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## Plasma Levels of Apparent Free Estradiol during Pregnancy

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### S u m m a r y

The plasma concentrations of apparent free estradiol were measured by radioimmunoassay without chromatography in plasma samples of patients at 6–38 weeks of pregnancy. The fraction of the unconjugated estradiol which is unbound to the plasma proteins was estimated by equilibrium dialysis at 37 °C. We found a significant decrease of apparent free estradiol from 2.2% to 1.3% during the first trimester of pregnancy.

Estradiol-17 $\beta$  in human plasma is bound to sex hormone binding globulin (SHBG) and albumin. The biologic effects may be due to the small unbound fraction.

Tulchinsky and Chopra (1973) observed a 20-fold increase of plasma estradiol levels during the first trimester of pregnancy associated with a 6-7-fold increase in the SHBG concentration over the nonpregnant levels.

The purpose of this study was to investigate the plasma concentrations of apparent free estradiol during the pregnancy.

### M a t e r i a l s a n d M e t h o d s

Total estradiol was measured by radioimmunoassay without chromatography as previously described (Freyman et al. 1977). This method is based on an antiserum of rabbits immunized with estradiol-6-(O-carboxymethyl)-BSA. The apparent free fraction of estradiol was estimated by equilibrium dialysis for 24 hr. at 37 °C (Rivarola et al. 1968). Plasma samples were obtained from 48 women at different stages of pregnancy. By comparison estradiol was measured in plasma samples from 5 normally menstruating women and from 2 women with anovulatory cycle.

### R e s u l t s a n d D i s c u s s i o n

The plasma levels of apparent free estradiol during pregnancy and menstrual cycle are presented in Table 1.

The concentrations of total (free and bound) estradiol increase at different stages of pregnancy from 2.0 ng/ml (6–12 weeks) to 16.0 ng/ml (30–38 weeks) and reach the 100-fold levels in comparison with the nonpregnant levels.

The SHBG-concentrations increase in correlation with those results during the pregnancy (Tulchinsky and Chopra 1973). During pregnancy we found a decrease of the percent of apparent free estradiol. This fraction is 2-fold lower than that found in the menstrual cycle.

**Table 1 Unconjugated and apparent free estradiol plasma levels (means  $\pm$  S. D.) during pregnancy and menstrual cycle**

	Number	Unconjugated Estradiol (ng/ml)	Percent of Apparent Free Estradiol	Concentrations of Apparent Free Estradiol (pg/ml)
Menstrual Cycle	35	0.160 $\pm$ 0.100	2.2 $\pm$ 0.4	3.5 $\pm$ 2.0
Anovulatory Cycle	14	0.050 $\pm$ 0.020	2.3 $\pm$ 0.3	1.0 $\pm$ 0.5
<b>Pregnancy:</b>				
6—12 weeks	9	2.0 $\pm$ 1.1	1.6 $\pm$ 0.4	32 $\pm$ 21
12—20 weeks	10	5.5 $\pm$ 2.2	1.3 $\pm$ 0.3	72 $\pm$ 39
20—30 weeks	12	10.8 $\pm$ 4.6	1.2 $\pm$ 0.3	130 $\pm$ 74
30—38 weeks	17	16.0 $\pm$ 7.0	1.2 $\pm$ 0.2	184 $\pm$ 103

The main decrease of the percent of apparent free estradiol is at the first trimester of pregnancy from 2.2% to 1.6%. These findings are in agreement with the results of Tulchinsky (1973). This author worked with a similar method of equilibrium dialysis and observed a decrease of the percent of free estradiol from 2.0% at nonpregnant women to 1.2% in the 10—14 weeks of pregnancy.

We found a little decrease of the percent of apparent free estradiol from 12 to 20 weeks of pregnancy from 1.6 to 1.2% and approximately constant values from 20 to 38 weeks of pregnancy. The concentrations of the apparent free estradiol in maternal peripheral plasma during the third trimester of pregnancy are 40—50 fold higher than those found during the menstrual cycle. Tulchinsky and Chopra (1973) observed, that at 8 weeks of pregnancy both SHBG and the total estradiol levels were 4-fold higher than nonpregnant levels, by 12 weeks of pregnancy the estradiol concentrations rose by another 4-fold increase, whereas the SHBG only increased by less than 2-fold.

Finally, the authors found another 6-fold increase of total estradiol from the second trimester of pregnancy to term, which was not associated with any further increase in plasma SHBG.

It is known that the SHBG concentrations in plasma are significantly affected by biologically active estradiol (Tulchinsky and Chopra 1973). On the other hand, it is possible that the increase of progesterone during pregnancy may antagonize the stimulatory effect of estradiol on SHBG (Forest 1968).

We found approximate results of excessively high estradiol levels after application of FSH and HCG in a nonpregnant women. 8 days after treatment the percent of apparent free estradiol decreased to 1.2% as in pregnancy.

#### References

1. Tulchinsky, D., I. J. Chopra: Competitive ligand-binding assay for measurement of sex-hormone-binding-globulin (SHBG). *J. clin. Endocrinol. & Metabol.* **37**, 873—891 (1973).
2. Freymann, E., W. Hubl, M. Büchner, H. Belleé: Eine spezifische, radioimmunologische Bestimmung des Plasma Östradiols ohne Chromatographie im Zyklus und in der Schwangerschaft und die Bestimmung des freien, nichtproteingebundenen Anteils mittels Dialyse. *Zbl. Gynäkol.* **99**, 321—329 (1977).

3. **Rivarola, M. A., M. G. Forest, C. J. Migeon**: Testosterone, androstenedione and dehydroepiandrosterone in plasma during pregnancy and at delivery: Concentrations and protein binding. *J. clin. Endocrinol. & Metabol.* **28**, 34—40 (1968).
4. **Tulchinsky, D.**: Placental secretion of unconjugated estrone, estradiol and estriol into the maternal and the fetal circulation. *J. clin. Endocrinol. & Metabol.* **36**, 1079—1087 (1973).
5. **Forest, M. G., M. A. Rivarola, C. J. Migeon**: Percentage binding of testosterone, androstendione and dehydroisoandrosterone in human plasma. *Steroids* **12**, 323—343 (1968).

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