A Possible Explanation for Falsely Positive Hydrocortisone Glucose Tolerance Tests During Pregnancy

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SUMMARY

Twenty-three pregnant subjects have been studied by means of the oral glucose tolerance test to compare the effect of hydrocortisone and prednisolone on blood glucose levels. In four patients an additional GTT, using twice the standard dose of prednisolone before the glucose load, was compared with the previous tests. In another two patients, the effect on glucose excretion was compared when hydrocortisone or prednisolone was administered.

The results suggest a potentiation in the biologic effect of hydrocortisone during pregnancy, but not with prednisolone as has been reported in nonpregnant subjects receiving estrogens. It appeared that to duplicate the glucocorticoid effect of hydrocortisone, a ratio of potency of prednisolone to hydrocortisone in pregnancy may be 2:1 rather than the 4:1 ratio observed during the nonpregnant state.

Prednisolone instead of hydrocortisone, as the provocative agent for the detection of subclinical diabetes in pregnancy, may be useful, or perhaps a smaller dose of hydrocortisone should be employed than is required for the nonpregnant subjects.

A potentiation of the biologic activity of exogenous hydrocortisone during estrogen administration has been shown in a previous paper.[1] This potentiation, as measured by the glycosuric response of diabetic patients, was not apparent following the administration of the 1-2 unsaturated synthetic corticoids, prednisolone or prednisone. To determine whether this is a physiologically significant effect in pregnancy and to study it as a mechanism to explain the reported discrepancies[2,3] between the provocative hydrocortisone glucose tolerance test and the prednisolone glucose tolerance test in pregnancy, twenty-three subjects, in various stages of gestation, were given oral glucose tolerance tests while receiving both steroids. The results suggest a potentiation of the biologic activity of the administered hydrocortisone in pregnancy by alteration of the glucose tolerance test and by increase in glucosuria similar to that observed in normal subjects treated with estrogens.

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MATERIALS AND METHODS

Twenty-three pregnant subjects, only one of whom had a family and obstetrical history suggestive of clinical prediabetes, were studied at the University of Southern California Clinical Research Center in the Los Angeles County General Hospital. Each patient received three oral glucose tolerance tests (GTT) with intervals of three to seven days between tests. For a few days prior to the GTT, a diet containing at least 150 gm. of carbohydrate was prescribed to prevent plateau or diabetic type curves.[4,5] All patients were ambulatory, and patients who experienced nausea or vomiting following glucose administration were not included in the study.[6]

After an overnight fast of twelve hours, 100 gm. of glucose, dissolved in 500 ml. of water, was given and venous blood was obtained before and 1, 1½, 2, 2½, 3, and 4 hrs. after the ingestion of the solution. For the second test, either 40 mg. of hydrocortisone was given orally 8½ and 2 hrs. before the glucose administration (HGTT) as recommended by Fajans and Conn,[7] or 10 mg. of prednisolone* was administered in the same way (PGTT). The third test then consisted of the steroid not previously administered. The order in which hydrocortisone and prednisolone were administered to normal subjects in a similar previous study also failed to influence the results.[1] In four patients, an additional GTT was performed following the administration of 20 mg. of prednisolone 8½ and 2 hrs. before the glucose load.

*Hydeltra® was kindly supplied by Dr. E. Alpert, Merck Sharp & Dohme Research Laboratories.

Two female subjects, in the second and third trimester of their pregnancy, one with diabetes mellitus (M.L.) and the other with renal glycosuria (N.S.), were studied. Each of these patients received a constant diet and twenty-four hour urine collections were obtained daily throughout the study. Urine glucose was measured and the completeness of the collections was checked by urinary creatinine determinations. After a three-day control period, each patient received 20 mg. of hydrocortisone orally every six hours for two days, and after three additional control days, 5 mg. of prednisolone was given in the same sequence. In patient N.S., an oral GTT was done on the second day of corticosteroid administration. Blood and urine glucose were measured by a glucose oxidase procedure.[8]

