Gestational Diabetes Mellitus: Does One Size Fit All? A Challenge to Uniform Worldwide Diagnostic Thresholds

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OBJECTIVE

To define the prevalence and pregnancy outcomes related to elevated fasting venous plasma glucose (FVPG) in a Danish pregnancy cohort.

RESEARCH DESIGN AND METHODS

This was an observational cohort study including 1,516 women without gestational diabetes mellitus (GDM) by Danish criteria. FVPG measured at 28 weeks' gestation was related to pregnancy outcomes.

RESULTS

With use of the World Health Organization (WHO) 2013 threshold of FVPG ≥5.1 mmol/L, 40.1% of the cohort qualified as having GDM. There was no evidence of excess fetal growth, hypertension in pregnancy, or cesarean delivery in women with FVPG <5.6 mmol/L.

CONCLUSIONS

The WHO 2013 FVPG threshold for GDM is unsuitable for Denmark. It inappropriately labels as having GDM an unmanageably large number of women who are at low absolute risk of pregnancy complications.

Worldwide diagnostic criteria for gestational diabetes mellitus (GDM), including fasting venous plasma glucose (FVPG) ≥5.1 mmol/L, were proposed by the International Association of Diabetes in Pregnancy Study Groups in 2010 (1). The World Health Organization (WHO) endorsed these in 2013 (WHO2013) but noted that the quality of evidence was "very low" (2).

The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study (3,4) demonstrated that the relative contribution of fasting versus postload glucose values to GDM varies substantially worldwide. Sacks et al. (4) reported, "Associations [between glucose and outcomes] did not differ among centers, indicating that HAPO study results are applicable to all centers." This has been interpreted to imply worldwide validity of WHO2013 criteria for GDM, even in countries outside those studied in HAPO. The Danish Society for Obstetrics and Gynecology has endorsed but not yet implemented WHO2013 criteria (5). GDM diagnosis in Denmark generally follows the methodology of Jensen et al. (6), with risk factor–based screening followed by a one-step 75-g oral glucose tolerance test (OGTT). GDM is diagnosed with 2-h venous plasma glucose (VPG) ≥9.0 mmol/L. FVPG is measured in some centers but not routinely used diagnostically.

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Egan et al. (7) reported that obese Danish women showed the highest WHO2013 GDM prevalence (54%) among nine European countries, due largely (78.5%) to early elevated FVPG. We wished to examine the frequency and impact of elevated FVPG in Denmark using a more representative cohort.

RESEARCH DESIGN AND METHODS

The Odense Child Cohort (OCC) is a single-center longitudinal Danish birth cohort (8), including 2,874 pregnant women recruited before 16 weeks' gestation in 2010–2012 (8). Participants received written and oral information about the study and provided written consent (8). The OCC was performed in accordance with the Helsinki Declaration II and was approved by the Regional Scientific Ethical Committee for Southern Denmark (S-20090130) and the Danish Data Protection Agency (13/15326).

Supplementary Fig. 1 outlines inclusion and exclusion of participants. Overnight FVPG was measured by the hexokinase method (ARCHITECT; Abbott Core Laboratory) at Odense University Hospital. Intra-assay coefficients of variation were between 5.2 and 5.4%, and interassay coefficients of variation were between 1.2 and 1.7% (9). Internal and external quality-control measurements were acceptable throughout the study period.

Maternal and birth data were obtained from hospital records. Maternal prepregnancy BMI was calculated as weight in kilograms divided by the square of height in meters. Ponderal index (PI) was calculated as birth weight (BW) in kilograms divided by length in meters cubed. BW *Z* score (BWZ) and large for gestational age (LGA) (BW >90th centile) were calculated using the Scandinavian formula of Marsal et al. (10), corrected for sex and gestation.

Data are expressed as mean (SD), median (interquartile range), or number (%) as appropriate. Differences in means were analyzed using unpaired *t* tests for normally distributed data, Mann-Whitney *U* tests for nonnormally distributed data, and χ^2 tests for dichotomous variables. Trends across glucose categories were analyzed with the Cuzick test (11). Adjustments for maternal BMI, parity, and age were performed using multiple logistic and linear regression. Significance was accepted at the 5% level on two-tailed testing. Data were analyzed using STATA/IC, version 15.0 (StataCorp, College Station, TX).

RESULTS

Of 1,540 women with FVPG results at 28 weeks' gestation, 351 (23%) had known risk factors for GDM, as listed in Supplementary Table 1. With exclusion of 24 women with GDM by Danish criteria, the final sample included 1,516 women. Supplementary Table 1 shows baseline characteristics for OCC (included/not included) and the Danish background population. Statistical differences of small magnitude are as noted.

