Influence of Pregnancy on the 75-g OGTT

A Prospective Multicenter Study

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This study reports the responses to a 75-g oral glucose tolerance test (OGTT) in 1009 pregnant women from throughout Europe. We reached the following conclusions. *1*) A pregnant woman tends to have blood glucose concentrations that are elevated for a longer period of time after an oral glucose load. Therefore, ~10% of women will reach or exceed 8 mM glucose at 2 h, but it is unlikely that 10% of European women have disordered carbohydrate metabolism. *2*) The fasting and 1-h values should be included in any analysis of the response of the patient. By doing this, many fewer women will have responses regarded as abnormal; in this series, it reduced the 79 women with a 2-h value >8 mM to 15 who were considered to have carbohydrate intolerance (2 with diabetes, 13 with impaired glucose tolerance [IGT]). *3*) By increasing the 2-h cutoff value to ≥9 mM, the number of women regarded as at risk would be reduced by >50% (from 79 to 32 in this series), but 10 of the 13 women with two abnormal values would still have been detected, as would the 2 diabetic women. *4*) From the obstetric viewpoint, mothers who screen positive do not have bigger babies, they deliver close to term, and they do not have particular stigmas such as a family history of diabetes or an increased tendency to smoke or to have an adverse obstetric outcome. However, they do tend to be older and heavier. This raises the question of whether the apparent longer-term consequences such as coronary artery disease and hypertension are not in some measure due to these factors rather than carbohydrate intolerance alone. *5*) We recommend that the screening test for disordered carbohydrate tolerance should be based on a 75-g OGTT with at least three blood samples: fasting, 60 min, and 120 min. The fasting value should not exceed 7 mM, the 1-h level should be <11 mM, and the 2-h value should be <9 mM. To diagnose IGT, either the fasting or 1-h concentration should be above the stated values in addition to a 2-h value >9 mM. Diabetes should be diagnosed with the existing World Health Organization criteria. *6*) The term *gestational diabetes* should be reserved for those in whom blood glucose levels are diagnostic of diabetes and not IGT. If the term *IGT during pregnancy* is too long, the abbreviation *gestational IGT* is a reasonable alternative. *Diabetes* 40 (Suppl. 2):8–13, 1991

During 1980, the World Health Organization (WHO) suggested criteria for diagnosing diabetes mellitus and impaired glucose tolerance (IGT) based on blood glucose concentrations after a 75-g oral glucose load; in 1985, a second WHO study group substantially endorsed these recommendations after some minor modifications (1). This report suggested that the criteria used to diagnose diabetes and IGT in the general population could be applied to pregnant women. A second report endorsed this view with the argument that the application of set diagnostic criteria to large groups of pregnant and nonpregnant individuals would make it possible to determine more specifically the effect of lesser degrees of glucose intolerance on maternal and child health (2). Neither report acknowledged that pregnancy itself imposes changes on the response to an oral glucose load and hence the possibility that glucose intolerance may be diagnosed in healthy women displaying normal physiological adaptation.

This study investigated prospectively the response to a 75-g oral glucose load in a general prenatal population drawn from a wide geographical area of western Europe. The tests were performed under the usual clinical and laboratory conditions prevailing in the units taking part with the guidelines suggested by the WHO (1,2). The minimum number of blood samples required was two: fasting and at 2 h. Many centers provided additional data from samples obtained at 30, 60, and 90 min.

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TABLE 1
Maternal characteristics in population studied

