Type 2 DM) and obesity. Differences exist in offspring risk of diabetes and obesity based on time and type of diabetes exposure in utero. There is a risk gradient, wherein type 2 DM exposure confers greater risk and reduces time to development of type 2 DM in the offspring compared with exposure to GDM and no diabetes exposure. These data suggest, glucose dose dependence in risk transmission. Given that the age of onset of prediabetes and type 2 DM is declining many reproductive age women may have undiagnosed diabetes or dysglycaemia when they become pregnant. This has great public health significance and it has become imperative that all pregnant women should be screened for hyperglycemia even if they have no symptoms. Ministry of Health, Government of India has developed the national guidelines for testing, diagnosis and management of hyperglycemia in pregnancy. These guidelines recommend early testing at booking, to be repeated again between 24-28 weeks if negative at first testing. The guideline also recommends that GDM can be diagnosed if the 2 hr PG is ≥140mg/dl after 75 gm of oral glucose administration without regard to the time of the last meal (i.e., fasting or non-fasting). This approach has also been endorsed by International Diabetes Federation (IDF), World Health Organization (WHO) and International Federation of Gynaecology and Obstetrics (FIGO) for resource constrained settings.

The aim should be to target new born baby's birth weight, appropriate for gestational age (2.5 to 3.5 kg) to prevent the offspring developing NCD in the future. For this to happen early diagnosis and tight maternal glucose control during pregnancy similar to glycaemic level in the normal pregnancy, (FPG between 80 and 90 mg, 2 hr. post prandial between 110 and 120 mg) is necessary.

Introduction

The IDF Diabetes Atlas 8th edition published in 2017[1] revealed an alarming 180% increase in the prevalence of diabetes in the world from 151 million in 2000 to 425 million in 2017. How can we arrest or slow down this rising trend and what should be the focus of public health policy? These are questions that need serious consideration. While several reasons are ascribed for this rising trend including aging population, urbanization, nutrition and lifestyle transition, genetic predisposition etc., one factor that has not received adequate attention is the concept of intrauterine programing.

David Barker's, "Fetal Origin of Adult Diseases theory" conceptualized that the body's susceptibility to "lifestyle" diseases was programmed in the intrauterine period. Intra uterine programming is a process whereby stimuli or stresses occurring at critical or sensitive periods of fetal development permanently change structure, physiology, and metabolism, thereby predisposing individuals to disease in adult life.

If the stimulus happens to be hyperglycemia in pregnancy (HIP), the consequent abnormal maternal metabolic environment affects the developing fetal tissues, organs and control systems in complex ways which eventually lead to permanent functional changes in adult life. The quantum of hyperglycemic exposure in terms of duration and degree are relevant, as is the timing of the onset of exposure in the course of pregnancy. Early exposure during fetal organogenesis and placental development has relatively more severe and lasting consequences then later exposure. Depending upon the timing and quantum of exposure to the aberrant fuel mixture (embryonic-fetal), different effects may occur including abortion, congenital anomalies, macrosomia and large of gestational age (LGA), intrauterine growth restriction (IUGR) and small for gestational age (SGA), intrauterine death and still births etc. In addition, independent of genetic risk, offspring of hyperglycaemic pregnancies are at increased risk of early onset type 2 DM and obesity. Differences exist in offspring risk of diabetes and obesity based on time and type of diabetes exposure in utero. There is a risk gradient wherein intrauterine type 2 diabetes exposure confers relatively greater risk and reduces time to development of type 2 diabetes in offspring compared to exposure to GDM and no diabetes exposure. These data suggest that there is glucose dose

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dependence not only in the immediate poor pregnancy outcomes but even in transmission of risks for future type 2 DM. As offspring of mothers with HIP are at a heightened risk of early-onset obesity, pre-diabetes, and T2DM;[2,3] female offspring of mothers with HIP also are highly vulnerable to hyperglycaemia during pregnancy thus creating a multigenerational impact. Pregnancy maybe considered a multiplier of the unfolding pandemic of diabetes, obesity and cardiovascular diseases.

A negative correlation has also been shown between severity of maternal hyperglycemia and offspring performance on various neurodevelopmental and behavioral tests.[4] Compared with children unexposed to diabetes in utero, children exposed to diabetes have been reported to be at higher risk for Attention Deficit Hyperactivity Disorders (ADHD)[5], Autism Spectrum Disorders (ASD) and intellectual disabilities (IDs).[6,7] A more marked effect has been reported with combined exposure to maternal pre-pregnancy obesity and diabetes.

