Evaluation of the Three-hour Oral Glucose Tolerance Test in Detection of Significant Hyperglycemia and Hypoglycemia in Pregnancy

D. A. Abell, M.B., B.S., M.G.O., M.R.C.O.G., F.C.O.G. (S.A.), and
N. A. Beischer, M.D., M.G.O., F.R.C.S. (Edin.), F.R.A.C.S., F.R.C.O.G.,
Melbourne, Australia

SUMMARY

Analysis of 2,000 consecutive patients who had a three-hour 50-gm. oral glucose tolerance test done in the third trimester of pregnancy has shown that the three-hour reading was not necessary for the diagnosis of gestational diabetes.

It was found that hyperglycemia and hypoglycemia (95th and 5th percentiles, respectively, for plasma glucose levels) were significantly associated with an increased risk for perinatal mortality. Furthermore, hyperglycemia was associated with an increased incidence of large-for-dates placentas and hypoglycemia with small-for-dates infants and small-for-dates placentas. These associations with hypoglycemia were seen to be greatest when this occurred at the three-hour level, and it was concluded that the three-hour *measurement should be retained until the clinical significance of* hypoglycemia in pregnancy is fully determined. DIABETES ***24*:874-80, October, 1975.**

It is well recognized that gestational diabetes is associated with a higher incidence of maternal and fetal complications than is seen in normal pregnancy.[1] It is to be hoped that the antenatal detection of gestational diabetes would be rewarded by allowing improvement in the rates of pregnancy complications and would enable the follow-up these women require in view of their increased risk of developing overt diabetes mellitus in later life.[2]

From the University of Melbourne Department of Obstetrics and Gynaecology, Mercy Maternity Hospital, East Melbourne, Australia. 3002

Address reprint requests to Dr. D. A. Abell, Department of Obstetrics and Gynaecology, Mercy Maternity Hospital, Clarendon Street, East Melbourne, Australia. 3002

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Screening of pregnant women for diabetes has been performed by complete glucose tolerance testing when indicated by the presence of certain clinical criteria. Macafee and Beischer[3] investigated the incidence of significantly abnormal glucose tolerance in the presence of a family history of diabetes mellitus, glycosuria, a previous large infant, maternal obesity, and advanced maternal age and concluded that maternal age of thirty years or more was the single most important indication. Likewise, O'Sullivan et al.,[1] in assessing the value of a previous large baby, a poor past obstetric history, and a family history of diabetes mellitus as criteria for performing a glucose tolerance test in pregnancy, found that the incidence of gestational diabetes was no higher in this group of selected patients than in the entire antenatal population. In addition, they found that 79 per cent of gestational diabetics were detected by a single blood glucose estimation performed one hour after ingestion of 50 gm. of glucose. While the sensitivity rate was increased to 88 per cent in gestational diabetic patients twenty-five years and older, the majority of pregnant women are younger than this age group, and it would appear that the only way to detect all gestational diabetics is to perform complete glucose tolerance testing on every patient.

There is reason to believe that milder degrees of hyperglycemia and hypoglycemia may be associated with increased pregnancy complications,[4] and routine complete glucose tolerance tests may prove beneficial in the detection of patients with these aberrations of carbohydrate metabolism as well as those with gestational diabetes.

Acknowledging the difficulties inherent in routine

glucose tolerance testing, the purpose of the present study was to assess whether a three-hour reading was necessary in an oral glucose tolerance test in pregnancy.

MATERIALS AND METHODS

All patients at the Mercy Maternity Hospital, Melbourne, have a glucose tolerance test performed at thirty-two to thirty-four weeks of gestation. The present study group consisted of 2,000 consecutive patients, 1,000 of whom were clinic and 1,000 private patients.

The only criterion for inclusion was that a glucose tolerance test had been performed. Patients not included in this series were those prematurely delivered before the time of performance of the glucose tolerance test and those admitted unbooked in labor or with emergency obstetric complications providing no opportunity to perform a glucose tolerance test before delivery. Excluded were known diabetics and patients with multiple pregnancies.

