Adrenal Cortical Capacity and Cortisol Utilization in Normal and Toxemic Pregnancies.*† (22623)

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It has been demonstrated that the plasma level of 17-hydroxycorticosteroids (17-OHCS) in pregnancy is elevated over normal, non-pregnant values(1-4). No difference in this steroid level was found between normal and toxemic pregnancies(3). Speculation as to the source or sources of the additional 17-OHCS has suggested several possibilities among which two appear probable: an increased rate of production by the maternal adrenal cortex, and faulty utilization by the maternal organism.

Samuels and his coworkers(5,6) have presented evidence for 1) elevation of 17-OHCS in surgery, 2) reduced rate of metabolism of infused cortisol by surgical patients, and by non-surgical patients with liver disease, and 3) correlation between impaired liver function and the magnitude of the rise in plasma 17-OHCS due to surgery. They also believe that there is evidence that liver function is depressed during other types of stress as well as during surgery(6). Hence, they concluded that the elevated levels of 17-OHCS seen in stress are due to both adrenal stimulation and impaired hepatic function(6).

In view of their findings, we decided to investigate the possibility that the increased levels of 17-OHCS in pregnancy are due to both adrenal stimulation and impaired utilization since pregnancy is regarded as a "stressful" situation. We used the test of adrenal cortical capacity or reserve as outlined by Eik-Nes *et al.*(7) to determine whether the stimulus received by the adrenal cortex during pregnancy was maximal. In addition, from the results of this test the functional status of the adrenal cortex might be judged. To determine whether diminished utilization is involved in the production of the high levels of these steroids found in pregnancy, the ability of the pregnant patient to handle infused cortisol was investigated. Both normally pregnant and toxemic pregnant patients were used in this study in the hope that some difference in the production, or utilization, of these steroids under the experimental conditions used might be disclosed, since no difference in these levels for normal and toxemic pregnancies under the influence of endogenous ACTH was found in the previous study(3).

Methods.§ These studies were performed on 39 pregnant patients who were hospitalized and at bed rest. Tables I and III give age, diagnosis, and length of gestation of the patients. The test of adrenal cortical capacity was carried out on 12 patients with normal pregnancy and 13 patients with toxemia of pregnancy. Each of these patients received 40 mg (40 I. U.) of Armour's ACTH in one liter of 5% aqueous dextrose by intravenous drip infusion over a period of 6 or 10 hours. The dose of ACTH employed was higher than that used by Eik-Nes because it was considered possible that the level of endogenous ACTH in the pregnant patient is elevated. If this is true, then the usual dosage of ACTH (25 mg) would be inadequate to produce a physiological response. Blood samples for the determination of 17-OHCS were taken immediately prior to the infusion (zero hour) and at 2, 4, 6, 8, and 10 hours.

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TABLE I. Effect of Intravenously Infused ACTH (40 mg) on Level of Plasma 17-Hydroxycorticosteroids in Normal and Toxemic Pregnancies.