Additionally women with GDM have a high vulnerability for future Type 2 DM and GDM is considered the most reliable marker for it[8] and cardio metabolic disorders in women;[9] with a proven possibility for prevention or delaying onset through appropriate post-partum lifestyle interventions.[10,11]

Maternal Glucose Level and Fetal Growth

Higher glucose transfer as a consequence of maternal hyperglycemia stimulates the developing fetal pancreatic β-cells to start secreting insulin earlier and in higher quantity resulting in fetal hyperinsulinemia which in turn increases fetal glucose utilization and fat deposition with resultant macrosomia. Once initiated fetal hyperinsulinemia becomes self-perpetuating. By improving glucose utilization in the fetal compartment it increases the glucose concentration gradient across the placenta, further increasing glucose flux to the fetus requiring more fetal insulin secretion.[12] This may sometimes help lower maternal glucose level as well, but favors a persistently high glucose flux even when maternal blood glucose is not very high. This phenomenon is called the "fetal glucose steal" syndrome; wherein, a hyperinsulinemic macrosomic fetus apparently helps to attenuate and "normalize" maternal glucose despite poor maternal metabolic control. It provides an explanation for why some mothers with fetuses with all the characteristics of diabetic fetopathy have apparently "good" glucose control[13]. Conversely, maternal hyperglycemia through its effect on poor placentation may cause IUGR. Compared to GDM, pre pregnancy diabetes (PDM) both type 1 and 2 is relatively more likely to be associated with poor placentation and SGA babies.

Postprandial hyperglycemia plays a more important role in causing fetal overgrowth. Data suggests that postprandial glucose levels more closely relate to macrosomia risk compared to fasting glucose levels.[14,15] Based on studies in preterm births renal threshold for glucose in the fetus is probably <110 mg/dl.[16] When maternal glucose level is >110 mg/dl, the fetal blood glucose load causes fetal glycosuria and consequently a glucose-enriched amniotic fluid. After 20 weeks of gestation, the fetus begins to swallow the amniotic fluid. In addition to the placental transfer of glucose, ingested high glucose amniotic fluid also stimulates insulin secretion. Thus, even transient elevations of blood glucose on the maternal side not only result in elevations of blood glucose on the fetal side but also provide for glucose ingestion by the fetus for many hours. Thus, post prandial hyperglycemia for <1 h once a day in the mother may produce fetal insulin stimulus, through the oral route for hours. Elevations of maternal glucose levels more frequently (after every meal, for example) may produce a more prolonged oral glucose load for the fetus resulting in an overfed fat fetus.[17]

Implications for public health policy

Whom to test?

Women with a history of GDM are at increased risk of future obesity, type 2 diabetes and cardio metabolic disorders, as are their children.[18] Thus, GDM may play crucial role in the increasing prevalence of diabetes and cardio metabolic diseases. One of the highest prevalence of HIP is highest in South Asia (26.6%). It is obvious that all pregnant women should be screened for hyperglycemia even if they have no symptoms.[19]

How to test?

Given the load of testing over 30 million pregnant women in India what should be the best testing strategy? Some organizations and countries while accepting universal testing recommend a two-step approach – a 50 g non fasting glucose challenge test (GCT) followed by a 75 g OGTT in women who test positive on initial screening. This reduces the number of OGTTs and ensures that women diagnosed with GDM have 'significant glucose intolerance'.[20] However, it does not take into account that the GCT also misses around 25% of cases with OGTT abnormalities and in particular fails to identify women manifesting only fasting hyperglycemia as they do not qualify for the OGTT.[20] Moreover, a significant proportion of women fail to complete the evaluation as they do not turn up for the OGTT.[21] This approach therefore may miss many women with HIP.

