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Proposed diagnostic thresholds for gestational diabetes mellitus according to a 75-g oral glucose tolerance test. Maternal and perinatal outcomes in 3260 Danish women

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Abstract

Aims To study if established diagnostic threshold values for gestational diabetes based on a 75-g, 2-h oral glucose tolerance test can be supported by maternal and perinatal outcomes.

Methods Historical cohort study of 3260 pregnant women examined for gestational diabetes on the basis of risk indicators. Information on oral glucose tolerance test results and clinical outcomes were collected from medical records.

Results There was an increased risk of delivering a macrosomic infant in women with 2-h capillary blood glucose of 7.8–8.9 mmol/l compared with women with 2-h glucose < 7.8 mmol/l. Despite treatment, 2-h glucose of 9.0–11.0 mmol/l and ≥ 11.1 mmol/l were both associated with increased rates of macrosomia, spontaneous preterm delivery, hypertensive complications, and neonatal hypoglycaemia. Adverse outcomes tended to be more frequent in women with 2-h glucose ≥ 11.1 mmol/l than in women with 2-h glucose of 9.0–11.0 mmol/l.

Conclusions The risk for several maternal and perinatal complications increased with the diagnostic threshold for 2-h glucose. Large-scale blinded studies are needed to clarify the question of a clinically meaningful diagnosis of gestational diabetes mellitus. Until these results are available, a 2-h threshold level of 9.0 mmol/l after a 75-g oral glucose tolerance test seems acceptable.

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Keywords diagnostic criteria, gestational diabetes mellitus, pregnancy, maternal-fetal outcome, preterm delivery

Abbreviations BMI, body mass index; BW, birth weight; DM, diabetes mellitus; DPSG, Diabetic Pregnancy Study Group of the European Association for the Study of Diabetes; GDM, gestational diabetes mellitus; GIGT, gestational impaired glucose tolerance; IGT, impaired glucose tolerance; LGA, large for gestational age; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test; WHO, World Health Organization

Introduction

Gestational diabetes mellitus (GDM) is defined as 'carbohydrate intolerance of varying degrees of severity with onset or first recognition during pregnancy' [1] and is present in about 2% of Danish women [2]. In most studies of perinatal and maternal outcomes related to GDM, diagnosis has been based on the results of a 100-g, 3-h oral glucose tolerance test (OGTT) [3–5], although alternative criteria are in widespread use [6–8]. Consequently a recent review called for outcome data to support the use of different diagnostic criteria based on the results of a 75-g, 2-h OGTT [9]. As this diagnostic test has been

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Table 1 Local screening criteria for gestational diabetes mellitus (GDM)

	Screening criteria
1	Family history of diabetes mellitus
2	≥ 20% pre-pregnancy overweight
3	Previous unexplained stillbirth
4	Previous macrosomic infant (birth weight ≥ 4500 g)
5	Age ≥ 35 years
6	GDM in previous pregnancy
7	Glucosuria

The urine was tested for glucose by a BM-Test Strip® (Boehringer-Mannheim®, Germany) on every visit throughout pregnancy. Women fulfilling these criteria were tested with two consecutive measurements of fasting capillary plasma glucose (FPG) or fasting capillary blood glucose (FBG). If the mean FBG level was ≥ 4.1 mmol/l (corresponding capillary plasma glucose value of 4.7 mmol/l) a diagnostic oral glucose tolerance test (75 g, 3 h) was performed. In women without GDM, the procedure was repeated in gestational week 30–32.

used in Denmark for many years, a large cohort with reliable data on OGTT results and outcome data could be provided.

The objective of this investigation therefore was to study if established diagnostic threshold values for gestational diabetes according to a 75-g, 2-h OGTT can be supported by maternal and perinatal outcomes.

Patients and methods

Screening and diagnosis

All pregnant women were considered for formal testing for GDM according to local screening procedures (Table 1) [10]. GDM was diagnosed when two or more glucose values exceeded the following capillary whole blood values: 5.7 mmol/l at 0 min, 11.9 mmol/l at 30 min, 12.0 mmol/L at 60 min, 9.7 mmol/l at 90 min, 8.9 mmol/l at 120 min, 8.5 mmol/l at 150 min and 7.4 mmol/l at 180 min [10–12]. These diagnostic criteria correspond closely to those advocated for 'Gestational Impaired Glucose Intolerance' by the Diabetic Pregnancy Study Group of the European Association for the Study of Diabetes (DPSG): ≥ 9.0 mmol/l at 120 min [8].

