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Evidence in support of the international association of diabetes in pregnancy study groups' criteria for diagnosing gestational diabetes worldwide in 2019

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Condensation: Recent data from the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Follow Up Study demonstrate clear long term adverse maternal and offspring effects from mild hyperglycemia in pregnancy

Short title: Gestational diabetes in 2019

Abstract

Gestational diabetes mellitus is the most frequent medical complication of pregnancy, affecting 5-6% of women in the USA using the currently predominant Carpenter Coustan criteria, which still represent the preferred approach of the American College of Obstetricians and Gynecologists. Alternative criteria proposed by the International Association of Diabetes in Pregnancy Study Groups (IADPSG) would likely increase gestational diabetes (GDM) prevalence to 15 – 20%, due both to a one step testing policy and the requirement for only one elevated glucose value for diagnosis. Increasing GDM prevalence relates to older maternal age and the increasing prevalence of overweight and obesity. This increased GDM prevalence is consistent with 29.3% prevalence of prediabetes and 4.5% prevalence of known diabetes outside pregnancy in US adults between 20 – 44 years of age. Gestational diabetes by the IADPSG criteria is associated with almost twice the risk of large for gestational age babies, increased fetal adiposity, neonatal hyperinsulinemia and pre-eclampsia and a 50% higher risk of preterm delivery and shoulder dystocia. The recent publication of the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Follow Up Study provides further evidence regarding the influence of gestational diabetes on long term maternal and infant health. This study clearly demonstrates that hyperglycemia in pregnancy, untreated and identified *post hoc* by IADPSG criteria, carries a 41.5% risk of maternal prediabetes (Odds ratio 3.72; 95% CI 3.09 – 4.47) and 10.7% risk of type 2 diabetes (Odds ratio 7.63; 95% CI 5.33 – 10.95) after 11.4 years follow up. Gestational diabetes was also associated with higher rates of childhood overweight and obesity (prevalence 39.3% with maternal gestational diabetes; Odds ratio 1.5; 95% CI 1.56 – 2.44). This paper places these findings in the context of other recent studies demonstrating that interventions including lifestyle measures and / or metformin offer a >50% reduction in the risk of women with GDM developing overt diabetes after their index GDM pregnancy. Although prevention of obesity and prediabetes in offspring by pregnancy treatment of gestational diabetes has not been demonstrated to date, we argue that the immediate pregnancy benefits and opportunities for long term improvements in maternal health justify a reevaluation of the current ambivalent approach taken by the American College of Obstetricians and Gynecologists to gestational diabetes diagnosis. These currently allow for a choice of alternative criteria. The Carpenter – Coustan or National Diabetes Data Group criteria, listed as preferred criteria by ACOG, markedly limit the frequency of gestational diabetes in comparison to IADPSG criteria and limit the opportunity for immediate and long term follow up and treatment. We consider that new information from the Hyperglycemia and Pregnancy Outcome Follow Up Study and other recent publications on long term maternal and offspring risk provides compelling arguments for a more comprehensive approach to the promotion of maternal and infant health through all the life cycle.

Keywords: pregnancy, diagnostic criteria, HAPO, follow up, type 2 diabetes, impaired fasting glucose, impaired glucose tolerance, hyperglycemia in pregnancy, health economic studies, one step testing, two step testing, FIGO, non – communicable disorder

The relationship between hyperglycemia in pregnancy and adverse pregnancy outcome is continuous, not dichotomous

Data from a blinded multinational cohort of 23,316 women and their singleton offspring the HAPO study, [1], provided clear evidence of the independent and continuous linear relationship between nondiabetic hyperglycemia and a range of pregnancy complications and neonatal outcomes. The primary outcomes were large for gestational age (LGA) infants (birthweight > 90th centile), primary cesarean delivery, clinical neonatal hypoglycemia (symptoms or treatment with a glucose infusion or a local laboratory report of a glucose value of 30.6 mg /dL or less in the first 24 hours after birth or 45.0 mg / dL or less after the first 24 hours) and fetal hyperinsulinemia (cord c peptide > 90th centile for the HAPO cohort). The major secondary outcomes included preterm birth, shoulder dystocia / birth injury, admission to newborn intensive care unit, hyperbilirubinemia and preeclampsia. Figure 1 provides a graphical depiction of the risk of the HAPO study primary outcomes across increasing categories of fasting glucose in the HAPO study. Similar trends are seen when considering one hour or two hour oral glucose tolerance test (OGTT) glucose results [1].

