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Maternal Serum Corticosteroids and Corticosteroids Binding Globulin in Cases of Anencephalus, Intrauterine Fetal Death and Hepatic Lesion during Pregnancy

(11-OHCS/CBG/abnormal pregnancy)

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We carried out studies to determine the relationship between the production of maternal steroid and function of the fetal adrenal gland and placenta during pregnancy.

The blood CBG levels in normal pregnant women increased gradually with increase in the number of weeks of gestation and reached a peak or 2 to 3 times that of early pregnancy at 39 to 40 weeks' gestation.

In pregnant women with anencephalus and intrauterine fetal death where the maternal estrogen decreases markedly, the maternal blood CBG showed a level lower than the normal range in normal pregnant women.

In pregnant women with hepatic lesion, it was confirmed that maternal blood 11-OHCS and CBG levels were lower than the normal range in normal pregnant women.

Thus, an overall increase in blood CDS in pregnant women is due not to an increase in free cortisol but rather to an increase in cortisol bound to CBG.

It is considered that CBG is synthesized and metabolized in the maternal liver and that estrogen acts in such way as to promote CBG synthesis in the liver.

The cortisol bound to CBG is probably pooled in the maternal blood and compensates for loss of the hormone in cases where the maternal hormonal secretion has decreased sharply by one reason or another.

Determination was made of serum 11-OHCS in normal pregnant women and pregnant women with anencephalus. As a result (1, 2), the blood 11-OHCS levels increased gradually with increase in the number of weeks of gestation and reached a peak at 10 months' gestation in cases of normal pregnancy.

In the case of pregnant women with anencephalus, the values for the blood 11-OHCS levels were close to those seen in normal nonpregnant women and

Abbreviations used are : CCLF, cephalin cholesterol floculation test ; TTT, thymolturbidity test ; ZTT, zinc sulfate test ; GOT, glutamate oxalacetic transaminase ; GPT, glutamate pyruvic transaminase ; 11-OHCS, 11-hydrocorticosteroids ; CBG, corticosteroids binding globulin ; CDS, corticosteroids ; LDH, lactate dehydrogenase.

within the normal range of levels observed in the early stage of pregnancy.

To study the relationship between blood CBG and urinary estrogen in normal pregnant women, determination was made of the values for these substances on a time-course basis in the same cases. As a result (3), a significantly high correlation was observed.

These results suggest that estrogen levels which increase markedly during pregnancy are concerned with the production of maternal CDS and CBG.

In the present work, blood 11-OHCS and CBG levels in pregnant women with anencephalus, intrauterine fetal death or hepatic lesion were determined in hopes of elucidating the cause of blood 11-OHCS levels in pregnant women which increase with the advance of gestational weeks. We also assessed the correlation between the mother and fetus, particularly the fetal adrenal gland in reference to adrenal steroids.

MATERIALS AND METHODS

Using 256 normal pregnant women, 6 pregnant women with anencephalus, 2 pregnant women with intrauterine fetal death and 6 pregnant women with hepatic lesion as the subjects, determination was made of serum 11-OHCS or CBG levels, and when necessary, urinary estrogen was also determined.

Collection of Blood and Urine in Pregnant Women

In pregnant women, 3—5 ml of blood were collected from the vena cubiti at around 10 a. m. ; and after centrifugation, serum was frozen to −10°C for storage until determination.

Twenty-four hour urinary specimens were used.

Determination of Various Hormones

1) Determination of Serum 11-OHCS

Serum 11-OHCS was determined by the method of Usui *et al.* (4, 5), an improved version of the original De Monr's method (fluorimetric determination).

2) Determination of Serum CBG

Serum CBG was determined by the method of Usui and Kawamoto (6, 7) using hydrophobic resin.

3) Determination of Urinary Estrogen

Estrogen in 24 hour urine was determined by the Amberlite XAD-2 method (8) with E_3Kit (Teikoku Zoki K.K.).

RESULTS

1. Serum 11-OHCS Levels in 2 Cases of Pregnant Women with Hepatic Lesion

Serum 11-OHCS was determined in 2 cases of pregnant women complicated with hepatic lesion.

The first case was a patient who had been placed on a prophylactic

chemotherapy after intrauterine curettage for hydatidiform mole and who was now in a second pregnancy. Clinical biochemical examination at 18 weeks' gestation revealed icteric index 3, CCLF (++), TTT 4.2 U, ZTT 5.3 U, GOT 110 and GPT 122 Karmen.

Under the diagnosis of hepatic lesion, a total of 12 mg of 16β-methyl-9α-fluoropredonisolone was administered. A marked improvement ensued with GOT 122 and GPT 51 Karmen.

One week after, however, GOT and GPT rose again to 180 and 79 Karmen, respectively.

