Journal of Steroid Biochemistry. 1971, Vol. 2, pp. 371–376. Pergamon Press. Printed in Great Britain

PLASMA OESTRONE IN NORMAL HUMAN PREGNANCY

WIGGO FISCHER-RASMUSSEN*
University Department of Obstetrics and Gynaecology, Rigshospitalet, Copenhagen, Denmark.
(Department Heads: Dyre Trolle and Børge Sørensen)

(*Received* 3 *December* 1970)

SUMMARY

The oestrone concentration in plasma from the 23rd to the 41st week of pregnancy was measured in a series of normal pregnant women by a gas–liquid chromatography method, in order to determine normal ranges in preparation for clinical studies. The results show a large spread around the mean value for each week of pregnancy, which depends more on variation between individuals than within individuals. Plasma oestrone concentrations and urinary oestrone excretion were firmly correlated.

In the whole material there was no significant increase in plasma oestrone values from the 24th to the 41st week of pregnancy, but if the 3 women with the highest plasma oestrone values are excluded from the material, a slight but significant increase is observable in plasma oestrone towards the end of pregnancy.

INTRODUCTION

RESULTS from an earlier measurement of plasma oestriol by gas chromatography in a series of normal pregnant women have been previously recorded [1]. Further development of the oestriol determination method has allowed measurement of oestrone and oestradiol-17β together with oestriol from the same 5 ml plasma sample [2]. This paper gives the results of the oestrone study in the same series of women in which oestriol was measured. The results of plasma oestradiol-17β are the subject of a later paper [3].

The motivation of all three studies was to determine normal ranges for plasma oestrogens, as a basis for subsequent studies of pathological states in pregnancy.

EXPERIMENTAL

Material

The original oestriol investigation was of 21 women. As the result of a laboratory error the oestrone analyses of one woman were lost; therefore, the current study comprises only 20 women. The age range (17–40 yr) and average (26 yr) were not affected.

As earlier recorded all the women had normal vaginal deliveries of normal babies. Average birth weight was 3270 g (2700–4100 g). There were 10 girls and 10 boys. Ten women were primiparae, and 10 were secundiparae. Pregnancies were uncomplicated. All the women came regularly to the prenatal clinic, and gave birth in the hospital. All deliveries occurred between the 38th and 42nd week of pregnancy.

*Address of the author: Fagerbo 19, 2950 Vedbæk, Denmark.

Methods

Beginning between the 22nd and 28th week of pregnancy, venous blood samples were taken at one to two week intervals till term. The women provided urine specimens from the 24 h immediately preceding clinic attendance. Oestrone and oestradiol-17β content in the urine was measured in the Hormone Department, Statens Seruminstitut, Copenhagen, by Svenstrup's method[4].

Plasma oestrone was measured in duplicate by the method described by the author[2]. The oestrone and oestradiol-17β plasma fraction was stored at -21°C until analysis was undertaken.

RESULTS

Table 1 gives the mean value of plasma oestrone concentration and urine excretion for the relevant weeks of pregnancy. Spread about the mean of the plasma measurements was large. On average the standard deviations were approx. 80% of the mean values.

Figure 1 is a semi-logarithmic scatter graph of the individual oestrone determinations in the 20 women. Linear regression analysis of the logarithmic values for the weeks of pregnancy was made. The mean value line is appended together with the 95% limits for all values (solid lines). In the whole material of 20 women there was no significant increase in the mean plasma oestrone values during the period of investigation: 24th–41st week of pregnancy ($0{\cdot}10 > P > 0{\cdot}05$).