RESULTS

Table 1 shows the values for blood glucose in the twenty-three subjects during fasting and 1, 1½, 2, 2½, 3, and 4 hrs. following ingestion of the glucose load. When hydrocortisone was administered, the mean value at the two-hour level was 143 mg. per 100 ml. of blood in comparison with a value of 118 mg. per 100 ml. of blood when prednisolone was given. This difference was significant at a P value $< .01$. The same probability estimate was obtained at the 2½-, 3-, and 4-hr. interval. Although the mean blood glucose values were higher with hydrocortisone than with prednisolone at fasting, one, and one and one-half hours, the difference was not significant ($P > .1$ and $> .2$ respectively). Figure 1 illustrates the mean response to the three GTT's performed in the twenty-three subjects. In the four patients, in whom an additional GTT was done while on 20 mg. of prednisolone rather than 10 mg., the blood glucose curve approximates that obtained with 40 mg. of hydrocortisone (table 2). The number of patients is not sufficient to show any difference between

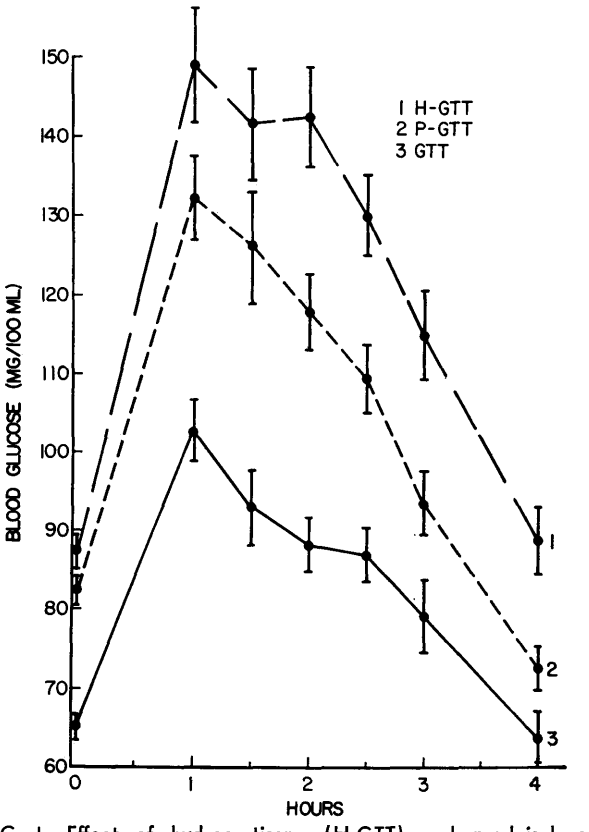

FIG. 1. Effect of hydrocortisone (H-GTT) and prednisolone (P-GTT) on the oral glucose tolerance test in twenty-three pregnant subjects. GTT represents mean response prior to corticoid administration. (Mean ± S.D. for these values is given in table 1.)

TABLE 1

Effect of hydrocortisone and prednisolone on the oral glucose tolerance test in twenty-three pregnant subjects

	(Fasting blood glucose)	Blood glucose levels mg. per 100 ml.					
Hours	0	1	1½	2	2½	3	4
GTT*	65± 7.6**	103±18.7	94±23.3	88±16.5	87±16.8	79±22.6	63±15.3
HGTT†	87±10.9	149±35.1	141±32.5	143±30.1	131±24.6	115±26.7	89±19.6
PGTT‡	82± 9.4	132±27.1	127±32.1	118±21.5	110±21.3	93±18.6	73±13.0
P§ between HGTT and GTT	<.001	<.001	<.001	<.001	<.001	<.001	<.001
P between PGTT and GTT	<.001	<.001	<.001	<.001	<.001	<.02	<.05
P between HGTT and PGTT	<.2	<.1	<.2	<.01	<.01	<.01	<.01

*GTT: glucose tolerance test.
†HGTT: hydrocortisone glucose tolerance test.
‡PGTT: prednisolone glucose tolerance test.
§P: significance of difference determined by the Student *t* test.
**Mean ± Standard Deviation.

