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Counterpoint: Establishing Consensus in the Diagnosis of GDM Following the HAPO Study

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Conflict of Interest

H. David McIntyre has board membership with the Mater Research Institute. He has received speakers' fees from Novo Nordisk, Eli Lilly, Sanofi-Aventis, and AstraZeneca. He has received travel/accommodations expenses covered or reimbursed for travel to meetings from Novo Nordisk, Sanofi-Aventis, and AstraZeneca.

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Boyd E. Metzger, Alan R. Dyer, David R. Hadden, Moshe Hod, Lynn P. Lowe, Jeremy J.N, and Bengt Persson declare that they have no conflict of interest.

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Abstract

The International Association of Diabetes in Pregnancy Study Groups (IADPSG) recommended a new protocol of one step testing with a 75 gram oral glucose tolerance test for gestational diabetes in 2010. Since that time these recommendations have been carefully scrutinized and accepted by a variety of organizations, but challenged or rejected by others. In the current review, we present more details regarding the background to the development of the IADPSG recommendations and seek to place them in context with the available epidemiologic and randomized controlled trial data. In this "counterpoint" we also provide specific rebuttal for errors of fact and disputed contentions provided by Long and Cundy in their 2013 article in Current Diabetes Reports.

Keywords

Gestational diabetes mellitus (GDM); Hyperglycemia and Adverse Pregnancy Outcome (HAPO); Study

Introduction

Since the publication of the primary results of the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study (1), substantial efforts have been made to use HAPO study data, in combination with other important observational epidemiologic and randomized controlled trial (RCT) data, to develop a consensus definition of gestational diabetes (GDM). On an international level, these efforts have been led by the International Association of Diabetes in Pregnancy Study Groups (IADPSG), which convened an initial consensus development conference in Pasadena, CA in June 2008 and subsequently published consensus guidelines in 2010 (2). Since that time, the IADPSG diagnostic process and diagnostic thresholds for the diagnosis of hyperglycemia in pregnancy including both "Overt Diabetes" (OD) and GDM, have been adopted, in whole or in substantial part, by a number of influential national and international bodies, including the American Diabetes Association (ADA), The Endocrine Society and the World Health Organization (WHO) (3–5).

However, no consensus exists in North America, where influential organizations such as the American College of Obstetricians and Gynecologists (ACOG) (6), and the *ad hoc* National Institutes of Health (NIH) consensus panel (7) have favored alternative diagnostic strategies for GDM. Epitomizing equivocation, the Canadian Diabetes Association guidelines (8) have included the IADPSG approach as an alternative, but not their preferred, strategy. Similarly, the ADA endorsed the IADPSG guidelines in 2011 (3) and then equivocated in 2014 (9), suggesting that either IADPSG or ACOG approaches are acceptable.

A number of individuals have also made alternative recommendations. In 2013, Current Diabetes Reports published a review by Long and Cundy (10) under the title of "Establishing consensus in the diagnosis of gestational diabetes: where do we stand?" These two authors are among the most vocal opponents of the developing international consensus regarding GDM diagnosis and presented their article as "a counterpoint to what we believe is an unjustified change of practice". Thus, the current article essentially comprises a "counterpoint to a counterpoint". We plan to present the evidence for the IADPSG consensus guidelines, outline the consensus process which guided their development, scrutinize the arguments advanced by Long and Cundy and point to important unresolved issues regarding the classification of hyperglycemia in pregnancy.

Definitions of gestational diabetes

Although coined by Carrington in 1957 (11), the term "gestational diabetes" gained wider recognition after the publications by John O'Sullivan in 1961 (12) and 1964 (13). These described overlapping cohorts of pregnant women tested with a100g oral glucose tolerance test (OGTT) at varying gestations in Boston in the late 1950s. In the first publication (12), O'Sullivan applied cutoff values for whole blood glucose of: Fasting 100; 1 hour 170; 2 hours 120; 3 hours 110 mg / dL and required three abnormal values for diagnosis of GDM. This interpretation appears similar to definitions used at the time for diabetes outside pregnancy. Women in this study (n=7061) were enrolled on the basis of additional risk factors and were tested repeatedly during pregnancy if the initial test proved negative. This study reported a GDM frequency of 0.9% and also reported recurrent GDM in 37% (14/38) of the GDM women who had subsequent pregnancies.