Patients continued their normal diet and were instructed to fast from 10 p.m. on the night before the test. At 9 a.m. a three-hour 50-gm. glucose tolerance test was commenced. Capillary blood was obtained from a finger prick, collected into a heparinized tube, and immediately centrifuged. Assays of plasma glucose were performed by the glucose oxidase method using a Beckman glucose analyzer (Beckman Instruments, Fullerton, Calif. 92634). A fasting plasma glucose specimen was obtained, then plasma glucose was measured in hourly blood specimens for three hours after the ingestion of glucose, the assays being performed immediately after collection of the respective specimens.

The percentiles were calculated for the plasma glucose ranges at each reading of the glucose tolerance test in this group of patients and were separately evaluated for the clinic and private patients (table 1). Hyperglycemia and hypoglycemia were defined as present when the plasma glucose equaled or exceeded the ninety-fifth percentile or equaled or was less than the fifth percentile, respectively, on one or more of the four readings obtained. Gestational diabetes was diagnosed when the plasma glucose level was 140 mg. per 100 ml. or above at two hours and in addition reached 180 mg. per 100 ml. at any time during the three-hour glucose tolerance test.

Infants were diagnosed as large-for-dates when the birth weight was above the ninetieth percentile and small-for-dates when the birth weight was below the tenth percentile according to gestational age for infants born in this community.[5] The ninetieth and tenth percentiles used for defining large- and small-for-dates placentas were those reported by Ratten et al.[6]

TABLE 1

Plasma glucose percentiles for clinic and private patients

Glucose tolerance test	Plasma glucose percentiles mg./100 ml.		
	Ninety-fifth	Fiftieth	Fifth
Fasting			
Clinic patients	93	76	61
Private patients	91	78	65
1-Hour			
Clinic patients	165	123	88
Private patients	172	127	95
2-Hour			
Clinic patients	128	95	68
Private patients	132	101	74
3-Hour			
Clinic patients	103	70	55
Private patients	106	71	56

Urinary estriol excretion was measured in all patients by the method of Brown et al.[7] and was regarded as subnormal when one or more values were obtained below a line joining 8 mg. per twenty-four hours at thirty weeks of gestation and 12 mg. per twenty-four hours at forty weeks and thereafter.[8]

All infants were examined within forty-eight hours of birth and again shortly before the mother's discharge from hospital, and the presence of abnormalities entailed referral to a pediatrician for thorough assessment. A malformation was regarded as major if it was of such severity that it interfered with the function of all or part of the infant. Minor abnormalities were not considered in this study.

Perinatal mortality included any stillbirth and deaths occurring in live-born infants within twenty-eight days of birth.

RESULTS

In all cases a three-hour glucose tolerance test was performed. To establish the results that would have been obtained had the glucose tolerance test been limited to two hours, the three-hour reading was not considered initially.

The percentiles were observed to differ between the socioeconomic groups (table 1), and so the appropriate percentile values were used when grouping both social classes of patients together into hyperglycemia and hypoglycemia groups.

Preliminary studies entailed the assessment of paired limits of 90th and 10th, 95th and 5th, and 97th and 3rd percentiles in this group of 2,000 patients (unpublished data). The ninety-fifth and fifth percentiles were selected as the limits of normality as they provided an apparent best and most complete selection of complicated pregnancies as well as a manageable incidence of patients designated as abnormal. The percentage abnormality rates at these limits are shown in table 2. There were twenty-seven patients who had an abnormal glucose tolerance test with both a hyperglycemic and a hypoglycemic result during the three-hour test, and these patients are included in the results of both types of abnormal glucose tolerance.

TABLE 2

Incidence of abnormal glucose tolerance test*

	Duration of glucose tolerance test			
	3 Hours		2 Hours	
	No.	(%)	No.	(%)
Hyperglycemia	315	(15.8)	243	(12.2)
Hypoglycemia	346	(17.3)	272	(13.6)

*In twenty-seven patients both hyperglycemic and hypoglycemic levels occurred during the three-hour glucose tolerance test.

When all four levels in the three-hour glucose tolerance test fell between the ninety-fifth and fifth percentiles the patient was considered to be normoglycemic. The percentage incidences in normoglycemia of abnormalities of birth weight, placental weight, major fetal malformations, perinatal mortality, and low estriol excretion may then be regarded as normality for comparative purposes (table 3).

