THE ADRENAL CORTEX AND THE PREGNANT DIABETIC*

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The diagnosis and clinical management of diabetes are based upon the detection and correction of an abnormal glucose-tolerance test. However, as this test is merely indicative of altered carbohydrate metabolism, 'true' control of the diabetic state can only be achieved by the accurate definition and treatment of the aetiological agents responsible in each individual patient.

The Natal Indian diabetic, for example, conforms to a pattern which is highly suggestive of adrenocortical hyperactivity. Thus these patients rarely develop ketosis, are relatively resistant to insulin, are frequently aglycosuric in the fasting state, and have hirsutes and trunk obesity.

As it is generally accepted that certain diseases have a racial prevalence, the following study was instituted with the object of comparing:

(*a*) The excretion pattern of the 17-hydroxycorticoids (17 - OHCS) and the 17-ketosteroids (oxosteroids or 17-KS) in pregnant non-diabetic Indian females during the third trimester of pregnancy with similar values in the pregnant Natal Indian diabetic.

(*b*) The effect (if any) of diabetic 'control' on glucocorticoid and ketosteroid activity as measured by their excretory products.

MATERIAL AND METHOD

Twenty Natal Indian diabetic women were admitted to the antenatal ward for routine investigation and treatment. Of these, 3 had received no treatment for their diabetes (being seen for the first time in the 38th week of gestation), 4 were on tolbutamide, 2 on chlorpropamide and 2 on insulin, and 9 were controlled on diet alone (Table I).

The 39 'controls' were patients of the same racial group who were hospitalized for conditions other than diabetes, this having been excluded on the grounds of normal glucose tolerance. Some of the patients regarded as 'normal pregnancies' were women who had been referred to the diabetes clinic for investigation because of a family history of diabetes, but who were found to have normal carbohydrate tolerance. The 10 patients with pre-eclamptic toxaemia all had mild signs and symptoms (blood pressure less than 160/100 mm.Hg; albuminuria + or less; oedema +) and most were controlled on bed rest and sedation alone. The rest of the controls were a miscellaneous group consisting of 3 cardiac patients; 3 patients with moderately severe iron-deficiency anaemia; and single cases of placenta praevia (on conservative treatment), suspected postmaturity, contact bleeding and premature rupture of membranes.

The diabetic and control groups were matched as regards age and parity.

Twenty-four-hour specimens of urine were obtained under identical basal resting conditions. The total 17-ketosteroids (oxosteroids) were assayed by the method of Norymberski *et al.*[1] and the 17-hydroxycorticoids by the method of Appleby *et al.*[2] A total of 112 determinations were performed in the diabetic group and 118 in the control group. All assays were performed by the same technician in the Department of Obstetrics and Gynaecology, University of Natal.

RESULTS

17-Ketosteroids (Tables II and III and Fig. 1)

A comparison of the mean 17-ketosteroid excretion rate in the two groups shows a similar pattern throughout the third trimester, with the output in the diabetic group being greater than that in the control group. Although fluctuations did occur during this period, the mean excretion level was 11·73 ± 4·6 mg./24 hours in the diabetics as opposed