Center	*n* tests by gestation (days)			Type of blood sample	Age at test (yr)		Height (cm)		Test weight (kg)		Body mass index (kg/m^2)	
	<117	118–195	196+		Mean	Range	Mean	Range	Mean	Range	Mean	Range
Aberdeen		110	2	CP	27	18–38	161	147–178	68	52–113	26	21–42
Belfast		83	17	VP	27	18–39	159	145–175	65	47–101	26	19–40
Berlin	89	133	105	CWB	25	17–37	165	146–178	65	47–98	24	19–33
Bonn		5	55	CWB,VP	31	17–43	165	149–179	80	60–127	29	22–47
Copenhagen			25	CWB,VP	29	23–36	166	150–175	67	48–80	24	19–30
London	11	31		VP	27	19–41	163	151–177	67	52–90	25	20–33
Newcastle upon Tyne	18	21	24	VP,VWB	29	22–36	163	147–183	68	43–104	25	18–36
Southampton	25	21	174	VP	26	15–38	162	138–184	64*	43–90*	NS	NS
Misda	2	50	61	VP	28	18–42	158	140–177	68	48–103	28	18–41
Vienna	12	29	39	CWB	25	17–35	165	146–180	62	46–84	23	17–32
Zagreb	10	30	5	CWB	28	20–48	166	156–178	68	48–109	25	17–40
Whole group	167	513	507		27	15–43	162	138–184	70	46–127	26	18–47

Because age and weight increase progressively throughout pregnancy, whole-group values for age, weight, and body mass index are for 3rd trimester. C, capillary; P, plasma; V, venous; WB, whole blood.
*Recorded at 1st visit and not at testing.

The only specified reason for exclusion of any patient from the trial was known insulin-dependent diabetes mellitus, although one center (Southampton) also excluded women who had a family history of diabetes in a first-degree relative.

RESEARCH DESIGN AND METHODS

Patient characteristics. Not all information is available on every patient. Thus, for example, maternal height was not recorded on some individuals, so these data do not relate to the total number of women investigated. Some of those investigated during early pregnancy subsequently aborted or, in a very few cases, delivered elsewhere; hence, the number of live births plus perinatal deaths do not add up to the total number of individuals studied. Finally, some women in the Berlin group were asked to have an oral glucose tolerance test (OGTT) during each trimester; thus, 149 women eventually contributed 327 tests. Precise details of all variables according to the participating center are available, but in the interest of brevity the data have been treated as coming from a single group unless specific differences between groups occurred.

Because in some centers relatively few women attend for their first prenatal visit before 13 wk gestation, the numbers recruited within this definition of the first trimester were low. Computer analysis showed that if an early pregnancy group was defined as up to 117 days from the last menstrual period, then seven centers would contribute data from 167 tests. On this basis the midpregnancy group was defined as 118–195 days (10 centers, 513 tests), and late pregnancy was ≥196 days (10 centers, 507 tests). The main epidemiological features are given against these gestational groupings in the tables.

The means and ranges for maternal age, weight, height, and body mass index (BMI) are given in Table 1. With an average weight increase by term of 12 kg, we would regard a BMI of up to 30 kg/m^2 by term as normal, between 31 and 35 kg/m^2 as overweight, and ≥36 kg/m^2 as obese. Each center studied a population in which most were well inside the normal range, but each had some women at the extremes of age, weight, and height.

Most of the mothers studied were recorded as nonsmokers, (Table 2), but one area was exceptional in this regard; Copenhagen recorded 60% of the mothers as smokers, but the total number studied was small (Table 2; 25). No smoking was allowed during the test in any center.

With the exception of Southampton, no attempt was made to exclude patients on the basis of family history. Although such details obtained by patient recall can be somewhat unreliable, the facts that 5% had a first-degree relative and 6% had a second-degree relative with diabetes suggest that our study population was generally representative in this respect (Table 2). One center (Misda) had 29% of their patients with a first-degree history of diabetes, but this is a feature of that population, and most of such relatives are non–insulin requiring.

Three-quarters of the population had not had a previous pregnancy loss before 28 wk gestation, and ~50% were being studied during their first pregnancy. It was not possible to determine how many previous abortions were spontaneous or induced, but in the center recording by far the biggest percentage of women (33%) having two or more previous pregnancy losses before 28 wk, most were induced terminations. Thus, we have no reason to suspect that the study population was unusual with respect to previous obstetric outcomes (Table 2).

Pregnancy outcome. Sonar facilities were available in every center taking part, and most of the women had a scan during the first half of pregnancy. The gestation at delivery is therefore the best estimate in each case by use of menstrual dates and ultrasonic measurements. All babies delivered very preterm were the result of spontaneous labor, and those going ≥43 wk were accepted to be genuinely postterm. The mean and range values for the length of gestation are shown in Table 3; the earliest were spontaneous abortions, and the gestation of 313 days was reliably determined from dates and sonar. The SD calculated for the whole group was 14 days.

