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Most Appropriate Gestational Age for OGTT amongst High-Risk Pregnant Patients? Need for RCT

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Abstract **Review Article**

High risk for gestational diabetes mellitus includes mothers with certain ethnicities, increasing maternal age, mothers with history of high or low birth weights, rising parity, previous macrosomic baby, stillborn baby, a family history or first degree relative with gestational diabetes (GDM) and type 2 diabetes mellitus, history of glucose intolerance or GDM, polycystic ovarian syndrome and maternal obesity. Timely screening, hence intervention can prevent complications of GDM to fetus and mother. Studies investigating, when during pregnancy should this high-risk group be screened, have established that 24-28 weeks OGTT have missed a few early onset GDM cases and booking visit OGTT/12 weeks gestational age OGTT may miss late onset GDM cases. All these studies have either been retrospective or comparison groups have been mis-matched. To date there is no prospective direct comparisons, comparing early OGTT results (12 weeks gestation) and late OGTT results (24—28weeks gestations). Physiologically speaking, stress of pregnancy is higher with advancing age of gestation and 24-28 weeks gestational age OGTT seems appropriate however evidence suggests that a few early onset GDM cases are missed. There is a need for prospective comparison at two different time intervals in same group of these high risk patients to answer this question.

Keywords: gestational diabetes (GDM), ethnicities, pregnancy, OGTT.

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INTRODUCTION

Gestational diabetes mellitus (GDM) is a well-known pregnancy-related complication, where hyperglycemia can lead to many complications for both mother and the baby [1].

International Diabetes Federation (IDF) recently published that gestational diabetes mellitus affects about 14% of pregnancies in the world, which accumulates to approximately 18 million births every year [2]. Timely diagnosis hence timely management can be immensely helpful for this relatively large, at risk population group.

On basis of Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study [3] outcomes and following the latest WHO recommendations, GDM is diagnosed if:

i. Fasting plasma glucose level is more than 92 mg/dl.
ii. 1 h level exceeds 180 mg/dl or
iii. 2 h level exceeds 153 mg/dl after glucose loading (OGTT international consensus criteria).

Any one of the above will warrant diagnosis of GDM and strict metabolic control would be deemed mandatory.

There is well-reported concern about the rising incidence of gestational diabetes mellitus, its complications for pregnant mothers and newborns and its effects on the public health [4]. Numerous risk factors are related to raising the likelihood of gestational diabetes mellitus. These include background of some ethnicities (South East Asian, African, Native American, Pacific Islander and Hispanic), increasing maternal age, the mother with history of high and low birth weights, rising parity, a previous macrosomic baby, stillborn baby, a family history or first-degree relative with GDM and diabetes mellitus [5], a past history of glucose intolerance or GDM [6], polycystic ovarian syndrome [7] and maternal overweight or obesity [8].

HORMONAL HOMEOSTASIS IN PREGNANCY

Placental hormones including human placental lactogen, prolactin, progesterone, cortisol, released heavily from mid-pregnancy onwards add to decreased

insulin action during pregnancy [9]. It has been hypothesized that these hormones are needed to make sure sufficient nutrients transport to the fetus promoting growth. In an uncomplicated pregnancy, the action of above mentioned placental hormones is adequately compensated through increased release of insulin, creating a regulated insulin release from the mother.

With abnormal glucose tolerance for the high-risk group patients, pregnant mother's insulin resistance resulting from being pregnant is not adequately compensated for, leading to further glucose intolerance. It is hypothesized that mothers who develop GDM must have underlying insulin resistance, for example, due to high maternal adiposity and beta-cell malfunction. Both these increase the insulin resistance of pregnancy [9-11]. Inflammation has been proposed as a possible cause of this phenomenon as well [11].

During pregnancy, a mother's body undergoes a number of compensatory physiological changes including insulin sensitivity, to accommodate the needs of the growing fetus. In earlier phases of pregnancy, insulin sensitivity does increase, leading to increased uptake of glucose into cells in preparation for the energy demands of later pregnancy [12]. But, as the pregnancy is advanced into middle and later stages, there is a surge amongst local and placental hormones, for example estrogen, progesterone, leptin, cortisol, placental lactogen, and placental growth hormone. Collectively this altogether worsens the state of insulin resistance [13].