New diagnostic criteria for gestational diabetes

The results of the HAPO study led to an international consensus process sponsored by the International Association of Diabetes in Pregnancy Study Groups (IADPSG) to redefine gestational diabetes (GDM), leading to recommendations for a one step approach to diagnosis and classification of hyperglycemia in pregnancy according to thresholds corresponding to adjusted odds ratios (aORs) of 1.75 compared to the mean for three neonatal outcomes - LGA, excess adiposity (% body fat > 90th percentile) and neonatal hyperinsulinemia [2]. This contrasts with the traditional US definition of GDM based on the risk of maternal progression to diabetes post-partum [3], using data derived from a small cohort of 752 women recruited by O'Sullivan et al in Boston in the late 1950s, later re-analyzed to provide the basis for current "two step" testing [4]. Strikingly, O'Sullivan reported that "16.2% were 20% or more above their ideal body weight", compared to the recent prevalence of obesity in US women aged 20 – 39 years of 37% [5].

The IADPSG approach has been endorsed by the World Health Organization (WHO) [6, 7] and the International Federation of Gynecology and Obstetrics (FIGO) [8], but has not been widely accepted in North America and varying opinions have been expressed in the pages of this journal [9, 10]. In the USA, the American College of Obstetricians and Gynecologists (ACOG) [11] has continued to favor the traditional two step approach. In Canada the Canadian Diabetes Association [12] has favored higher diagnostic thresholds, primarily based on concerns regarding increased frequency of GDM diagnosis with the IADPSG approach. Table 1 summarizes both immediate and longer-term outcomes in the HAPO study, according to the presence or absence of gestational diabetes by IADPSG criteria.

Ten to fourteen year follow up of infants and mothers enrolled in the HAPO study

The recent publication of the HAPO Follow up Study (FUS) [13] (see Table 1), provides a long term view of the maternal and offspring consequences of pregnancy hyperglycemia; thus offering another opportunity to review issues relating to GDM informed by 10 – 14 year follow up of both mothers and infants from the original study and to place these in the context of other research published over the last decade. HAPO FUS included 4747 mothers and 4834 infants from the original study, drawn from 10 of the 15 initial HAPO Field Centers. Median time post-birth at follow up was 11.4 years.

Overall, 52.2% of mothers with GDM based on IADPSG criteria, who were blinded and untreated during their index pregnancy developed prediabetes (composite of impaired glucose tolerance (IGT); impaired fasting glucose (IFG)) or Type 2 diabetes (T2D) at follow up as compared to 20.1% of those without IADPSG GDM. The fully adjusted odds ratio (including adjustment for maternal BMI at follow up) for impaired glucose metabolism was 3.44 (95% CI 2.85 – 4.14) and for T2D 5.44 (95%CI 3.68 – 8.08). Thus, a diagnosis of GDM based on IADPSG criteria at the index pregnancy carried a very strong risk for future metabolic abnormalities.

IADPSG GDM in the mother was also associated with offspring overweight or obesity (39.5 vs. 28.6%), with a stronger trend for obesity alone (19.1 vs. 9.9%). The combined outcome of offspring overweight and obesity just failed to reach statistical significance after adjustment for field center, pubertal status and maternal variables at the OGTT visit:- age, height, family history of diabetes, mean arterial pressure, parity, smoking status, alcohol consumption, gestational age and BMI (OR 1.21; 95% CI 1.00 – 1.46) but obesity remained significant (OR 1.58; 95% CI 1.24 – 2.01)

The HAPO FUS also published additional analyses comparing long term outcomes in women and their offspring classified *post hoc* as having gestational diabetes by IADPSG or the more stringent Carpenter -Coustan criteria commonly used in the USA [14]. As expected due to the more marked maternal hyperglycemia identified by the Carpenter – Coustan criteria, the frequency of maternal impaired glucose metabolism following GDM was 68.4% and of T2DM 20.0% when Carpenter - Coustan criteria were used. Although not presented in the recent publication, the relationships between maternal glycemia during pregnancy and later maternal and child outcomes were continuous, as reported for immediate pregnancy outcomes in earlier publications.