The lowest–birth weight baby (550 g) was an apparent stillbirth because it delivered after 28 wk, but the clinical evidence suggested fetal demise some weeks before this.

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TABLE 2
Percentages of nonsmokers and those with family history of diabetes and previous pregnancy outcomes

Center	Nonsmokers (%)	Family history of diabetes (%)			Distribution of previous pregnancies (%)					
					<28 wk			>28 wk		
		0	1st degree	2nd degree	0	1	2	0	1	2
Aberdeen	83	79	5	16	76	20	4	62	28	10
Belfast	60	87	8	5	84	14	2	30	35	35
Berlin	92	90	1	9	76	22	2	49	40	11
Bonn	NR	NR	NR	NR	63	20	17	32	37	31
Copenhagen	40	100	0	0	64	36	0	72	24	4
London	68	95	3	2	57	31	12	57	33	10
Newcastle upon Tyne	94	91	3	6	78	18	4	48	44	8
Southampton	70	100	0	0	71	20	9	64	22	14
Misda	68	61	29	10	89	10	1	45	35	20
Vienna	77	100	0	0	73	18	9	56	34	10
Zagreb	96	100	0	0	43	24	33	27	60	13
Group mean	75	89	5	6	76	17	6	51	34	15

NR, not recorded.

Only 9 infants of the 986 with recorded weights exceeded 4.5 kg and came from a wide geographic distribution: 1 each in Aberdeen, Belfast, Newcastle, and Southampton; 2 in Bonn; and 3 in Berlin. The SD of birth weight around the mean was 508 g (Table 3).

The term *vaginal delivery* includes cephalic and breech presentations, *forceps* includes the use of vacuum extraction, and *cesarean section* is the total of elective and emergency procedures. The average data given in Table 4 for the group as a whole are broadly representative of the individual groups. For example, the cesarean section rate varied between 6 and 16% with one exception: the rate for Bonn was 25% in the 55 mothers contributing to the trial and reflected a slight excess of emergency operations. Interestingly, the lowest operation rate at 6% was also in Germany (Berlin).

There were three spontaneous abortions, seven stillbirths, and one neonatal death (Table 3). Two of the stillbirths were so classified because delivery occurred after 28 wk gestation, although fetal death had occurred before this in both cases. The neonatal death occurred in a baby that had lethal cardiac anomalies (Table 4). Neither the spontaneous abortions nor the neonatal death occurred in mothers with test results suggestive of carbohydrate intolerance. One of the seven mothers delivering a stillbirth had a capillary plasma glucose level of 8.2 mM 2 h after the 75-g glucose load, but the WHO cutoff value for this blood sample type is 8.9 mM. In addition, this mother's fasting value was only 4.8 mM, and the peak value (at 90 min) was only 8.4 mM. Thus, none of the mothers with an adverse pregnancy outcome had diabetes or IGT by WHO criteria.

OGTT procedure. The 75-g OGTT was used following the test recommendations in Annex 1 of the WHO report (2). Four centers collected venous whole-blood samples and determined the glucose concentration on the plasma, three centers used capillary samples and determined whole-blood glucose values, one center determined capillary plasma values, two centers collected simultaneous paired samples of capillary and venous blood and reported capillary whole-blood and venous plasma values, and one center obtained venous whole blood and measured glucose in this and the separated plasma from the same sample (Table 5).