Animal studies have revealed that the pregnant females develop hypertrophy and hyperplasia of pancreatic β-cells, along with increased glucose-stimulated insulin secretion (GSIS) to cope with changing physiological demands [14].

Maternal hyperglycemia leads to increased glucose transfer to the fetus across the placenta, leading to fetal hyperinsulinemia and may be responsible for later on increased glucose intolerance in life of the fetus [3].

Widely accepted prevention strategy & treatment for gestational diabetes mellitus, other than lifestyle changes involving diet with exercise and sometimes insulin therapy, seems lacking. Although some oral hypoglycemic medications, like metformin and glyburide, are showing good results, however their long-term safety for the mother and the child stands in question [15].

With previous lack of consensus amongst international leads on the definitive threshold for the diagnosis of GDM, the latest recommendation as it stands for now is to use International Association of Diabetes and Pregnancy Study Group (IADPSG) cut-offs be used in the diagnosis of GDM (16) as derived from outcomes from Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) Study—a large multinational and multicenter study including 23,000 pregnant women [3].

One significant finding of the HAPO Study was a continuous risk of adverse maternal and fetal outcomes with increasing maternal glycaemia, even when below the diagnostic threshold for GDM. Raising the question that the criteria for intervention needed to be lowered. The IADPSG, therefore, recommended that all women undergo a fasting plasma glucose (FPG) test at their first prenatal visit (with a reading ≥of 92 mg/dL confirms gestational diabetes diagnosis). The pregnant ladies with fasting plasma glucose below 92 mg/dL undergo a 2-h 75 g oral glucose tolerance test (OGTT) sometime between 24 and 28 weeks gestation. However, doing 2hrs OGTT being traditionally more accurate towards diagnosing GDM, would be a better option to help diagnose GDM early on, rather than by 24—28weeks gestation, therefore helping avoid missing early onset GDM cases. Equally, lowering the diagnostic criteria can increase the cost of care substantially [17].

Recently there has been a debate between specialists around the world on the IADPSG criteria whether it needs to be modified, “only” for women at-risk, in other words, ladies with advanced age, overweight or obese, those from the high-risk ethnicity groups, or those with diabetes mellitus in the family. Contrary to this though, some studies suggest that such efforts are likely to miss a substantial number of GDM cases without significantly reducing the costs [18-20]. These opposing studies just worked on risk factor groups vs generalized assessment however both groups were tested at same age of gestation and not as soon as possible versus 28-32 weeks gestation. To-date, general IADPSG criteria are the most widely advised and practiced guidelines today. Table 1 below shows different cut offs used internationally for diagnosing GDMs. Only National institute for clinical excellence of the United Kingdom (NICE) suggests doing “OGTT as early in pregnancy as possible” for high-risk pregnant patients.

Table 1: Plows *et al*., (21) showing various criteria for gestational diabetes mellitus (GDM) diagnosis using oral glucose tolerance test

CRITERIA	PREGNANCIES	TIMING OF OGTT	STEPS	GLUCOSE LOAD (g)	GLUCOSE THRESHOLD (mmol/L)			
					FASTING	1h	2h	3h
IADPSGA, 2010 WHO, 2013 ADA, 2016	All	24---28 weeks	1	75	5.1	10.0	8.5	---
NICE 2020	High risk	As early as possible	1	75	5.6	---	7.8	---
American Diabetes Association (ADA) 2004	High and medium risk	14---18 weeks for high risk and 28—32 weeks for medium risk	2	100	5.3	10.0	8.6	7.8
WHO, 1999	All	24—28weeks	1	75	7.0	-------	7.8	---
O'Sullivan 1964	All	24—28weeks	2	100	5.0	9.2	8.1	6.9

These inconsistencies in diagnostic criteria of GDM, make estimates of GDM related outcomes and comparisons among different research studies difficult. However, based on IADPSG's criteria, the International Diabetes Federation (IDF) estimated that around 18 million births (14%) were affected by gestational diabetes, worldwide in 2017 alone [21]. South-East Asia with 24.2% had the highest prevalence of gestational diabetes mellitus, whereas Africa has the lowest prevalence at 10.5%. About 90% of cases of hyperglycemia during pregnancy had occurred in the low- and middle-income countries, where access to maternal healthcare had been limited [22].