Subsequently, the more frequently cited paper by O'Sullivan and Mahan (13) reported an unselected cohort of 986 women enrolled over a four month period. A subgroup of this cohort, comprising 752 women, underwent both the 50 gram non-fasting glucose challenge test (GCT) at their first antenatal presentation and later a formal 100 gram OGTT. The result of the GCT was not used to determine which women should progress to an OGTT, so their results are similar to those from a "one step" protocol for GDM diagnosis. These 752 women comprise the historic basis for the diagnosis of GDM in the USA. Their OGTT values were used to derive 97.7 percentile levels (2 standard deviations above the cohort mean) for the 100g OGTT and after rounding of the 2 and 3 hour values, these results provided the initial threshold whole blood glucose values for GDM of: Fasting 90; one hour 165; two hour 145; three hour 125 mg / dL, with the equally arbitrary decision ("it was considered expedient…") that two elevated values would be required for diagnosis.

The OGTT values described above were then applied to a cohort of 1013 women who were involved in an (apparently) separate long term follow up study and a diagnosis of GDM was found to be strongly predictive of post pregnancy development of diabetes. O'Sullivan did not report BMI data for the cohort of 752 women, but noted that "16.2% were 20% or more over their ideal body weight" (13). This appears idyllic compared to an obesity prevalence of 31.9% in women aged 20 – 39 years in recent NHANES data (14).

These original “O’Sullivan criteria” for GDM diagnosis, modified for changes in laboratory methodology by Carpenter and Coustan and the National Diabetes Data Group (NDDG) (15), still form the basis for current recommendations by ACOG (6) and were endorsed in 2013 by the NIH consensus panel (7). They have achieved wide acceptance, despite recognized methodologic flaws (16) and the fact that they were derived from an empirical analysis of a small cohort of women in Boston in the late 1950s and developed as predictors of later diabetes, without consideration of their relationship to pregnancy outcomes.

The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study

In the years since publication of the “O’Sullivan criteria”, a veritable Tower of Babel has developed across the world in terms of varying diagnostic pathways and threshold values for the detection of GDM (17). For many years, reviews on this topic centered primarily on the differences between alternative tests of glycemia in relation to their ability to predict OGTT results, often without reference to pregnancy outcomes and called for a definitive epidemiologic study.

The HAPO study was subsequently designed and conducted to examine the independent associations of maternal glycemia at 24–32 weeks gestation with perinatal outcomes. HAPO has been described in detail elsewhere (1, 18–20). It was a large, multicenter, multinational, epidemiologic study of 23,316 women (over 30 times larger than the O’Sullivan cohort) who underwent blinded 75 gram OGTTs at 24 – 32 weeks’ gestation. The key finding of HAPO was a linear relationship between fasting, one hour and two hour glucose values on the OGTT and a broad range of pre-defined, carefully ascertained and adjudicated adverse clinical and biochemical pregnancy outcomes. Further, the independent associations of hyperglycemia with pregnancy outcomes persisted after extensive adjustment for potential confounders including maternal BMI, age, height, mean arterial pressure and parity.

The HAPO data are downplayed and in some instances misrepresented by Long and Cundy (10). The study was designed to evaluate the relationship between milder degrees of hyperglycemia and pregnancy outcomes, not, as contended by Long and Cundy, because the investigators were “hoping to find” a presumed inflection point for GDM diagnosis. However, if such an inflection point or threshold had been found, it would have obviated the need for consensus. Contrary to their other contentions, the HAPO Study was not powered to detect a difference in perinatal mortality and for ethical reasons the protocol was designed to minimize risk of perinatal mortality. Further, and again contrary to Long and Cundy’s assertions, BMI was not more strongly associated with the primary study outcomes than glycemia (21–23) and the effects of these two variables were additive without a statistically significant interaction (21).

Long and Cundy (10) argue that it is unlikely that maternal-fetal hyperglycemia recorded in pregnancies complicated by gestational diabetes has any long term consequences for the offspring since the rate of early onset of type 2 diabetes is not epidemic in children born to mothers with type 1 diabetes despite having been exposed to marked hyperglycemia in utero. In fact, childhood glucose intolerance and defective insulin secretion have been described in the offspring of women (but not men) with Type 1 diabetes (24), suggesting an

effect related to *in utero* exposure to hyperglycemia. Furthermore, the interaction between type 2 diabetes genes and fetal hyperglycemia that may occur in gestational diabetes represents a quite different pathophysiological situation. In Pima Indian women, the rate of diabetes in pregnancy and GDM in the second generation were found to be associated with their mother's 2-hr OGTT glucose during pregnancy (25).

