THE RAPID INTRAVENOUS GLUCOSE TOLERANCE TEST IN PREGNANCY*

By FELIX A. SILVERSTONE, EDWARD SOLOMONS AND JEANETTE RUBRICIUS

(From the Department of Obstetrics and Gynecology and the Department of Medicine, State University of New York, Downstate Medical Center, and the Maimonides Hospital of Brooklyn, N. Y.)

(Submitted for publication May 9, 1961; accepted August 30, 1961)

Pregnancy may precipitate frank diabetes (1–5) or aggravate diabetes with regard to the clinical course and insulin requirements (6–10). Not all susceptible females are equally affected and some escape deterioration of carbohydrate metabolism during a particular pregnancy (10–14). The detrimental effects are frequently interrupted early in the puerperium (1, 2, 14–16). Consideration of the diabetogenic factors involved has focused attention on the contra-insulin effects of cortisone and growth hormone (2, 5, 17). Insulin degradation by one of the products of conception, the placenta (18), and insulin inactivation by plasma protein (19) represent other potential factors. The contra-insulin effects have been interpreted as a challenge to the insulin-producing capacity of the maternal pancreas (2, 3).

The limitations of the oral glucose tolerance test, particularly during pregnancy (20–23), cast doubt on interpretations indicating impaired tolerance in nondiabetic women (24–27). Intravenous tolerance tests have been inconclusive (28) with some values (29) indicating that glucose tolerance may improve during uncomplicated pregnancy. There is at present no convincing evidence of altered glucose tolerance in the nondiabetic pregnant female, despite the multiplicity of metabolic changes during pregnancy and the adverse effects upon the diabetic state. Failure to disclose significant alterations in tolerance may have resulted from: *1*) inadequacies of the oral glucose tolerance test because of the interaction between glucose absorption and glucose uptake by tissues; *2*) insensitivity of the intravenous test methods employed, since only a rough estimate of tolerance can be derived from the fall in blood glucose concentration within a preselected interval, usually 2 hours (30); or *3*) the absence of a net change in glucose tolerance during pregnancy. The last possibility could reflect a balance between the effects of increased insulin production and contra-insulin mechanisms. This possibility also offers a basis for the maintenance of tolerance during pregnancy in the nondiabetic and the deterioration of tolerance in the diabetic female, assuming a relative inability of the diabetic to meet a demand for more insulin.

This investigation was directed at revaluating the pattern of glucose tolerance during uncomplicated pregnancy in nondiabetic women. The slope of the tolerance curve after the injection of a standard dose of glucose served as the index of glucose tolerance. Previous experience with this technique has shown it to be sufficiently sensitive to reveal changes in glucose tolerance among nondiabetic male subjects on the basis of differences in age (30).

EXPERIMENTAL METHODS

Subject selection. One hundred sixteen ambulatory female subjects, aged 16 to 41 years, were screened by a detailed history, physical examination, urinalysis and fasting blood glucose determination. Subjects presenting any of the following were excluded from the study: *1*) a history or evidence of diabetes or glycosuria; *2*) a family history of diabetes; *3*) a suspicious obstetrical history including babies of excessive weight (exceeding 4.0 kg) and unexplained stillbirths; *4*) alcoholism, hepatomegaly, cirrhosis or other liver disease; *5*) thyroid or other endocrine disturbance; *6*) cardiac decompensation, edema, toxemia and abnormalities of pregnancy; *7*) gastrointestinal upsets; *8*) the taking of steroid drugs (all other medication was omitted for 24 hours before the test); and *9*) infection, temperature elevation, or trauma (including surgical) within 1 week of the test, except for the postpartum group which was tested after the third postpartum day. The previous diet provided 2,000 calories daily for at least 1 week, again with the exception of

* This study was supported by Grant A-1842 from the National Institute of Arthritis and Metabolic Diseases of the National Institutes of Health, United States Public Health Service.

TABLE I

Subject characteristics

Variable		Non-pregnant	Pregnant (trimester) First	Second	Third	All	Post-partum
N		30	21	20	20	61	25
Age (*yrs*)	Mean	26.0	24.3	24.4	23.2	24.0	26.4
	Range	19–35	17–34	17–34	17–37	17–37	16–41
Height (*cm*)	Mean	162.7	160.0	159.6	159.2	159.6	156.4
	Range	150–179	153–173	152–176	150–173	150–176	147–167
Weight (*kg*)	Mean	59.7	60.4	59.0	65.5	61.6	58.2
	SE of mean	2.3	2.5	2.3	2.7	1.5	1.9
	Range	47–95	48–101	45–89	49–100	45–101	44–86
Fasting blood glucose (*mg/100 ml*)	Mean	65.9	61.3	59.1	59.6	60.0	56.1
	SE of mean	1.2	1.5	1.6	1.9	1.0	2.0
	Range	52–84	50–75	45–77	44–78	44–78	40–91