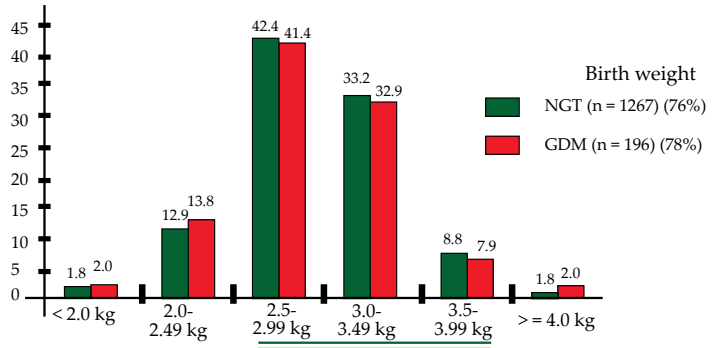
There is also the issue of one abnormal reading versus two abnormal readings as required by some guidelines (Carpenter and Coustan and NDDG). All dysglycaemic states (diabetes, IFG, IGT) are diagnosed based on single abnormal values. Surely, pregnancy where any degree of dysglycaemia has multi-generational consequences should be taken more seriously!

International Association of Diabetes in Pregnancy Study Group (IADPSG) guideline[22] while recommending universal testing using a one step procedure and one abnormal value as being diagnostic may still not be relevant and applicable everywhere, and in particular countries like India. For sake of uniformity while it would be desirable to have uniform global diagnostic cut off values, in view of the continuous linear association between maternal glycaemia and perinatal outcomes any set of diagnostic criteria proposed will need to evolve from a consensus approach, balancing risks and benefits in particular social, ethnic, economic and clinical contexts.[23] The IADPSG 2 hr cut off value is based on the 1.75 odds ratio for macrosomia of the HAPO cohort (Caucasian population) and it may not be as efficient in identifying women

Table 1: GDM diagnosis and management – DIPSI guidelines (RCT)

Parameter	Control (n=140)	GDM with treatment (n=70)	GDM not accepted Rx (n=62)	P value
Still birth	-	-	3 (4.84)	
Preterm* < 37 weeks	4 (2.8%)	3 (4.2%)	10 (16.13%)	0.006
Respiratory distress syndrome RDS	-	-	2 (3.23)	
Macrosomia > 4 kg	4 (1.4%)	1 (2.8%)	6 (9.6%)	0.03

This study proves advantages of adhering to DIPSI guidelines in the diagnosis (2 hr PG ≥ 140 mg/dl) and management of GDM for a significantly positive effect on pregnancy outcome



The birth weight distribution was similar between NGT and GDM women. The GDM status (2-h PG ≥ 140 mg/dl) of the pregnant women after intervention was not associated with macrosomia [Adjusted OR 0.752; 95% CI (0.406-1.390); p = 0.363)]

Fig. 1: Neonate birth weight distribution of women with NGT and GDM

at risk for fetal overgrowth as those identified by having a 2-h glucose corresponding to a slightly lower odds ratio, e.g. 1.5. The latter corresponds to the older WHO criteria 2 h. value of 7.8 mmol/L or 140 mg/dl. This maybe of importance in the developing countries particularly in South Asia where women are relatively small and a larger baby may pose greater obstetric risk[19] as well as be a marker for higher future diabetes risk. IADPSG guideline validity has become questionable as one of the authors of IADPSG guideline has recently commented that "even at centers", that accepted IADPSG recommendation, the approach varies and needs revision for standardization of the strategy for diagnosing GDM.[24] South Asian population phenotype is different, one size does not fit all, and where possible, diagnostic threshold should be adapted using local data.[19,25] The guideline and diagnostic criteria should be simple and feasible on the ground particularly when applied on a large scale at a public health program level.[26]

WHO while endorsing the IADPSG criteria described the quality of evidence for its recommendation as "very low" and the strength of its recommendation is "weak". "WHO made a few important and pertinent observations with regard to GDM testing. OGTT is resource intensive and many health services, especially in low-resource settings, are not able to routinely perform OGTTs in pregnant women. In these circumstances, many health services do not test for hyperglycemia in pregnancy. For a pregnant woman, the request to attend fasting for a blood test may not be realistic because of the long travel distance to the clinic in many parts of the world, and increased tendency to nausea in the fasting state. Consequently, non-fasting testing may be the only practical option.[28]

Diabetes in Pregnancy Study Group India (DIPSI) and South Asian Initiative for Diabetes in Pregnancy (SAIDIP) recommend "a single step procedure" for diagnosing GDM using a single 2 hr PG value ≥ 140 mg/dl after 75g oral glucose administration without regard to the time of the last meal (i.e., fasting or non-fasting).[29]