Pregnancy outcomes in OCC according to the WHO2013 FVPG threshold and divided into eight glucose categories are presented in Table 1 and Supplementary Table 2. Percentages are reported using the number of women in HAPO categories C1–7 (n = 1,446) as the denominator (3). C8 included women in the final OCC cohort (n = 70 ["extra" 4.8%]) with FVPG >5.8 mmol/L. Such women were unblinded and treated in HAPO but not in the OCC. Supplementary Fig. 2 graphically illustrates FVPG distribution in the HAPO and OCC cohorts limited to the seven HAPO quantiles (C1–7) (3).

In total, 620 women (40.1%) had WHO2013 GDM based on FVPG. Pregnancies with WHO2013 GDM demonstrated higher maternal age, BMI, BW, BWZ, and PI and higher frequencies of maternal overweight/obesity, multiparity, family history of diabetes, LGA, BW >4,000 g, and hypertensive disorders of pregnancy (HDP). After adjustment for maternal BMI, parity, and age, the differences remained significant only for BW (P = 0.002), BWZ (<0.001), and PI (0.006).

Of the 639 women (347 with prespecified risk factors) who underwent an OGTT, 81 (13%) had GDM by 1-h glucose and 66 (10%) by 2-h glucose using WHO2013 criteria (2).

There was a significant increasing trend across C1–8 for maternal age, prepregnancy BMI, and overweight/obesity and for the pregnancy outcomes: BW, BWZ, LGA, BW >4,000 g, PI, neonatal abdominal circumference, and HDP.

CONCLUSIONS

GDM in Denmark currently affects 2.3% of singleton pregnancies (12). Clearly, the distribution of FVPG in OCC was substantially higher than reported in HAPO (3). Following WHO2013, using only FVPG ≥5.1 mmol/L, >40% of women in OCC would be classified as having GDM. WHO2013 GDM based on 1- or 2-h OGTT glucose values affected 10–13% of women. Our sample size of 1,540 is >5 of 15 HAPO centers (4). However, as in the HAPO study, we are unable to definitively affirm that our sample is representative of the underlying population. The selective nature of OGTT testing in the OCC is a limitation of this study, but clearly postload WHO2013 GDM was much less prevalent, despite the fact that more than half of those with available data had additional risk factors.

Further, our data demonstrate minimal adverse outcomes in OCC women with mildly elevated FVPG. Women with untreated WHO2013 GDM gave birth to slightly larger babies, but mean BWZ was −0.01, and only 10.4% were LGA. Excepting the very small number of women in C1 (n = 8), mean Z score was <0.0 and LGA <10% until C7 (5.6–5.8 mmol/L). There was no evidence of excessive fetal growth or excess HDP in OCC women with untreated WHO2013 GDM and FVPG <5.6 mmol/L. Cesarean section and stillbirths showed no association with FVPG.

Ehrlich et al. (13), studying a Californian cohort, reported a high frequency of LGA in women with FVPG ≥5.3 mmol/L, but these women were selected due to prior elevated postload glucose.

Sesmilo et al. (14) recently described the FVPG distribution and pregnancy outcomes using HAPO quantiles in 5,203 unblinded, untreated women from Catalonia. The FVPG distribution in this cohort resembled HAPO, with 53% of women falling in C1 and 2. In this report, LGA frequency first exceeded 10% in C4 (FVPG ≥4.8 mmol/L), and LGA, HDP, and preterm delivery appeared to increase substantially with FVPG ≥5.3 mmol/L (C6).

We are unable to determine the cause for the marked difference in fasting glucose distribution in the OCC compared with other cohorts. Agarwal et al. (15) have noted that laboratory variations, well within acceptable limits, may be associated with a halving or doubling of GDM prevalence. The Danish Inter99 population study (outside pregnancy) reported that lowering the threshold for impaired fasting glucose (IFG) from 6.0 mmol/L (recommended by WHO) to 5.5 mmol/L (recommended by the American Diabetes Association) would create a "pandemic" of prediabetes (16), increasing IFG from 12 to 38% in their cohort.