Patient	Age	Length of gestation, wk	17-hydroxycorticosteroids in μg/100 ml plasma						Max change and time of occurrence		
			0 hr	2 hr	4 hr	6 hr	8 hr	10 hr	2 hr	4 hr	6 hr
Normal pregnancies											
7-D	28	40	54.2	107.0	101.6	119.0					64.8
1-F	40	38	54.0	80.8	100.0	101.5					47.5
9-F	20	40	85.4	100.8	100.5	122.2					36.8
8-G	16	36	40.3	68.4	80.0	95.7					55.4
8-K	20	37	58.7	112.9	111.6	126.9					68.2
2-M	20	38	48.4		97.0	105.8					57.4
7-M	20	39	77.5	86.7	109.0	134.0					56.5
1-N	15	40	67.7	101.3	113.8	117.2					49.5
5-N	18	40	42.3	91.6	91.1	80.4			49.3		
9-N	17	40	48.8	78.5	87.4	94.2					45.4
3-O	23	35	61.7	59.4	116.4	107.9				54.7	
4-Y	24	35	49.6	75.7	93.6	108.8	123.9	131.9			59.2
Median		38.5	54.1	86.7	100.3	108.4					55.95
Toxemic pregnancies											
2-E	18	36	44.2	104.0	109.4	83.3				55.2	
7-E	30	38	59.0	104.3	86.3	74.7			45.3		
5-F	18	36	86.6	101.8	102.9	98.8				16.3	
7-H	20	37	67.6	51.4	77.1	71.1				9.5	
1-I	20	38	72.3	73.0	108.4	118.0					45.7
7-I	18	32	68.7	73.8	73.9	94.4					25.7
1-J	19	34	59.3	94.6	95.1	92.1				35.8	
9-J	22	36	41.9	69.5	90.4	77.0				48.5	
4-K	20	38	28.6	50.1	51.6	60.7					32.1
8-L	21	36	66.1	98.5	102.4	112.9					46.8
4-V	19	42	55.1	83.4	106.9	138.9	117.2	89.0			83.8
8-X	28	31		58.5	72.2	75.7	77.0	81.7			
2-CC	19	32	35.3	70.3	104.2	88.9	105.0	109.4		68.9	
Median		36	59.2	73.8	95.1	88.9	105.0	89.0		42.2	45.7

The test of the metabolism of cortisol was performed on 8 normal and 6 toxemic pregnant patients. Each of these was given 75 mg of cortisol in 250 ml of 5% aqueous dextrose by intravenous drip infusion over a period of one-half hour. Blood samples were drawn immediately prior to the infusion (zero hour) and at 1, 2, 4, 6, and 8 hours after the start of the infusion. The level of plasma 17-OHCS of all of the samples was determined by the method described elsewhere(3). The sulfuric acid blanks recommended by Bayliss and Steinbeck were not used in our determinations since use of these makes it impossible to run duplicates of the samples from normal, non-pregnant subjects. We feel that duplicates are essential; however, we realize that omission of these blanks might produce non-physiological differences in the values for the 2 groups of patients studied.

Results. Adrenal cortical capacity. The data obtained for the levels of 17-OHCS in this test are shown in Table I. Examination of these values shows that a rise occurred in response to exogenous ACTH in all of the patients studied. In the cases of normal pregnancy it is not possible to judge whether the rise was maximal at 6 hours or not, except in the case studied for 10 hours (Y-4) in which the increase was still proceeding. Most of the toxemic pregnant patients showed a less pronounced rise which reached a peak at 4 or 6 hours. The median rise observed at *6 hours* in response to 40 mg of infused ACTH was about 100% in cases with normal pregnancies, and about 50% in those with toxemia of pregnancy. The maximal median rise obtained by Eik-Nes *et al.*(7) in 39 normal, non-pregnant subjects under similar conditions was 300%. Calculations given in Table II, however, show that the rise in normal pregnancy due to the combined effect of exogenous and endogenous

TABLE II. Effect of Endogenous and Exogenous ACTH (40 mg) on Level of Plasma 17-Hydroxycorticosteroids in Normal and Toxemic Pregnancies.

	Endogenous ACTH Median values		Exogenous ACTH Median values		Endogenous ACTH + exogenous ACTH (6 hr) Median values	
	μg/100 ml plasma	% rise	μg/100 ml plasma	% rise	μg/100 ml plasma	% rise
Normal late pregnancy	54.1				108.4	
Non-pregnant control	28.5				28.5*	
Difference	25.6	89.9			79.9	280.5
Normal late pregnancy						
6 hr			108.4			
0 "			54.1			
Difference			54.3	100.2		
Toxemic pregnancy	59.2				88.9	
Non-pregnant control	28.5				28.5*	
Difference	30.7	107.8			60.4	212.0
Toxemic pregnancy						
6 hr			88.9			
0 "			59.2			
Difference			29.7	50.2		

* Endogenous ACTH only.

ACTH compared with our non-pregnant value is equivalent to the rise found by Eik-Nes.‖ In the toxemic pregnancies this combined rise is about one-fourth lower. In another study of adrenal cortical capacity, Christy *et al.* (8) studied a small number of patients over a period of 4, instead of 6 hours. They reported finding a rise in plasma 17-OHCS in pregnant patients in excess of the rise in normal subjects in response to exogenous ACTH.