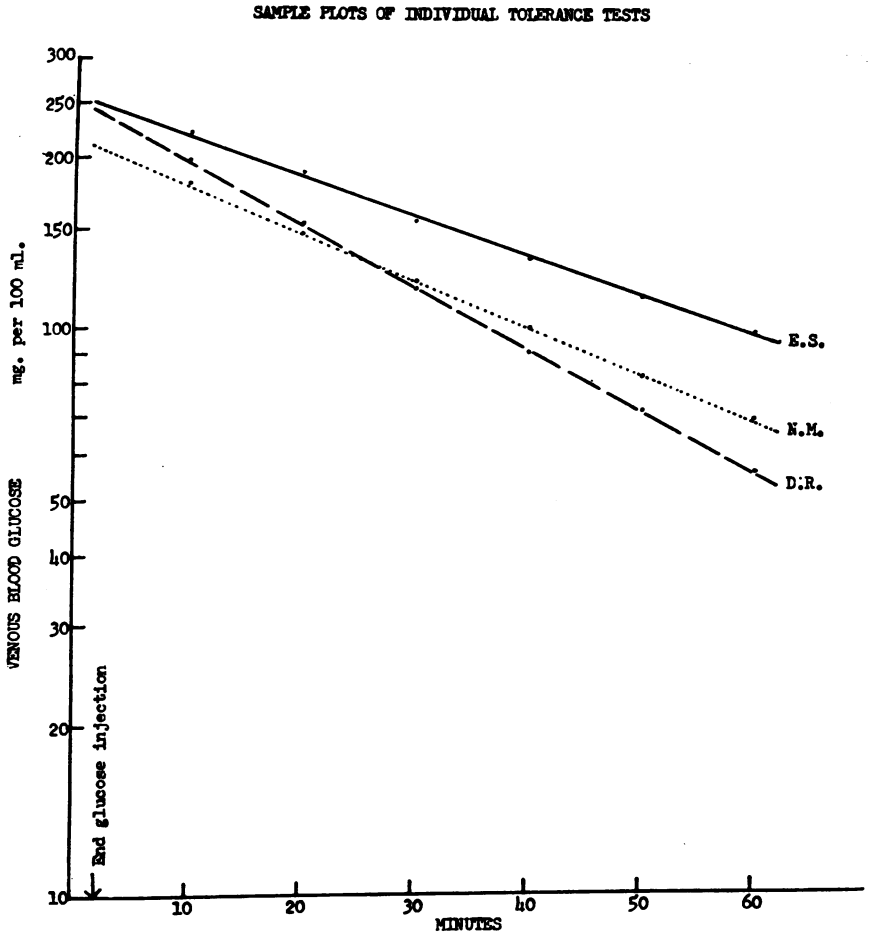

FIG. 1. LOG GLUCOSE CONCENTRATION IN VENOUS BLOOD (MILLIGRAMS PER 100 ML) PLOTTED AGAINST TIME (MINUTES) FOR INDIVIDUALS SELECTED FROM THE FOLLOWING GROUPS: NONPREGNANT (SOLID LINE), THIRD TRIMESTER (DOTTED LINE), AND FIRST TRIMESTER (DASHED LINE).

the postpartum group, in which the minimal period was 3 days.

Experimental procedure. With the subject in the basal state, a modified Lindeman needle was inserted into an antecubital vein 20 minutes before the test and left in place until completion of the procedure. Patency of the needle was maintained by heparinization of the stylus. This needle was used only for the subsequent drawing of blood specimens without a tourniquet (31) and for obtaining a fasting sample a few minutes before zero time. The latter was recorded at the beginning of the injection of 50 ml of 50 per cent glucose in water into a vein of the opposite arm over a period of 2 minutes.

Blood samples were collected at 10 minutes and at 10-minute intervals thereafter until 60 minutes. The blood was immediately placed in dried heparin-fluoride tubes and analyzed on the day of the test by the Nelson-Somogyi method (32). Determinations were in duplicate and read on a Klett-Summerson photoelectric colorimeter.

Data analysis. The observations obtained between 10 and 60 minutes for each glucose tolerance test (GTT) were fitted to the equation, $\log_e y = \log_e A - kt$, where y is the blood glucose concentration in milligrams per 100 ml, A is the intercept with the vertical axis, and t is the lapsed time in minutes. The value of k, the index of tolerance for the study, was computed for each subject from the visually fitted slope to a plot of the log glucose concentration against time.[1] Glucose spaces were derived by extrapolating the GTT plots to the intercept at zero time without applying a correction factor (33) for the concentration of solids in whole blood.[2] Changes in glucose tolerance were evaluated by comparing the k values of the following groups: nonpregnant, nonmenstruating (30 subjects); pregnant, first trimester (21 subjects); pregnant, second trimester (20 subjects); pregnant, third trimester (20 subjects); pregnant, total (61 subjects); and postpartum, fourth through the sixth day (25 subjects).

RESULTS

Reliability of methods. The standard error of estimate of repeated glucose determinations on a single blood filtrate was ± 0.61 mg per 100 ml (N = 55, mean glucose concentration = 122 mg per 100 ml). Corresponding values for duplicate filtrates prepared from the same blood specimen were ± 0.92 mg per 100 ml (N = 100, mean glucose concentration = 119 mg per 100 ml).

General description of results. No significant differences in age were found among the subject

[1] The derivation of k by least squares has been compared with graphic estimates obtained from visual fits (30). The results were in sufficiently close agreement for the GTT (R = 0.96) to substantiate the use of the visual method.