TABLE 2

Comparison of the effect of prednisolone, hydrocortisone, and a doubled dose of prednisolone on the oral glucose tolerance test in four pregnant women

	Mean blood glucose levels mg./100 ml.							
Hours	(FBS) 0	1	1½	2	2½	3	4	Total mg. corticoid given
GTT*	74	87	83	95	84	86	66	0
HGTT†	92	142	140	125	134	106	88	80
PGTT‡	90	133	124	117	100	89	81	20
2 PGTT§	86	156	143	126	117	107	81	40

*Glucose tolerance test.
†Hydrocortisone glucose tolerance test (40 mg.) 8½ and 2 hrs. before the test.
‡Prednisolone glucose tolerance test (10 mg.) 8½ and 2 hrs. before the test.
§Prednisolone glucose tolerance test (20 mg.) 8½ and 2 hrs. before the test.

the trimesters of pregnancy in which the studies were performed.

Figures 2 and 3 show the glycosuric effect of both corticoids when administered to two pregnant subjects. The glycosuric response was, as had been seen previously in patients receiving estrogens, greater with hydrocortisone than prednisone. Figure 3 also shows the blood

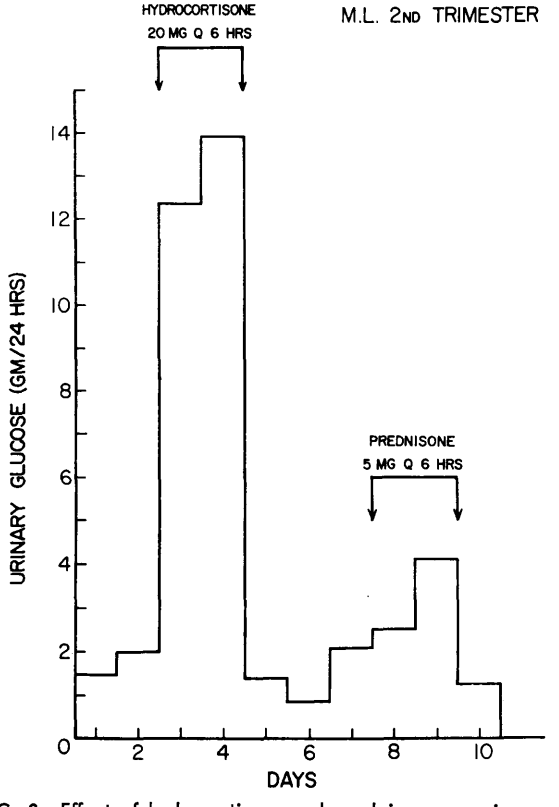

FIG. 2. Effect of hydrocortisone and prednisone on urinary glucose excretion in a pregnant, diabetic subject.

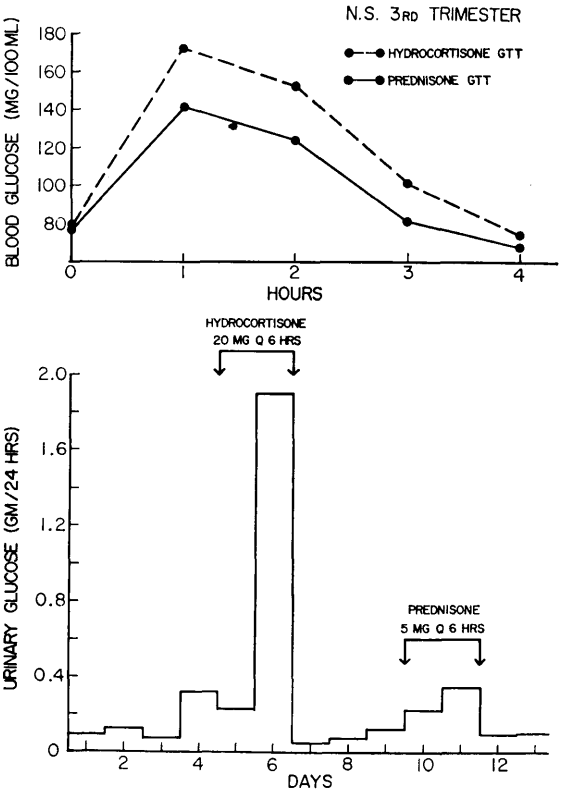

FIG. 3. Effect of hydrocortisone and prednisone administration on urinary glucose and on the oral glucose tolerance test in a pregnant subject with renal glucosuria.

glucose levels in patient N.S. when a load of 100 gm. of glucose in 500 ml. of water was given the second day of corticoid administration. The response is similar to that in the twenty-three previously described patients.