Other observational epidemiologic studies

The HAPO study, although unique in its scale and the formal blinding of OGTT results from caregivers and participants, is not the only large scale observational epidemiologic study of hyperglycemia in pregnancy and was not the sole basis for the IADPSG recommendations. A summary of glucose values noted in these epidemiologic studies and RCTs is included as Table 1.

In 1995, Sacks et al published an open observational study with the apparently optimistic title "Toward universal criteria for gestational diabetes: The 75-gram glucose tolerance test in pregnancy" (26). Interestingly, when offered the alternatives of two step testing with GCT + potential OGTT or a primary 75 gram OGTT, 86% of women agreed to the latter test. These 3505 women underwent a 75 gram OGTT without prior GCT. The OGTT results were not blinded, but women were treated for GDM only if fasting glucose was ≥ 5.8 or 2-hour glucose ≥ 11.1 mmol/L (105 or 200 mg/dl respectively). Thus, these women represent a spectrum of OGTT glucose values that are similar to those in the HAPO Study participants.

Congruent with the later HAPO Study data, Sacks et al demonstrated a continuous relationship between fasting, 1 hour and 2 hour glucose and both birth weight centile (adjusted for maternal race, parity, BMI and mean weight gain) and macrosomia (defined as birth weight > 90^{th} percentile). Detailed analysis of the data failed to demonstrate any threshold above which macrosomia increased dramatically and the authors commented that criteria for GDM "will probably be established by consensus".

In the same year, Sermer et al (27) published the findings of the Toronto Tri-Hospital Gestational Diabetes Project. This study recruited 3836 women, all of whom underwent both a 50 gram GCT and a 100 gram OGTT, performed without regard to the GCT results. The results were blinded to caregivers unless NDDG criteria for GDM were met (27), leaving a study cohort of 3637 women. The primary outcomes were pre eclampsia, macrosomia (birth weight > 4000g) and cesarean section, all of which increased progressively across quartiles for each glucose measurement. As confirmed later in HAPO (1), these investigators noted that individual glucose measures on the OGTT were poorly correlated, suggesting independent associations with outcomes. They developed a variety of regression models and the overall report of their findings was "a clear graded relationship between values of the oral GTT, as well as glucose challenge results and a variety of adverse maternal – fetal outcomes". As in the Sacks study, no definite inflection point or threshold in maternal glycemia was associated with a marked increase in risks.

Jensen et al reported the results of a Danish epidemiologic study of mild GDM in 2001 (28). Their testing protocol was selective, involving a combination of historical risk factors and laboratory measurement of either plasma or blood glucose from a capillary sample, as well

as repeated urine glucose testing. They did not resort to a GCT, but rather performed a 75 gram OGTT if random plasma glucose exceeded 4.7 mmol/L (85 mg/dl) on two or more occasions. Their threshold for "abnormality" on the OGTT required two or more values to exceed the Mean+3 standard deviations for a small group (n=40) of healthy, non-pregnant, non-obese women. In contrast with the other epidemiologic reports, all women in the final cohort of 2904 participants had either one or more risk factors for GDM or previously demonstrated mild hyperglycemia. The prevalence of macrosomia rose significantly across quartiles of both fasting and 2 hour glucose, whilst hypertension, emergency cesarean section and shoulder dystocia were associated only with the 2 hour glucose values.

An epidemiologic study from Brazil, authored by Schmidt et al was published in 2001 (29) and included 4977 women who also underwent a primary 75 gram OGTT without prior GCT. The OGTT results were not blinded, but it was noted that women with mild GDM did not routinely receive treatment in Brazil at the time of the study. Rather than reporting overall relationships between OGTT values and pregnancy outcomes, this study used *post hoc* classification of OGTT results according to the divergent WHO and ADA thresholds in use at the time. Both sets of criteria identified women at risk of developing pre eclampsia or delivering a macrosomic infant. The more stringent ADA criteria also identified a group of babies at higher risk of perinatal death.

In summary, the epidemiologic association of mild pregnancy hyperglycemia with adverse pregnancy outcomes is now well understood. The major studies have generally been performed with a 75 gram OGTT, without prior GCT. The results, in particular the associations with excess fetal growth and its complications and the risk of pregnancy hypertension, remain consistent despite varying methods of analysis and some variations in reported statistical significance (most likely due to sample size in the smaller cohorts). No study found a clear diagnostic threshold or "inflection point" for any glucose measure above which risk increased sharply. In addressing the challenges of GDM or "hyperglycemia in pregnancy" we need to be mindful of these consistent findings.