[2] Glucose space (liters) = $\frac{\text{injected dose (25 g)}}{\text{0 time concentration} - \text{fasting concentration (g/L)}}$

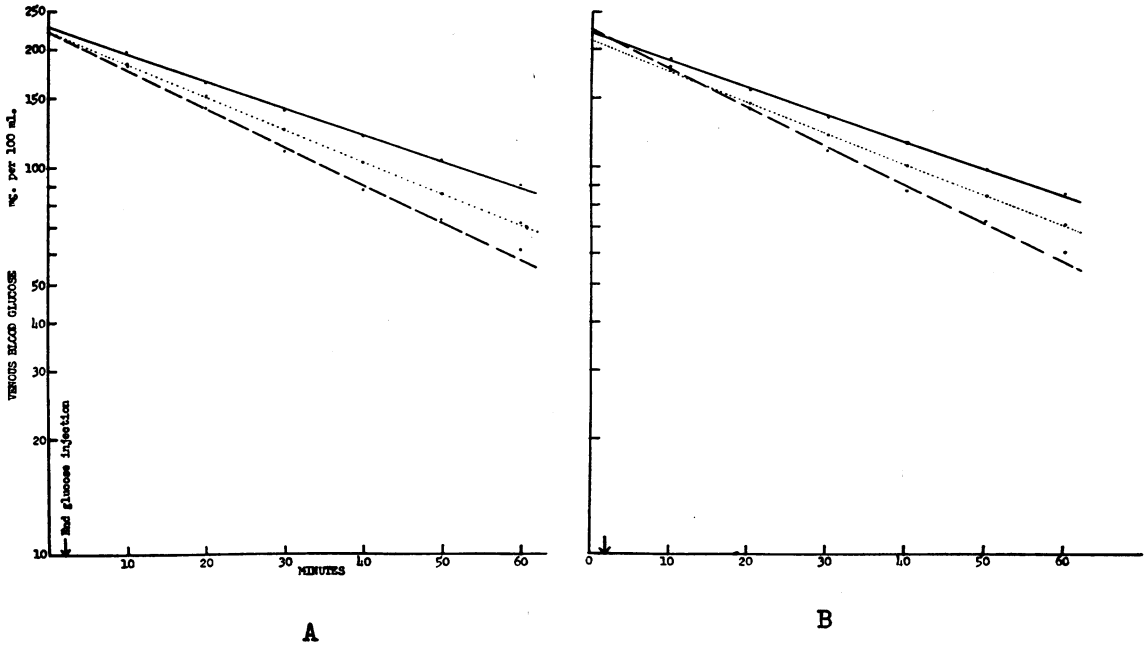

FIG. 2. CHANGES IN THE RAPID INTRAVENOUS GLUCOSE TOLERANCE TEST IN PREGNANCY. Logs of average venous blood sugar values (milligrams per 100 ml) for each group plotted against time (minutes) after the intravenous injection of 25 g of glucose. A. Nonpregnant (solid line), second trimester (dotted line), first trimester (dashed line). B. Postpartum (solid line), third trimester (dotted line), first trimester (dashed line).

TABLE II

Nonpregnant women of childbearing age (30 subjects)

Subject	Age	Ht	Wt	Blood levels after 25 g glucose i.v. (mg/100 ml at time in min) 0	10	20	30	40	50	60	k	Glucose volume
	yrs	*cm*	*kg*								*%/min*	*L*
M.J.	25	170	94	66	180	153	130	117	100	89	1.50	17.6
J.K.	21	161	47	67	231	186	165	144	127	112	1.65	12.3
B.D.	33	166	51	69	200	167	144	124	109	92	1.64	15.0
DJ.V.	30	164	82	80	223	198	173	156	140	133	1.40	14.7
P.G.	19	166	50	69	218	196	164	145	130	108	1.18	15.2
P.P.	23	157	60	70	197	170	147	131	116	100	1.31	16.5
N.L.	35	159	49	60	185	149	126	108	100	88	1.81	15.4
E.S.	29	159	51	64	222	189	152	130	113	99	1.76	12.4
H.R.	28	179	63	66	182	151	123	109	96	84	1.73	16.9
L.S.	20	164	50	66	224	117	155	136	124	112	1.50	14.3
G.C.	24	164	75	75	186	167	150	136	123	116	1.07	18.9
J.O.	29	172	56	70	188	159	140	129	115	99	1.35	17.4
P.C.	25	161	52	64	201	173	161	145	134	121	1.39	15.7
O'S.J.	26	166	62	64	194	150	127	104	83	72	2.04	14.5
E.F.	29	155	56	68	215	174	155	150	136	125	1.07	16.1
M.K.	23	154	56	60	200	172	139	122	112	94	1.57	14.5
D.L	23	155	49	62	237	204	181	159	139	119	1.33	12.2
L.R.	32	150	48	60	198	151	119	92	78	59	2.47	13.3
B.M.	27	159	50	60	239	162	130	103	85	80	2.25	12.7
C.C.	23	167	59	52	170	150	133	115	102	92	1.25	18.1
M.P.	26	172	66	65	181	126	97	79	59	49	2.73	15.2
E.W.	22	154	49	62	188	150	124	97	80	66	2.14	14.6
M.V.	32	157	61	65	162	138	125	104	92	89	1.43	20.8
J.B.	21	172	60	64	194	145	114	92	80	70	2.09	15.6
R.T.	25	169	58	62	150	131	112	88	74	72	1.59	15.8
N.S	25	161	59	66	204	158	133	110	91	80	1.90	14.7
I.I.	30	162	64	57	208	171	147	129	115	94	1.54	13.5
Q.N.	23	157	56	71	231	177	140	124	111	88	1.78	14.1
G.J.	24	169	64	69	182	139	108	80	71	62	2.44	17.3
T.J.	27	160	95	84	205	177	155	141	126	116	1.28	17.6
Mean	26.0	162.7	59.7	65.9	199.8	163.7	139.0	120.0	105.4	92.7	1.67	15.4

TABLE III

Pregnant women in the first trimester (21 subjects)