Gestational diabetes frequency and impaired glucose metabolism outside pregnancy

The most frequent concern among those opposed to the IADPSG diagnostic criteria is the marked increase in GDM frequency. In the USA, a 2013 National Institutes of Health (NIH) panel estimated that GDM frequency would rise from 5 – 6% using Carpenter - Coustan criteria to 15 – 20% with the IADPSG approach [15]. Indeed, in the US based HAPO field centers, IADPSG GDM frequency ranged from 17.3 % in Chicago IL to 25.5% in Bellflower CA [16]. In this context it is important to note that the US population data from the most recent National Health and Nutrition Examination (NHANES) surveys demonstrate that 4.5% of US adults age 20 – 44 years have overt diabetes [17] and a further 29.3% prediabetes (HbA1c 5.7 – 6.4 and / or fasting glucose 100 – 126 mg /dL and / or 2 hour OGTT glucose 140 – 199 mg / dL) [18]. Even at age 12 – 19 years, diabetes affects 0.6% and prediabetes 13.2% of US females [19]. Thus, if women of reproductive age were routinely tested prior to pregnancy, over 30% would be found to have prediabetes or diabetes. The fact that many cases of GDM represent preexisting prediabetes or diabetes has been recognized for many years [20], but is not always adequately considered when discussing likely GDM prevalence. More recent data from the US based CARDIA study [21] which recruited women before pregnancy (Age 18 – 30 years) and followed them longitudinally, clearly demonstrate that abnormalities in glucose and lipid metabolism are detectable many years before a GDM diagnosis is made.

Given that pregnancy is a potent "metabolic stressor" due to increased insulin resistance and the need for beta cell adaptation [22-24], why should there be surprise that up to 25% US women might be diagnosed with GDM? Refusal to accept GDM as a very common condition reflects a denial of the facts and a refusal to address the problems posed by concurrent epidemics of diabetes and obesity affecting women of child bearing age. Besides the immediate perinatal outcomes, hyperglycemia in pregnancy is a highly reliable marker of future type 2 diabetes; relative risk (RR) 7.43 (95% CI 4.79–11.51). [25]; cardio metabolic disorders (RR 1.66, 95% CI 1.30-2.13) and renal disease (Odds ratio (OR) 2.3, 95% CI 1.4-3.7) [26-28]. Other pregnancy complications including the development of gestational hypertension [29], early term delivery [30]and occurrence of placental complications [31] may also help to identify future cardiometabolic risks. In women with prior GDM, post-partum lifestyle intervention has been reported to reduce progression to diabetes by 35% and metformin by 40% [32]. Breast feeding for > 10 months has been reported to decrease the risk of diabetes at two years postpartum by 57% in women with a history of GDM [33].

The HAPO FUS clearly confirms that pregnancy is a window of opportunity to identify mothers and offspring with substantial future health risks. Given the continuous association between glucose exposure and both immediate pregnancy complications and later cardiometabolic risks, there is no "perfect" set of glucose thresholds, during or following pregnancy, that will identify most women and children at risk. Questions both of individual clinical and broader public health risks and benefits,

opportunity costs and health economics must be considered when deciding on diagnostic processes and cut-offs.

Randomized trials – health benefits and health economic benefits

There is clear evidence from the landmark Crowther [34] and Landon [35] trials that GDM treatment improves immediate pregnancy outcomes related to excess fetal growth (LGA in both studies, neonatal fat mass also measured in the Landon study) and hypertensive disorders of pregnancy by 40 - 50%. Of note, the sole inclusion criterion for the Crowther study was a 2 hour OGTT glucose ≥ 140 mg / dL, representing less severe hyperglycemia than the IADPSG GDM definition. Direct health economic analysis of the Crowther study reported that GDM treatment was highly cost effective, at AUD60,506 per perinatal death prevented and AUD2988 per quality adjusted life year (QALY) gained [36]. A US based analysis using data from the Landon study also suggested an acceptable cost / benefit ratio of USD20412 / QALY gained [37]. More indirect "modelling" studies provide more varied results [38-40], but all conclude that treatment is highly cost effective if interventions to reduce future maternal diabetes risk are included.

One step vs. two step testing and one vs. two abnormal values on oral glucose tolerance testing

Table 2 provides a comparison of current diagnostic thresholds for GDM. The 2018 guidelines from the American College of Obstetricians and Gynecologists [41] remain highly ambivalent, stating only that "practitioners and institutions should select a single set of diagnostic criteria". This inconclusive approach tacitly endorses even the largely discredited National Diabetes Data Group (NDDG) thresholds for GDM diagnosis [42-44], contrary to current recommendations from the American Diabetes Association [45]. Although the substantially higher NDDG glucose cut – offs limit the number of GDM diagnoses, they have the capacity to increase overall healthcare costs by virtue of increased maternal and neonatal complications [46]. ACOG continues to endorse "two step" testing (glucose 1 hour post non-fasting 50 gram glucose load, followed by OGTT if positive) as its preferred option, without clearly stating what glucose result should prompt a full OGTT. We note that this approach systematically does not detect around 25% of women with GDM [47], delays diagnosis (and thus therapy) and leads to a risk of process errors, in particular failure to follow up on a "positive screen" [48, 49].

