**Special Editorial**

**Towards a global consensus on GDM diagnosis: light at the end of the tunnel?**

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Hyperglycemia is one of the most common medical complications of pregnancy. The International Diabetes Federation (IDF) estimates that, globally, 1 in 6 of the twenty million annual live births (16.8%) occur to women with some form of hyperglycemia; 16% of these relate to Diabetes in Pregnancy (either pre existing or diagnosed during the index pregnancy) and the remaining 84% to gestational diabetes mellitus (GDM). [1]

**Definitions**

Hyperglycemia in pregnancy (HIP) is a broad term that encompasses various forms of glucose dysregulation seen during pregnancy. It includes diabetes in pregnancy (DIP) as well as gestational diabetes mellitus (GDM). DIP maybe either preexisting diabetes (type 1 or type 2) antedating pregnancy, or overt diabetes (defined by severe hyperglycemia consistent with definitions of diabetes outside pregnancy) that is first diagnosed during pregnancy. When hyperglycemia is first detected on routine testing anytime during the course of pregnancy in women with no previous history of known diabetes, and meets any of the following criteria for diagnosis of diabetes in the non-pregnant state (Fasting Plasma Glucose (FPG) ≥ 7.0 mmol/l or 126 mg/dl and /or 2hr. 75 g OGTT value ≥ 11.0 mmol/l or 200 mg/dl or Random Plasma Glucose (RPG) ≥ 11.0 mmol/l or 200 mg/dl associated with signs and symptoms of diabetes), the condition is called DIP. Hyperglycemia first detected in pregnancy during routine testing (often between 24-28 weeks) which does not meet the criteria for overt diabetes is called GDM. Various diagnostic criteria and glucose cut off values have been proposed by different organizations and professional groups to diagnose GDM.

**Previous controversies**

In the past, diagnostic cut off values for GDM were validated by the future risk of type 2 diabetes with scant attention paid to perinatal outcomes particularly among women with so called ‘mild gestational hyperglycemia’. As a consequence, in many countries around the world only women with risk factors for diabetes are tested for hyperglycemia, and/or testing protocols and diagnostic cut off values are designed to only identify women with more severe hyperglycemia (two step test and two abnormal readings on OGTT often using a higher glucose load and longer testing - 100 g and 3hr versus the normal 2hr 75g OGTT used outside pregnancy). These multiple policies are confusing, cumbersome and difficult to implement in busy clinics and some of them actually impede, rather than facilitate GDM diagnosis!

**New strategies following the HAPO Study**

After the publication of the HAPO study, [2] the International Association of Diabetes in Pregnancy Study Groups (IADPSG) recommended a new diagnostic protocol (universal, single step test using 2-hr 75 g OGTT with one elevated glucose value sufficient for diagnosis). [3] This approach was endorsed by the World Health Organization (WHO) [4] and received support and endorsement of the International Federation of Obstetrics and Gynecology (FIGO) [5] and the IDF [6]. FIGO developed a pragmatic guide for diagnosis, management and care of GDM that accommodated challenges in resource poor settings in different parts of the world. The FIGO pragmatic guide received widespread endorsement from several professional organizations around the world particularly from Europe and high burden low resource countries in the developing world. [5]

GDM according to the IADPSG and WHO criteria is associated with almost twice the risk of large-for-gestational-age babies, increased fetal adiposity, neonatal hyperinsulinemia and preeclampsia, and a 50% higher risk of preterm delivery and shoulder dystocia. [7] The recent publication of the Hyperglycemia and Adverse Pregnancy Outcome Follow Up Study [8] provides further evidence regarding the adverse impact of GDM on long-term maternal and infant health.

Studies in the last decade have already shown significant association between adverse pregnancy outcomes and levels of maternal glucose considered within the nondiabetic range [2, 9,10] and have clearly demonstrated that treatment of this 'mild gestational hyperglycemia' improves pregnancy outcomes [11,12].

**Maternal health after a GDM pregnancy**

Apart from affecting immediate perinatal outcomes, GDM is the most reliable marker for future type 2 diabetes [13] and cardio metabolic disorders in women [14,15], with a proven possibility of prevention or at least delaying onset, through appropriate post-partum lifestyle interventions and/or medications [10,16,17]. In this context it should be noted that, women with previous GDM have an increased risk of cardiovascular disease even if they do not develop inter-current type 2 diabetes and women with previous GDM who progress to type 2 diabetes have a higher risk of cardiovascular disease than those who develop type 2 diabetes without having had GDM during a preceding pregnancy. [18] A recent systematic review and metaanalysis showed that compared with those who did not have GDM, women with GDM had a twofold higher risk of future cardiovascular events (RR 1.98 [95% CI 1.57, 2.50]). Meta-regression analysis showed that the rates of incident type 2 diabetes across the studies did not affect this risk (p = 0.34). Moreover, when restricted to women who did not develop type 2 diabetes, GDM remained associated with a 56% higher risk of future cardiovascular events (RR 1.56 [95% CI 1.04, 2.32]). GDM conferred a 2.3-fold increased risk of cardiovascular events in the first decade postpartum (RR 2.31 [95% CI 1.57, 3.39]). [19]

There is also evidence that excessive weight gain between pregnancies especially due to retention of previous pregnancy weight gain is associated with more complications in subsequent pregnancies, including higher risk of stillbirth. [20] Additionally, offspring of mothers with GDM are at a significantly heightened risk of early onset obesity, type 2 diabetes and cardio-metabolic disorders as a consequence of intrauterine developmental programing [21, 22]. Whether good control of GDM helps prevent or reduce offspring risks is currently unknown and requires further well designed intervention studies.