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TABLE I. ANALYSIS OF 20 NATAL INDIAN DIABETICS STUDIED

Name	Age in years	Parity	GTT mg./100 ml. Fasting	GTT mg./100 ml. 2 hours	Treatment	Mean 17-KS value	3rd trimester 17-OHCS value	Result of pregnancy
R.A.	24	5	100	188	Nil	9·1	10·2	Live F (7/4)*
P.P.	21	3	90	180	Nil	11·7	12·4	Live F (8/12)
A.P.	32	4	85	143	Nil	11·1	14·1	Live F (6/14)
P.P.	23	0	81	186	Diet	15·9	18·5	Live F (5/8)
C.R.	27	2	96	173	Diet	15·3	15·9	Live M (8/4)
K.S.	30	2	130	250	Diet	14·5	14·9	Live F (10/4)
N.B.	32	6	122	217	Diet	9·5	10·2	Live F (8/9)
J.G.	27	5	75	195	Diet	4·9	5·5	Live F (6/6)
K.S.	27	1	64	195	Diet	16·8	17·2	Live M (6/10)
D.M.	40	5	140	293	Diet	14·2	14·7	Live F (7/10)
R.O.	32	4	77	144	Diet	7·2	8·7	Live F (5/4)
E.P.	32	6	107	198	Diet	15·1	16·0	Live F (7/2)
C.H.	17	0	93	180	Tolbutamide	13·2	14·8	Live M (5/8)
P.G.	30	6	115	203	Tolbutamide	13·9	14·5	Live M (8/8)
M.S.	26	3	155	197	Tolbutamide	9·2	9·7	Absconded
D.G.	25	3	210	634	Tolbutamide	1·8	2·9	Stillborn M (5/1)
M.N.	30	3	95	190	Chlorpropamide	15·5	16·0	Live M (7/0)
A.G.	25	1	167	360	Chlorpropamide	7·2	7·5	Live F (8/9)
S.N.	36	3	122	203	Insulin	9·3	10·8	Live M (8/0)
B.M.	30	2	100	213	Insulin	16·2	16·9	Live F (7/10)

* Figures in parenthesis indicate birthweight in lb. and oz.

to 9·3 ± 4·3 mg./24 hours in the control group. This difference is statistically significant ($p = < 0.05$).

17-Hydroxycorticoids (Tables II and III and Fig. 2)

A similar pattern was obtained when the mean 17-hydroxycorticoid excretion rates were compared in the two groups. The mean excretion rate in the diabetic group was 12·6 ± 4·5 mg./24 hours and that of the control group 11·00 ± 6·8 mg./24 hours. The difference was found to be just short of statistical significance ($p = > 0.05$).

Diabetic Control and 17-Ketosteroid and Hydroxycorticoid Excretion

A comparison of the degree of diabetic control and the 17-ketosteroid excretion rate was studied in an attempt to determine the relationship (if any) between 'control' (as judged by the glucose-tolerance test) and adrenal function (as judged by 17-ketosteroid excretion). Only those patients who had had a glucose-tolerance test on the same day on which the urine specimens were collected, were included. Although the number of patients analysed was small, reference to Fig. 3 indicates that the 17-ketosteroid excretion level was not in any way related to the 2-hour blood-sugar level. A similar effect was noted when 17-hydroxycorticoid values were compared.

DISCUSSION

The results of this study therefore confirm the clinical impression[3,4] that some Natal Indian diabetics have certain hyperactive adrenocortical function. The full significance of these results, however, is more clearly defined when they are discussed in relation to the following features.

TABLE II. 24-HOUR URINARY EXCRETION VALUES OF 17-KETOSTEROIDS AND 17-HYDROXYCORTICOIDS IN 20 PREGNANT NATAL INDIAN DIABETICS

28 weeks		*32 weeks*		*34 weeks*		*36 weeks*		*38 weeks*		*40 weeks*	
17-KS	*17-OHCS*	*17-KS*	*17-OHCS*	*17-KS*	*17-OHCS*	*17-KS*	*17-OHCS*	*17-KS*	*17-OHCS*	*17-KS*	*17-OHCS*
12·5	12·6	12·8	15·2	11·7	12·1	7·4	9·6	8·6	9·7	9·2	9·7
15·4	14·9	14·5	13·2	12·9	13·8	12·9	13·1	13·6	14·4	9·6	11·2
14·7	15·1	16·3	18·4	13·2	13·7	16·4	17·6	18·9	25·2	14·2	17·3
1·8	2·9	15·4	15·6	14·8	15·6	10·0	10·3	2·2	4·2	13·8	13·8
15·1	15·1			8·2	10·1	21·0	21·7	5·4	6·8	14·2	16·2
				7·8	7·9	10·7	11·1	14·2	15·3	15·2	15·5
				5·6	5·9	10·7	11·1	15·4	14·9	15·8	16·4
				9·2	9·7	11·6	11·9	14·9	15·3	16·2	16·9
						14·2	14·7	18·6	19·2	7·2	7·5
								9·2	9·7	4·2	4·4
								14·2	15·2	14·8	15·3
								4·9	4·5		
								4·9	7·1		
								4·8	5·5		
								16·8	17·2		
								6·8	10·4		
								7·4	8·4		
								11·1			
								14·2	14·1		
Mean values of 17-ketosteroid and 17-hydroxycorticoid excretion expressed in mg./24 hours											
11·90	12·12	14·80	15·90	10·42	11·10	12·80	13·50	10·80	12·10	12·21	13·10