However, in 3 women the regression lines of plasma oestrone were at or over the 95% upper limit, as calculated from the values in the other 17 women. These 3 women were not represented in the last weeks of the investigation, but did not

Table 1. Mean value ± standard deviation for plasma concentration and urine excretion of oestrone in individual weeks of pregnancy. 20 normal women

Week of pregnancy	Plasma (μg/l) Mean ± SD	Number	Urine (mg/24 h) Mean ± SD	Number
23	67	3	0·69	3
24	86	5	1·00	5
25	98 ± 81	6	0·83 ± 0·25	7
26	103 ± 79	10	1·07 ± 0·51	9
27	78 ± 74	14	1·08 ± 0·55	11
28	92 ± 84	15	1·07 ± 0·56	16
29	66 ± 56	17	1·07 ± 0·76	16
30	92 ± 74	16	1·09 ± 0·51	14
31	89 ± 87	15	1·18 ± 0·66	16
32	89 ± 72	15	1·19 ± 0·59	15
33	83 ± 53	14	0·89 ± 0·33	15
34	106 ± 83	15	1·26 ± 0·69	15
35	109 ± 95	16	1·34 ± 0·76	13
36	106 ± 73	16	1·30 ± 0·63	16
37	104 ± 96	15	1·34 ± 0·68	19
38	132 ± 91	14	1·35 ± 0·75	15
39	80 ± 55	15	1·20 ± 0·42	14
40	65 ± 46	10	1·21 ± 0·64	9
41	86	5	1·05	5
		236		233

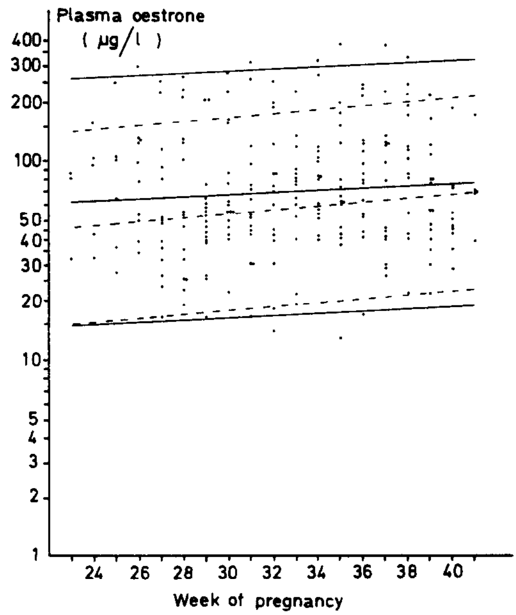

Fig. 1. Plasma oestrone concentration in different weeks of pregnancy. Regression line and zone of $\pm s_{y \cdot x} \cdot t_{0 \cdot 05}$ (solid lines.) Data from 20 normal pregnant women. Logarithmic ordinate. Regression equation for mean values: Log $Y = 1{\cdot}6628 + 0{\cdot}0057 \cdot X$ ($0.10 > P > 0{\cdot}05$).

The dashed lines represent the regression line and zone of $\pm s_{y \cdot x} \cdot t_{0 \cdot 05}$ after excluding 3 women with particularly high plasma oestrone levels from the material. The regression equation for mean values is then: Log $Y = 1{\cdot}4253 + 0{\cdot}0103 \cdot X$ ($0{\cdot}010 > P > 0{\cdot}005$). See text.

apparently differ from the other members. If a regression analysis is made for the 17 women only, a significant increase in mean plasma oestrone values during the period of investigation is seen ($0{\cdot}010 > P > 0{\cdot}005$). In Fig. 1 the mean value line, together with the 95% limits (dashed lines) for the 17 women is shown.

As earlier mentioned there is a large spread about the means in Table 1. In study of this spread, the variation in individuals was compared with the variation between individuals.

The variation in the individuals was calculated by application of the following formula:

$$s^2 = \frac{\Sigma_{\text{women}}(\Sigma(y_i - Y_i)^2)^*}{\Sigma_{\text{women}}(N-2)},$$

giving $s = \pm 29 \mu g/l$.

An expression of the variation between the individuals is given by the standard deviations of the ordinates of the regression lines of each individual in a certain week (the abscissa). As examples, these standard deviations were calculated in weeks 28, 32, and 36. The respective standard deviations were ± 63, ± 66 and ± 73 $\mu g/l$. The corresponding means were 75, 84, and 94 $\mu g/l$.