Additionally, we would note that the lower GDM diagnosis rates with Carpenter - Coustan or NDDG criteria are due largely to the requirement for two values > threshold on the diagnostic OGTT for a confirmed GDM diagnosis. All other dysglycemic states (diabetes, IFG, IGT) are diagnosed based on a single abnormal value. Surely, pregnancy is one situation where any degree of dysglycaemia with its multi-generational consequences should be taken seriously! The "two abnormal values" caveat is essentially an historical quirk, empirically proposed *post hoc* by O'Sullivan in Mahan in 1964 with the cryptic comment: "it was considered expedient" following their early cohort studies [3]. Indeed, in 1961, O'Sullivan reported GDM diagnoses generally requiring three abnormal OGTT values [50]. The continued insistence two abnormal values for diagnosis serves to reduce GDM frequency, but not in any logical fashion [51-53]. It is almost thirty years since a randomized trial by Langer and colleagues demonstrated that treatment of women with one abnormal value on OGTT improved pregnancy outcomes [54]. Postpartum follow up studies also clearly demonstrate that even women with a positive glucose screen and a negative OGTT, and certainly women with a single abnormal OGTT value, have worsening β cell function and dysglycemia within the first year postpartum [55].

Do we need a new, "definitive" randomized controlled trial?

A further argument advanced by critics is that the IADPSG cut-offs values have not been formally used in any randomized trial [15]. We acknowledge this issue, but note that the Crowther [34] and Landon

[35] trials included women whose OGTT results, age and BMI substantially overlap with women who would be diagnosed under the IADPSG criteria [56]. Given the known continuous relationship between glucose exposure and risk, it seems most unlikely that a new study specifically using IADPSG cut – offs would deliver a different result. Furthermore, with definite clinical benefits including reduction of excess fetal growth and its consequences and reduction in hypertensive disorders of pregnancy now well established on systematic review [57] any further study would pose ethnical issues.

Implementation and pre / post cohort studies

Issues related to implementation of the IADPSG GDM diagnostic strategy have recently been reviewed by Brown and Wyckoff [58] , who note that women diagnosed *post hoc* as GDM by IADPSG criteria have worse outcomes that those with normal glucose tolerance, "indicating a likely opportunity to improve outcomes with treatment." Cohort studies conducted on a pre / post basis after a "whole of system" change from two step Carpenter - Coustan testing to one step IADPSG testing have shown variable results. Duran et al [59] reported a threefold increased frequency of GDM diagnoses (from 10.6 to 35.5%) with this change, but noted that the increased costs of treatment were more than offset by a reduction in peripartum costs, principally related to reduced rates of cesarean delivery and newborn intensive care unit admission. Of note, the percentage of women requiring insulin therapy under the IADPSG criteria was constant at around 20%, suggesting that the change in approach did not result in the detection of trivial or clinically insignificant hyperglycemia in pregnancy.

By contrast, a US based cohort study from Kaiser Permanente California [60], also evaluating a change from Carpenter - Coustan testing to IADPSG testing, reported an increase in GDM from 17 to 27% without any change in pregnancy outcomes. However, in addition to the change in standard GDM screening, this group also introduced early glycosylated hemoglobin (HbA1c) testing into routine clinical practice. The majority of the increase in GDM prevalence appeared due to early HbA1c testing, with a consequent increase in what they termed "pre-diabetes" from 4 to 11%. This clearly suggests a high rate of pre-pregnancy impaired glucose metabolism in their population. Such women are known to be at higher risk and may benefit less from routine treatment [61]. Further, clinical practice in this center clearly changed over the course of the study, with glyburide replacing insulin as the predominant mode of pharmacotherapy. This may also have contributed to worsening of outcomes [62, 63]. A more recent report from Kaiser Permanente Washington State [64] also reported an increase in GDM from 6.9 to 11.4% after a similar change in diagnostic protocol, without improved overall pregnancy outcomes. Of note, their "post IADPSG" rate of GDM diagnosis was still substantially lower than any US based center in the HAPO study [16], suggesting a population at low overall risk. Again, this study introduced early HbA1c testing at the same time, but failed to separately document the rate of abnormal early testing.

Saccone et al have recently published a systematic review of all randomized studies comparing the "two step" and "one step" approaches [65]. They conclude that overall perinatal outcomes are improved with the IADPSG approach, with evidence for reduction in LGA, NICU admission and neonatal hypoglycemia.