Showing no abnormalities other than high levels of GOT and GPT, she was followed as an out-patient, and a normal vaginal delivery was made at 37 weeks' gestation. The levels of GOT and GPT one week after the delivery were normal with 32 and 30 Karmen, respectively.

Serum 11-OHCS levels were determined repeatedly from the 18th to the 35th week of gestation, results of which are as shown in Fig. 1.

These values were lower than the mean value minus SD (2) in the normal pregnant women.

The second case (9) developed acute fatty liver at 36 weeks' gestation and went into a state of shock immediately after delivery. Administration of prednisolone, hydrocortisone, etc., resulted in a complete restoration.

Clinical biochemical examination revealed urinary bilirubin (++), LDH 1070 Wroble, GOT 154, GPT 198 Karmen and icteric index 65, which clearly

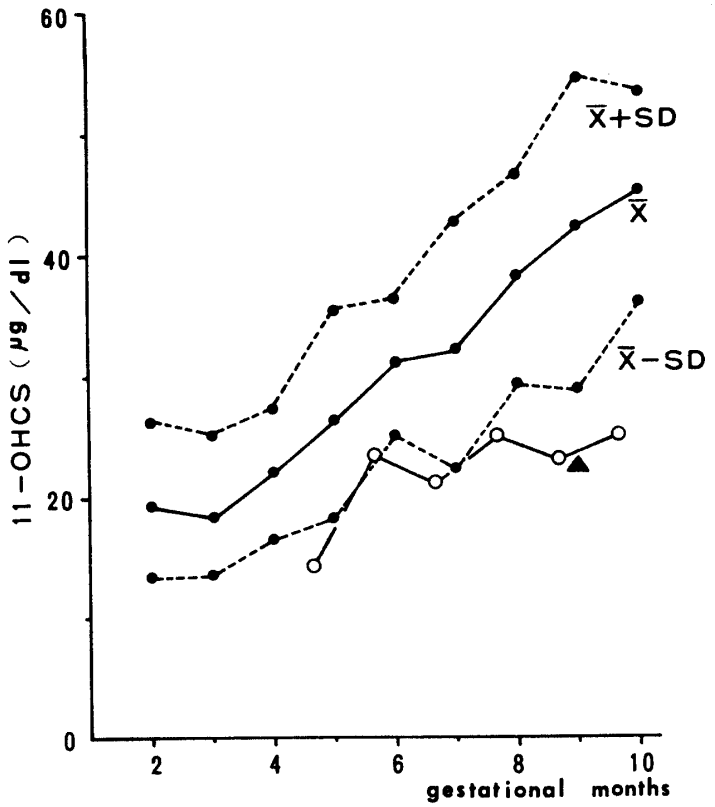

Fig. 1. Maternal serum 11-OHCS levels in cases of pregnant women with hepatic lesion.
○ : first case, ▲ : second case

represented the presence of hepatic lesion. As shown in Fig. 1, the serum 11-OHCS level was 22.5μg/dl, which is lower than the mean value minus SD in normal pregnant women (2).

2. Variations in Serum CBG Values at Each Stage of Pregnancy in Normal Pregnant Women

As shown in Fig. 2, the blood CBG levels rose with the advance of pregnancy and reached a peak at 39 to 40 weeks' gestation, to show an increase about 2.2 times that seen during 11 to 12 weeks' normal gestation.

3. Maternal Blood CBG Level in Cases of Anencephalic Pregnancy

In six cases diagnosed as anencephalus by abdominal roentgenogram and the level of maternal urinary estrogen being 5mg/day or less, the maternal blood CBG levels were considerably low compared to those at each gestational week in normal pregnant women, as shown in Fig. 2.

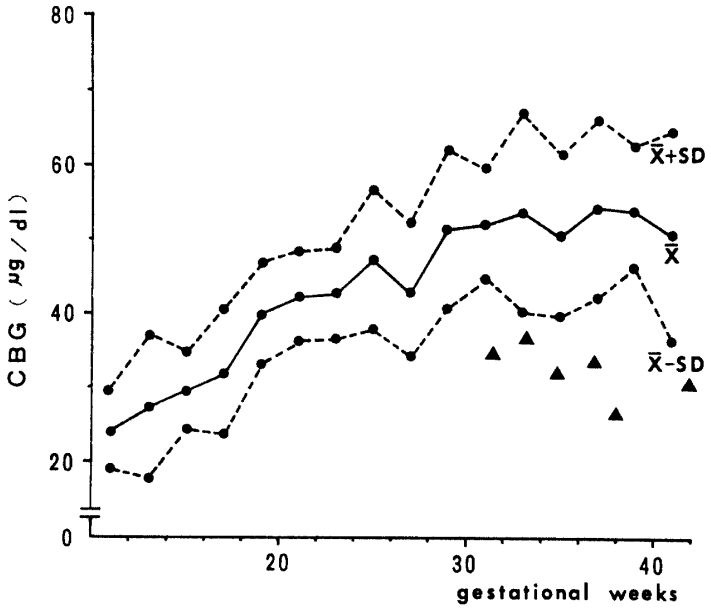

Fig. 2. Maternal serum CBG values in cases of anencephalic pregnancy (▲).