All studies highlight the multi factorial nature of the associations and clearly identify the potential importance of other factors, particularly maternal obesity. None of the adverse pregnancy outcomes described is uniquely associated with maternal hyperglycemia. Several of the commonly used outcomes, since they are defined in terms of the frequency > 90th percentile, e.g. birth weight, neonatal fat mass, hyperglycemia and hyperinsulinemia, have a "natural" frequency of approximately ten percent. From the epidemiologic background data, it is clear that no set of potential diagnostic glucose measurements will ever be able to clearly identify all women who are destined to develop adverse pregnancy outcomes.

The randomized controlled trials

The randomized trials performed by Crowther et al (ACHOIS) (31) and Landon et al (MFMU) (32) are misrepresented by Long and Cundy. They inaccurately contend that the participants in the Landon trial were "less hyperglycemic than those of the ACHOIS cohort" and that this explains the lower rate of insulin usage in the Landon study. Review of the mean glucose values for participants in each RCT (30–32) (Table 1) shows the reverse to be

true. Furthermore, participants in the MFMU RCT had 2 or more of the 1, 2, or 3 hour OGTT glucose concentrations equal or greater than the threshold values of 10, 8.6 or 7.8 mmol/l (180, 155, 140 mg/dl).

It is worthwhile to summarize the similarities and differences between these major trials, both in terms of the cohorts studied and the relevant outcomes.

Crowther et al followed the prevailing WHO criteria for GDM in recruiting women for their trial. Although recruitment of women on the basis of risk factors without a prior glucose challenge test (GCT) was allowed under their protocol, 93% of included participants did undergo an initial GCT, followed by a two sample (fasting and 2 hour) 75 gram OGTT. Contrary to the tabulation provided by Long and Cundy, the fasting venous plasma glucose (VPG) value was used only to exclude women, initially using fasting VPG≥ 7.8 mmol/L (later changed to 7.0 mmol/L after a change in WHO recommendations). Thus, it would have been possible for women with marked fasting hyperglycemia to be included in this trial. However, since this degree of fasting hyperglycemia is very uncommon in pregnancy when the 2-hour plasma glucose is <11.1 mmol/L (200 mg/dL), this criterion was rarely invoked and the women actually included in the trial demonstrated a single abnormal OGTT value of 7.8 – 11.0 mmol/L at 2 hours in a 75 gram OGTT. Their mean fasting plasma glucose of 4.8 mmol/L (86 mg/dL) is the same as the mean FPG in the MFMU RCT.

Landon et al also performed a 50 gram GCT, followed in their study by a 100 gram, four sample OGTT. They also used the fasting glucose value only for exclusion, but applied a much more stringent criterion, excluding women with fasting VPG ≥ 5.3 mmol/L (95 mg/dL), presumably because they believed that this level of fasting glucose abnormality definitely required treatment. They followed the US convention of requiring two (by definition “post load”) values ≥ threshold (1 hour - 10.0 mmol/L [180 mg/dL]; 2 hours - 8.6 mmol/L [155 mg/dL]; 3 hours - 7.8 mmol/L [140 mg/dL]) for inclusion. The mean glucose values of included participants in their study are shown in Table 1.

Long and Cundy also display bias when presenting the results of the major RCTs. They deconstruct and attempt to “explain away” the positive results of ACHOIS in great detail, whilst summarizing the Landon study as a “clear negative result”. In fact there is a high degree of congruence in the results of these two studies and given the fact that they took respectively 10 (31) and 6 (32) years to perform, it seems worthwhile to further examine their outcomes.

Both studies showed a reduction in fetal overgrowth and related complications with identification and active treatment of mild GDM. This was seen both in terms of mean birth weight, frequency of LGA (31, 32) and reduction in fat mass (32) and in reduction of rarer complications such as shoulder dystocia (32). Hypertensive disorders of pregnancy (gestational hypertension and pre eclampsia) were also substantially reduced by active GDM treatment (31, 32). Maternal weight gain was lessened by active therapy (31, 32). Induction of labor was increased by active treatment in the Crowther study (31), but not in the Landon study (32). Caesarean section frequency was unchanged in the Crowther study (31) and reduced in the Landon report (32). A subsequent systematic review has concluded that the

observed reductions in LGA, shoulder dystocia and pre eclampsia are consistent across these and other available reports (33).