Maternal GDM treatment, breast feeding and offspring risks

Offspring exposed to maternal hyperglycemia in pregnancy, independent of maternal obesity, are at a significantly heightened risk of early onset obesity, type 2 diabetes and cardio-metabolic disorders as a consequence of intrauterine developmental programing [13, 66, 67]. A report from Germany including adjustment for maternal BMI and other potential confounders comparing GDM and non GDM offspring yielded an OR of 1.81 (95% CI 1.23-2.65) for childhood overweight and 2.80 (95% CI 1.58-4.99) for, respectively. Similar results were obtained for the risk of childhood abdominal adiposity (OR 1.64, 95% CI 1.16-2.33) by maternal gestational diabetes. A study from Israel has also reported an association between diet treated GDM and offspring cardiovascular morbidity: (RR 1.6, 95% CI 1.2–2.2) [68]. The effects of maternal GDM treatment on offspring risk of obesity and impaired glucose

metabolism are much less clear. Follow up from the Crowther [69] and Landon [70] randomized trials has failed to demonstrate any clear overall benefit of maternal GDM treatment for the offspring, although the Landon study suggested some possible improvement in metabolic status for girls whose mothers were treated for GDM. Recent US based evidence from Gunderson et al shows that breast feeding can attenuate some of these risks, with weight for length Z score reduced by 0.36 to 0.45 SD units at 12 months of age in GDM offspring who were intensively breast fed [67], but definitive evidence of longer term benefit is lacking.

GDM as a global health issue

Thus far, our commentary has focused primarily on GDM as it affects US – based clinical practice. However, the issues are even more pressing on a global scale [71, 72]. Hyperglycemia in pregnancy is estimated to have affected 21.4 million live births in 2013, with over 90% of cases occurring in low - middle income countries which lack sufficient resources to provide optimal care [71]. Moreover, in populous low and middle income countries (South Asia 37 million and China 18 million pregnancies annually) with limited resources, the recommendation for a two-step approach for diagnosis is impractical and will result in only a small fraction of the target population being tested. The International Federation of Gynecology and Obstetrics (FIGO) has addressed this pressing health issue by producing and promoting pragmatic worldwide guidelines for diagnosis and treatment of hyperglycemia in pregnancy [8]. In collaboration with the International Diabetes Federation (IDF), FIGO has produced firm declarations regarding the importance of hyperglycemia in pregnancy [73, 74]. This is the first time that such a broad global consensus has been achieved. These declarations have been endorsed by governments in many areas of the world. A global consensus document was signed at the FIGO 2018 world congress. FIGO has also formed a "Pregnancy and prevention of early non – communicable disease" (NCD) subcommittee to effectively address the prevention of NCDs by highlighting the importance maternal nutrition, obesity, hyperglycemia and hypertension and pre term delivery as major antecedents to and markers of later NCD risk [75].

In conclusion, we consider that the HAPO FUS has provided important evidence to demonstrate that identification of hyperglycemia in pregnancy may identify a large number of women may benefit from interdisciplinary medical intervention in pregnancy and post-partum follow up. Without appropriate diagnostic strategies and careful follow up, this opportunity will be lost and the current epidemics of obesity and diabetes will continue unchecked.

What is now needed is not further contemplation but rather action, impeded in the USA by denial of what we consider compelling evidence that IADPSG GDM, although it is somewhat less severe than the hyperglycemia identified by older criteria, merits detection and treatment. We strongly urge our US based colleagues, both individually and through major groups such as ACOG and the Society for Maternal - Fetal Medicine (SMFM), to realistically address the challenges posed by hyperglycemia in pregnancy, to promote women's health by taking a "whole of life" approach to this and other maternal risk factors and to energetically support efforts to reduce the personal, economic and societal harms caused by this global epidemic.

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Table 1. Perinatal and long-term outcomes in untreated women subsequently classified as gestational diabetes mellitus (GDM) or non GDM by International Association of Diabetes in Pregnancy Study Groups criteria in the Hyperglycemia and Adverse Pregnancy Outcome study participants and their offspring

Outcome	IADPSG GDM (%)	Non GDM (%)
Perinatal outcomes [56] (from HAPO study)		
Pre-eclampsia**	9.1	4.5
Preterm delivery (< 37 weeks)**	9.4	6.4
Primary cesarean delivery**	24.4	16.8
Shoulder dystocia / birth injury*	1.8	1.3
Birthweight > 90th centile**	16.2	8.3
Newborn % body fat > 90th centile**	16.6	8.5
Cord c peptide > 90th centile**	17.5	6.7
Clinical neonatal hypoglycemia**	2.7	1.9
Admission to newborn intensive care*	9.1	7.8
Long term outcomes [13] (from HAPO Follow Up Study)		
Maternal diabetes**	10.7	1.6
Maternal prediabetes**	41.5	18.4
Offspring overweight or obesity**	39.5	28.6
Offspring obesity**	19.1	9.9
Offspring body fat > 85th centile**	21.7	13.9

Perinatal outcomes relate to the 23316 women and their singleton offspring in the blinded Hyperglycemia and Adverse Pregnancy Outcome (HAPO) cohort. Long-term outcomes relate to 4697 women and 4832 offspring from the HAPO follow up cohort, examined at a mean of 11.4 years post birth. International Association of Diabetes in Pregnancy Study Groups (IADPSG) gestational diabetes mellitus (GDM) was defined as one or more values greater than or equal to the following on the 75 gram OGTT (mg/dL): Fasting 92; 1 hour 180; 2 hour 153. ** = $p < 0.001$; * $p < 0.01$ comparing IADPSG GDM and non GDM groups.