4. Maternal Blood CBG Levels in Cases of Pregnant Women with Intrauterine Fetal Death and Hepatic Lesion

In two cases diagnosed as intrauterine fetal death, the maternal blood CBG levels were lower than the mean value minus SD in normal pregnant women, as shown in Fig. 3.

The serum CBG values in 4 pregnant women diagnosed as hepatic lesion by clinical findings and clinical biochemical examinations were lower than the mean value minus SD in normal pregnant women, as shown in Fig. 3.

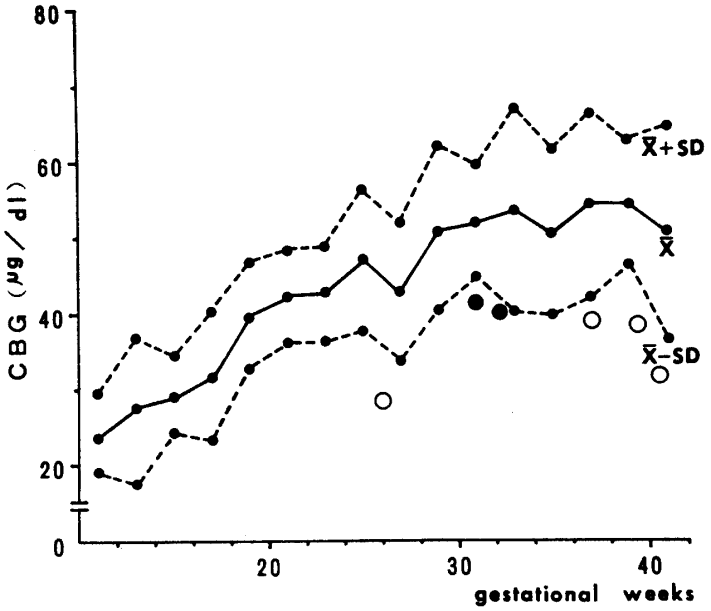

Fig. 3. Maternal serum levels in cases of pregnant women with intrauterine fetal death and hepatic lesion.
● : intrauterine fetal death, ○ : hepatic lesion

DISCUSSION

Tahara (1), Kitao *et al.* (2), Bryans and Belither (10) and Friedman (11) reported that the blood CDS levels in normal pregnant women began to rise from the third month of pregnancy, increased gradually with the advance of gestational weeks and reached a peak at the 10th month of pregnancy to show an increase by 2 to 3 times that of the early stage of pregnancy.

Furthermore, Kitao *et al.* (2) maintained that the blood CDS levels in pregnant women with anencephalus or intrauterine fetal death who show a significantly low levels of maternal urinary estrogen are lower than those of normal pregnant women, suggesting that maternal estrogen might be concerned with synthesis of CDS in pregnant women.

As is seen in our present work, the blood CBG level in pregnant women increases gradually with the advance of gestational weeks and reaches a peak in the 39th—40th week of pregnancy to show an increase by 2—3 times that in the early stage of pregnancy, as does the maternal blood CDS value.

The maternal blood CBG in anencephalic pregnancy and intrauterine fetal death also shows a considerably low value compared with the CBG level in normal pregnancy.

Regarding low levels of blood 11-OHCS and CBG in pregnant women with anencephalus or intrauterine fetal death showing low levels of maternal urinary estrogen, Ueda *et al.* (3 maintained that estrogen is concerned with CBG synthesis in pregnant women, on the ground that the blood CBG level in pregnant women showed a high coefficient of correlation with the amount of urinary estrogen in the same pregnant women. Doe *et al.* (12) reported

that administration of estrogen in animal experiments resulted in an increase in the blood CBG level.

Novak *et al.* (13) and Beisel *et al.* (14) stated that blood CBG, that is, transcortin increases and its capacity to combine with CDS increases under the influence of estrogen. These levels increase markedly during pregnancy but protein binding CDS being not easily metabolized nor excreted from the kidney is pooled in the blood.

Judging from the fact that symptoms ascribable to an increase in free cortisol, that is, Cushing's syndrome do not appear in pregnant women and also from results of the present experiment, it is possible that an overall increase in blood CDS levels in pregnant women is due not to an increase in free cortisol with potent biological activity such as is seen in glucocorticoid but rather to an increase in cortisol bound to globulin free of biological activity.