DISCUSSION

Since Fajans and Conn[7] reported a provocative oral GTT for the detection of the subclinical diabetic state with the use of cortisone, the test, when used in pregnancy, has shown a surprisingly high number of abnormal responses in subjects who do not have any of the clinical manifestations of the so-called prediabetic syndrome.[2,9] Baldi et al.,[3] using prednisolone as the provocative agent in the GTT during pregnancy, found a much smaller number of positive results in thirty-one pregnant subjects. The two-hour blood glucose value was used as the reference point of the test in these studies.

It is generally accepted that the relative biologic potency of prednisolone and hydrocortisone, in regard to glucocorticoid activity, is in the range of 4-5 to 1.[10,11] West[12] showed that the relative activity of the two compounds in producing an increase in blood glucose in normal subjects fasting and after glucose admin-

istration is similar when this ratio of steroid is used for treatment. The results presented in this study suggest that during pregnancy a potentiation of exogenous hydrocortisone biologic activity occurs similar to that seen during estrogen therapy.[1] An alternative, but less likely explanation in the authors' opinion, would be a decreased effectiveness of prednisolone during pregnancy. This explanation is made less likely by the similarity between two-hour blood glucose found in the pregnant subject in our study and in normals by West[12] following prednisolone administration. The difference in relative biologic activity of the two steroids during pregnancy probably accounts for the different results obtained by Jackson[2] and Baldi et al.[3] in pregnancy, as mentioned previously. Forty milligrams of hydrocortisone appeared to produce an effect on the blood levels of glucose similar to that produced by 20 mg. of prednisolone, suggesting that during pregnancy the relative biologic effect of the two steroids is altered.

Possible explanations for the increase in biologic activity of hydrocortisone during estrogen therapy have been discussed previously.[1] The studies reported here indicate that a similar alteration in activity may occur during pregnancy. This effect produces an apparent doubling of biologic activity of administered hydrocortisone and would appear to explain the increased number of positive HGTT's seen during pregnancy. Further studies are underway to determine whether the use of prednisolone, or halving the quantity of hydrocortisone employed, does make this test a more satisfactory one during pregnancy, as is suggested by the results presented here.

SUMMARIO IN INTERLINGUA

Un Possibile Explication pro Falsemente Positive Tests a Hydrocortisona de Tolerantia de Glucosa Durante Pregnantia

Vinti-tres subjectos pregnante esseva studiate per medio del oral test de tolerantia de glucosa pro comparar le effectos de hydrocortisona e prednisolona super nivellos de glucosa sanguinee. In quatro patientes un additional test de tolerantia de glucosa, con un dosage de prednisolona duple le dosage standard, administrate ante le carga de glucosa, esseva comparate con le previe tests. In duo altere patientes le effecto super excretion de glucosa del administration de hydrocortisona o prednisolona esseva comparate.

Le resultatos suggestiona un potentiation del effecto biologic de hydrocortisona durante le pregnantia, sed non de prednisolona (como ha essite reportate in subjectos nonpregnante qui recipe estrogenos). Il pare que pro duplicar le effecto glucocorticoide de hydrocortisona, le proportion del potentia de prednisolona comparate a hydrocortisona pote esser 2:1 in pregnantia plus tosto que le proportion 4:1 que es observate durante le stato nonpregnante.

Prednisolona pote esser utile in loco de hydrocortisona como le agente provocative pro le detection de diabete subclinic in pregnantia, o forsan un minus grande dosage de hydrocortisona debe esser empleate que lo que es requirite pro subjectos nonpregnante.

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