In reverting from a three-hour to a two-hour glucose tolerance test, patients excluded from the abnormal groups will be those in whom the three-hour reading only was abnormal. The pregnancy outcome in these patients is shown in table 4. For comparison

TABLE 4

Pregnancy complications when a single plasma glucose abnormality was confined to the three-hour reading

Complications	Type of plasma glucose abnormality			
	Hyperglycemia		Hypoglycemia	
	No.	(%)	No.	(%)
Subnormal urinary estriol excretion	8	(11.1)	12	(16.2)
Small-for-dates baby	5	(6.9)	16	(21.6)
Large-for-dates baby	6	(8.3)	3	(4.1)
Small-for-dates placenta	6	(8.3)	16	(21.6)
Large-for-dates placenta	8	(11.1)	8	(10.8)
Major fetal malformations	5	(6.9)	3	(4.1)
Perinatal mortality	1	(1.4)	0	0
Patients	72		74	

the pregnancy outcome where there were abnormalities at the various points of the glucose tolerance test is shown in table 5; it should be noted that in this table all patients with an abnormal reading at three hours are included—that is, those who had a single abnormality confined to the three-hour reading (table 4) plus those who had an additional abnormality at some other time during the glucose tolerance test.

If the plasma glucose value at three hours exceeded that at two hours, the pregnancy outcome was as shown in table 6. These patients constituted 8.9 per cent of the series and were regarded as those with a delayed rise in plasma glucose levels, perhaps due to delayed gastric emptying.

Fourteen patients with gestational diabetes were detected; plasma glucose levels were elevated above the ninety-fifth percentile in the two-hour reading in all and the one-hour reading in thirteen. In seven of the fourteen patients the ninety-fifth percentile was exceeded in the fasting specimen, but in only three was it exceeded at three hours (table 7). There was no significant excess of large-for-dates babies or placentas and only one stillbirth in this group of patients.

TABLE 3

Pregnancy complications in the presence of normoglycemia, hyperglycemia, and hypoglycemia—three-hour glucose tolerance test*

Complications	Glucose tolerance test result					
	Normoglycemia		Hyperglycemia		Hypoglycemia	
	No.	(%)	No.	(%)	No.	(%)
Subnormal urinary estriol excretion	121	(8.9)	37	(11.7)	42	(12.1)
Small-for-dates baby	116	(8.5)	30	(9.5)	54	(15.6)
Large-for-dates baby	127	(9.3)	30	(9.5)	27	(7.8)
Small-for-dates placenta	147	(10.8)	31	(9.8)	47	(13.6)
Large-for-dates placenta	118	(8.6)	46	(14.6)	34	(9.8)
Major fetal malformations	53	(3.9)	9	(2.9)	15	(4.3)
Perinatal mortality	8	(0.6)	10	(3.2)	9	(2.6)
Patients	1,366		315		346	

*In twenty-seven patients both hyperglycemic and hypoglycemic levels occurred during the three-hour glucose tolerance test.

TABLE 5

Pregnancy complications associated with all abnormalities of plasma glucose at the fasting, one-, two-, and three-hour readings

Complications	Type of plasma glucose abnormality							
	Hyperglycemia				Hypoglycemia			
	Fasting (%)	1 hr. (%)	2 hrs. (%)	3 hrs. (%)	Fasting (%)	1 hr. (%)	2 hrs. (%)	3 hrs. (%)
Subnormal urinary estriol excretion	11.9	16.5	12.4	10.3	13.5	7.8	13.9	16.7
Small-for-dates baby	11.9	10.7	7.1	7.5	15.6	9.8	13.9	20.4
Large-for-dates baby	12.9	7.8	7.1	8.4	8.3	8.8	8.3	6.5
Small-for-dates placenta	8.9	13.6	9.7	8.4	13.5	13.7	8.3	18.5
Large-for-dates placenta	18.8	13.6	10.6	11.1	9.4	10.8	9.3	9.3
Major fetal malformations	3.0	1.9	2.7	5.6	6.3	3.9	3.7	3.7
Perinatal mortality	6.9	3.9	3.5	1.9	4.2	2.0	3.7	0.9
Patients	101	103	113	107	96	102	108	108

