Changes in Oral Glucose Tolerance During the Menstrual Cycle*

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Impairment of carbohydrate tolerance occurs in a proportion of normal women taking either combined oestrogen/progestogen contraceptive preparations or oestrogens alone (Gershberg *et al.*, 1964; Buchler and Warren, 1966). It seems that it is the oestrogen component of the contraceptive drugs which produces this impairment, for treatment with a progestational agent alone does not alter glucose tolerance (Puchulu *et al.*, 1967) or may even improve it (Benjamin and Casper, 1966). This suggested the possibility that changes in endogenous oestrogen levels occurring during the normal menstrual cycle might be associated with changes in carbohydrate tolerance. We report here the results of repeated oral glucose tolerance tests in a small group of menstruating women and the relation between glucose tolerance and the phase of the menstrual cycle.

Results of Repeated Oral Glucose Tolerance Tests in 10 Menstruating Women. The Days of the Cycle are Numbered from the First Day (Day 1) of Bleeding. Blood Sugar Fasting = 0 and the Subsequent Half-hourly Blood Sugars are Numbered 1–4

Subject	Day of Cycle	Blood Sugar (mg./100 ml.) 0	1	2	3	4	G.T.T. Area
1	24	72	106	81	50	60	606
	2	86	150	86	90	67	805
	10	79	128	90	79	71	744
	16	75	130	92	68	75	730
2	22	66	136	112	100	88	850
	3	80	159	111	110	75	915
	17	70	151	79	69	69	737
3	23	66	131	96	65	64	714
	8	75	116	78	84	75	706
	15	83	119	90	71	79	722
	22	62	98	75	80	75	642
4	21	85	118	92	93	85	776
	28	74	120	98	89	78	766
	3	74	103	84	94	92	728
5	1	84	116	105	94	81	793
	9	86	153	133	82	96	918
	25	88	137	104	84	80	818
6	1	84	123	114	81	71	790
	9	94	171	117	73	80	896
	14	89	151	125	75	90	882
	3	90	142	86	69	73	757
7	21	75	116	116	115	71	840
	1	78	132	122	110	62	868
	7	70	85	126	118	62	790
	14	90	163	162	78	74	969
8	27	87	131	171	133	103	1,060
	7	74	132	120	99	83	859
	14	81	148	145	98	89	952
	21	83	143	154	111	84	983
9	3	75	115	102	62	73	706
	10	100	155	110	84	84	882
	17	93	140	126	85	82	877
	24	108	145	132	82	82	908
10	16	68	155	105	75	58	796
	23	87	190	160	100	78	1,065
	30	85	177	113	101	88	955
	7	74	127	108	99	83	825

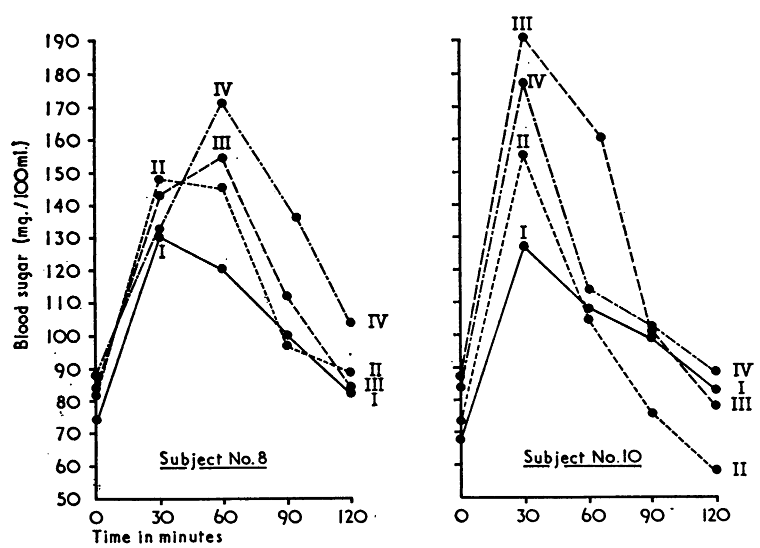

FIG. 1.—Glucose tolerance curves in Subjects 8 and 10, showing pronounced variation in peak blood sugar levels.