The IADPSG recommendations

From the available observational epidemiologic data, it is clear that the risk of adverse pregnancy outcomes increases in a continuous fashion with increases in any commonly used measure of maternal glycemia, including fasting and post load OGTT glucose concentrations and glycosylated hemoglobin (34). Therefore any decision regarding threshold values for GDM diagnosis will, by definition, be arbitrary, based on an individual or consensus view of the level of risk which is "sufficient" to merit the GDM label. Further, the exact diagnostic process and cutoff values finally recommended by the IADPSG panel (2) did not precisely concord with any prior set of (equally arbitrary) OGTT values in wide usage in any jurisdiction.

The underlying principles of the IADPSG consensus process were (1) that women with equivalent levels of glucose-associated risk should be classified in a similar manner and (2) that glucose criteria should be standardized internationally. Long and Cundy (10) argue that the diagnostic pathway of GCT followed by OGTT ensures that women diagnosed with GDM have "significant glucose intolerance". This presents only one side of the argument, as the GCT will miss around 25% of cases with OGTT abnormalities (35) and in particular fail to detect fasting hyperglycemia, which is clearly associated with risks equivalent to those seen with elevations in glucose after an oral glucose load (1). Long and Cundy (10) also erroneously argue that the IADPSG proposal is deficient because different ethnic / geographic groups will have varying proportions of GDM cases identified by fasting vs. post load glucose values. This finding relates to the underlying distribution of glucose abnormalities in the various HAPO centers and their associated ethnic groups. It should be considered a strength of the primary 75 gram OGTT diagnostic approach, as it offers the opportunity to correctly identify and classify glycemic risk across varying ethnicities, particularly in ethnically heterogeneous populations.

Long and Cundy also seek to trivialize the association of GDM with adverse pregnancy outcomes (10). After considerable discussion, the consensus panel chose to use features of diabetic fetopathy, namely the frequency of birth weight > 90^{th} percentile, percent body fat > 90^{th} centile and cord c peptide > 90^{th} centile for determination of diagnostic glucose thresholds. These are key phenotypic features of babies affected by maternal hyperglycemia, directly related to the likely causal pathways. The selected thresholds also identify an increased risk of more severe and less frequent adverse pregnancy outcomes (30). We continue to support this decision.

Long and Cundy also criticize the selection of "such a small odds ratio of 1.75" to select diagnostic thresholds. This issue has been addressed in detail elsewhere (30), but in summary represents a compromise between elements of sensitivity (desire to identify and make treatment available to significant numbers of pregnancies at risk of complications) and specificity (desire not to include an excess of women at low risk in the "GDM" group). It is important to remember that the adjusted odds ratio of 1.75 was in comparison to individuals

with glucose values at the mean. When gravidas in the HAPO study who would be diagnosed with GDM by IADPSG criteria are compared to those without GDM, this represents a risk ratio of approximately 2.0 for the major outcomes considered (30). We concede that the OR threshold of 1.75 represents a compromise (consensus) viewpoint, but contend that it is well reasoned.

Further, the recommended diagnostic thresholds were also influenced by the results of the Crowther (31) and Landon (32) studies. In the Crowther study, women were enrolled solely on the basis of an elevated 2-hour glucose value ≥ 7.8 mmol/L. This is below the 2-hour threshold recommended by IADPSG and in fact lies close to the OR 1.5 threshold. As seen from Table 1, the median two hour glucose of this cohort was actually close to the IADPSG recommended 2 hour diagnostic threshold, meaning that if this value alone were to be used for diagnosis, around 50% of these women, who benefited from intervention, would not be diagnosed with GDM. This finding would likely be mitigated by the use of additional glucose measures, but as 1-hour post load values were not measured in the ACHOIS study, it is impossible to precisely confirm this belief.

Long and Cundy provide some muted support for the proposition, first advanced by Ryan (36, 37), that the alternative diagnostic thresholds corresponding to an OR of 2.0 in the HAPO cohort might be used to define GDM, arguing that these are “closer to the GDM definition *(sic)* used in the ACHOIS and MFMU trials”. Examination of Table 1 shows this contention to be erroneous, as the recorded inclusion criteria for the RCTs clearly lie much closer to the OR 1.75 values endorsed by the IADPSG panel.