Subjects

The study took place in four centres: The University Hospitals of Copenhagen (Copenhagen County Hospital and Rigshospitalet), Aarhus and Odense from 1 January 1992 to 31 December 1996. Only the first pregnancy during this period was included. All participants were tested with a 75-g OGTT, and if two consecutive tests had been performed during one pregnancy, the results of the most recent were used. GDM patients diagnosed by markedly elevated fasting or random glucose alone (i.e. not by an OGTT) were not included. Other exclusion criteria were: pre-gestational diabetes, multiple pregnancies and referral from other hospitals because of a chronic disease. Women without GDM received standard obstetric care, and blood glucose was only measured in new-borns when clinically indicated. GDM patients were treated with home blood glucose monitoring and a diet with a daily energy intake of 5000–8000 kJ. Insulin treatment was instituted in 38 patients according to local protocols (therapeutic goals of mean blood glucose ≤ 7.0 mmol/l and in one centre post-prandial (1.5 h after breakfast) blood glucose value ≤ 7.0 mmol/l). Clinical supervision was offered at intervals of 1–2 weeks including ultrasound examinations with intervals of 4–6 weeks following diagnosis. Labour was induced at 40 weeks of gestation if spontaneous labour had not occurred. During labour, glucose monitoring was performed every 1–2 h aiming at blood glucose levels of 4–7 mmol/l, and treatment with glucose infusion and human insulin (Actrapid; Novo-Nordisk®, Gentofte, Denmark) was initiated if necessary. Blood glucose in new-borns was measured 2 h after delivery, and hypoglycaemia was treated with early feeding and if necessary intravenous infusion of glucose. Data were collected from patient records and data on the background population from Danish population-based investigations [13,14]. The local ethics committees of the participating centres approved the project.

A total of 3401 pregnant women had a diagnostic OGTT during the study period. Although the 2-h threshold value is identical in the local Danish and the DPSG criteria, the criteria are not completely identical, as the Danish criteria require two elevated glucose values (the 2-h value not necessarily elevated). Furthermore, dietary treatment was, for various unspecified reasons, instituted in a small number of women with a normal OGTT. To facilitate interpretation of the analyses, we excluded these treated women with 2-h OGTT values < 9.0 mmol/l as well as women with 2-h OGTT values ≥ 9.0 mmol/l who for some reason were untreated. Thus, from the first-mentioned group 88 out of 2973 women were excluded from the analyses, while 38 out of 428 from the latter group were excluded. Furthermore, 15 women were excluded because of treatment with sulphonylureas. Thus a total of 3260 pregnant women were eligible for the analysis.

The OGTT results were categorized into four groups according to proposed diagnostic thresholds for 2-h blood glucose (Fig. 1):
1 2-h OGTT value < 7.8 mmol/l (normal by WHO criteria) and not treated (n = 2596).
2 2-h OGTT value 7.8–8.9 mmol/l (normal by DPSG but impaired glucose tolerance (IGT) of pregnancy by WHO criteria) and not treated (n = 289).
3 2-h OGTT value 9.0–11.0 mmol/l (abnormal by DPSG and also IGT of pregnancy by WHO criteria) and treated (n = 278).
4 2-h OGTT value ≥ 11.1 mmol/l (diabetic by both WHO and DPSG criteria) and treated (n = 97).

Groups 1 and 2 did not receive any treatment focused on glucose tolerance, while dietary treatment was used in groups 3 and 4. Fourteen (5.0%) women in group 3 and 24 (24.7%) women in group 4 also received insulin treatment.

Outcomes

Hypertensive complications were defined as persistently elevated blood pressure (clinic blood pressure ≥ 140/90 mmHg on more than two occasions) with or without proteinuria. Shoulder dystocia was defined when obstetrical manoeuvres in addition to downward traction, episiotomy and a mild suprapubic pressure were required to deliver the shoulders. The diagnosis was re-evaluated by an obstetrician. Preterm delivery was defined as