Methods

In the first part of the investigation three or four oral glucose tolerance tests were made on 10 volunteer subjects. The first test was performed at an arbitrary time in individual menstrual cycles, usually determined solely by the most convenient day for the subject to attend for testing. Subsequent tests were performed at weekly intervals. The blood sugar level was measured in the fasting state and at half-hourly intervals for up to two hours after drinking 50 g. of glucose (Lucozade). From an ear lobe 0.1-ml. capillary blood samples were taken and added to 3 ml. of 1% potassium fluoride, and the blood sugar was measured by the micromethod (ferricyanide reduction) on the AutoAnalyzer (Technicon).

Three subjects had further oral glucose tolerance tests repeated over several cycles, and two of these recorded their basal oral temperature in order to determine the approximate time of ovulation.

The 10 volunteers ranged in age from 19 to 39 years. Three were multiparae, the remainder were nulliparae. Nine had regular cycles of approximately 28 days and one had a regular cycle of approximately 21 days.

In order to facilitate comparison of glucose tolerance tests the area under the glucose curve was calculated, and is referred to as the G.T.T. area. The calculation is:

$$\text{Area} = a + 2b + 2c + 2d + e$$

where a is the fasting blood sugar and b, c, d, and e are the subsequent half-hourly measurements. The area thus measured is bounded by straight lines joining the five points, the ordinates and the abscissa.

Results

The Table shows the individual results in the preliminary study. Subjects 4–10 appear to share a common pattern, the glucose tolerance test area being least, or tolerance greatest, at the beginning of the cycle. The actual glucose tolerance test curves of two of these (Subjects 8 and 10) are shown in Fig. 1, which indicates that most of the variation occurs in the level of the peak blood sugar.

In three of this group (Subjects 5, 6, and 7) further tests were made in subsequent cycles, the complete results for each individual being shown in Fig. 2. It is clear that the pattern observed in the initial series of tests is repeated in subsequent cycles. In the two

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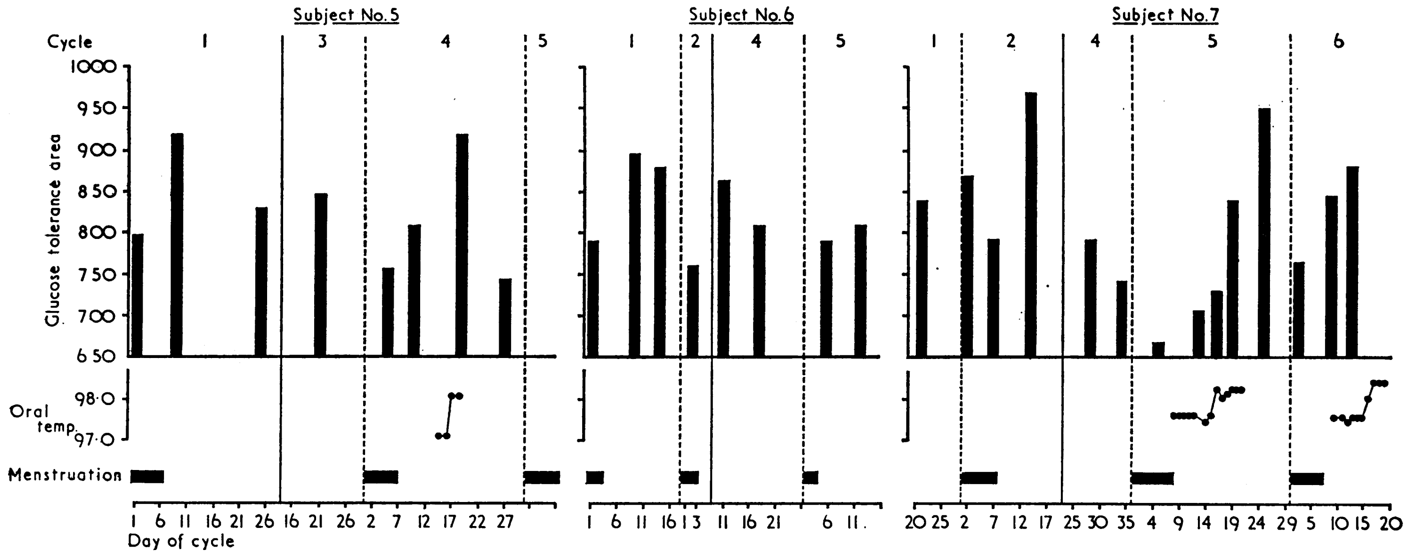