Subject	Age	Ht	Wt	Blood levels after 25 g glucose i.v. (mg/100 ml at time in min) 0	10	20	30	40	50	60	k	Glucose volume
	yrs	*cm*	*kg*								*%/min*	*L*
E.K.	32	161	52	61	180	106	75	58	46	41	3.45	13.1
S.D.	34	157	56	60	180	152	126	115	105	93	1.31	14.0
G.G	21	173	71	62	154	117	85	70	59	53	2.62	18.1
R.S.	20	157	48	50	179	113	81	42	35	27	3.38	14.6
D.C.	26	161	62	69	187	129	102	73	69	59	2.56	16.1
E.M.	26	170	66	62	170	145	79	76	65	56	2.46	17.1
J.P.	24	165	59	67	162	105	64	55	43	41	3.23	18.9
G.M.	21	154	61	55	165	140	118	100	99	71	1.73	17.7
I.V.	18	155	49	57	197	161	128	95	75	58	2.44	12.9
S.V.	23	166	53	60	208	178	128	102	99	63	2.38	12.3
T.C.	28	156	57	62	172	145	115	106	95	88	1.70	17.7
C.R.	20	166	59	71	186	138	100	77	58	53	3.20	14.1
M.P.	23	165	72	64	184	150	123	106	97	87	1.85	17.2
D.G.	24	157	66	75	180	156	138	115	102	91	2.99	18.9
P.M.	31	155	101	71	164	132	106	87	74	68	2.33	17.4
L.S.	22	155	56	57	185	143	101	86	75	72	2.53	14.3
M.McM.	29	161	62	58	184	156	138	123	110	106	1.36	16.3
D.R.	27	153	50	57	198	153	117	89	72	56	2.53	12.9
A.A.	21	157	55	50	179	142	107	84	72	54	1.91	17.4
F.M.	23	155	62	66	230	180	156	132	113	90	1.71	12.3
A.R.	17	161	52	54	180	129	96	60	48	45	3.15	13.2
Mean	24.3	160.0	60.4	61.3	182.1	141.4	108.7	85.5	76.7	65.3	2.42	15.6

TABLE IV

Pregnant women in the second trimester (20 subjects)

Subject	Age	Ht	Wt	Blood levels after 25 g glucose i.v. (mg/100 ml at time in min) 0	10	20	30	40	50	60	k	Glucose volume
	yrs	*cm*	*kg*								*%/min*	*L*
C.R.	32	152	49	77	231	184	171	148	129	109	1.27	13.0
M.G.	28	156	54	71	216	184	160	139	117	101	1.43	14.5
D.B.	28	162	66	61	178	135	105	77	63	49	2.52	16.3
R.R.	20	162	75	63	175	142	110	87	73	61	2.19	16.7
H.A.	34	162	71	65	182	155	128	112	93	78	1.68	18.3
I.C.	21	155	61	54	190	153	119	89	72	58	2.42	12.9
C.D'A.	22	157	60	55	189	153	131	110	93	79	1.75	15.2
M.O'F.	22	166	56	59	149	145	125	106	94	78	1.45	19.1
J.R.	25	173	54	59	195	157	133	102	88	77	2.03	13.8
T.K.	27	157	56	51	169	129	106	88	70	61	2.14	16.5
B.L.	23	176	47	53	187	149	116	85	73	60	2.40	13.4
E.S.	22	159	61	56	164	136	121	103	91	75	1.50	18.8
C.L.	21	154	60	53	217	176	147	118	101	88	1.93	12.0
A.R.	28	161	58	68	187	165	147	130	115	103	1.29	17.5
G.R.	17	157	60	56	160	132	104	87	75	63	2.15	27.2
M.F.	20	162	58	57	169	131	102	82	71	63	2.38	16.1
H.M.	21	157	45	56	198	168	144	122	104	88	1.60	14.3
R.B.	23	153	48	62	200	155	120	94	73	58	2.50	12.8
S.G.	28	155	51	61	203	156	122	102	87	76	1.76	13.4
O.K.	26	155	89	45	160	130	102	76	65	57	2.05	10.4
Mean	24.4	159.6	59.0	59.1	186.0	151.8	125.7	102.9	87.4	74.1	1.92	15.6

groups (Table I). A small decrease in weight occurred ($p = < 0.05$) in the postpartum subjects compared with the third trimester group. This is an anticipated finding in a random sample of women after childbirth. Fasting blood sugar concentrations throughout pregnancy and the postpartum period showed small, but statistically significant, decreases from the nonpregnant level.

A linear relationship was obtained when the log glucose concentration for each test was plotted

TABLE V

Pregnant women in the third trimester (20 subjects)

Subject	Age	Ht	Wt	Blood levels after 25 g glucose i.v. (mg/100 ml at time in min) 0	10	20	30	40	50	60	k	Glucose volume
	yrs	*cm*	*kg*								*%/min*	*L*
M.C.	18	155	56	54	204	164	132	100	79	71	2.12	12.8
D.C.	18	159	59	61	206	161	130	109	91	70	2.07	13.2
A.H.	19	164	100	67	156	135	114	103	92	82	1.41	23.2
R.H.	23	159	59	64	213	164	123	94	73	60	2.67	11.6
D.L.	23	167	66	61	155	130	103	80	62	49	2.40	18.7
A.C.	17	150	49	64	203	163	130	104	84	69	2.21	13.2
B.R.	25	154	56	78	196	162	136	119	102	90	1.68	18.1
Z.B.	19	156	66	61	175	145	117	95	78	64	2.14	16.3
A.L.	37	156	76	55	171	143	116	103	88	74	1.75	17.4
G.L.	30	157	80	63	140	119	104	94	89	78	1.24	27.2
N.M.	22	156	62	51	182	146	121	100	82	70	1.94	14.9
A.C.	28	173	50	62	206	171	150	131	112	96	1.51	14.2
D.G.	21	164	79	66	149	125	105	85	72	66	2.40	22.5
R.M.	26	159	68	56	140	119	90	76	66	53	2.00	21.6
E.G.	25	159	68	44	164	132	117	106	97	82	1.35	18.3
B.C.	19	166	61	48	149	117	101	79	67	59	1.98	19.2
H.M.	23	162	59	49	170	139	121	104	88	80	1.62	17.0
J.C.	22	153	60	67	215	168	137	116	91	74	2.87	13.3
M.R.	17	157	61	68	209	173	150	130	112	97	1.53	14.8
E.D.	32	157	75	53	166	139	121	109	95	83	1.37	18.4
Mean	23.2	159.2	65.5	59.6	178.5	145.8	120.9	101.9	86.0	73.4	1.91	17.3