Risk factor based screening fails to identify substantial proportion of women [23–25], supporting the contention that identification of women with hyperglycemia in pregnancy (HIP) requires testing of all pregnant women [5].

**Ongoing controversy regarding GDM detection and frequency**

Some countries including the United States and professional organizations (American College of Obstetrics and Gynecology) while accepting universal testing recommend a two-step approach – a 50 g non fasting glucose challenge test (GCT) followed by a 75 g or a 100 g OGTT in women who test positive on initial screening; a positive OGTT also requires two elevated readings. [26] This protocol reduces the number of women requiring full OGTTs and ensures that women diagnosed with GDM have ‘significant glucose intolerance’ [27]. However, it does not take into account the fact 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.[27] In this context it must be noted that a substantial portion of women identified with IADPSG / WHO GDM in the US based HAPO study centers were diagnosed only with high fasting glucose. [2] Moreover, a significant proportion of women fail to complete the evaluation as they do not return for the OGTT [28]. This approach therefore may miss many women with HIP.

The continued use of risk based testing, the two step process and two elevated values criteria in many developed economies appears to be due to the frequently expressed concern that universal testing using a single test with one abnormal reading as recommended by the IADPSG criteria will markedly increase GDM frequency, thereby increasing need for interventions and place significant additional burden on stretched health care resources.

The counter argument is that these concerns fail to take into account the fact that the occurrence of HIP parallels the prevalence of prediabetes, overweight, obesity and type 2 diabetes in a given population. These conditions are on the rise; also affecting younger people in the reproductive age, thus more women entering pregnancy are vulnerable to HIP and therefore the increased frequency seen by IADPSG criteria is not unnatural. It also does not take into account the overall health and economic benefits that accrue from identifying and treating GDM both in the short term (perinatal complications) and the long term through post-partum lifestyle interventions to prevent or delay the onset of type 2 diabetes, obesity and cardiovascular diseases both in the mother and offspring.

**FIGO and the global perspective**

Since the publication of the FIGO HIP pragmatic guide, the FIGO HIP working group (now incorporated into the Pregnancy and Non Communicable Disease (PNCD) committee) has taken several steps to highlight the issue and bring it to the forefront of maternal and new born child health and the non-communicable disease agenda. These include several publications, post graduate training, creation of infographics, developing regional and global declarations on HIP in collaboration with and participation of several like-minded stakeholders including the IDF, WHO, IADPSG, European Association of Perinatal Medicine (EAPM), European Board and College of Obstetrics and Gynecology (EBCOG), Diabetic Pregnancy Study Group (DPSG), South Asia Initiative for Diabetes in Pregnancy (SAIDIP), Chinese Society of Perinatal Medicine, Diabetes in Pregnancy Study Group of India (DIPSI), Diabetes in Pregnancy Study Group of Latin America, Australian Diabetes in Pregnancy Society (ADIPS), African Federation of Obstetrics and Gynaecology (AFOG), Federation of Obstetrics and Gynecology Societies of India (FOGSI) South Asian Federation of Obstetrics and Gynecology (SAFOG), Egyptian Society of Gynecology and Obstetrics, Obstetrical and Gynecological Society of Sudan, Lebanese Society of Obstetrics and Gynecology, World Diabetes Foundation (WDF), Women Deliver and Jhpeigo. In 2018 the FIGO HIP Working Group and FIGO Working Group on Adolescent and Maternal Nutrition merged into the FIGO Committee on Pregnancy and Non Communicable Diseases with the aim to continue the focus on the links between maternal health and NCDs.

**GDM Debate at the Annual Meeting of the Society of Maternal Fetal Medicine (SMFM**)

In February 2019, a postgraduate course at the Society of Maternal Fetal Medicine (SMFM) Annual Meeting offered the opportunity to compare current recommendations for detecting and diagnosing gestational diabetes from the American College of Obstetrics and Gynecology (ACOG) with those of FIGO. Speakers focused on similarities and differences between the two and provided data supporting the use of one or the other approach.