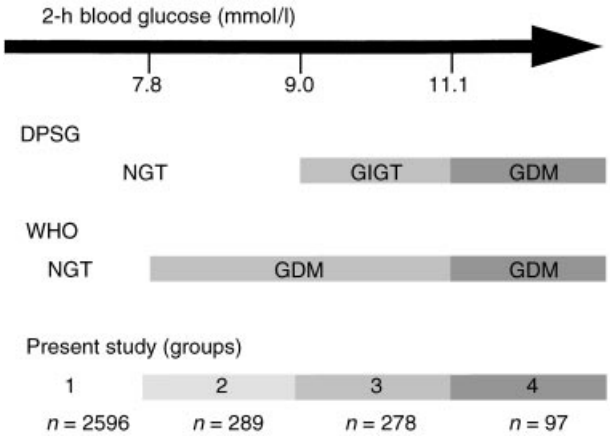

Figure 1 Proposed diagnostic threshold values for gestational diabetes mellitus according to the 75-g oral glucose tolerance test. DPSG, The Diabetic Pregnancy Study Group of the European Association for the Study of Diabetes [10]; WHO, World Health Organization [9]; NGT, normal glucose tolerance; GIGT, gestational impaired glucose tolerance; GDM, gestational diabetes mellitus.

delivery before 37 completed weeks. Macrosomia was defined by birth weight (BW) ≥ 4000 g or large for gestational age (LGA) defined as BW ≥ 90th percentile for a Danish standard population [15]. Jaundice required treatment with phototherapy, hypoglycaemia was defined as the need for intravenous glucose during the first 48 h of life and infants with respiratory distress were treated with continuous positive airway pressure for at least 30 min.

Statistical analysis

All statistical analyses were performed with the statistical program STATA 6.0 (Stata Corporation, College Station, TX, USA). The effects of various diagnostic threshold values were analysed by comparing the frequencies of adverse outcomes in the four groups by a univariate logistic regression analysis with group 1 (2-h blood glucose < 7.8 mmol/l) as the baseline category. The overall effect of 2-h glucose levels during OGTT was evaluated, using a Wald test. Similarly, multivariate logistic regression analysis was performed with adjustments for the risk factors: pre-pregnancy body mass index (BMI), maternal age, parity, smoking, weight gain during pregnancy, gestational age, anamnestic risk indicators for GDM, ethnic background and clinical centre. Here, the overall effect of 2-h glucose was evaluated, using a likelihood-ratio test. The results of the logistic regression analyses are expressed as odds ratios (OR) and the corresponding 95% confidence intervals (CI) and *P*-values. Data are given as median and interquartile range or number and percent. Differences between two groups were tested with Mann–Whitney's test. Trends across the four groups were evaluated by Cuzick's non-parametric test for continuous variables and with logistic regression analysis for categorical variables. A significance level of 0.05 was chosen (two-sided tests).

Results

The women in the study were significantly older (mean 30.5 vs. 28.8 years, $P < 0.001$) and more obese (mean pre-pregnancy BMI 26.6 vs. 23.8 kg/m^2, $P < 0.001$) than the background population. Fourteen percent had a non-Caucasian background. Among these, 31% were immigrants from the middle-east region, 25% from Turkey, 20% from India or Pakistan, 9% from China or Vietnam, 8% from Africa (predominantly Somalia) and 7% from other locations. OGTTs were performed at 31.3 (27.6–33.6) weeks of gestation. Maternal and infant characteristics are listed in Table 2.

Maternal and fetal outcomes. Univariate analyses

The results of the univariate logistic regression analysis are summarized in Table 3. The frequencies of shoulder dystocia,

Table 2 Maternal and fetal characteristics according to 2-h blood glucose values during a 75-g, 2-h oral glucose tolerance test

Group	1 (*n* = 2596)	2 (*n* = 289)	3 (*n* = 278)	4 (*n* = 97)
2-h blood glucose (mmol/l)	< 7.8	7.8–8.9	9.0–11.0	≥ 11.1
Maternal age (years)*	29.8 (26.6–33.5)	30.8 (27.9–34.7)	31.8 (28.7–36.1)	31.9 (28.7–35.0)
Pre-pregnancy BMI (kg/m^2)*	25.8 (21.8–30.0)	25.6 (21.6–29.7)	26.9 (22.7–32.4)	27.0 (24.2–32.1)
Weight gain during pregnancy (kg)*	14.6 (10.5–18.9)	14.6 (10.7–18)	11.0 (6.0–16.0)	9.0 (5.0–13.7)
Caucasians*	2248 (87.4)	242 (84.6)	206 (76.6)	62 (66.0)
Nulliparous*	1227 (47.3)	120 (41.5)	96 (34.7)	34 (35.1)
Family history of diabetes mellitus	1038 (41.0)	98 (34.2)	123 (45.2)	49 (52.7)
History of macrosomia	127 (4.9)	15 (5.2)	25 (9.1)	5 (5.1)
History of stillbirth	48 (1.9)	6 (2.1)	7 (2.5)	2 (2.1)
History of GDM*	36 (1.4)	15 (5.2)	29 (10.4)	11 (11.3)
Glucosuria*	381 (14.8)	77 (26.9)	74 (29.1)	49 (53.9)
Birth weight (g)	3600 (3250–4000)	3750 (3300–4070)**	3580 (3180–3900)	3590 (3260–4050)
Length (cm)*	52 (51–54)	53 (51–54)	52 (50–53)	52 (50–53)
Gestational age at delivery (weeks)*	40.3 (39.1–41.1)	40.0 (39.0–41.0)	39.3 (38.3–40)	39 (37.9–39.9)