TABLE 6

Pregnancy complications when the plasma glucose value at three hours exceeded that at two hours

Complications	Incidence	
	No.	(%)
Subnormal urinary estriol excretion	19	(10.7)
Small-for-dates baby	20	(11.3)
Large-for-dates baby	15	(8.5)
Small-for-dates placenta	13	(7.3)
Large-for-dates placenta	18	(10.2)
Major fetal malformations	4	(2.3)
Perinatal mortality	1	(0.6)
Patients	177	

There were twenty-six perinatal deaths in the 2,000 pregnancies; eighteen occurred when glucose tolerance was abnormal, but only one of these was associated with an abnormal reading confined to the three-hour level. Table 8 shows the clinical details of these pregnancies; maternal weight was measured at the time of the glucose tolerance test. Major malformations were detected in seventy-six infants; twenty-three of these were associated with abnormalities of glucose tolerance, and eight occurred when the abnormality was confined to the three-hour reading.

DISCUSSION

It has been reported that simplified screening has limited sensitivity and specificity in the detection of gestational diabetes.[1] If routine glucose tolerance testing is adopted only for the diagnosis of gestational diabetes with 100 per cent sensitivity, a detection rate of 0.7 per cent, as in this series, may not justify the considerable laboratory and staffing facilities required.

TABLE 7

Glucose tolerance tests and pregnancy outcome in patients diagnosed as gestational diabetics

Patient No.	Glucose tolerance test Plasma glucose, mg./100 ml.				Urinary estriol excretion	Birth weight (gm.)	Placental weight (gm.)	Fetal outcome
	Fasting	1 hr.	2 hrs.	3 hrs.				
Clinic								
1	137*	188*	194*	154*	Normal	1,940‡	500	Alive, patent ductus arteriosus
2	110*	203*	148*	76	Normal	3,760	600	Alive
3	110*	192*	145*	102	Normal	3,700	630	Alive
4	97*	189*	143*	71	Subnormal	2,280	660†	Stillborn, Down's syndrome, multiple malformations
5	95*	191*	150*	76	Normal	2,450	580	Alive
6	88	198*	141*	71	Subnormal	1,060	240	Alive
7	86	182*	339*	57	Normal	3,980	505	Alive
8	85	212*	156*	72	Normal	2,690†	530	Alive
9	85	166*	228*	152*	Normal	4,200†	770†	Alive
10	75	195*	160*	65	Subnormal	1,770‡	310‡	Alive
Private								
11	118*	201*	166*	79	Subnormal	3,480	780†	Alive
12	116*	198*	149*	119*	Normal	3,070	660	Alive
13	85	184*	145*	66	Normal	3,810	640	Alive
14	72	167	183*	85	Normal	3,790	540	Alive

*Above the ninety-fifth percentile.
†Large-for-dates.
‡Small-for-dates.

TABLE 8

Clinical details of perinatal deaths

Patient No.	Glucose tolerance				Maternal age	Maternal weight (kg.)	Urinary estriol excretion
	Fasting	1 hr.	2 hrs.	3 hrs.			
1 Normoglycemia	80	144	94	62	38	108	Subnormal
2 Normoglycemia	77	158	80	61	19	56	Normal
3 Normoglycemia	77	113	84	67	32	90	Subnormal
4 Normoglycemia	74	142	88	57	18	64	Normal
5 Normoglycemia	74	98	98	66	17	73	Normal
6 Normoglycemia	72	125	126	92	16	59	Normal
7 Normoglycemia	71	136	75	64	22	46	Normal
8 Normoglycemia	62	136	113	61	18	70	Subnormal
9 Gestational diabetes	97	189	143	71	46	82	Subnormal
10 Hyperglycemia	122	112	112	91	17	92	Normal
11 Hyperglycemia	98	180	130	84	22	59	Normal
12 Hyperglycemia	98	114	95	79	20	61	Normal
13 Hyperglycemia	96	122	98	85	26	66	Normal
14 Hyperglycemia	94	179	141	97	33	79	Subnormal
15 Hyperglycemia	91	146	137	98	30	64	Normal
16 Hyperglycemia	91	140	116	103	24	65	Normal
17 Hyperglycemia	73	174	102	73	42	82	Subnormal
18 Hyperglycemia & Hypoglycemia	61	169	146	131	22	51	Normal
19 Hypoglycemia	86	94	94	85	25	80	Normal
20 Hypoglycemia	82	126	70	62	28	78	Normal
21 Hypoglycemia	78	111	65	74	36	58	Subnormal
22 Hypoglycemia	73	131	65	60	24	60	Subnormal
23 Hypoglycemia	69	82	87	71	21	69	Normal
24 Hypoglycemia	65	150	127	84	30	60	Subnormal
25 Hypoglycemia	63	112	109	83	23	57	Normal
26 Hypoglycemia	50	118	47	36	43	73	Subnormal