FIG. 2.—Results of glucose tolerance tests, repeated over several cycles, in three subjects.

subjects in whom ovulation was timed by basal temperature recording, the glucose tolerance test area, low during the first few days of the cycle, increased before ovulation occurred but was maximal after ovulation.

Discussion

The changes in oestrogen and progesterone secretion during the menstrual cycle have been described by Loraine and Bell (1963), who measured the urinary excretion of oestrogens, pregnanediol, and pregnanetriol. In general, oestrogen excretion was low in the first part of the cycle, reached a peak towards mid-cycle, and remained elevated, with a secondary peak, during the luteal phase of the cycle. Thus if endogenous oestrogen modifies carbohydrate tolerance one would expect tolerance to be greatest when oestrogen levels are lowest—that is, during the phase of menstrual flow—with subsequent deterioration in tolerance as oestrogen production increases. This pattern was, in fact, observed in the three subjects studied over several cycles.

It would be surprising if a possible relation between carbohydrate tolerance and the menstrual cycle had not previously been investigated. Though the recent literature is devoid of references, a number of studies were performed 30 or more years ago. Okey and Robb (1925) found that during oral glucose tolerance tests the initial rise in blood sugar was less and " secondary hypoglycaemia " greater during the period of menstrual flow and that lessened tolerance occurred before and after this time. Asinelli and Casassa (1937) reported that the peak blood sugars in the oral glucose tolerance test were 30–40 mg. higher during the " premenstrual time " and that " normal " values returned after the first days of menstruation. Garafi and Ruggeri (1933), on the other hand, reported that blood sugars during oral glucose tolerance tests were lowest at about the time of ovulation, though the timing of this event was not measured ; a rise in blood sugar levels occurred during the premenstruum and reached a maximum at or about the onset of menstruation. Considering the different methods of evaluation, the results of these three studies are reasonably consistent with our own.

McDonald, Fisher, and Burnham (1965) have shown that in men considerable individual variation may occur in the results of repeated oral glucose tolerance tests. It is likely that similar random variation occurs in women. Despite this it is clear that some variation may be attributable to the hormonal changes occurring during the menstrual cycle, though it seems that such changes do not occur in all menstruating women. It may be that in these individuals random variation masks the cycle variation. Alternatively, there may be individual variation in sensitivity to the effects of oestrogens. This latter explanation would be consistent with the reported observations that only a proportion of women receiving oral oestrogens show changes in carbohydrate tolerance.

One curious feature remains to be explained. In diabetic females a number of observers have noted deterioration of control of the diabetes, even to the extreme of acidosis, occurring at or about the time of menstruation (Cramer, 1942). On the basis of the results in non-diabetics, one might reasonably have expected control to be easiest at this time. However, where carbohydrate tolerance is already impaired, oestrogens perhaps have an opposite effect. Thus Gershberg *et al.* (1967) have reported improved carbohydrate tolerance in some patients with maturity onset diabetes when treated with oestrogens.

Summary

The possibility that endogenous oestrogen affects carbohydrate tolerance was investigated by relating the results of repeated oral glucose tolerance tests to the phases of the menstrual cycle. In a preliminary study, 7 out of 10 women showed changes in their oral glucose tolerance tests over one or two cycles, glucose tolerance being greatest in the earliest phase of the menstrual cycle, when endogenous oestrogen levels would be expected to be at their lowest. In three women this pattern was repeated in tests performed over several subsequent cycles.

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