From the fact that blood 11-OHCS and CBG in pregnant women with hepatic lesion showed considerably low values and also from the report of Doe *et al.* (12) that the blood CBG level increases following administration of estrogen to animals but falls off in the presence of hepatic lesion, it may be assumed that estrogen acts on the liver to promote the CBG synthesis.

These data together with those of Takagi (15) that the CDS value is significantly higher in umbilical arterial blood than in umbilical venous blood, in a mode of delivery which is accompanied by greater stress there, arise two theories, namely, one that estrogen increasing markedly during pregnancy acts on the liver to promote CBG synthesis and subsequently increase blood CBG, to which is bonded cortisol for an increase in secretion of cortisol from the adrenal gland of the mother, thereby resulting in a gradual increase in the total amount of CDS, and the other that cortisol produced in the fetal adrenal gland enters the maternal blood through the placenta to combine with CBG, which results in an increase in the total amount of CDS.

Probably, these two factors are combined to increase the blood CDS level in pregnant women.

The results of the previous experiment (2) and the present experiment, suggest that it is possible to estimate the maternal estrogen levels and the function of the fetoplacental systetm including the function of the fetal adrenal gland, the placenta and of the maternal liver by determination of maternal serum 11-OHCS and CBG.

Thus, our studies have aided in clarification of the complex endocrinological environment during pregnancy centering around maternal blood CDS.

Significant differences of each case could not be examined because of very rare diseases, but this problem will be further investigated in our studies.

REFERENCES

1) Tahara, T. (1977) Studies on the variations of 11-OHCS in maternal serum as well as 17-KS and 17-OHCS in the urine during pregnancy. *J. Yonago Med. Assoc.* **28**, 293–308 (in Japanese)
2) Kitao, M., Tahara, T., Hasegawa, K., and Iba, N. (1978) Maternal serum 11-hydroxycorticosteroids during normal pregnancy and abnormal pregnancy particularly in cases of anencephalus. *Shimane J. Med. Sci.* **2**, 70–80
3) Ueda, T., Kaneda, K., and Kitao, M. (1977) Studies on the relationship between serum corticosteroid binding globulin and partial urinary estrogen/creatinine ratio. *Acta Obstet. Gynaecol. Jpn.* **29**, 101–102 (in Japanese)
4) Usui, T. and Kawamoto, H. (1970) Fluorimetric determination of serum 11-hydroxysteroids, Calculation correction of deviation in complex fluorescene specta. *Clin. Chim. Acta* **30**, 663–669
5) Usui, T., Kawamoto, H., Shimao, S., and Sakurai, K. (1970) Determination of serum 11-hydroxycorticosteroids (11-OHCS) in the clinic examining room. *Horumon to Rinsho* **18**, 151–156 (in Japanese)
6) Usui, T. and Kawamoto, H. (1971) Estimation of serum 11-OHCS as a routine test in the clinical laboratories. *Rinshobyori* **19**, 337–340 (in Japanese)
7) Usui, T. and Kawamoto, H. (1972) A new method for estimation of corticosteroid binding globulin with hydrophobic resin. *Clin. Chim. Acta* **37**, 151–155
8) Kanbegawa, A. (1971) Simple determination method for pregnant urinary estriol—E_3Kit method—. *Horumon to Rinsho* **19**, 355–368 (in Japanese)
9) Kitao, M., Tahara, T., Hasegawa, K., Umezawa, T., and Gomyoda, M. (1974) A rescued case of acute yellow liver atrophy in late pregnancy. *Yonago Acta Med.* **18**, 9–17
10) Bryans, F. E. and Belither, A. (1961) 17-hydroxycorticosteroid levels in pregnancy. *Am. J. Obstet. Gynecol.* **82**, 52–55
11) Friedman, M. (1966) Plasma 11-hydroxycorticosteroids in pregnancy and the puerperium. *J. Obstet. Gynecol. Brit. Cwlth.* **73**, 123–130
12) Doe, R. P., Fernandey, R., and Seal, V. S. (1964) Measurement of Corticosteroid-Binding Globulin in Man. *J. Clin. Endocrinol. Metab.* **24**, 1029–1039
13) Novak, E. R., Jones, G. S., and Jones, H. W. (1970) Novak's Textbook of Gynecology, p. 17, Wilkins, Baltimore
14) Beisel, W. R., Diraimond, V. G., and Forsham, P. H. (1964) Cortisol transport and disappearance. *Ann. Intern. Med.* **60**, 641–652
15) Takagi, K. (1975) 11-hydroxycorticosteroids and nonesterified falty acid in maternal and umbilical blood in labor. *J. Yonago Med. Assoc.* **26**, 1–20 (in Japanese)