In addition, further examination of the data in Table I discloses that whereas 42% of the toxemic pregnant patients may have reached their maximum level at 6 hours after the administration of ACTH, 50% showed the maximum change at 4 hours, and 8% at 2 hours. In contrast, 83% of the normally pregnant patients may not have reached the maximum level at 6 hours, whereas, only 17% showed a maximum change at 4 hours, and none showed it at 2 hours. These data appear to show that the adrenal cortex of the pregnant patient is submaximally stimulated by endogenous ACTH, and that the response to exogenous ACTH is normal in the cases of normal pregnancy and somewhat reduced in toxemic pregnancy.

Comparison of the data obtained by Sandberg *et al.*(5) for the level of plasma 17-OHCS in surgical patients with our data for normally pregnant patients suggests that the stress of surgery produces a somewhat greater rise in the plasma 17-OHCS than does the stress of pregnancy, but that the adrenal cortical reserve of these 2 groups of patients is similar. The toxemic pregnant patients, on the other hand, show a reduced adrenal cortical reserve when compared with normally pregnant patients and surgical patients.

Cortisol metabolism. The data obtained for plasma levels of 17-OHCS in normal and toxemic pregnancy before and after infusion of cortisol are given in Table III. The difference in the zero hour values for the 2 groups is probably due to the smallness of the groups and the difference in duration of pregnancy. The one hour value (½ hour after the end of the infusion) was the highest in both groups of patients. Calculations given in Table IV show that 95% of the exogenous cortisol had been removed from the blood at the end of one hour in both normal and the toxemic pregnancies. It would seem unlikely that the

‖ After this manuscript was prepared Migeon *et al.* (*J. Clin. Invest.*, 1956, v35, 488) reported finding that the adrenal cortical capacity of normally pregnant women is equivalent to that of non-pregnant women.

TABLE III. Effect of Intravenously Infused Cortisol (75 mg) on Level of Plasma 17-Hydroxycorticosteroids in Normal and Toxemic Pregnancies.

Patient	Age	Length of gestation, wk	17-hydroxycorticosteroids in μg/100 ml plasma 0 hr	1 hr	2 hr	4 hr	6 hr	8 hr
			Normal pregnancies					
9-O	17	37	55.2	117.9	118.1	60.8	69.6	83.7
5-P	20	37	77.2	194.0	150.3	102.9	91.9	88.2
1-Q	19	40	57.4	126.3	124.8	94.5	56.3	61.8
7-Q	19	38	43.4	154.2	143.9	126.9	86.9	89.8
8-S	21	38	72.2	222.5	156.0	121.5	93.7	92.0
4-T	25	38	70.4	173.0	176.2	106.5	88.8	77.2
1-U	17	35	91.2	214.5	149.4	87.0	87.1	69.0
8-U	26	39	65.9	173.2	111.1	91.3	83.0	70.7
Median		38	68.2	173.1	146.7	98.7	87.0	80.5
			Toxemic pregnancies					
3-R	19	32	49.0	164.2	149.2	124.2	88.4	132.0
10-R	34	36	73.6	148.8	101.9	93.9	57.6	48.4
1-X	29	26	24.0	85.0	67.1	65.0	52.2	47.6
5-AA	16	28	10.0	137.0	79.5	59.1	53.5	42.8
1-BB	19	36	19.8	111.5	94.8	56.4		
6-BB	19	32	56.5	142.9	135.6	105.8	65.5	48.5
Median		32	37.0	140.0	98.4	79.5	57.6	48.4

elevated level of plasma 17-OHCS found in pregnancy was due to faulty utilization, since the amount of cortisol removed in the one hour period was more than 100 times the amount of 17-OHCS due to pregnancy (pregnancy level minus non-pregnancy level).

Discussion. The additional rise produced in the plasma levels of 17-OHCS in pregnancy by infused ACTH appears to indicate that the adrenal cortex in both normal and toxemic pregnancy is submaximally stimulated by the endogenous ACTH. In the normally pregnant patient, however, the combined rise due to the exogenous and the endogenous ACTH is similar to that seen in non-pregnant subjects after infusion of ACTH. This suggests that the adrenal cortex is functionally normal.