RISK FACTORS

A number of risk factors have been associated with GDM. These include maternal overweight/obesity [23], excessive gestational weight gain [24], westernized diet [25], ethnicity [26], genetic polymorphisms [27], advanced maternal age [28], intrauterine environment with low or high birth weight [29], family and personal history of GDM [30], and miscellaneous pathologies involving insulin resistance, for example polycystic ovarian syndrome (PCOS) [31]. Each of these risk factors is either directly or indirectly associated with impaired β-cell function and/or insulin sensitivity.

Diets high in the saturated fats, refined sugars, and red and processed meats are consistently associated with an increased risk of GDM, while diets high in fiber, micronutrients, and polyunsaturated fats are incessantly associated with a reduced risk of GDM [32-34].

Saturated fats directly interfere with insulin signaling [35], and they can also instigate inflammation and endothelial dysfunction—both these factors are pathognomic in GDM [36]. On the other hand, fatty acids derived from fish and seafood including n-3 polyunsaturated fatty acids, have anti-inflammatory properties [32]. The association between processed meat and GDM remains strong, even after amendment for fatty acids, cholesterol, heme iron, and protein content [33]. It has been hypothesized that the by-products of processing of any meat could be caustive factors—such as nitrates (a commonly used preservative in processed meats), or advanced glycation end products (AGEs), which have both been implicated in β-cell toxicity [37, 38]. The inverse association between dietary fibre and GDM perhaps may have been the result of lowered appetite or reduced glucose absorption, reducing demand on β-cells and insulin signaling mediators [33].

Low and high birth weight are likely to risk factors for GDM because of their association with insulin resistance. Low birth weight usually results from undernutrition whilst in the womb, either because of maternal malnourishment or insufficiency of placenta. It is believed that the fetus compensates the lack of nutrition in utero by epigenetically altering the genes expression which are then involved in storing fats, energy consumption, and regulation of appetite. Additionally, animal studies suggest that undernutrition in utero is associated with a reduced β-cell number [39]. These adaptations persist after birth—a phenomenon referred to as "developmental programming" [40]. Whilst potentially beneficial in times of famine, a mismatch between nutritional status in the womb and nutritional status once born may contribute to the development of obesity and metabolic disease [41]. Overnutrition on the other hand, whilst in the womb, which may occur in GDM—can lead to fetal overgrowth. These individuals are more likely to have been exposed to hyperglycemia hence β-cell fatigue even antenatally, making them susceptible to hyperglycemia during times of later on metabolic stress, such as during pregnancy [42].

TIMING FOR SCREENING IN GDM:

The American College of Obstetricians and Gynecologists (ACOG) recommends that "early" GDM screening be considered for high-risk groups (previous history of GDM, known impaired glucose metabolism, and obesity. Hong *et al*., [43] retrospectively studied pregnant ladies with GDM diagnosis who had at least one criterion that would potentially warrant early screening.

Indications for early screening for their study were:

1. Obesity (pre-pregnancy body mass index (BMI) ≥30 kg/m2
2. GDM in a prior pregnancy.
3. Delivery of a macrosomic infant (≥4000 g) in a prior pregnancy

Outcomes were examined for whether a woman underwent early screening (first GDM testing <20 weeks gestation) or routine screening (first GDM testing 24---28 weeks gestation) for GDM. This study found not much benefit of early screening for high-risk mothers however it was retrospective study.

A meta-analysis [44] published in 2018 on GDM in India including Indian studies only, has touched the subject of when to screen during pregnancy. This meta-analysis included studies with data on