TABLE III. 24-HOUR URINARY EXCRETION VALUES OF 17-KETOSTEROIDS AND 17-HYDROXYCORTICOIDS IN 33 'CONTROL' PREGNANT NATAL INDIANS

28 weeks		*30 weeks*		*34 weeks*		*36 weeks*		*38 weeks*		*40 weeks*	
17-KS	*17-OHCS*	*17-KS*	*17-OHCS*	*17-KS*	*17-OHCS*	*17-KS*	*17-OHCS*	*17-KS*	*17-OHCS*	*17-KS*	*17-OHCS*
2·8	2·8	10·1	14·3	7·0	9·7	13·2	12·6	2·8	4·2	11·3	11·0
9·7	13·3	9·7	13·8	7·2	8·4	14·9	15·4	9·7	10·4	16·2	17·9
11·2	15·7	8·4	13·2	4·8	5·9	14·8	16·0	6·8	8·3	10·2	12·6
11·0	15·8	13·3	15·4	5·0	7·0	7·2	8·4	7·2	10·4	11·3	11·2
10·7	13·2	11·6	12·1	8·6	8·9	10·3	9·9	9·6	9·6	12·8	13·4
11·2	13·4	4·1	9·7	5·7	6·3	10·9	14·9			8·7	12·7
10·8	12·2	13·6	14·9			13·4	14·9			10·4	12·6
9·2	10·8	1·3	2·1			14·8	15·8			15·8	18·6
						11·0	10·8			8·6	9·8
						15·2	16·2			7·8	7·9
						11·1	12·4			5·6	9·3
						8·7	11·2			8·0	10·4
						8·7	7·3			9·2	9·8
						6·7	6·0			5·1	6·6
						4·9	5·4				
						4·9	5·8				
						5·3					
Mean values of 17-ketosteroids and 17-hydroxycorticoids expressed in mg./24 hours											
9·60	12·15	9·01	11·93	6·38	7·70	10·49	11·44	7·22	8·58	10·07	11·70

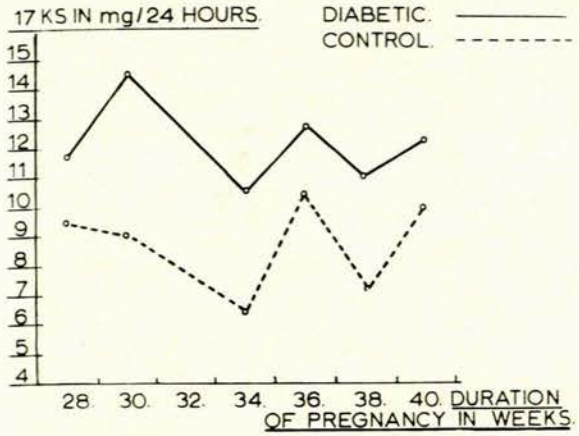

Fig. 1. A comparison of the mean 17-ketosteroid excretion rate in 20 pregnant diabetics and 33 pregnant controls.

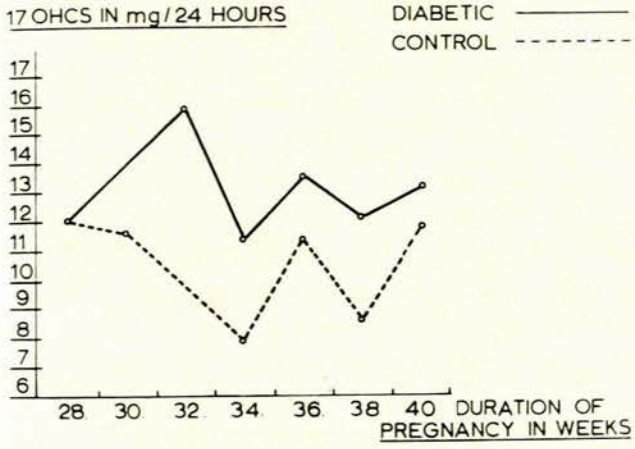

Fig. 2. A comparison of the mean 17-hydroxycorticoid excretion rate in 20 pregnant diabetics and 33 pregnant controls.