Table 1—Pregnancy outcomes according to third-trimester FVPG in OCC

			HAPO FVPG category number							
	Non-GDM (n = 896 [59.1%])	GDM (n = 620 [40.1%])	C1 (2.5–4.2 mmol/L)	C2 (4.2–4.4 mmol/L)	C3 (4.5–4.7 mmol/L)	C4 (4.8–4.9 mmol/L)	C5 (5.0–5.2 mmol/L)	C6 (5.3–5.5 mmol/L)	C7 (5.6–5.8 mmol/L)	OCC FVPG C8 (>5.8 mmol/L)
HAPO cohort (blinded) (n = 23,217 for fasting glucose)			17.4%	32.3%	26.6%	11.8%	8.1%	2.9%	0.9%	Excluded; 2.9% unblinded
OCC (n = 1,516)			8 (0.6)	99 (6.8)	311 (21.5)	336 (23.2)	377 (26.1)	235 (16.3)	80 (5.5)	70 (extra 4.8)
BW, g (n = 1,493)†§	3,480 (3,145–3,825)	3,598 (3,280–3,920)	3,408 (3,268–3,700)	3,403 (3,105–3,700)	3,500 (3,180–3,805)	3,485 (3,128–3,840)	3,535 (3,215–3,900)	3,594 (3,280–3,900)	3,655 (3,360–3,933)	3,700 (3,293–4,078)
BWZ (n = 1,490)†§	−0.23 (−0.87 to 0.42)	−0.01 (−0.61 to 0.75)	0.39 (−0.97 to 0.51)	−0.41 (−1.04 to 0.05)	−0.19 (−0.78 to 0.40)	−0.25 (−0.92 to 0.42)	−0.11 (−0.75 to 0.62)	−0.04 (−0.59 to 0.65)	0.18 (−0.34 to 0.85)	0.35 (−0.65 to 1.07)
LGA neonate (n = 1,490)*§	57 (6.5)	64 (10.4)	1 (16.7)	1 (1.0)	20 (6.6)	21 (6.3)	33 (8.8)	17 (7.3)	14 (17.5)	14 (20.6)
PI, kg/m^3 (n = 1,483)†§	24.8 (23.2–26.4)	25.3 (23.7–26.9)	24.4 (22.9–25.9)	24.4 (22.9–26.0)	25.0 (23.3–26.9)	24.6 (23.3–26.3)	25.2 (23.5–26.5)	25.2 (23.8–26.9)	26.2 (24.3–27.4)	25.5 (23.8–27.1)
Abdominal circumference, cm (n = 1,489)§	33 (32–35)	33 (32–35)	33.5 (32.5–34)	33 (32–34)	33 (32–34)	34 (32–35)	33 (32–35)	34 (32–35)	34 (32–35)	34 (32–36)
Gestational hypertension and preeclampsia*‡	46 (5.1)	58 (9.4)	0	5 (5.0)	15 (4.8)	16 (4.8)	35 (9.3)	15 (6.4)	9 (11.3)	9 (12.9)
C-section (n = 1,494)	194 (22.1)	130 (21.1)	1 (12.5)	21 (21.9)	67 (22.3)	69 (20.8)	78 (20.8)	51 (21.8)	14 (17.5)	23 (33.8)
Stillbirth (n = 1,494)	1 (0.1)	2 (0.3)	0	0	1 (0.3)	0	1 (0.2)	0	0	1 (1.4)

Data are presented as median (range) or n (%) unless otherwise indicated. GDM defined as fasting WHO2013 criterion (≥5.1 mmol/L). C1–7 follow the FVPG quantiles used in HAPO. FVPG C1–7 cover the range 2.5–5.8 mmol/L to enable matching with the blinded HAPO cohort; C8 includes OCC women with FVPG >5.8 mmol/L. The HAPO study unblinded women with any of the following: FVPG >5.8 mmol/L, 2-h OGTT VPG >11.1 mmol/L, any VPG <2.5 mmol/L, or random VPG in late pregnancy ≥8.9 mmol/L; 2.9% of the study population was unblinded. The number of women unblinded in HAPO owing to FVPG >5.8 mmol/L has not been reported. Women treated for GDM according to Danish diagnostic criteria were excluded. Outcome variables are missing in a small number of women delivering in hospitals other than Odense University Hospital; in these women, perinatal outcomes were not reported to the OCC database. LGA comparisons between adjacent fasting glucose categories (C1–8) are as follows: C2 vs. C1, P = 0.007; C3 vs. C2, P = 0.03; C4 vs. C3, P = 0.88; C5 vs. C4, P = 0.22; C6 vs. C5, P = 0.51; C7 vs. C6, P = 0.008; and C8 vs. C7, P = 0.63. LGA frequency in C7–C8 combined vs. C1–C6 combined: $P < 0.001$. *$P < 0.05$ (FVPG <5.1 vs. ≥5.1 mmol/L); †$P < 0.01$ (FVPG <5.1 vs. ≥5.1 mmol/L); ‡$P < 0.05$ across HAPO categories; §$P < 0.01$ across HAPO categories.