Data are given as median (interquartile range) or number (%). For some of the variables, the total number is less than 3260 due to missing values.
*Significant trends (Cuzick's non-parametric trend test and logistic regression analysis) across the four groups; **$P < 0.05$ vs. adjacent groups (Mann–Whitney).

Table 3 Maternal and fetal outcomes according to 2-h blood glucose values during a 75-g, 2-h oral glucose tolerance test (OGTT). Univariate logistic regression analysis with group 1 as baseline

	Group	No. affected	No. not affected	Percent affected	OR vs. baseline	95% CI	*P*-value*
Preeclampsia and pregnancy-induced hypertension†	1	158	2418	6.1	1.0	–	0.09
	2	16	271	5.6	0.9	0.5–1.5	
	3	25	249	9.1	1.5	1.0–2.4	
	4	10	86	10.4	1.8	0.9–3.5	
Shoulder dystocia‡	1	33	2109	1.5	1.0	–	0.004
	2	8	227	3.4	2.2	1.0–4.9	
	3	9	194	4.4	3.0	1.4–6.3	
	4	4	74	5.1	3.5	1.2–10.0	
Spontaneous preterm delivery§	1	73	2523	2.8	1.0	–	< 0.001
	2	11	278	3.8	1.4	0.7–2.6	
	3	15	263	5.4	2.0	1.1–3.5	
	4	13	84	13.4	5.2	2.9–10.0	
Caesarean section¶	1	450	2146	17.3	1.0	–	0.0015
	2	54	235	18.7	1.1	0.8–1.5	
	3	75	203	27.0	1.8	1.3–2.3	
	4	19	78	19.6	1.2	0.7–1.9	
Large for gestational age infant**	1	515	2074	19.9	1.0	–	< 0.001
	2	83	206	28.7	1.6	1.2–2.1	
	3	83	193	30.1	1.7	1.3–2.3	
	4	36	61	37.1	2.4	1.6–3.6	
Birth weight ≥ 4000 g	1	696	1897	26.8	1.0	–	0.005
	2	98	191	33.9	1.4	1.1–1.8	
	3	57	220	20.6	0.7	0.5–1.0	
	4	27	70	27.8	1.0	0.7–1.7	
Hypoglycaemia††	1	63	2516	2.4	1.0	–	< 0.001
	2	6	281	2.1	0.9	0.4–2.0	
	3	26	246	9.6	4.2	2.6–6.8	
	4	25	71	26.0	14.1	8.4–23.7	
Jaundice‡‡	1	83	2468	3.3	1.0	–	< 0.001
	2	6	281	2.1	0.6	0.3–1.5	
	3	20	253	7.3	2.4	1.4–3.9	
	4	10	85	10.5	3.5	1.8–7.0	
Respiratory distress§§	1	192	2387	7.4	1.0	–	< 0.001
	2	24	263	8.4	1.1	0.7–1.7	
	3	28	248	10.1	1.4	0.9–2.1	
	4	23	74	23.7	3.9	2.4–6.3	

†Hypertension with and without proteinuria in women without hypertension prior to pregnancy.
‡Shoulder dystocia in vaginal delivereries only.
§Spontaneous delivery before 37 completed weeks.
¶Total caesarean section rate.
**Birth weight > 90th percentile for a Danish reference population.
††Intravenous glucose during the first 48 h of life.
‡‡Treatment with phototherapy.
§§Treatment with continuous positive airway pressure for at least 30 min.
*Wald test. Baseline is defined as 2-h blood glucose < 7.8 mmol/l. Groups 1–4 according to 2-h glucose value during OGTT: group 1, < 7.8 mmol/l; group 2, 7.8–8.9 mmol/l; group 3, 9.0–11.0 mmol/l; group 4, ≥ 11.1 mmol/l. For some of the variables, the total number is < 3260 due to missing values.