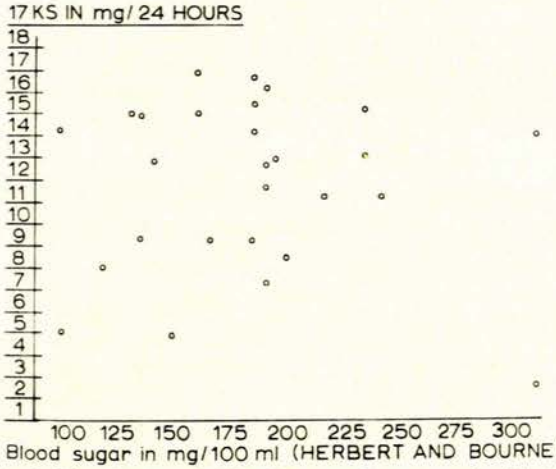

Fig. 3. The degree of diabetic control compared with 17-ketosteroid excretion.

Race

Friedman[5] and Henrotte *et al.*[6] have shown that the South Indian has a smaller 24-hour excretion of 17-ketosteroids than a comparable group of White controls. The socio-economic status of these individuals is of importance, since the decrease of ketosteroid production is associated with poor nutrition and a reduction in body size.[6]

Most of the patients studied by me are of South Indian stock and come from the lower income and social groups. Therefore, although the mean 17-ketosteroid excretion in the diabetic group (11·7 ± 4·6 mg./24 hours) may be well within the normal limits (12 - 36 mg./24 hours) for Whites,[1] comparison with normal pregnant Natal Indian 'control' (9·3 ± 4·3 mg./24 hours) indicates that the diabetic mean level is in fact significantly elevated.

Individual Assessment

The results of this study are representative of the group as a whole, but it is essential that patients be considered individually, for some diabetics may have normal adrenal function, whereas in others it may be markedly increased. Dancaster and Jackson[7] conclude that the output of adrenal steroids is not significantly altered in diabetics, yet scrutiny of their results reveals that the mean 17-OHCS was higher in their White diabetics than in the White controls. Similar conclusions were published by Jakobson,[8] yet, once again, the response of urinary 17-ketogenic steroids to the intravenous administration of corticotrophin to a group of his diabetic patients was found to be significantly greater than in a non-diabetic control group.

Is it therefore apparent that although the mean value of an excretory product may not be significant when analysed statistically, individual assessments provide an entirely different picture, and in the final reckoning it is the management of the individual which counts.

Pregnancy

The results of adrenal function obtained during pregnancy (if based on urinary excretion) may be fallacious, as long-term hormonal studies have indicated that oestrogen decreases the excretion of cortisol and its metabolites.[9] Furthermore, it is well known that the elevated levels of cortisol commonly found during pregnancy are largely biologically inactive, due to binding with an oestrogen-induced globulin. Therefore, when one considers adrenal function during pregnancy, oestrogen metabolism should also be taken into account, since raised levels of cortical steroids with adequate oestrogen production may have a lesser effect on carbohydrate balance than a lower level of cortical activity with a poor oestrogen supply. In this regard, the observations of Boulle[10] are of interest, as he found the level of oestrogen excretion to be much lower in the pregnant Natal Indian diabetic when compared with patients of the same racial group and duration of pregnancy. Davis and Plotz[11] have similarly described an increased excretion of urinary ketosteroids (androsterone and etiocholanolone) in the presence of a diminution of oestrogen synthesis by the placenta in pregnant diabetics. As androsterone and testosterone are the principal hormonal precursors of oestrogen during pregnancy, they have postulated that the observed biochemical status in

these patients is probably due to the inhibition of the enzyme system responsible for this conversion.