In toxemic pregnant patients, although the elevation in these steroid levels under endogenous stimulation does not differ from that of normally pregnant patients, the response to exogenous ACTH is lower and less sustained. Thus, it would appear that the reserve capacity of the adrenal cortex in toxemic pregnancy is reduced. This reduction might be attributed to one, or both, of two factors. If the adrenal cortex is under elevated stimulation during pregnancy, it is possible that reduction in the adrenal reserve in toxemia is due to fatigue of the gland. In addition, and this appears more likely, there may be a shift in the normal ratio of production of gluco- and mineralocorticoids with an increase in the latter. Since the chief mineralocorticoids are not measured by the Porter-Silber reaction, an increase in the plasma mineralocorticoids would not be detected by use of this assay method. Thus the reduction in adrenal cortical reserve found in toxemia of pregnancy may be a reduction in glucocorticoids only. When a chemical method for determination of mineralocorticoids in blood becomes avail-

TABLE IV. Utilization of Cortisol in Normal and Toxemic Pregnancies. Median values of plasma 17-hydroxycorticosteroids.

Time of collection	Normal pregnancies, μg/100 ml	Toxemic pregnancies, μg/100 ml
1 hr	173.1	140.0
0 "	68.2	37.0
Difference	104.9	103.0
	μg/3.2 l* plasma	μg/3.8 l* plasma
Total 17-hydroxycorticosteroids at 1 hr above 0 hr level	3457	3914
Infused cortisol remaining at 1 hr	4.6%	5.2%

* The plasma vol in pregnancy has been found to be greater at 32 wk (toxemic pregnancies) than at 38 wk (normal pregnancies) (9).

able, this aspect should be investigated. It has been suggested that toxemia of pregnancy is similar in a number of respects to the syndrome of DOCA intoxication(10). It also has been found that the sodium-retaining activity of urine is increased during late pregnancy with the greatest increase found in toxemia of pregnancy(11). These findings appear to lend support to the aforementioned suggestion.

It was not feasible to study the ability of the maternal organism to utilize exogenous cortisol after delivery. Hence, no estimate can be made of the significance of the per cent of exogenous cortisol remaining in the plasma at a given time, except to say that the maternal organism has the ability to use an amount of cortisol greatly in excess of the increment found in 17-OHCS in pregnancy. It would appear, then, that an increased rate of production, rather than a decreased rate of utilization, is responsible for much, or all, of the elevated level of 17-OHCS seen in pregnancy. It is recognized that the data presented herewith do not rule out the possibility that the placenta and, or, the fetal adrenals may contribute to the elevated level of plasma 17-OHCS.

Summary. Adrenal cortical capacity and cortisol utilization were studied in 20 patients with normal pregnancy and 19 patients with toxemia of pregnancy. It was found that the level of plasma 17-OHCS in late pregnancy can be further elevated by the action of exogenous ACTH. The reserve capacity of the adrenal cortex in normal pregnancy is similar to that in non-pregnant subjects; in toxemia of pregnancy it is somewhat reduced. Utilization of infused cortisol in both normal and toxemic pregnancies does not appear to be faulty; thus utilization does not seem to be a factor in the elevated levels of plasma 17-OHCS found in pregnancy.

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The *in vitro* and *in vivo* Effect of Synkavite on *Histoplasma capsulatum*.* (22624)

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De Saint-Rat and Luteraan(1) demonstrated that 5-hydroxy-2-methyl-1, 4-naphthoquinone in concentrations of 1:50,000 was active, *in vitro*, against *H. capsulatum*. Synkayvite, Roche (tetrasodium 2-methyl-1, 4-naphthohydroquinone diphosphoric acid ester), is a synthetic water-soluble compound of similar basic structure, potent vit. K activity, and relatively low toxicity. These characteristics, together with stability to heat and easy availability, resulted in the selection of this drug for this study.

It was the purpose of the following experi-

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