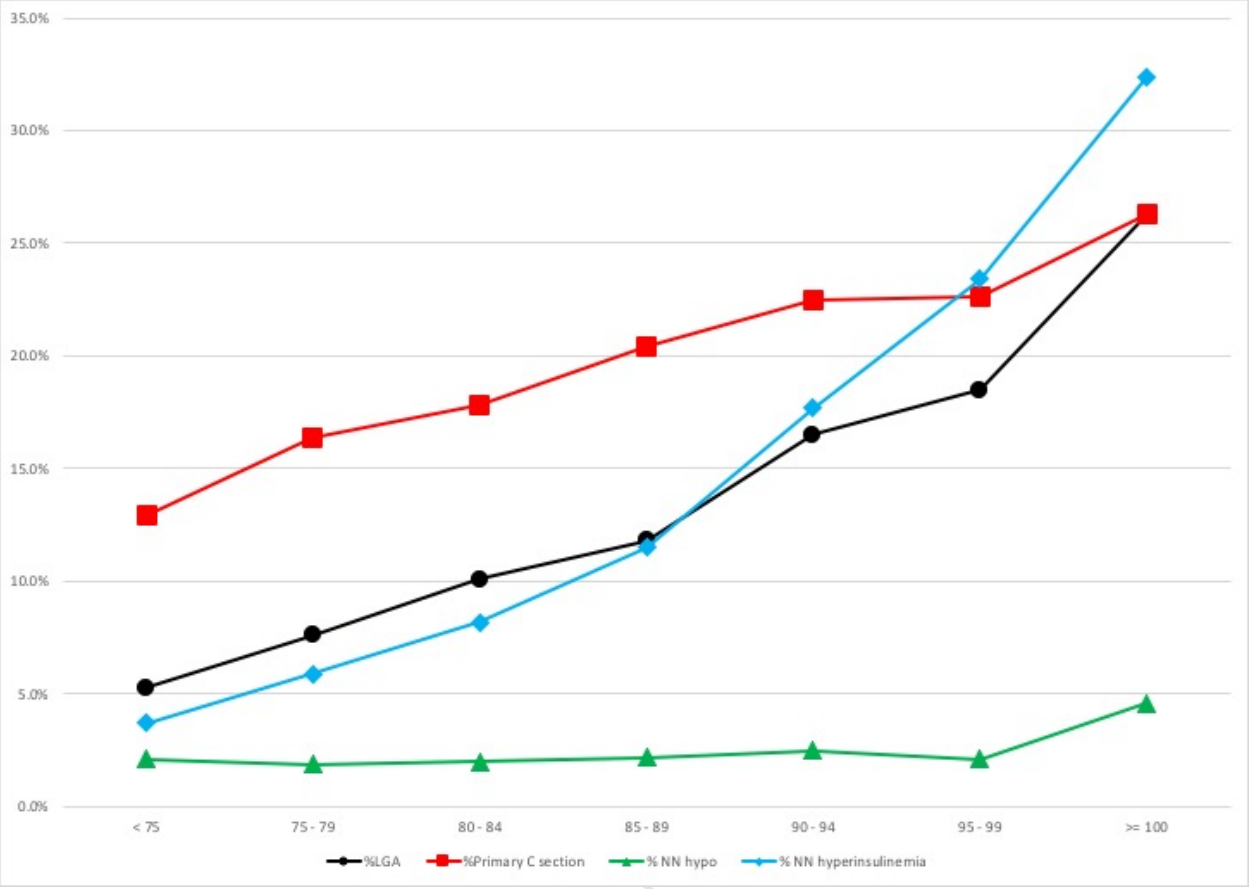
Table 2. Criteria for gestational diabetes using thresholds recommended by Carpenter Coustan, National Diabetes Data Group and International Association of Diabetes in Pregnancy Study Groups

Criteria	Fasting glucose (mg/dL)	1 hour glucose (mg/dL)	2 hour glucose (mg/dL)	3 hour glucose (mg/dL)
Carpenter Coustan	95	180	155	140
National Diabetes Data Group	105	190	165	145
IADPSG	92	180	153	N/C

Comparison of diagnostic venous plasma glucose cutoff values for gestational diabetes according to various criteria using the oral glucose tolerance test (OGTT). Carpenter Coustan [14] and National Diabetes Data group [41] criteria generally relate to a 100 gram OGTT, include an additional glucose measurement at 3 hours post load and require two values ≥ threshold for diagnosis. International Association of Diabetes in Pregnancy Study Group (IADPSG) criteria [2] relate to at 75 gram OGTT and require only one value > threshold for diagnosis. N/C = Not Considered.