The value of any test in pregnancy is related to its rate of detection of an abnormality that in itself shows an associated incidence of pregnancy complications. If milder degrees of hyperglycemia and hypoglycemia in pregnancy are significant parameters of pregnancy risk, then their detection may justify routine complete glucose tolerance testing of all pregnant women.

The two-hour oral glucose tolerance test may be advantageous to the patient and the laboratory, but this must be weighed against the loss of detection of patients with complicated pregnancies who would have been identified by an abnormal result confined to the three-hour value (table 4).

In this study the incidence of abnormal glucose tolerance when the ninety-fifth and fifth percentiles were adopted as the limits of normality was approximately 32 per cent in a three-hour test and 25 per cent in a two-hour test (table 2). It is important to note the finding that the percentile values for the private patients were higher than those in the clinic patients ($p < 0.01$ by nonparametric analysis). It is known that patients of higher socioeconomic status have increased fetal birth weight and placental weight,[6] and these observations may be explained by dietary considerations.

In the diagnosis of gestational diabetes the definition used ensured that the two-hour reading was above the ninety-fifth percentile. The glucose tolerance tests in these patients revealed that a delayed rise in the values was not a diagnostic feature (table 7). The fact that thirteen of the fourteen gestational diabetics had two or more plasma glucose levels above the ninety-fifth percentile and that the three-hour level was not required to establish the diagnosis has shown that a two-hour glucose tolerance test is sufficient to diagnose gestational diabetes.

Empirically it could be expected that the three-hour plasma glucose reading would approach fasting levels, and if that was so then this reading would be regarded as unnecessary. However, delayed gastric emptying time may result in occurrence of the highest concentration of glucose at two or three hours rather than at one or two hours.[9] Patients with plasma glucose levels higher at three hours than at two hours (table 5) proved to have pregnancy outcomes similar to those with normal glucose tolerance ($p > 0.05$ for all values). Similarly, when hyperglycemia was confined to the three-hour reading (table 4) the results were not significantly different from normal. These findings indicated that the three-hour reading confers

TABLE 8 (*continued*)

