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Free Estrone, Estradiol, Estriol, Progesterone and Total Corticosteroids Levels during Pregnancy, Labor and Puerperium

(serum estrogen/progesterone/corticosteroids)

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In 9 women with a normal pregnancy, delivery and puerperium, measurement was made of free estrone (E_1), free estradiol (E_2), free estriol (E_3), free progesterone (P) and total corticosteroids (CDS), continuously in each period.

The maternal blood E_1, E_2, E_3, P and CDS levels at 39 weeks' gestation were higher and the concentration of three fractions of estrogen was higher in the order of $E_2 > E_3 > E_1$.

When a comparison was made of maternal blood levels of various hormones at 39 weeks' gestation and at the onset of labor, a significant increase in E_1 and CDS was observed at the onset of labor.

As for maternal blood levels of various hormones with the advance of delivery, an increase in E_1 and CDS was observed at expulsion of the fetus, and the concentration of three fractions of maternal blood estrogen at this time was higher, in the order of $E_1 > E_2 > E_3$.

Maternal blood levels of various hormones after the expulsion of the placenta decreased rapidly. Particularly, E_2 and E_3 showed a marked decrease, thus suggesting that the fetoplacenta is closely concerned with the production of maternal blood E_2 and E_3.

With the advent of radioimmunoassay, the secretion estrogen, progesterone and corticosteroids in maternal blood can be monitored during pregnancy, delivery and the puerperium. Blood estrogen of pregnant women is mostly produced in the fetoplacental system and thus can be used as an index for fetoplacental function.

The role of endocrines in the mechanism of delivery, particularly before and after the onset of labor is being clarified by observing the behavior of corticosteroids, progesterone and estradiol in sheep maternal blood or by the behavior of corticosteroids, progesterone and estradiol in human maternal blood.

Defense mechanisms and the role of endocrines in both the mother and fetus during delivery can be elucidated by assessing the behavior of ACTH and corticosteroids or corticosteroids and estrogen in the blood of the mother and fetus during delivery.

In women who had completed a normal pregnancy, delivery and puerperium,

we measured the total corticosteroids (CDS), free estrone (E_1), free estradiol (E_2), free estriol (E_3) and free progesterone (P) continuously in each period and the behavior of each hormone.

MATERIALS AND METHODS

The subjects were 9 healthy primipara at 39 weeks' gestation who subsequently had spontaneous labor pains and went through normal transvaginal delivery and an uneventful puerperium. Five to seven hours passed from the onset of labor to delivery. Blood was collected from V. mediana cubiti of the mother at 39 weeks' gestation, on admission with the onset of labor pains, immediately after expulsion, 2 hr after the expulsion of fetus and on the 3rd day of puerperium.

The sera were immediately isolated and stored at −20°C. Blood E_1, E_2, E_3, CDS and P were determined using the CIS-RIA Kit.

The rejection limit method was used for the statistical analysis and the t-test for calculation of significant differences.

RESULTS

Peripheral Blood Levels of Various Hormones in Pregnant Women at 39 Weeks' Gestation

Maternal blood levels were 7.0−34.0 ng/ml for E_1, 7.6−60.0 ng/ml for E_2, 5.0−28.0 ng/ml for E_3, 70−145 ng/ml for P and 40−720 ng/ml for CDS.

As to the concentration of E_1, E_2 and E_3, E_2 was significantly high compared with E_1 and E_3 ($P<0.005$) and E_3 tended to show high values compared with E_1 ($0.05<P<0.1$), as shown in Table I.

TABLE I. *Changes in Serum Unconjugated Estrogen, Progesterone and Total Corticosteroids from 39 Weeks of Pregnancy to the 3rd Day of Puerperium*

	A	B	C	D	E	Comparison of A, B, C, D, E
E_1 (ng/ml)	8.2±9.3	10.6±8.1	23.2±9.1	8.4±7.1	0.92±0.51	B>A (0.025<P<0.05) C>B (0.01<P<0.025) C>D (P<0.05)
E_2 (ng/ml)	24.7±14.2	22.2±12.9	21.8±6.4	3.1±1.8	0.47±0.24	C>D (P<0.001)
E_3 (ng/ml)	13.4±7.7	11.8±6.0	13.2±4.9	1.1±1.2	0.44±0.37	C>D (P<0.001)
E_1 : E_2 : E_3 (Comparison)	$E_2>E_3>E_1$ (P<0.005) (0.05<P<0.10)	$E_2>E_3$, E_1 (P<0.001)	$E_1>E_3$, E_2 (P<0.005)	$E_1>E_2>E_3$ (0.025<P<0.05) (0.01<P<0.02)	$E_1>E_2$, E_3 (0.025<P<0.05)	
Progesterone (ng/ml)	93.8±27.2	93.3±12.2	109.2±53.2	34.5±12.0	3.47±0.96	C>D (P<0.001)
Corticosteroids (ng/ml)	228.0±178.0	320.0±202.0	450.0±213.0	235.2±75.3	190.0±117.0	B>A (P<0.05) C>B (P<0.05)