TABLE VI

Women in the first postpartum week (25 subjects)

Subject	Age	Ht	Wt	Blood levels after 25 g glucose i.v. (mg/100 ml at time in min) 0	10	20	30	40	50	60	k	Glucose volume
	yrs	*cm*	*kg*								*%/min*	*L*
R.B.	23	149	48	54	203	150	122	96	71	61	2.45	12.5
F.F.	32	157	62	52	197	173	144	126	116	112	1.32	14.7
M.N.	23	153	71	73	196	155	140	115	113	103	1.46	17.2
E.K.	38	155	75	56	168	146	128	110	95	79	1.44	18.4
B.C.	19	166	54	56	191	160	148	137	125	116	1.05	16.1
M.D.	25	165	58	49	182	145	115	91	80	71	2.14	14.8
J.C.	22	150	54	91	218	166	124	103	80	71	2.46	13.6
R.M.	20	159	57	52	192	166	136	133	101	85	1.52	15.2
A.P.	41	165	63	53	164	140	127	114	97	82	1.25	18.9
A.R.	20	155	59	55	194	160	130	115	97	84	1.70	14.8
I.D.	34	153	61	50	174	150	128	112	95	76	1.44	16.8
M.M.	31	167	52	55	178	119	108	83	72	53	2.15	16.7
M.N.	22	157	51	55	188	161	137	128	113	104	1.23	16.2
I.P.	24	150	44	47	175	128	102	92	77	67	1.53	18.2
O.R.	19	157	56	66	185	156	127	106	96	78	1.79	15.5
H.C.	38	153	57	54	175	149	138	112	92	86	1.51	16.9
L.D.	20	153	54	47	191	173	157	139	120	115	1.09	14.4
C.C.	25	153	51	53	214	166	155	134	126	112	1.21	15.6
G.D.	24	160	69	56	177	139	116	94	79	71	1.97	15.9
M.P.	29	155	59	40	206	156	140	120	103	94	1.57	14.2
V.F.	27	147	59	56	222	192	171	157	141	124	1.16	12.9
V.R.	16	156	48	48	200	165	140	114	101	88	1.71	13.4
B.E.	31	150	48	70	220	186	160	140	122	103	1.51	13.7
S.J.	23	167	60	56	186	168	146	136	120	113	1.09	16.9
K.F.	35	159	86	58	161	115	102	83	82	74	1.68	19.7
Mean	26.4	156.4	58.2	56.1	190.3	155.4	133.6	115.6	100.6	88.9	1.58	15.7

from 10 to 60 minutes. There was a tendency for small upward deviations at the 10- and 60-minute points. Figure 1 shows individual log plots selected from the nonpregnant, first trimester, and third trimester groups. Log plots of the mean glucose values for five groups of subjects are separated into Figures 2A and 2B because of the nearly identical curves in the second and third trimester and the nonpregnant and postpartum groups, respectively. The rate of decline of blood glucose concentration appears greatest in the first trimester of pregnancy and recedes to an intermediate level in the second trimester. No change occurred between the second and third trimesters. During the first postpartum week the rate returns to that of the nonpregnant controls.

The slope, k, computed for each subject's GTT (Tables II–VI), provided numerical data for estimates of the variability within groups. Table VII summarizes the k values. Average values of k, expressed as per cent per minute, were as follows for each subject group: nonpregnant, 1.67;

TABLE VII

*Rate (k) of disappearance of glucose from venous blood after intravenous injection of 25 g glucose and extracellular distribution volume of glucose**

		Non-pregnant	Pregnant (trimester) First	Second	Third	All	Post-partum
N		30	21	20	20	61	25
k (*%/min*)	Mean	1.67	2.42	1.92	1.91	2.09	1.58
	SE of mean	0.08	0.14	0.09	0.10	0.07	0.08
Glucose volume (*L*)	Mean	15.4	15.6	15.6	17.3		15.7
	SE of mean	0.4	0.5	0.8	0.9		0.4

* Glucose volume = dose administered/blood glucose concentration at zero time − fasting concentration. No correction was made for concentration of water in whole blood.

first trimester, 2.42; second trimester, 1.92; third trimester, 1.91; and postpartum, 1.58. The overall effect of pregnancy, combining the three trimesters, was an increase in k from the nonpregnant level of 1.67 to 2.09.[3]

Extrapolated, extracellular distribution volumes of glucose were comparable in all groups, except the third trimester (Table VII). The volume increase of 1.9 ± 1.0 L (difference in means $\pm$ standard error of the difference) in the third trimester over the nonpregnant group was significant at $p = < 0.05$.

DISCUSSION

Subjects, activity and diet. Differences in age (30), activity (34) and diet (35) influence glucose tolerance. The age range was comparable in all groups. However, the postpartum group underwent the stress of childbirth (36), including 1 day of restricted food intake. Although not confined to bed, they were less active physically. These circumstances tend to depress glucose tolerance, and may have contributed to the fall in k during the postpartum period.