In summary, using FVPG ≥5.1 mmol/L for GDM diagnosis appears inappropriate for Denmark. It would classify an unmanageable number of women as having GDM who are at low absolute risk of pregnancy complications and divert finite health care resources from other areas. Although specific to Denmark, our data raise serious questions about uniform application of GDM diagnostic thresholds across the world. For GDM diagnosis, "one size does not fit all." Where possible, diagnostic thresholds should be adapted using local data.

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Duality of Interest. H.D.M. has served as a speaker for Sanofi, Eli Lilly, Novo Nordisk, and AstraZeneca. D.M.J. has served as a speaker and investigator for Novo Nordisk. M.A. has served as an investigator for Novo Nordisk, Novartis, and Sonics. No other potential conflicts of interest relevant to this article were reported.

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References

1. Metzger BE, Gabbe SG, Persson B, et al.; International Association of Diabetes and Pregnancy Study Groups Consensus Panel. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. Diabetes Care 2010;33:676–682

2. World Health Organization. *Diagnostic Criteria and Classification of Hyperglycaemia First Detected in Pregnancy*. Geneva, World Health Organization, 2013

3. Metzger BE, Lowe LP, Dyer AR, et al.; HAPO Study Cooperative Research Group. Hyperglycemia and adverse pregnancy outcomes. N Engl J Med 2008;358:1991–2002

4. Sacks DA, Hadden DR, Maresh M, et al.; HAPO Study Cooperative Research Group. Frequency of gestational diabetes mellitus at collaborating centers based on IADPSG consensus panel-recommended criteria: the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study. Diabetes Care 2012;35:526–528

5. Benhalima K, Mathieu C, Van Assche A, et al. Survey by the European Board and College of Obstetrics and Gynaecology on screening for gestational diabetes in Europe. Eur J Obstet Gynecol Reprod Biol 2016;201:197–202

6. Jensen DM, Damm P, Sørensen B, et al. Proposed diagnostic thresholds for gestational diabetes mellitus according to a 75-g oral glucose tolerance test. Maternal and perinatal outcomes in 3260 Danish women. Diabet Med 2003;20:51–57

7. Egan AM, Vellinga A, Harreiter J, et al.; DALI Core Investigator Group. Epidemiology of gestational diabetes mellitus according to IADPSG/WHO 2013 criteria among obese pregnant women in Europe. Diabetologia 2017;60:1913–1921

8. Kyhl HB, Jensen TK, Barington T, et al. The Odense Child Cohort: aims, design, and cohort profile. Paediatr Perinat Epidemiol 2015;29:250–258

9. Finnbogadóttir SK, Glintborg D, Jensen TK, Kyhl HB, Nohr EA, Andersen M. Insulin resistance in pregnant women with and without polycystic ovary syndrome, and measures of body composition in offspring at birth and three years of age. Acta Obstet Gynecol Scand 2017;96:1307–1314

10. Marsal K, Persson PH, Larsen T, Lilja H, Selbing A, Sultan B. Intrauterine growth curves based on ultrasonically estimated foetal weights. Acta Paediatr 1996;85:843–848

11. Cuzick J. A Wilcoxon-type test for trend. Stat Med 1985;4:87–90

12. Ovesen PG, Jensen DM, Damm P, Rasmussen S, Kesmodel US. Maternal and neonatal outcomes in pregnancies complicated by gestational diabetes. a nation-wide study. J Matern Fetal Neonatal Med 2015;28:1720–1724

13. Ehrlich SF, Crites YM, Hedderson MM, Darbinian JA, Ferrara A. The risk of large for gestational age across increasing categories of pregnancy glycemia. Am J Obstet Gynecol 2011;204:240.e1–240.e6

14. Sesmilo G, Meler E, Perea V, et al. Maternal fasting glycemia and adverse pregnancy outcomes in a Mediterranean population. Acta Diabetol 2017;54:293–299

15. Agarwal MM, Dhatt GS, Othman Y. Gestational diabetes mellitus prevalence: effect of the laboratory analytical variation. Diabetes Res Clin Pract 2015;109:493–499

16. Borch-Johnsen K, Colagiuri S, Balkau B, et al. Creating a pandemic of prediabetes: the proposed new diagnostic criteria for impaired fasting glycaemia. Diabetologia 2004;47:1396–1402