* i = week in which a measurement was performed.
y_i = measured plasma oestrone in an individual in week i.
Y_i = ordinate of the regression line of this individual at the week i.
N = number of measurements in an individual.

This emphasizes that the spread depends more on variation between than within individuals.

Figure 2 gives the correlation between plasma and urinary oestrone. The correlation is firm. The 3 women with high plasma oestrone levels also had high urinary excretion of oestrone.

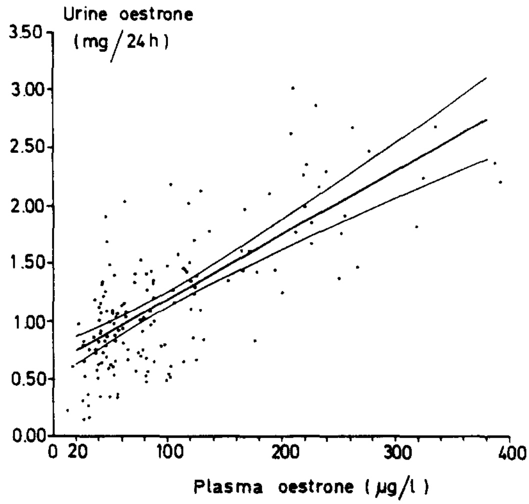

Fig. 2. Correlation between oestrone in plasma and urine. $N = 211$. The regression line and the 95% confidence intervals are appended ($Y = 0{\cdot}6265 + 0{\cdot}0056 \cdot X$, $P < 0{\cdot}0001$).

DISCUSSION

The findings are in accordance with those of other authors that there is a considerable variation in plasma oestrone concentrations in human pregnancy [5–7]. Some authors [5, 8] report an increase as pregnancy proceeds, but one [9] found that a plateau was reached in the last weeks.

Plasma determination has an advantage over urine determination in that a blood sample is more easily obtained. The collection of a 24 h urine specimen is laborious and it cannot always be relied on, especially when dealing with out-patients. Diurnal variation might invalidate plasma determination, but Roy and Mackay [5] found no significant diurnal variation in plasma oestriol, oestrone, and oestradiol-17β. Two other reports [10. 11] found no significant variation in plasma oestriol values in blood samples taken in the morning and evening. In the latter [11] a significantly lower level was found at 4:30 p.m. In the present study diurnal variation has not influenced the spread as all samples were taken between 8 and 9 a.m.

It must be emphasized that although the concentration of plasma oestrone during late pregnancy is in the same range as oestriol, the urinary excretion of oestrone is very low compared with oestriol. It is not clearly understood why the renal clearance of these two oestrogens is so different. It may be related to differences in the conjugation of the two steroids, and to the fact that oestrone and oestriol are produced by different metabolic pathways [12].

In Fig. 1 a regression analysis is shown, excluding the 3 women with particularly high plasma oestrone levels. In other respects they did not seem to differ from the other members: one, in her fifth pregnancy, gave birth to her second child—a 2700 g girl; the second, in her first pregnancy, gave birth to a 3100 g girl, and the third, in her fourth pregnancy, gave birth to her second child—a 2950 g girl. Investigation did not show significant correlation between high plasma oestrone and girl children or number of pregnancies, even though in this study girls were more frequently born of mothers with high plasma oestrone.

The large variation in plasma oestrone makes comparison of results, achieved by different methods, difficult. Table 2, nevertheless, makes such a comparison.

Table 2. Late pregnancy values of oestrone concentration in plasma or blood found by different investigators. Mean value and range (μg/l)

Investigators	Period of pregnancy	Number	Mean	Range	Biological fluid
Roy and Mackay [5]	38th–40th week	29	47 (78)	11–83·5 (18–139)	Blood Plasma*
Smith and Arai [6]	37th–43rd week	4	113	43–250	Plasma
Schwers [13]	Term	12	20·3	6·5–42·1	Plasma
Rado *et al.* [7]	Labor	4(5)	48	16–105 (347)†	Plasma
Ittrich *et al.* [8]	9th month	5	40 (67)	28–50 (47–83)	Blood Plasma*
Adlercreutz [14]	Late pregnancy	10	31·3 (52·2)	9·5–66.2‡ (15·8–110·3‡)	Blood Plasma*
Touchstone and Murawec [17]	3rd trimester	Pool	59·6		Plasma
Present investigation	39th–40th week	25	74	22–220	Plasma

*Based on a haematocrit value of 40%.
†Twin pregnancy.
‡Conjugated oestrone.