DIPSI guideline is evidence based. In an RCT by Wahi et al[30] to test the validity of the DIPSI guideline 272 pregnant women were studied. Of these 140 were normal glucose tolerant (Group 1), 70 women with GDM received treatment (Group 2) and 62 women declined treatment (Group 3). The incidence of macrosomia and preterm birth was 1.4% and 2.8% in Group 1, 2.1% and 4.2% in Group 2 and 9.6% and 16.1% in Group 3. The prevalence of large babies > 4 kg was significantly higher in GDM without treatment group (p =0.02, c2 = 5.19) when compared to GDM with treatment. The study demonstrated that compared to normal glucose tolerant Indian women, those diagnosed with GDM using DIPSI guideline and not receiving standard treatment were at much higher risk of macrosomia and preterm birth, whereas the risk of these complications were considerably reduced among women with GDM who received treatment. The study concluded that the use of DIPSI guideline to diagnose and manage GDM has a significantly positive effect on pregnancy outcome[30] (Table 1). In another study Balaji et al included 1267 pregnant women who had normal glucose tolerance (NGT) and 196 with GDM diagnosed using DIPSI guideline and who received treatment. Follow up, showed that the birth weight distribution between NGT and GDM women was similar because the GDM status was corrected by treatment[31] (Figure 1). It can be concluded from the above and other published studies[31,32] that the diagnosis of GDM with 2-h PG ≥ 140 mg/dl and treatment is worthwhile and is associated with a decreased incidence of macrosomia, fewer emergency cesarean sections, serious perinatal morbidity and improved health-related quality of life.

The Ministry of health and family welfare Govt. of India has also endorsed the DIPSI guideline and recommends the single step testing using 75g oral glucose and measuring plasma glucose 2 hour after ingestion of 75g glucose dissolved in 300 ml water irrespective of whether the woman comes in the fasting or non-fasting state and irrespective of the last meal time.[33] A plasma standardised glucometer should be used to evaluate blood glucose 2hour after the oral glucose load. If vomiting occurs within 30 min of oral glucose intake, the test has to be repeated the next day, if vomiting occurs after 30 minutes, the test is continued. The threshold plasma glucose level of ≥140 mg/dl (more than or equal to 140) is taken as cut off for diagnosis.[33] Laboratory glucose measurement is often not available in less resource settings and testing with a portable glucometer is the only option.[28]

The International Federation of

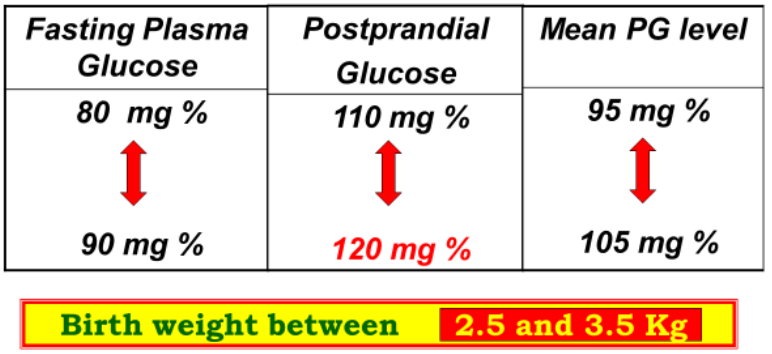


Fig. 2: Target blood glucose level and birth weight

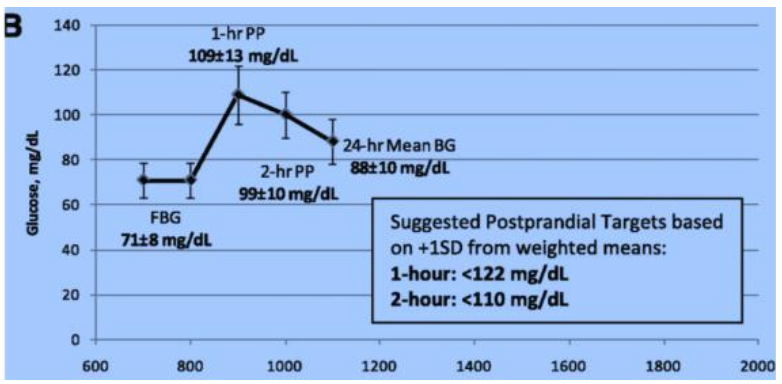


Fig. 3: Pattern of glycaemia in normal pregnancy (adopted from Hernandez)

Gynecology and Obstetrics (FIGO) in its pragmatic and widely accepted International guideline endorsed the DIPSI single step approach and recommended its use in the Indian sub-continent.[19]

The FIGO and IDF joint statement and declaration on hyperglycemia in pregnancy states that all pregnant women attending health facilities should be tested for hyperglycemia using a single-step procedure, as advocated by FIGO, IDF and WHO.[34]

When to test?