Conclusion

The relationship between hyperglycemia and adverse pregnancy outcomes is now well defined through a large volume of congruent observational epidemiologic data. The continuous nature of the risk associations mean that there is no “natural” set of diagnostic thresholds and that determination of GDM diagnostic thresholds is (by definition) an arbitrary process, which can be diligently and carefully undertaken and reasonable in its recommendations but never absolutely “right”. We consider that the IADPSG recommendations represent a well-reasoned consensus view as to the levels of glycemia which are “sufficient to merit identification and treatment”. They do not (and no set of criteria ever could) identify all women at risk of adverse pregnancy outcomes. They require some modification of ingrained diagnostic algorithms and patterns of practice in all jurisdictions. We strongly disagree with Long and Cundy, who believe GDM diagnosis by the IADPSG criteria will “medicalize… hitherto healthy pregnancies” (10). Rather, they will allow identification of previously ignored risks. We consider that, if thoughtfully implemented, they will appropriately identify and allow treatment of the metabolic abnormalities of GDM, with well-established benefits in terms of immediate pregnancy outcomes and likely benefits in terms of future maternal and offspring health.

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Table 1

OGTT values in observational epidemiologic studies and clinical trials

Study	**n =**	**Fasting glucose mmol/L *mg/dL* Mean(SD) or Median[IQR][1]**	**1 hour glucose mmol/L *mg/dL* Mean (SD) or Median[IQR][1]**	**2 hour glucose mmol/L *mg/dL* Mean (SD) or Median[IQR][1]**	**3 hour glucose mmol/L *mg/dL* Mean(SD) or Median[IQR][1]**
Observational					
HAPO 2008 (1)	23316	4.5(0.4) *80.9(6.9)*	7.4(1.7) *134.1(30.9)*	6.2(1.3) *111.0(23.5)*	NR
Sacks 1995 (26)	3505	4.7(0.5) *83.7(9.2)*	7.2(1.8) *130.0(33.5)*	6.1(1.4) *109.0(25.3)*	NR
Sermer 1995 (27)	3637	4.25[4.1–4.5] *76.5[74–82]*[2]	7.55[6.4–8.7] *135.9[116–158]*[2]	6.45[5.6–7.3] *116.1[101–132]*[2]	5.15[4.3–6.0] *92.7[78–109]*[2]
Jensen (2001)(28)	2904	4.35[4.1–4.5] *78.3[74–82]*	NR	6.35[5.7–7.1] *114.3[103–128]*	
Schmidt 2001(29)	4977	NR	NR	NR	NR
IADPSG GDM *post hoc* in HAPO cohort 2013 (30)	3754	4.9 *88.2*	9.6 *172.8*	7.6 *136.8*	NR
RCTs					
Crowther 2005 (31)	1000	4.8(0.6) *86.4(11)*	NR	8.6 [8.1–9.2] *154.8[146–166]*	NR
Landon 2009 (32)	958	4.8 (0.3) *86.4(5.7)*	10.7 (1.1) *192.6(20.6)*	9.6(1.1) *173.5(20.7)*	7.5(1.7) *135.7(30.3)*
Diagnostic thresholds					
IADPSG OR 1.5 (30)	23316	5.0 *90*	9.3 *167*	7.9 *142*	-
IADPSG OR 1.75* (30)	23316	5.1 *92*	10.0 *180*	8.5 *153*	-
IADPSG OR 2.0 (30)	23316	5.3 *95*	10.6 *191*	9.0 *162*	-
Crowther (31)	1000	Exclusion ≥ 7.0 *126*	-	7.8 *140*	-
Landon (32)	958	Exclusion ≥ 5.3 *95*	10.0 *180*	8.6 *155*	7.8 *140*

[1] Mean(SD) or Median[IQR] values (depending on availability) are reported firstly in mmol/L and *in italics in mg/dL* both for the observational studies and for the cohorts included in the randomized controlled trials. The Sacks and Landon studies reported venous plasma glucose in mg / dL, other studies used mmol/L. A conversion factor of 1mmol/L = 18 mg/dL was used for all conversions, starting with the units used in the primary report.

[2] The median glucose values for the Sermer and Jensen studies were calculated as the midpoint between the upper limit of the second quartile and the lower limit of the third quartile. The diagnostic thresholds relate to a 75 gram OGTT with one value ≥ threshold considered as GDM, except for Landon et al which used a 100 gram OGTT and required two values ≥ threshold. OR – adjusted odds ratio compared to mean.

* Consensus thresholds recommended by IADPSG