Clinical details of perinatal deaths

Patient No.	Gestation (wk.)	Birth weight (gm.)	Placental weight (gm.)	SB or NND	Remarks
1 Normoglycemia	42	4,380†	950†	SB	Obese, hypertensive grand-multigravida
2 Normoglycemia	40	3,500	640	SB	Chronic maternal anemia, salicylate addict
3 Normoglycemia	39	3,550	560	NND day 11	Anomalous pulmonary venous drainage
4 Normoglycemia	34	1,520*	480	SB	Abruptio placentae
5 Normoglycemia	42	3,220	630	SB	Cord tight around neck
6 Normoglycemia	40	3,400	650	SB	Intrauterine hypoxia
7 Normoglycemia	35	2,340	500	NND 1 hr.	Idiopathic hydrops fetalis
8 Normoglycemia	36	1,840*	360	NND day 2	Hyaline membrane disease
9 Gestational diabetes	33	2,280	660†	SB	Down's syndrome, multiple malformations
10 Hyperglycemia	40	3,070	550	SB	Intrapartum hypoxia
11 Hyperglycemia	41	2,850*	485*	SB	Intrapartum hypoxia
12 Hyperglycemia	40	3,320	790†	NND day 6	Coliform septicemia
13 Hyperglycemia	42	3,260	620	SB	Intrapartum hypoxia
14 Hyperglycemia	35	2,300	640	SB	Rh immunized, hydrops fetalis
15 Hyperglycemia	40	3,170	550	NND day 2	Hypoplastic heart, pulmonary hemorrhage
16 Hyperglycemia	38	2,730	540	NND 10 mins.	Hydrocephaly, micrognathia, cleft palate
17 Hyperglycemia	33	1,100*	200*	SB	Maternal hypertension
18 Hyperglycemia & Hypoglycemia	39	2,350*	420*	NND day 2	Respiratory distress syndrome
19 Hypoglycemia	35	2,560	580	NND 5 hrs.	Congenital heart disease, multiple malformations
20 Hypoglycemia	38	4,130†	800†	SB	Intrauterine hypoxia
21 Hypoglycemia	36	2,580	490	SB	Abruptio placentae
22 Hypoglycemia	32	1,310	315	NND day 3	Respiratory distress syndrome
23 Hypoglycemia	36	2,170	370	SB	Abruptio placentae
24 Hypoglycemia	40	2,230*	385*	NND 2 hrs.	Diaphragmatic hernia
25 Hypoglycemia	37	1,880*	285*	NND 2 hrs.	Potter's syndrome
26 Hypoglycemia	37	2,470	450	SB	Abruptio placentae in labor

SB = Stillbirth. NND = Neonatal death. * = Small-for-dates. † = Large-for-dates.

no advantage by detecting delayed glucose tolerance with late elevation of plasma glucose values.

Hyperglycemia was associated with increased placental weight ($p < 0.01$) (table 3), this association being greatest when there was fasting hyperglycemia (table 5). Significantly, hypoglycemia was more likely to result in small-for-dates babies and small-for-dates placentas (table 3), the yield being highest when the hypoglycemia occurred at the three-hour value (table 5). When hypoglycemia was confined to the three-hour reading, all other readings of the glucose tolerance test being normal (table 4), it was associated with the highest incidences of small-for-dates infants ($p < 0.001$) and placentas ($p < 0.01$), and, possibly as a consequence of this, subnormal urinary estriol excretion was present more frequently ($p < 0.05$). The glucose tolerance tests of such patients demonstrate reactive hypoglycemia. Jung et al.[10] found that asymptomatic reactive hypoglycemia, by an arbitrary definition, occurred in about 17 per cent of surveyed healthy women and was more frequently associated with lower fasting blood glucose values. However, although this may be regarded as a phenomenon of normal glucose tolerance, the data presented here suggest that this condition is a clinical entity in obstetrics, as this could result in insufficient transfer of glucose across the placenta. We believe that there is a group of clinically normal patients whose infants are stillborn because of growth retardation due to this mechanism.[11]

Eighteen of the twenty-six perinatal deaths occurred when glucose tolerance was abnormal in the three-hour test; statistical analysis showed that this association of abnormal glucose tolerance and perinatal mortality was highly significant ($p < 0.001$). Retention of the three-hour assay would not be justified in the selection of this association, as there was only one perinatal death when the abnormality was confined to the three-hour reading. It appeared that the incidence of major fetal malformations was unrelated to maternal plasma glucose levels. Hyperglycemia and hypoglycemia were associated with incidences of major malformations of 2.9 per cent and 4.3 per cent, respectively, which did not differ significantly from the value in normoglycemic patients (3.9 per cent) (table 3), nor were the differences significant

when plasma glucose abnormalities were confined to the three-hour reading (table 4).

The two-hour glucose tolerance test is convenient to laboratory staff and patients, and it detected all cases of gestational diabetes. Abnormal glucose tolerance, defined as being outside the ninety-fifth and fifth percentile limits, was associated with a higher incidence of perinatal deaths, but not of major fetal malformations. As hypoglycemia at the three-hour level was associated with increased incidences of small-for-dates babies and placentas, we believe that the three-hour glucose tolerance test should be retained until the clinical significance of milder degrees of hyperglycemia and hypoglycemia has been fully determined.

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