The standard practice is to test women for GDM between 24 and 28 weeks of gestation, however these recommendations are changing. The fact that undiagnosed diabetes in pregnancy has much severe consequences for both the mother and the fetus, it is now recommended that pregnant women without known diabetes should be tested for hyperglycemia at first booking to rule out any preexisting diabetes.[19]

There is also evidence to suggest that women may manifest hyperglycemia early in pregnancy as a consequence of higher insulin resistance and/or reduced capacity to increase insulin secretion resulting in earlier decompensation manifesting as early onset GDM.[35] There are reports that claim that between 40% and 66% of gestational diabetes can be detected in early pregnancy.[36-38] A cross-sectional observational study from India reported that 31.5% and 43.2% of all GDM cases were diagnosed during testing in the first and second trimester respectively.[39] Similar high rates of GDM diagnosis in the first and second trimester have been reported from Sri Lanka. Given this one would recommend testing at booking and if negative testing again in second and third trimester particularly if risk factors such as overweight and obesity, high maternal age, bad obstetric history, excessive weight gain and family history of diabetes particularly maternal diabetes are associated.[40] For this, the glycemic control has to be optimized from the early weeks of pregnancy. Testing for glucose intolerance only between 24 – 28 weeks is not prudent.

How good should glycemic control be?

Glycaemic control has to be optimal from early weeks of pregnancy to prevent the development of fetal hyperinsulinemia. As observed by Norbert Freinkel "No single period in human development provides a greater potential (than pregnancy) for long-range 'pay-off' via a relatively short-range, period of enlightened metabolic manipulation". In the Indian setting achieving new born birth weight between 2.5 and 3.5 kg (Figure 2) should be the aim, as both low birth weight babies and large for gestational age babies are prone to develop diabetes in the future.

Hernandez et al.[41] have systematically reviewed and pooled more than 45 years of normal pregnancy glucose data. They showed that normal glucose pattern were very similar across different studies, and glucose level were generally lower than expected, including FBG of 3.9 ± 0.4 mmol/L, one-hour postprandial glucose of 6.0 ±0.72mmol/L, two-hour postprandial glucose of 5.5 ± 0.55mmol/L, and 24hour mean of 4.9 ± 0.55mmol/L.

Historically, the treatment goal in pregnancies complicated by diabetes has been to mimic pattern of glycaemia in normal pregnancy.[42]

The success of prevention of type 2 DM entirely depends on aiming for target glycemic level, that is, maternal glucose should be maintained similar to non-diabetic pregnant women Figure 3.

It has been documented that occurrence of macrosomia has a continuous relationship to the 2hr plasma glucose above 120 mg/dl (adjusted odds ratio 3.02 [95% CI 1.30 – 7.00], $P < 0.05$]);[43] and to fasting plasma glucose which becomes significant above 90 mg/dl (adjusted odds ratio 2.08 [95% CI 1.24 – 3.48], $P = 0.005$].[44] FBG < 90 mg/dl prevents macrosomia as well as other adverse outcomes, such as preeclampsia and contrary to belief, neonatal hypoglycemia doesn't occur in women with GDM.[45] Pregnant women experience less hypoglycemia in response to exogenous insulin in comparison to non-pregnant subjects.[46] Hence, any recommendation to maintain FPG at 95 mg/dl is not equipoise.

Conclusion

Preventive measures against Type 2 DM should ideally start even before conception (being conceived by healthy parents is the best gift a child can receive) but certainly during intra uterine period and continue throughout life from early childhood. It is necessary to optimize metabolic control early in pregnancy. This will necessitate pre-

pregnancy planning for women with pre-existing diabetes, as well as for those at increased risk of GDM, and better means to normalize glycemia. It also requires that all women are tested early and appropriately using a single step procedure and receive good care to ensure optimal glucose control is achieved early in pregnancy and is maintained throughout pregnancy.

1. One test with 75gm oral glucose in the fasting or non-fasting state.
2. One value to diagnose GDM. 2hr PG ≥140mg/dl.
3. One target for monitoring Mean Plasma Glucose 105 mg/dl

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