The tolerance equation in pregnancy. The glucose tolerance equation, $y = Ae^{-kt}$, graphically applied in the log form, $\log_e y = \log_e A - kt$, gathers the experimental, absolute glucose levels of each test and expresses them as a single derived value in the rate constant k (30, 37–39). This method has both the convenience and the limitations of a simple analytical curve used as a graduation device for expressing differences in the rate of disappearance of glucose. The rate constant is closely correlated with glucose clearance from the blood. Its reproducibility has been confirmed and adjustment of the glucose load to body size is unnecessary (30, 40). Comparable values of k in male subjects (30) are in close agreement with those of the nonpregnant female group, being 1.68 ± 0.9 and 1.67 ± 0.08, respectively. Cleempoel, Conard and Bastenie (41) reported normal values at 1.80 ± 0.16.

In vitro perfusion studies with nonmetabolized, glucose-like molecules (sorbitol) indicate rapid, extracellular equilibration, occurring well within 10 minutes (42). Generally, the phase of extracellular mixing in the GTT is likewise sufficiently completed by 10 minutes after the glucose injection to be indistinguishable from the body of the tolerance curve derived from venous blood samples. Interaction of the mixing phase with k is suggested in some individual curves by slight upward deflection of the 10-minute glucose values. Simultaneous estimates of the thiocyanate and glucose spaces, using the absolute glucose tolerance equation for estimates of the latter, have been in close agreement (39). Urinary excretion of glucose within 1 hour after an intravenous dose of 25 g was measured in 10 pregnant and 6 nonpregnant female subjects. The mean glucose excretion was 0.90 g, or 3.6 per cent of the dose, during pregnancy, and 0.80 g, or 3.2 per cent of the dose, in the nonpregnant state. Johnson and Bonsnes (29) also found the average urinary excretion of glucose after the intravenous injection of 25 g to be substantially the same in pregnant subjects (7.2 per cent) as in nonpregnant controls (6.8 per cent). These amounts represent a small fraction of the administered glucose load. The urinary losses occur during the early part of the tolerance curve when blood glucose levels and renal tubular loads are high and may, as pointed out by West and Wood (40), contribute to the early, slightly upward deviation of the tolerance curve from linearity. The latter part of the GTT curve involves an interaction with glucose release from the liver (43) which, in turn, probably accounts for late, upward nonlinearity, particularly when the curve is at or below fasting levels.

Greville (44) and Hlad, Elrick and Witten (45) computed an asymptotic value of blood sugar concentration, c, using the equation $\log_e(y - c) = \log_e A - kt$. This method partitions the expression of tolerance test data between the rate constant and the asymptote, since both terms are derived from the same set of experimental points.

[3] Differences in the mean values of k were significant at $p < 0.01$ between pairs of the following groups: nonpregnant and first trimester; first trimester and second trimester; and nonpregnant and the total of all trimesters. Differences in k were significant at $p < 0.05$ between the following paired groups: combined second and third trimesters and nonpregnant; and third trimester and postpartum. When regrouped into three classes for an analysis of variance—*A*) nonpregnant, *B*) first trimester, and *C*) second trimester—the differences in k between classes were significant at the 0.001 point. Combination of the second and third trimesters in class C, or substitution of the third for the second trimester group in class C or the postpartum for the nonpregnant group in class A, resulted in similar statistical estimates.

All k values are thereby rendered more nearly alike, and differences in glucose tolerance are projected into the asymptote. Recalculations, by this method, of the data from both the present study and a comparable, previously published report involving age differences in k (30) resulted in qualitative conclusions regarding glucose tolerance which were like those obtained without the asymptote (asymptote = zero).

The substitution of the fasting blood sugar level for a computed asymptote (46, 47) has been critically reviewed by Ikkos and Luft (48) and by West and Wood (40).

Changes in k during pregnancy. The index of tolerance was increased throughout pregnancy, but mainly in the first trimester. There is no evidence supporting an augmented response to insulin during pregnancy, other than some uncertainties pertaining to the rapidly growing conceptual products and the elevated metabolic rate (49). While the increased insulin effect indicated by k may have resulted from a greater release of insulin, other factors are involved. Growth and redistribution of body fluids occur as pregnancy progresses (50-52). Glucose crosses the placenta (53) and is utilized by the fetus (54). Chesley, Valenti and Uichanco estimated the total water gain of pregnancy as 6.3 L and the average gain in extracellular fluid (sucrose space) as 3.95 L, with 2.65 L as the maternal fraction (50). The increment of extracellular fluid was taken as 3.8 L by Seitchik and Alper (55), with 2.5 L for the maternal fraction. By comparison, the increment in glucose space, measured from the nonpregnant state to the third trimester, is 1.9 ± 1.0 L. While this figure is in fairly good agreement with estimates of the maternal fraction, it must be extended to its upper error range (2 standard errors) to approach other estimates of total extracellular fluid gain. However, of the 20 subjects in the third trimester, 11 were at less than 32 weeks' duration of pregnancy, 3 were beyond 36 weeks, and only 1 had reached 39 weeks. This distribution does not represent full-term growth and fluid attainment. Furthermore, failure to correct for hemodilution, reported with advancing pregnancy (52), may have introduced an underestimate of the increase in glucose volume. The effects of increasing cell mass and body fluid are minimal in the first trimester and progressively reach a maximum in later pregnancy. In contrast, the pattern of k changes (Table VII) proceeds in the opposite direction. This trend is not attributable to progressively increasing distribution volumes, although the latter probably contribute to the over-all elevation of k in pregnancy.