Legend for Figure 1

Frequency of primary outcomes in the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study, classified by fasting venous plasma glucose categories (ranges in mg/dL). LGA (black circles) – large for gestational age (birthweight > 90th centile); Primary C section (red squares) - primary cesarean section delivery; NN hypo (green triangles) – clinical neonatal hypoglycemia; NN hyperinsulinemia – (blue diamonds) cord c peptide > 90th centile



Hyperglycemia and Pregnancy

Hyperglycemia is one of the **most common medical conditions women encounter during pregnancy**

1 in 6 live births occur to women with some form of hyperglycemia

84% *of which are due to GDM*

- Age of onset of diabetes and pre-diabetes is decreasing and age of child bearing is rising thus more women are vulnerable to hyperglycemia in pregnancy
- Rates of over weight and obesity in reproductive age women are rising
- Women born small or large are at high risk of GDM

Hyperglycemia in Pregnancy is Grossly Neglected

In most parts of the low, low middle and upper middle income countries which account for

85 %
Global deliveries

90%
Maternal & Perinatal deaths & Poor pregnancy outcomes.

80%
Global diabetes burden

And HIP contributes to increased risk of maternal and newborn morbidity and mortality due to

- Obstructed labor
- Pre eclampsia
- Postpartum Hemorrhage
- Preterm delivery
- Neonatal asphyxia
- Birth injury
- Future DM and CVD in both mother and offspring

Majority of women are not tested for diabetes during pregnancy.

Hyperglycemia in pregnancy is a reliable marker of future

- Type 2 diabetes; relative risk (RR) 7.43 (95% CI 4.79–11.51). [Bellamy L et al Lancet 2009;373:1773-9.]
- Cardio metabolic disorders (RR 1.66, 95% CI 1.30-2.13) [Retnakaran R, Shah BR. CMAJ 2009;181:371-6; Kessous R et al. Heart 2013; 99: 1118-21]
- Renal disease (OR) 2.3, 95% CI 1.4-3.7). [Beharier O et al. J Clin Endocrinol Metab 2015;100:1412-6.]

In women with prior GDM post-partum intervention reduces progression to diabetes

- Lifestyle by 35% and metformin by 40%. [Aroda VR et al. J Clin Endocrinol Metab 2015;100:1646-53.]

- Breast feeding for > 10 months by 57% within two years [Gunderson EP. et al. Annals of internal medicine 2015;163:889-98.27.]

If US women of reproductive age were routinely tested prior to pregnancy, over 30% would be found to have prediabetes or diabetes

National Health and Nutrition Examination (NHANES) surveys demonstrate that among US adults age 20 – 44 years

- 4.5% have overt diabetes [. JAMA 2015;314:1021-9.]
- 29.3% have prediabetes (HbA1c 5.7 – 6.4 and / or fasting glucose 100 – 126 mg /dL and / or 2 hour OGTT glucose 140 – 199 mg / dL) [Menke A et al. Ann Epidemiol 2018.15.]
- Even at age 12 – 19 years, diabetes affects 0.6% and prediabetes 13.2% of US females [Menke A et al JAMA 2016;316:344-5.]

In utero exposure to maternal hyperglycemia, independent of maternal obesity, significantly increases risk of early onset obesity, type 2 diabetes and cardio-metabolic disorders