spontaneous preterm delivery, LGA infant, neonatal hypoglycaemia and jaundice were significantly higher in groups 3 and 4 than in group 1. Furthermore, the occurrence of shoulder dystocia, LGA infant and BW ≥ 4000 g was significantly increased in group 2 compared with group 1, while the frequency of BW ≥ 4000 g decreased in group 3. The caesarean section rate was increased in group 3, but not in group 4. There was a significant overall effect of the 2-h glucose level except for hypertensive complications ($P = 0.09$).

Maternal and fetal outcomes. Multivariate analyses

The results of the multivariate logistic regression analysis are summarized in Table 4. The frequencies of spontaneous

Table 4 Maternal and fetal outcomes according to 2-h blood glucose values during a 75-g, 2-h oral glucose tolerance test. Multivariate logistic regression analysis with group 1 as baseline

	Group	OR vs. baseline	95% CI	*P*-value*
Preeclampsia and pregnancy-induced hypertension†	1	1.0	–	0.03
	2	0.9	0.5–1.8	
	3	1.6	0.9–2.7	
	4	2.9	1.3–6.2	
Shoulder dystocia‡	1	1.0	–	0.73
	2	1.3	0.4–3.9	
	3	1.8	0.7–4.7	
	4	1.2	0.2–5.8	
Spontaneous preterm delivery§	1	1.0	–	< 0.001
	2	1.7	0.8–3.5	
	3	2.0	1.0–3.6	
	4	5.1	2.4–11.0	
Caesarean section¶	1	1.0	–	0.09
	2	1.0	0.7–1.4	
	3	1.4	1.0–2.0	
	4	0.7	0.4–1.4	
Large for gestational age infant**	1	1.0	–	< 0.001
	2	1.7	1.1–2.4	
	3	2.0	1.4–2.8	
	4	3.0	1.8–5.1	
Birth weight ≥ 4000 g	1	1.0	–	0.02
	2	1.5	1.1–2.2	
	3	1.2	0.8–1.7	
	4	2.1	1.1–3.8	
Hypoglycaemia††	1	1.0	–	< 0.001
	2	0.7	0.2–2.2	
	3	3.4	2.0–5.9	
	4	8.1	3.9–16.7	
Jaundice‡‡	1	1.0	–	0.36
	2	0.5	0.2–1.6	
	3	1.3	0.7–2.4	
	4	0.7	0.2–2.2	
Respiratory distress§§	1	1.0	–	0.14
	2	1.2	0.7–2.2	
	3	0.9	0.6–1.5	
	4	2.0	1.1–3.6	

†Hypertension with and without proteinuria in women without hypertension prior to pregnancy.
‡Shoulder dystocia in vaginal delivereries only.
§Spontaneous delivery before 37 completed weeks.
¶Total caesarean section rate.
**Birth weight > 90th percentile for a Danish reference population.
††Intravenous glucose during the first 48 h of life.
‡‡Treatment with phototherapy.
§§Treatment with continuous positive airway pressure for at least 30 min.
*Likelihood-ratio test. Baseline is defined as 2-h blood glucose < 7.8 mmol/l. Groups 1–4 according to 2-h glucose value during oral glucose tolerance test: group 1, < 7.8 mmol/l; group 2, 7.8–8.9 mmol/l; group 3, 9.0–11.0 mmol/l; group 4, ≥ 11.1 mmol/l.

preterm delivery, LGA infant and neonatal hypoglycaemia were significantly higher in groups 3 and 4 than in group 1. The incidence of BW ≥ 4000 g was increased in groups 2 and 4 (but not group 3) compared with baseline. The caesarean section rate was higher in group 3, whereas the rate in group 4 did not differ from baseline. There was a significant overall effect of 2-h glucose level for the outcomes: hypertensive complications, spontaneous preterm delivery, LGA infant, BW ≥ 4000 g and neonatal hypoglycaemia.

Discussion

This large Danish cohort study provides outcome data according to diagnostic threshold values during an OGTT (75 g; 2 h) as proposed by DPSG [8] and WHO [7]. Our results confirm the findings of other investigators: that a number of maternal and perinatal outcomes are associated with glucose levels in pregnancy [16–20]. Women with diagnosed GDM (groups 3 and 4) were subjected to a special programme and this

should obviously be considered in the interpretation of our results.