It is therefore tempting to postulate that the observed increased adrenal cortical function found in some of the pregnant Natal Indian diabetics assumes even greater significance as an indicator of possible diabetogenic activity.

Fractionation of Cortical Steroids

When assessing adrenal function, it is important to measure as many metabolites as is practical, for the corticoids often vary independently of one another—for example, patients with Cushing's syndrome have elevated levels of hydroxycorticoids and normal ketosteroid values, while in certain cases of hirsutism the reverse is true. Similarly, during pregnancy a marked increase in the corticoids occurs, whereas 17-ketosteroid remains fairly constant.[11,12] The elevated values for ketosteroid excretion obtained in the present series are once again in keeping with the clinical impression that these patients have some hyperactive adrenal function. Thus McKechnie,[4] in a clinical survey of 100 female diabetics, reported that 74% had significant hirsutes (sideburns, and excessive hair on the upper lip, chest and limbs) as opposed to 15% in a control group of 93 patients.

The results obtained might have been even more significant if the total 17-ketosteroids had been fractionated, for it has been shown that the beta-ketonic fraction (dehydro-isoandrosterone) is markedly increased in adrenal hyperplasia and other pathological conditions of the adrenal cortex. Both the beta- and alpha-ketonic fractions (androsterone, etiocholanolone: 11-oxygenated ketosteroids) are normally not increased during pregnancy.[11]

Diabetic Control and Cortical Activity

It was partly the object of this study to investigate the effect (if any) of diabetic 'control' on adrenocortical function. Although the numbers involved are small, reference to Fig. 3 indicates that there is no apparent relationship whatsoever between diabetic control (as judged by the glucose-tolerance test) and cortical activity (as determined by 17-ketosteroid and 17-hydroxycorticoid excretion). Jakobson similarly concluded that the degree of control of the diabetic state did not significantly affect adrenocortical function. These observations serve to illustrate the importance of defining and treating the cause of the disordered carbohydrate balance, rather than its symptom—the elevated blood sugar.

'Adrenal Facts and Fancies'

Cope[13] has recently indicated that the urinary 17-ketosteroid excretion rate is of little practical value, in that 80% of the estimate is due to other non-specific chromogens. Furthermore the results depend upon the accuracy of collection and storage of the specimen, while the variations which must occur in the hormonal balance during a 24-hour period have also to be considered. The same is true of 17-ketogenic steroid excretion. Isotopic studies, using radioactive labelled tritium, are the most accurate methods available for assessing the functional state of the adrenal cortex, but since their use is contraindicated during pregnancy, fluorometric determination of the free 11-hydroxycorticoids in plasma is the best alternative. In order to establish the 'true' state of adrenocortical activity during pregnancy, it would probably be necessary to base one's findings on the levels of free cortisol in the blood before and after stimulation, by drugs such as Synacthen.[14]

CONCLUSIONS

Based on the results of investigations of adrenocortical activity in the pregnant Natal Indian diabetic, it can be concluded that:

1. The pregnant diabetic subject has increased levels of 17-ketosteroid and 17-hydroxycorticoid excretion when compared with the pregnant non-diabetic controls.

2. It is important to assess patients individually as only some diabetics will have evidence of adrenocortical hyperfunction.

3. Abnormal values should always be based on a comparison with normal values obtained in the same racial group.

4. Adrenocortical function during pregnancy (and especially the pregnant diabetic) should be studied in conjunction with oestrogen assays, since the level of free and therefore biologically active cortisol is directly related to the degree of binding with an oestrogen-induced globulin.

5. The suggestion is made that every diabetic should be screened before the institution of treatment whenever adrenal hyperactivity is thought to be of some aetiological significance, since it would appear that 'true' control cannot be achieved by suppressing the blood-sugar level.

SUMMARY

A study was instituted with the object of comparing adrenocortical function, as measured by the urinary excretion pattern of the 17-hydroxycorticoids and the 17-oxosteroids, in the pregnant diabetic and non-diabetic Natal Indian. The results indicate that the individual pregnant diabetic is more liable to disturbed adrenocortical activity than the non-diabetic control. The significance in relation to the management of diabetics is commented upon.

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