1. Screening on GDM
2. Diagnostic criteria for GDM
3. Prevalence of GDM

Out of 1252 studies initially identified, 64 remained after inclusion and exclusion criteria applied. On the question of "when to screen" high risk cases for gestational diabetes, descriptive analysis showed that 11- 60% had develop GDM as early as the first trimester. Equally many GDM cases (16-40%) were missed if screened only at first visit. They advised a first trimester as well as 28th week OGTT to make sure no cases are missed. However that would have significant bearing on the cost. Maternal outcomes, studied were cesarean delivery (any), primary cesarean, preeclampsia, type 2 diabetes (defined on basis of requiring any hypoglycemic medication), and insulin use. Cesarean delivery and preeclampsia were chosen as outcomes because treatment of GDM has been demonstrated to reduce its risk. Use of medications to treat GDM was selected as a marker of severity of GDM. Neonatal outcomes included birth weight, macrosomia (defined as birth weight ≥4000 g), large for gestational age (>90th percentile16), small for gestational age (< 10th centile), birth injury (shoulder dystocia, skull/clavicular/humerus fracture, or brachial plexus injury), gestational age at delivery, and preterm delivery (<37weeks) all of which have been associated with GDM and its treatment.

Corrado and colleagues from Italy in 2012, using IADPSG diagnostic criteria, found that OGTT done in 28 weeks gestation had found prevalence of GDM 11.9% out of 738 pregnant ladies however when using fasting glucose in first trimester as diagnostic criteria, retrospectively, (fasting > 5.1, they found another 29 cases of GDM [45]. However, this was a retrospective study hence limited influence. They concluded advising to do a booking fasting glucose using IADPASG criteria to enhance early diagnosis of GDM.

In an attempt to see if first trimester fasting glucose level could replace 28 weeks OGTT, Lopez [46] studied retrospectively 1425 pregnant ladies, obtaining the sensitivity and specificity of first trimester using fasting glucose levels ≥ 92mg/dL as diagnostic criteria. They found them to be 46.4% and 88.8% when compared against the diagnosis of GDM using Carpenter and Coustan criteria [47]. They concluded that fasting glucose in first trimester was not a good substitute for diagnosing gestational diabetes early.

Trying to evaluate latest evidence for screening with subsequent treatment of GDM, Immanuel and Simmons [48] in 2017 published a systematic review. They concluded based on their evidence that a significant proportion (15-70%) of GDM patients may be diagnosed early in pregnancy depending upon settings used, criteria implemented and screening strategy. In this meta-analysis comprising 13 cohort study they concluded that:

i. Perinatal mortality (relative risk (RR) 3.58 [1.91, 6.71])
ii. Neonatal hypoglycemia (RR 1.61 [1.02, 2.55]) and
iii. Insulin use (RR 1.71 [1.45, 2.03])

Were greater among early-onset GDM women compared to late-diagnosed GDM women, despite the treatment. This raised the question that if despite treatment, outcomes were no different. Therefore, would there be any point in further evaluating this diagnostic query. As they were unable to make a direct comparison between early diagnosed vs late diagnosed GDM, they emphasized the need for randomized controlled trials to investigate benefits from early diagnosis and treatment of early onset gestational diabetes.

Recently, exploring options of screening in first trimester GDM amongst high risk population group, using Tree Age 2016 ® software (Tree Age Software Inc, Williamstown, MA) Walker and colleague [49] published a theoretical decision analytical analysis which led to conclusion that screening was not cost-effective because of an incremental ratio of cost effectiveness as 5.87 when compared against screening with a positivity threshold of Hba1c of 6.4% however with 5.9% threshold cut-off would provide an overall cost savings of $29.72 million.

Another study (50) published their decision analytical model work recently touching similar areas of diagnosis of GDM. Studying ladies with age more than 35yrs they concluded that first trimester fasting plasma glucose screen was cost-saving and more effective.

These two theoretical model publications add to further need to do a proper randomized controlled trial among high risk of GDM pregnancies during early OGTT to get a real time definitive answer.

CONCLUSION

Answer to the question, whether we should be doing OGTT early on in pregnancy amongst high-risk patients has been raised in a number of retrospective studies however there is no direct head-to-head prospective randomized trials comparing early against late OGTT outcomes.

Among high-risk pregnant patients, there is need to do a randomized controlled trials comparing outcomes of the best diagnostic tool for GDM, the oral glucose tolerance test (OGTT) done at 12 weeks/booking visit against 24-28weeks gestational age to get a definitive answer whether should it be a routine to do OGTT as early as possible for at-least this pregnant mothers with high-risk or can be delayed until 24-28weeks gestational age.

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