The frequency of spontaneous preterm delivery increased dramatically with deteriorating carbohydrate intolerance. Even after adjustment for possible confounders, there was a five-fold greater risk when GDM was associated with a 2-h OGTT value ≥ 11.1 mmol/l. This finding is in accordance with the results of a previous Danish study [21] indicating a relationship between preterm delivery and the degree of metabolic disturbance and the findings in Type 1 diabetic pregnancies [22].

The frequency of macrosomia showed a > 50% increase in group 2 compared with baseline, whereas the risk of shoulder dystocia was only increased in the univariate analyses. In a previous publication, we reported a significant association between the 2-h OGTT value tested as a continuous variable and both macrosomia and shoulder dystocia in this range of glucose values [10]. This discrepancy is probably caused by the dichotomizing of the 2-h OGTT values < 9.0 mmol/l in the present study and the corresponding loss of statistical power. For women in groups 3 and 4, the risk of BW ≥ 4000 g declined compared with group 2, and also here the risk of shoulder dystocia was not significantly increased, suggesting an effect of treatment. The caesarean section rate increased from about 18% in the untreated groups [1,2] to 27% in group 3 where treatment had been instituted in accordance with previous findings [18]. In contrast, the caesarean section rate in group 4 was not increased, probably due to the increased rate of spontaneous preterm delivery in this group.

Despite intervention with diet and glycaemic control, the rate of LGA increased in groups 3 and 4 compared with groups 1 and 2. The therapeutic goals in our study were comparable to those recommended in the consensus report from The 4th International Workshop Conference on GDM [1], but treatment was instituted later since the time for screening for GDM was later. The slight variation in therapeutic goals in the four centres was accounted for by entering clinical centre in the multivariate model. It is likely that intervention at an earlier stage would have been more effective in preventing LGA infants. The low frequency of insulin treatment in women with GDM might be explained by the fact that the more severe cases of GDM, who were diagnosed by fasting hyperglycaemia alone, are not included in our study. If these patients had also been included, the effect of glucose intolerance on adverse outcomes might have been even more pronounced. It has been shown that birth weight is higher for white Caucasians than for most other ethnic groups [23]. In our study, the proportion of women with non-Caucasian background increased with increasing glucose intolerance. Thus the LGA rate in these groups might be somewhat underestimated, since ethnically adjusted growth curves are not used in Denmark. However, as the non-Caucasian group was very heterogeneous ethnically and statistical adjustments were made for non-Caucasian background in the analyses, the contribution of each ethnic minority is not likely to have had a major impact on the overall results. There is a well-known relationship between obesity and adverse pregnancy outcomes, including macrosomia, shoulder dystocia and preterm delivery [24]. However, the relationship between 2-h OGTT results and most complications remained significant after adjustment for BMI and other confounders, indicating that hyperglycaemia *per se* is a predictor for adverse outcome.

An association between hypertension and carbohydrate intolerance in pregnancy has previously been reported [25,26], although the results are conflicting [27]. The risk of neonatal hypoglycaemia tended to increase progressively in groups 3 and 4, whereas the incidences were similar in groups 1 and 2. A serious bias in comparing groups 1 and 2 with groups 3 and 4 is that infants in the latter groups were subjected to routine measurement of glucose. However, our definition was rather conservative and required the use of intravenous glucose infusion, whereas infants treated successfully with early feeding were considered normal.

In conclusion: (i) the risk of macrosomia is increased in women with 2-h blood glucose of 7.8–8.9 mmol/l compared with women with 2-h glucose < 7.8 mmol/l; (ii) despite treatment, 2-h glucose of 9.0–11.0 mmol/l and ≥ 11.1 mmol/l are associated with increased rates of LGA infants, spontaneous preterm delivery, hypertensive complications, neonatal hypoglycaemia and caesarean section; (iii) adverse maternal/perinatal outcomes tend to be more frequent in women with 2-h glucose ≥ 11.1 mmol/l than in women with 2-h glucose of 9.0–11.0 mmol/l. Thus, the results support the contention that no joint threshold level exists for all outcomes. Furthermore, a 2-h threshold of 9.0 mmol/l after a 75-g glucose load seems acceptable until data from large-scale prospective studies are available.

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