Hyperinsulinism of pregnancy. Simultaneous injection of glucose and insulin results in marked elevation of k (30). High k values have been observed in association with carcinoma of the pancreatic islets (46), presumably due to increased levels of endogenous insulin. The increased levels of k, particularly in early pregnancy, indicate a state of mild hyperinsulinism, possibly secondary to chronic pancreatic stimulation.

Welsh and Sims (56) found higher levels of plasma insulin-like activity in some of their pregnant subjects than in nonpregnant controls. Hoet and Lukens (2) have emphasized the hypertrophy and hyperplasia of the islets of Langerhans observed in the human and animal maternal pancreas during pregnancy, with marked regression of these changes in animals within 4 days after the birth of a litter.

SUMMARY

Glucose tolerance in pregnancy was studied by the intravenous glucose tolerance test under standardized conditions, using 25 g of glucose and venous blood samples. The rate of fall, k, obtained from a visual fit of the experimental sugar levels between 10 and 60 minutes to the equation $\log_e y = \log_e A - kt$, served as the index of tolerance. A total of 116 healthy women was tested, including 30 nonpregnant, 25 postpartum, and 61 subjects with uncomplicated pregnancies. There was a significant elevation in k during pregnancy, particularly in the first trimester, with a prompt return to nonpregnant levels in the postpartum period. The glucose space was slightly increased in the third trimester. It is proposed that k elevations may result from both mild hyperinsulinism and increased distribution volumes in pregnancy.

ACKNOWLEDGMENTS

The authors wish to express their appreciation to Miss Nechama Singer for technical and computational assistance, to Dr. Martin Bernstein, Dr. Eli Weil and Mr. Jerome Dobkin for assistance with clinical and laboratory aspects of the study, and to the Nursing Staff at Maimo-

nides Hospital for supplying many of the nonpregnant female subjects.

REFERENCES

1. Bergqvist, N. The influence of pregnancy on diabetes. Acta endocr. (Kbh.) 1954, **15**, 166.
2. Hoet, J. P., and Lukens, F. D. Carbohydrate metabolism during pregnancy. Diabetes 1954, **3**, 1.
3. Jackson, W. P. U. A concept of diabetes. Lancet 1955, **2**, 625.
4. Wilkerson, H. L. C. Maternal prediabetes and outcome of pregnancy: A preliminary report. Amer. J. publ. Hlth 1959, **49**, 1032.
5. Jackson, W. P. U. Present status of prediabetes. Diabetes 1960, **9**, 373.
6. Jones, W. S. The severity of diabetes in pregnancy. Amer. J. Obstet Gynec. 1956, **71**, 318.
7. Long, W. N., Hartmann, W. L., Futcher, P. H., and Eastman, N. J. Diabetes mellitus and pregnancy. Obstet and Gynec. 1954, **3**, 160.
8. White, P., and Hunt, H. Pregnancy complicating diabetes. A report of clinical results. J. clin. Endocr. 1943, **3**, 500.
9. Hurwitz, D., and Higano, N. Diabetes and pregnancy. New Engl. J. Med. 1952, **247**, 305.
10. Duncan, G. G., and Fetter, F. The effect of pregnancy on the insulin requirement of the diabetic. Amer. J. med. Sci. 1934, **187**, 347.
11. Pederson, J. Course of diabetes during pregnancy. Acta endocr. (Kbh.) 1952, **9**, 342.
12. Hall, R. E., and Tillman, A. J. B. Diabetes in pregnancy. Amer. J. Obstet. Gynec. 1951, **61**, 1107.
13. Lawrence, R. D., and Oakley, W. Pregnancy and diabetes. Quart. J. Med. 1942, **11**, 45.
14. Hagbaard, L. Pregnancy and diabetes mellitus. A clinical study. Acta obstet. gynec scand. 1956, **35**, suppl. 1.
15. Burt, R. L. Carbohydrate metabolism in pregnancy. Clin. Obstet. and Gynec. 1960, **3**, 310.
16. Hurwitz, D., and Irving, F. C. Diabetes and pregnancy. Amer. J. med. Sci. 1937, **194**, 85.
17. Randle, P. J. Endocrine factors in the syndrome of diabetes mellitus *in* Modern Trends in Endocrinology, H. Gardiner-Hill, Ed. New York, Paul B. Hoeber, 1958, p. 70.
18. Freinkel, N., and Goodner, C. Carbohydrate metabolism in pregnancy. I. The metabolism of insulin by human placental tissue. J. clin. Invest. 1960, **39**, 116.
19. Yalow, R. S., and Berson, S. A. Plasma insulin in man. Amer. J. Med. 1960, **29**, 1.
20. Tunbridge, R. E., and Allibone, E. C. The intravenous dextrose tolerance test. Quart. J. Med. 1940, **9**, 11.
21. Hansen, A., Zur Physiologie des Magens in der Schwangerschaft. Zbl. Gynäk. 1937, **61**, 2306.
22. Williams, N. H. Variable significance of heartburn. Amer. J. Obstet. Gynec. 1941, **42**, 814.
23. Moyer, J. H., and Womack, C. R. Glucose tolerance tests; relative validity of 4 different types of tests. Tex. St. J. Med. 1950, **46**, 763.
24. Selman, J. J. The results of glucose tolerance tests in pregnant women. Ohio St. med. J. 1932, **28**, 184.
25. Hurwitz, D., and Jensen, D. Carbohydrate metabolism in normal pregnancy. New Engl. J. Med. 1946, **234**, 327.
26. Weiden, S. Investigation of carbohydrate metabolism in normal pregnancy. Med. J. Aust. 1948, **1**, 646.
27. Cobley, J. F. C. C., and Lancaster, H. O. Carbohydrate tolerance in pregnancy. Med. J. Aust. 1955, **1**, 171.
28. Burt, R. L. Peripheral utilization of glucose in pregnancy and the puerperium. Obstet and Gynec. 1954, **48**, 58.
29. Johnson, D. G., and Bonsnes, R. W. The intravenous glucose tolerance test in pregnancy. J. clin. Invest. 1948, **27**, 745.
30. Silverstone, F. A., Brandfonbrener, M., Shock, N. W., and Yiengst, M. J. Age differences in the intravenous glucose tolerance tests and the response to insulin. J. clin. Invest. 1957, **36**, 504.
31. Loughlin, W. C., Mosenthal, H. O., and Halpern, R. Effect of tourniquets on venous blood sugar values. J. Lab. clin. Med. 1943, **28**, 1165.
32. Nelson, N. A photometric adaptation of the Somogyi method for the determination of glucose. J. biol. Chem. 1944, **153**, 375.
33. Ikkos, D., and Luft, R. On the volume of distribution of glucose in man. Acta endocr. (Kbh.) 1957, **25**, 335.
34. Blotner, H. Effect of prolonged physical inactivity on tolerance of sugar. Arch. intern. Med. 1945, **75**, 39.
35. Himsworth, H. P. Dietetic factors influencing the glucose tolerance and the activity of insulin. J. Physiol. (Lond.) 1934, **81**, 29.
36. Frawley, T. F., Kistler, H., and Shelley, T. Effects of anti-inflammatory steroids on carbohydrate metabolism, with emphasis on hypoglycemic and diabetic states. Ann. N. Y. Acad. Sci. 1959, **82**, 868.
37. Pijoan, M., and Gibson, J. G., II. The rate of disappearance of intravenously administered dextrose in the human subject. Amer. J. Physiol. 1938, **121**, 534.
38. Hamilton, B., and Stein, A. F. The measurement of intravenous blood sugar curves. J. Lab. clin. Med. 1942, **27**, 491.
39. Conard, V., Franckson, J. R. M., Bastenie, P. A., Kestens, J., and Kovacs, L. Étude critique du triangle d'hyperglycémie intraveineux chez l'homme normal et détermination d'un "coefficient d'assimilation glucidique." Arch. int. Pharmacodyn. 1953, **93**, 277.
40. West, K. M., and Wood, D. A. The intravenous glucose tolerance test. Amer. J. med. Sci. 1959, **238**, 25.