A : 39 weeks of pregnancy
B : time of admission with labor pain
C : immediately following birth of the child
D : 2 hrs after delivery
E : the 3rd day of puerperium

Maternal Peripheral Blood Levels of Various Hormones on Admission at the Onset of Delivery

Maternal blood levels were 3.4−31.7 ng/ml for E_1, 7.6−52.0 ng/ml for E_2,

5.5—25.0 ng/ml for E_3, 77.2—120 ng/ml for P and 56—520 ng/ml for CDS.

As to the concentration of E_1, E_2 and E_3, E_2 was significantly high compared with E_3 and E_1 and there was no significant difference between E_3 and E_1 as shown in Table I.

Maternal Peripheral Blood Levels of Various Hormones Immediately after Expulsion of Child

Maternal peripheral blood levels were 3.9—39.7 ng/ml for E_1, 13.0—32.0 ng/ml for E_2, 6.8—22.0 ng/ml for E_3, 61.2—225.0 ng/ml for P and 60—720 ng/ml for CDS.

As to the concentration of E_1, E_2 and E_3 in maternal blood, E_1 was significantly high compared with E_2 and E_3 and there was significant difference between E_2 and E_3 as shown in Table I.

Maternal Peripheral Blood Levels of Various Hormones at the 2 Hr after Delivery

Maternal peripheral blood levels were 2.4—26.5 ng/ml for E_1, 1.0—6.8 ng/ml for E_2, 0.2—4.0 ng/ml for E_3, 16—525 ng/ml for P and 88—390 ng/ml for CDS.

The concentration of E_1, E_2 and E_3 in maternal blood was higher in the order of $E_1 > E_2 > E_3$, as shown in Table I.

Maternal Peripheral Blood Levels of Various Hormones at the 3rd Day of Puerperium

Maternal blood levels were 0.5—1.9 ng/ml for E_1, 0.2—0.9 ng/ml for E_2 0.2—1.2 ng/ml for E_3, 2.8—4.6 ng/ml for P and 90—460 ng/ml for CDS.

As for the concentration of E_1, E_2 and E_3 in maternal blood, E_1 was high compared with E_2 and E_3, as shown in Table I.

Changes in Hormone Levels with Pregnancy, Delivery and Puerperium

1) Changes in maternal blood E_1 levels during delivery and puerperium.

The maternal blood E_1 level increased significantly from 8.2 ± 9.3 ng/ml at 39 weeks' gestation to 10.6 ± 8.1 ng/ml on admission at the onset of labor pains and 23.2 ± 9.1 ng/ml immediately after expulsion of fetus and decreased to 8.4 ± 7.1 ng/ml 2 hr after expulsion, showing a decrease of 38.2 ± 18.3 % compared with the level on expulsion of the fetus. It decreased further to 0.9 ± 0.5 ng/ml at the 3rd day of puerperium (Table I).

2) Changes in maternal blood E_2 levels during delivery and puerperium.

The maternal blood E_2 level did not change significantly with 22.2 ± 12.9 ng/ml on admission at the onset of labor pains and 21.8 ± 6.4 ng/ml immediately after expulsion of fetus from 24.7 ± 14.2 ng/ml at 39 weeks' gestation and decreased to 3.1 ± 1.8 ng/ml 2 hr after expulsion of fetus, showing a decrease of 84.1 % over the level immediately after delivery (Table I).

3) Changes in maternal blood E_3 levels during delivery and puerperium.

The maternal blood E_3 level showed changes similar to those with E_2. There was no significant change in the maternal blood E_3 level with $13.4 \pm$

7.7 ng/ml at 39 weeks' gestation, 11.8±6.0 ng/ml on admission at the onset of labor and 13.2±4.9 ng/ml immediately after expulsion of fetus. Two hr after expulsion, it decreased to 1.1±1.2 ng/ml, showing a decrease of 90.3± 9.9% over the level immediately after expulsion of fetus. The level was lower in the puerperium (Table I).

4) Changes in maternal blood P levels during delivery and puerperium.