TABLE 3
Length of gestation, birth weight, method of delivery, and infant outcome

Center	Gestation at delivery (days)		Birth weight (g)		Method of delivery (%)			Outcome of present pregnancy (*n*)				
	Mean	Range	Mean	Range	Vaginal	Forceps	CS	LB	SB	NND	Ab	NS
Aberdeen	280	193–306	3355	980–4640	75	17	8	109	1	1 (1)	1	
Belfast	281	246–302	3447	2270–4540	77	14	9	100 (4)	0	0		
Berlin	279	143–313	3359	1390–4670	90	4	6	139	1	0	2	7
Bonn	273	203–294	3301	550–4740	67	8	25	58	1	0		1
Copenhagen	281	246–311	3347	2260–4170	84	0	16	25	0	0		
London	279	230–307	3377	2100–4080	70	18	12	40	0	0		1
Newcastle upon Tyne	279	245–311	3451	2660–4500	71	21	8	98	1	0		1
Southampton	272	210–294	3348	1620–4650	74	15	11	216	0	0		6
Misda	278	243–295	3373	1530–4200	86	7	7	112	1	0		
Vienna	274	196–292	3341	1750–4460	94	0	6	77	1	0		1
Zagreb	272	230–293	3326	1700–4030	91	0	9	44	1	0		
Whole group	278	143–313	3367	550–4740	81	9	10	921	7	1	3	17

Number in parentheses indicates infants with anomalies. CS, cesarean section; LB, live birth; SB, stillbirth; NND, neonatal death; Ab, abortion; NS, not stated.

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TABLE 4
Clinical details of 7 stillbirths and 1 neonatal death occurring in total group

Infant outcome	Gestation (days)	Weight (g)	Comment
Stillbirths			
1	240	2850	Unexplained IUD at autopsy
2	254	2350	Severe accidental hemorrhage
3	203	550	Missed abortion delivered after 28 wk
4	263	2740	Unexplained IUD at autopsy
5	275	1530	Growth-retarded IUD (nil found at autopsy)
6	196		Missed abortion delivered after 28 wk
7	265	2690	Unexplained IUD at autopsy
Neonatal death			
1	285	3740	Multiple heart defects

IUD, intrauterine death.

All centers used autoanalyzer techniques employing enzyme methods for glucose determination. Six samples of freeze-dried serum were prepared in Newcastle upon Tyne and sent to each center for determination of glucose content. The tubes were simply labeled 1–6 with no indication of the likely glucose content; tubes 4–6 were actually the same sample. Six centers assayed the samples within a short time of receiving them; in two centers, there was a considerable delay in assaying them, and the values were so low that it seems likely degradation had occurred; in the final three instances the participating doctors had moved to other centers. Analysis of the data from the six centers determining the glucose values soon after receipt showed that each would assay to within 0.5 mM of the mean concentration of the samples, which covered a range of 2–8 mM.

Because some centers determined glucose concentrations in paired blood samples, it has been possible to see whether a reasonable relationship exists between capillary whole-blood and venous plasma glucose concentrations (Table 5). Although physiologically it can be postulated that such a relationship should exist, such was not the case in our data. Under everyday clinical and laboratory conditions, random errors can occur that prevent any useful extrapolation of values from venous plasma values to capillary levels; tests with venous plasma samples should be interpreted against standards derived from venous plasma glucose values; similarly, tests with capillary blood should not be interpreted from adjusted venous blood values.

RESULTS

There were 1009 mothers in the whole group providing data from 1187 separate test occasions; this arose because of the mothers from Berlin who agreed to have additional tests later in pregnancy. In addition, some centers obtained two types of blood sample in the course of the same test, so one woman could appear both in the analysis of capillary whole-blood results and venous plasma results. Therefore, there were 1296 test results available for analysis.

The 5th, 50th, and 95th percentile values for venous plasma and capillary whole blood at timed intervals after the 75-g oral glucose load during the three stages of pregnancy are shown in Table 6. The 95th percentile value for the fasting venous plasma concentration during the second trimester was influenced by a cluster of patients from one center who had unusual test responses. Thirteen women recorded a fasting level of ≥6.9 mM during the second trimester (12 from Belfast, 1 from Misda); of these, 5 were nondiabetic (2-h value <8 mM), 7 were classified as having IGT (2-h value 8–11 mM), and 1 was diabetic. They thus formed the top 5% of the 211 values available; by comparison, the 95th percentile value was only 4.7 mM for the 196 women having second trimester fasting values measured on capillary whole blood and 5.1 mM for the 110 capillary plasma samples. Indeed, only one other woman had a fasting value >6.9 mM in the whole series, suggesting that the 95th percentile value for venous plasma fasting glucose in a general prenatal population is probably ~4.7 mM.