41. Cleempoel, H., Conard, V., and Bastenie, P. A. Carcinoma of the islets of Langerhans; a test for hyperinsulinism. Lancet 1955, **2**, 801.
42. Morgan, H. E., Henderson, M. J., Regen, D. M., and Park, C. R. Regulation of glucose uptake in heart muscle from normal and alloxan-diabetic rats: The effects of insulin, growth hormone, cortisone, and anoxia. Ann. N. Y. Acad. Sci. 1959, **82**, 387.
43. Bondy, P. K., Bloom, W. L., Whitner, V. S., and Farrar, B. W. Studies of the role of the liver in human carbohydrate metabolism by the venous catheter technic. II. Patients with diabetic ketosis before and after the administration of insulin. J. clin. Invest. 1949, **28**, 1126.
44. Greville, G. D. The intravenous glucose tolerance equation. Biochem. J. 1943, **37**, 17.
45. Hlad, C. J., Jr., Elrick, H., and Witten, T. A. Studies on the kinetics of glucose utilization. J. clin. Invest. 1956, **35**, 1139.
46. Duncan, L. J. P. The intravenous glucose tolerance test. Quart. J. exp. Physiol. 1956, **41**, 85.
47. Amatuzio, D. S., Stutzman, F. L., Vanderbilt, M. J., and Nesbitt, S. Interpretation of the rapid intravenous glucose tolerance test in normal individuals and in mild diabetes mellitus. J. clin. Invest. 1953, **32**, 428.
48. Ikkos, D., and Luft, R. On the intravenous glucose tolerance test. Acta endocr. (Kbh.) 1957, **25**, 312.
49. Buxton, C. L. Thyroid function in pregnancy. Clin. Obstet. Gynec. 1958, **1**, 79.
50. Chesley, L. C., Valenti, C., and Uichanco, L. Alterations in body fluid compartments and exchangeable sodium in the early puerperium. Amer. J. Obstet. Gynec. 1959, **77**, 1054.
51. Haley, H. B., and Woodbury, J. W. Body composition and body water metabolism in normal pregnancy. Surg. Gynec. Obstet. 1956, **103**, 227.
52. Lund, C. J., and Sisson, T. R. C. Blood volume and anemia of mother and baby. Amer. J. Obstet. Gynec. 1958, **76**, 1013.
53. Davies, J. Permeability of rabbit placenta to glucose and fructose. Amer. J. Physiol. 1955, **181**, 532.
54. Page, E. W. Physiology of the human placenta at term. Clin. Obstet. Gynec. 1960, **3**, 279.
55. Seitchik, J., and Alper, C. Estimation of changes in body composition in normal pregnancy by measurement of body water. Amer. J. Obstet. Gynec. 1956, **71**, 1165.
56. Welsh, G. W., 3rd, and Sims, E. A. H. The effects of pregnancy on glucose metabolism in the human (abstract). Acta endocr. (Kbh.) 1960, suppl. 51, XIVb.