The maternal blood P level showed no significant change, with 93.8±27.2 ng/ml at 39 weeks' gestation, 109.2±53.2 ng/ml immediately after expulsion of fetus. It decreased to 34.5±12.0 ng/ml 2 hr after expulsion of fetus (Table I).

5) Changes in maternal blood CDS levels during delivery and puerperium.

The maternal blood CDS level showed no significant changes with 228.0± 178.0 ng/ml at 39 weeks' gestation and 320.0±202.0 ng/ml on admission at the onset of labor pains.

The level increased further to 450.0±213.0 ng/ml immediately after expulsion of fetus ($P<0.02$) (Table I).

The level decreased to 235.2±75.3 ng/ml 2 hr after expulsion and 190.0± 117.4 ng/ml at the 3rd day of puerperium (Table I).

DISCUSSION

According to a report of Uehara (1), the blood level in women in the later stages of pregnancy is 9.9 ng/ml for unconjugated E_1, 43 ng/ml for E_2 and 19.3 ng/ml for E_3, while the essential value is the highest for E_2, followed by E_3 and E_1 is the lowest.

These results were relatively consistent with ours and the same was also true of the concentrations of E_1, E_2 and E_3. With regard to differences in concentrations between unconjugated E_1, E_2 and E_3, Smith and Arai (2) attributed such to the fact that human blood E_2 is present mostly in the unconjugated type and that E_1 and E_3 are mostly of the conjugated type.

According to our results, no particular change in the P level was observed except high levels at 39 weeks' gestation and low levels 2 hr after expulsion of fetus. Blood CDS in pregnant women at 39 weeks' gestation likewise showed high levels.

Such is attributed to increases in the adrenal functions of the mother (3) and also to the cortisol binding globulin (CBG) increased by action of increased levels of estrogen (4, 5).

The "progesterone block theory" of Csap (6), or a decrease in maternal blood P level and a rise in 17-β estradiol and cortisol before delivery in experiments with sheep and the behavior of cortisol in fetuses all suggest the involvement of the adrenal gland of fetuses in the mechanism of the onset of delivery (7).

According to reports dealing with clinical findings and endocrinic behavior, a relationship between the onset of delivery and high E_2 levels is suggested by the high E_2 levels in cases of premature delivery than in normal cases (8),

a relationship between the P/E_2 ratio and the onset of delivery is implied by the fact that there is no difference in the E_2 level between the cases of threatened premature delivery and the control and that there is a difference in the P/E_2 ratio (9), or that delivery is imminent when E_2 reaches a certain fixed level, judging from the fact that the P level stops increasing from three weeks before delivery, while the E_2 level increases further (10).

We found a significant increase in maternal blood E_1 and CDS levels at 39 weeks' gestation and on the onset of labor pains.

Even during delivery, only maternal peripheral blood E_1 and CDS showed a significant rise, and there was no significant change in E_2, E_3 and P.

Donald *et al.* (11) reported that levels during delivery in 6 patients showed no significant changes in estrogen.

Townsley *et al.* (12) also reported that fractions of blood estrogen showed little variation and maintained rather fixed levels. On the other hand, Kuwabara (13) reported an increase in maternal blood DHA-S and in the fractions of estrogen in primiparae.

With regard to the behavior of CDS during the course of delivery, other investigators also found that the CDS level increases with the advance of delivery (14, 15). They maintained that increases in the adrenal function of the mother and fetus are related to the rise in the estrogen and CDS levels during the course of delivery, thus suggesting the biological defense reaction of the mother and fetus during delivery.

After expulsion of the fetus and placenta, levels of various hormones decreased rapidly and there was a difference in the decrease rate.

According to a report of Shoda (16), the free E_1+E_2 level decreased to 33.7 ± 14.4 % one hour after expulsion of the placenta.

Rado *et al.* (17) reported a decrease of E_1 to 68.8 % and E_2 to 45.5 % at one hr after expulsion of the fetus and placenta. Roy and Harkness (18) maintained that E_2 showed the most rapid decrease down to 30—40 % five minutes after, followed by E_1 and E_3 is the latest.

Our results concern values measured 2 hr after expulsion of the fetus and three fractions of estrogen showed a significant decrease rate in the order of $E_3<E_2<E_1$ ($P<0.05$).

E_3 and E_2 showed a significant decrease rate over P and CDS.

From the changes observed in the concentration of hormones after delivery, it was surmised that the fetoplacental system may be mostly concerned with the production of E_3 and E_2 in maternal blood.

Accordingly, measuring maternal blood E_3 and E_2 levels as a method to assess the fetoplacental function is considered to be of clinical value.

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