During the discussions it was highlighted that the US population data from the most recent National Health and Nutrition Examination Surveys (NHANES) demonstrates that 4.5% of US adults age 20-44 years have overt diabetes mellitus [29] and a further 29.3% have prediabetes (glycosylated hemoglobin [HbA1c] 5.7-6.4 % and/or fasting glucose 100-125mg/dL and/or 2- hour OGTT glucose 140-199 mg/dL).[30] Even between the ages of 12 to 19 years, diabetes mellitus affects 0.6% and prediabetes affects 13.2% of females.[31] Thus, if women of reproductive age were tested routinely before pregnancy, over 30% would be found to have prediabetes or diabetes mellitus. Given that pregnancy is a potent “metabolic stressor” because of increased insulin resistance and the need for beta-cell adaptation, why should there be any surprise that up to 25% US women might be diagnosed with GDM?

The fact that many cases of GDM represent preexisting prediabetes or diabetes mellitus has been recognized for many years but is not always given credence in the discussion on GDM prevalence.

Refusal to accept GDM as a very common condition reflects a denial to accept factual evidence regarding the prevalence of pre diabetes and diabetes in women of reproductive age and take steps to address the problem This is a barrier to addressing adverse health impacts posed by the concurrent epidemics of diabetes mellitus and obesity that are increasingly affecting women of child-bearing age.

A meta-analysis of 4 RCTs, including 2,617 women (and 152 total cases of GDM), showed that, comparing the Two Step with the One Step approach, the incidence of GDM increased non-significantly from 4.4 to 8.3%, mothers gained 1.3kg less weight, and had a non-significant 34% and 17% reduction in incidence of preeclampsia and cesarean delivery, respectively [32]. The One Step approach was also associated with several neonatal benefits, including significantly decreased incidence of large for gestational age (LGA) by 57%, neonatal hypoglycemia by 48%, and neonatal intensive care unit (NICU) admission by 51%. Neonatal death occurred in 1 baby of a mother randomized to the One Step test, and 4 babies of mothers randomized to the Two Step approach (a 74% non-significant decrease for the One Step test). [32] Thus, there is now Level 1 evidence from RCTs supporting the use the One Step approach for diagnosing gestational diabetes in USA, and to reconsider the current US recommendations.. [33]

Besides the immediate perinatal outcomes, hyperglycemia in pregnancy, as mentioned earlier is a highly reliable marker of future type 2 diabetes mellitus (relative risk, 7.43; 95% CI, 4.79-11.51), [13] cardio vascular disorders (RR 1.98 [95% CI 1.57, 2.50]), [19] and renal disease (OR, 2.3; 95% CI, 1.4-3.7).[34] Other pregnancy complications, which include the development of gestational hypertension, [35] early term delivery,[36] and occurrence of placental complications [37] may also help to identify future cardio metabolic risks. In women with previous GDM, postpartum lifestyle intervention has been reported to reduce progression to diabetes mellitus by 35%, and metformin has been reported to reduce progression to diabetes mellitus by 40%. [17]

A recent study showed that metformin continues to exert its diabetes prevention effect even 15 years post randomization in the Diabetes Prevention Program (DPP) and the Diabetes Prevention Program Outcomes Study (DPPOS). The effect is significantly higher for women with a history of prior GDM (HR 0.59, RD 24.57 cases/100 person-years) compared with parous women without GDM (HR 0.94, RD 20.38 cases/100 person-years.[38] Breast feeding for >10 months has been reported to decrease the risk of diabetes mellitus at 2 years after delivery by 57% in women with a history of GDM.[39]

The arguments and counter arguments for the FIGO and ACOG approach were elegantly debated in the session. [40] A cell phone-based poll of attendees at the session was administered prior and at the end of the session. All participants supported universal testing and using a fasting plasma glucose cutoff of 95 mg/dL both before and after the debate; however, the key change at the end of the debate was that most participants (over 90%) switched their preferences from the two-step to the one-step approach, and from requiring two elevated values to requiring one elevated value. [40]

**Key practice points following the SMFM Debate**

Based on the discussions in the meeting and available evidence, the following approach was suggested for implementation in the USA:

1. Universal testing for GDM at 24-28 weeks’ gestation.

2. Utilize a ***one-step procedure***, with a 75 gram, 2-hour OGTT

3. Diagnose GDM when ***one or more*** of the below mentioned thresholds is met or exceeded.

1. fasting plasma glucose 95 mg/dL (5.3 mmol/L),
2. 1-hour plasma glucose 180 mg/dL (10.0 mmol/L),
3. 2-hour plasma glucose 153 mg/dL (8.5 mmol/L).

Although not numerically identical to the recommendations in the FIGO pragmatic guide (fasting glucose threshold only differs), this process and these thresholds are very close to those recommended by IADPSG / WHO and would represent a major step forward in harmonization of the US and other jurisdictions.

We note that these conclusions represent the opinions of those present at the session and do not form part of official policies from any US based groups. If accepted more widely, adoption of this approach and these criteria would represent an important milestone in dissipating the long standing confusion and contention regarding GDM diagnosis and in creating a global consensus.

**Synopsis**

The diagnostic criteria for GDM continue to be debated. The arguments presented here may help dissipate confusion and help build global consensus

**Authors Contribution**

**Anil Kapur and David McIntyre prepared the first draft which was reviewed, commented and approved by all the other authors**

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