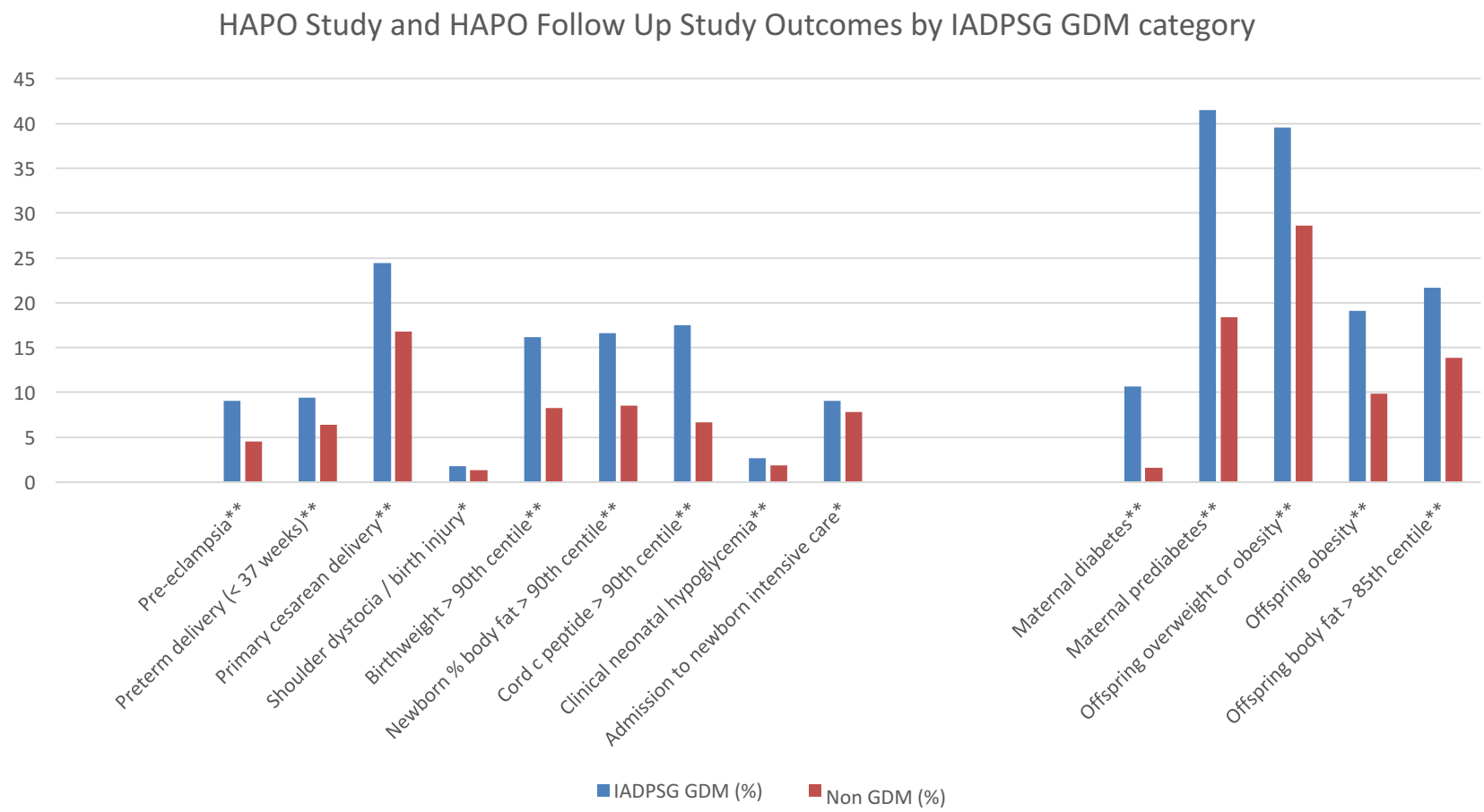
Lowe WL et al. JAMA 2018; 320:1005-16;
Nehring I et al. Diabet Med 2013; 30: 1449-56;
Dablea D et al. Diabetes Care 2008;31:1422-6.

Significant association between insulin as well as diet treated GDM and offspring cardiovascular morbidity: (RR 1.6, 95% CI 1.2–2.2)

Leybovitz-Haleluya N et.al Acta Diabetol. 2018 Jun 23. doi: 10.1007/s00592-018-1176-1

The effects of maternal GDM treatment on offspring risk of obesity and impaired glucose metabolism are less clear

Immediate and Long Term Outcomes IADPSG GDM



Pregnancy Outcomes

Long Term Outcomes

GDM vs non GDM comparisons: * $p < 0.01$; ** $P < 0.001$

Treatment of GDM Reduces Adverse Outcomes – Crowther Study *

OUTCOME	ROUTINE CARE (N = 510)	INTERVENTION (N = 490)	P
Birth Weight	3482 ± 660	3335 ± 551	< .001
LGA	22%	13%	< .001
Macrosomia	21%	10%	< .001
Preeclampsia	18%	12%	0.02
SGA	7%	7%	ns

***Crowther CA, et al. NEJM 352:2477-86, 2005**

Treatment of GDM Reduces Adverse Outcomes – Landon Study*

Outcome	NICHD RCT		P
	Not treated	Treated	
BW >90th percentile	14.5	7.1	<0.001
C-peptide >95th percentile	22.8	17.7	0.07
NICU admission	11.6	9.0	0.19
Shoulder Dystocia	4.0	1.5	0.02
Preeclampsia	5.5	2.5	0.02

*Landon MB et al. NEJM 361:1339-48, 2009

GDM Clinical and Cost Effectiveness Model