The percentile values for capillary plasma have not been given, because the data came from one center only (Aberdeen) and were obtained during the second trimester only.

INTERPRETATION OF RESULTS

As pregnancy progressed, the concentration of glucose in blood increased whether determined on venous plasma or capillary whole blood, with the mean concentrations at 60, 90, and 120 min significantly higher during the third trimester compared with the same times during early pregnancy ($P <$

TABLE 5
Relationship between plasma and whole-blood glucose concentrations in paired samples of capillary and venous blood

		Glucose concentration (mM)						
Center	*n*	VP (*n* = 147)	CWB (*n* = 177)	CWB − VP (*n* = 147)	VWB (*n* = 66)	CWB − VWB (*n* = 66)	CP (*n* = 79)	CP − VP (*n* = 79)
Belfast	36	4.60 ± 0.71	4.70 ± 0.70	0.07 ± 0.44	4.20 ± 0.58	0.53 ± 0.44	5.10 ± 0.87	0.45 ± 0.49
Berlin	30		4.60 ± 0.80		4.50 ± 0.63	0.06 ± 0.50		
Copenhagen	43	5.10 ± 1.19	4.80 ± 1.10	−0.15 ± 0.70			5.30 ± 1.20	0.24 ± 0.52
Newcastle upon Tyne	15	4.90 ± 0.53	4.30 ± 0.51	−0.56 ± 0.46				
Misda	13	4.00 ± 0.35	4.20 ± 0.68	0.15 ± 0.57				
Zagreb	40	3.80 ± 0.64	4.30 ± 0.63	0.55 ± 0.26				
Mean ± SD		4.50 ± 0.97	4.60 ± 0.82	0.08 ± 0.6	4.30 ± 0.62	0.31 ± 0.52	5.21 ± 1.03	0.33 ± 0.51

VP, venous plasma; CWB, capillary whole blood; VWB, venous whole blood; CP, capillary plasma. Belfast determined glucose levels on VP, VWB, CP, and CWB, allowing relationships between all samples to be examined, whereas Newcastle upon Tyne determined VP and CWB levels on simultaneously paired blood samples.

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TABLE 6
Glucose concentrations at timed intervals after 75-g oral glucose load for venous plasma and capillary whole-blood samples throughout pregnancy

		Sample time (min)			
	Fasting	30	60	90	120
Venous plasma glucose (mM)					
<117 days	(55)	(31)	(55)	(31)	(55)
5th percentile	3.6	5.2	3.3	2.8	2.6
50th percentile	4.2	6.2	5.4	5.2	4.7
95th percentile	4.9	9.1	7.8	8.7	6.8
118–195 days	(211)	(190)	(163)	(143)	(209)
5th percentile	3.7	5.0	4.3	4.0	3.8
50th percentile	4.6	7.4	6.9	6.3	5.7
95th percentile	6.9	10.6	10.1	9.0	9.0
≥196 days	(354)	(182)	(291)	(121)	(353)
5th percentile	3.5	4.9	4.7	4.2	4.2
50th percentile	4.1	6.8	7.3	7.2	6.1
95th percentile	5.2	9.4	10.5	10.4	9.0
Capillary whole-blood glucose (mM)					
<117 days	(111)	(110)	(111)	(101)	(111)
5th percentile	2.9	5.2	4.3	4.4	3.4
50th percentile	3.8	6.9	6.3	5.6	5.3
95th percentile	4.8	8.9	8.7	7.6	7.3
118–195 days	(196)	(191)	(196)	(161)	(196)
5th percentile	3.0	5.2	4.7	4.2	3.8
50th percentile	3.8	6.7	6.5	5.8	5.5
95th percentile	4.7	8.6	8.7	7.9	7.2
≥196 days	(228)	(174)	(229)	(168)	(229)
5th percentile	3.1	5.2	5.2	4.4	4.1
50th percentile	3.8	6.9	7.3	6.5	5.9
95th percentile	4.5	8.9	10.2	8.8	8.2

Numbers in parentheses are *n* observations.