In five reports [5–7, 13, 14] the same basic method [15] was used, or a modification with colorimetric measurements. One study [8] involved fluorometry [16], and in two studies [17, present investigation] gas–liquid chromatography was used. One report [14] concerns only conjugated oestrone, while the others measure "total" oestrone after hydrolysis of plasma or blood. Where blood was used, the table results are expressed as for plasma after correction based on a haematocrit value of 40% [18]. Only late pregnancy studies are included.

Comparison of the findings in this study with those of the largest of the others [5] shows that mean values and lower limits were roughly similar. In the study of conjugated oestrone [14] the mean value was 52 μg/l. On the assumption that approx. 75% of plasma oestrone is conjugated [17, 19], correction for "total" oestrone gives a value of approx. 70 μg/l. in late pregnancy which agrees well with the findings both of Roy and Mackay and of this author.

Large individual variation and the relatively small numbers studied are probably responsible for most differences evident in the table. Any differences dependent on different extraction techniques and recovery rates are obscured by these other considerations.

ACKNOWLEDGEMENTS

I should like to thank B. Svenstrup, M.Sc., Hormonafdelingen, Statens Seruminstitut, Copenhagen, who performed the urinalyses, and F. Rønnike, M.D., Ph.D., University Department of Obstetrics and Gynaecology, Rigshospitalet, Copenhagen, who advised on the statistical presentation.

This study was supported by a grant from "Konsul Ehrenfried Owesén og hustrus fond".

REFERENCES

1. W. Fischer-Rasmussen: *J. steroid Biochem.* **1** (1970) 121.
2. W. Fischer-Rasmussen: *J. steroid Biochem.* **2** (1971) 251.
3. W. Fischer-Rasmussen: *J. steroid Biochem.* **2** (1971) 377.
4. B. Svenstrup: (To be published).
5. E. J. Roy and R. Mackay: *J. Obstet. Gynaec. Br. Commonw.* **69** (1962) 13.
6. O. W. Smith and K. Arai: *J. clin. Endocr.* **23** (1963) 1141.
7. A. Rado, C. D. Crystle and J. D. Townsley: *J. clin. Endocr.* **30** (1970) 497.
8. G. Ittrich. A. Jakobovitz and H. Igel: *Zbl. Gynäk.* **82** (1960) 1772.
9. O. W. Smith: *Acta endocr., kbh. Suppl.* **104** (1966).
10. D. J. MacRae and S. M. Mohamedally: *J. Obstet. Gynaec. Br. Commonw.* **77** (1970) 1088.
11. M. Selinger and M. Levitz: *J. clin. Endocr.* **29** (1969) 995.
12. P. K. Siiteri and P. C. MacDonald: *J. clin. Endocr.* **26** (1966) 751.
13. J. Schwers: *Les Oestrogènes au Cours de la Seconde Moitié de la Grossèsse.* Arscia, Bruxelles (1965).
14. H. Adlercreutz: *Acta med. scand. Suppl.* **412** (1964) 133.
15. E. J. Roy and J. B. Brown: *J. endocr.* **21** (1960) 9.
16. G. Ittrich: *Hoppe-Seyler's Z. physiol. Chem.* **320** (1960) 103.
17. J. C. Touchstone and T. Murawec: *Biochemistry* **4** (1965) 1612.
18. H. Adlercreutz and G. Tallqvist: *Scand. J. clin. lab. Invest.* **11** (1959) 1.
19. O. W. Smith and D. D. Hagerman: *J. clin. Endocr.* **25** (1965) 732.