0.001). Therefore, it could be anticipated that this physiological response would cause some women to exceed the arbitrary level of 8 mM at 2 h. Our data show that ~10% of all mothers will exceed this limit and raise the question of whether such a high proportion of pregnant women have a true disorder of carbohydrate metabolism or whether most are merely displaying the extremes of normal pregnancy response.

To investigate this, the women were divided into two groups according to whether they achieved or exceeded a 2-h value of 8 mM. Because those who did were relatively few in number, this cutoff value was adopted whether measured on venous plasma or capillary whole blood. However, because capillary plasma glucose levels are appreciably higher, this group of mothers has been excluded from these particular analyses.

Features associated with 2-h blood glucose values >8 mM. There were 79 women in whom the 2-h blood glucose value reached or exceeded 8 mM. There was no preponderance of first-degree relatives having diabetes in those mothers having a high 2-h level. Whether the mothers were smokers did not influence the test responses. To keep the numbers as large as possible, women in their first pregnancy were compared with those in their second or subsequent pregnancy. No parity differences were noted in the blood glucose response groups. There was no difference in the mean height of the two groups. Both groups delivered close to term (mean ± SD gestation 276 ± 15 and 274 ± 15 days for women with 2-h blood glucose <8 and ≥8 mM, respectively). Both groups delivered babies of comparable weight (3367 ± 508 and 3366 ± 556 g, respectively). Age was accurately recorded (i.e., as date of birth) in 760 normally responsive mothers and 58 of those with ≥8 mM blood glucose; the latter group was significantly older at 29.0 ± 5.3 yr relative to 26.0 ± 4.6 yr ($P < 0.001$). Because maternal weight increases progressively throughout pregnancy, we compared the 290 mothers with normal levels tested during the last trimester against the 35 with raised 2-h levels. The latter group was heavier (74.8 ± 15.9 to 69.8 ± 11.0 kg) and had an increased BMI (28.3 ± 5.2 to 26.1 ± 3.9 kg/m^2; $P < 0.02$). None of the abortions, stillbirths, or neonatal deaths were associated with a high 2-h blood glucose level.

If blood glucose levels are elevated at 2 h, the presumption might be that one or more of the preceding test values were also elevated as part of a more generalized impairment of response. In most cases, this was not so: only 9 women had a fasting value ≥6.9 mM, and 7 of these came from one center; 13 women had a 60-min value ≥11 mM, 4 of whom were from the same Belfast group. The remaining 9 mothers with an elevated 1-h value had normal fasting values. Because the women were asymptomatic for diabetes, it could be argued that only those with two abnormal blood glucose levels should be regarded as having IGT or diabetes, in which case, 2 women had frank diabetes, and 13 had IGT.

If, during pregnancy, a 2-h value of 9 mM is adopted, then 32 women exceeded this value in our series; the 2 diabetic women and 10 of the 13 patients with a 60-min value ≥11 mM would still have been detected. However, inspection of

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the data again reveal that maternal age and BMI may influence the way glucose is handled. The mean age at test was 30.8 ± 4.0 yr for the 32 women with a 2-h value >9 mM relative to 26.4 ± 4.7 yr for the remainder ($P < 0.001$), and the BMIs were 29.2 ± 6.2 and 25 ± 4 kg/m^2, respectively ($P < 0.003$). The lengths of gestation did not differ (273 ± 14 and 276 ± 15 days, respectively) nor did infant birth weight (3422 ± 604 and 3366 ± 510 g, respectively).

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These data were presented at a syposium held in Aberdeen, UK (3).

APPENDIX 1

The centers taking part: Aberdeen, UK (H.W. Sutherland); Vienna, Austria (A. Pollak); Copenhagen, Denmark (L. Molsted-Pedersen, C. Kuhl); Belfast, Northern Ireland (D.R. Hadden); Newcastle upon Tyne, UK (T. Lind); Bonn, Germany (O. Bellmann); Zagreb, Yugoslavia (A. Drazancic); Misda, Malta (E.S. Grech, C. Savona-Ventura); London, UK (M. Maresh); Berlin, Germany (K. Fuhrmann); Southampton, UK (M. Hatem).

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