Comparative Measurements of Serum Estriol, Estradiol, and Estrone in Non-pregnant, Premenopausal Women: A Preliminary Investigation

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Abstract

Little to no data exists in the literature for serum estriol values in non-pregnant, premenopausal women. The current medical community opinion holds that estriol has no significant role in non-pregnant women relative to the other estrogens. It is a possibility that estriol's primary function has yet to be discovered. Accordingly, the first step is to understand cycle-dependent serum estriol concentrations. We have made a preliminary investigation of serum estriol concentration in 26 women during the known cycle peaks of estrone and estradiol. Five of the women were also tested for serum estriol on various days throughout the cycle in order to develop a cycle-dependent concentration profile. The result of these experiments show that serum estriol was always significantly higher than the sum of estrone and estradiol and less fluctuating. We conclude that estriol is probably a significant estrogen component.

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Introduction

While reference values are readily available for serum estrone and estradiol, serum estriol levels are listed in reference books for only pregnant women. Figure 1 demonstrates the biosynthesis of estrogens. The conventional medical practice has been to virtually ignore estriol as being an insignificant hormone. Prior to the 1970s, the technology was not sophisticated enough to accurately analyze estriol in non-pregnant patients. By the time estriol could be analyzed accurately, researchers had already conclusively demonstrated that estriol was a much weaker hormone than estradiol and estrone; therefore, it was believed to be of no known consequence.

Because the quantitative research on estriol to date had been focused on concentrations in pregnant women, we concluded that to determine normal serum estriol levels in healthy non-pregnant, premenopausal women, a reliable test needed to be developed.

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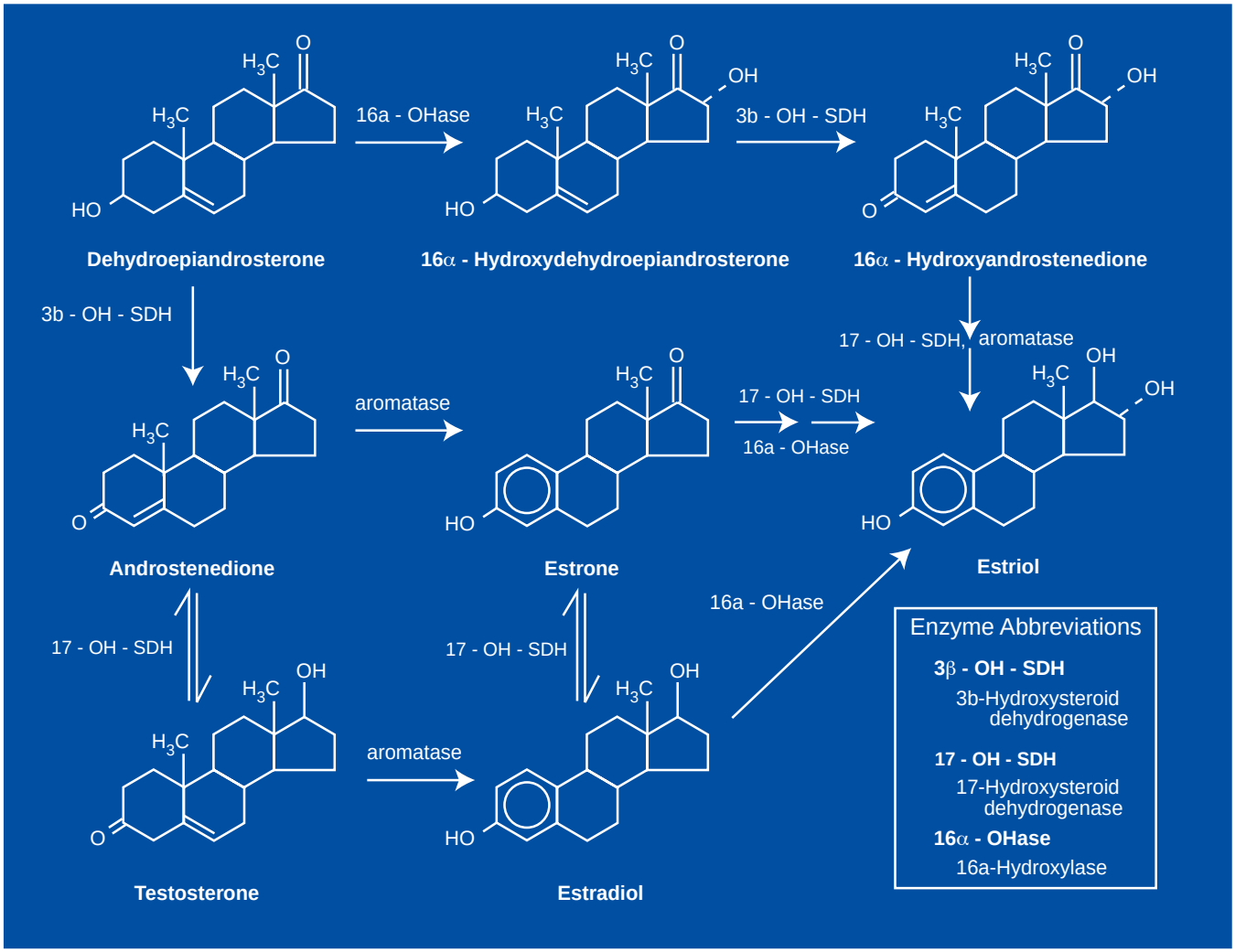
Figure 1. Biosynthesis of Estrogens



Method

A solid-phase competitive-binding radio-immunoassay (RIA) procedure for estriol was developed. A commercially prepared kit produced by Diagnostic Products Corporation of Los Angeles, California was modified to accurately detect estriol in the lower range necessary for the analysis of non-pregnant patient samples. Estriol purchased from Sigma Chemical Corporation in St. Louis, Missouri was utilized to prepare the spiked samples used for method validation. The calibrators from the kit were diluted appropriately for the purpose of quality control. A six-point calibration curve from 0 to 2000 pg/mL estriol was used to calculate quantitative values for the samples. Patient values initially over 2000 pg/mL for estriol were diluted 1:2 and retested. Serum estrone and estradiol concentrations were determined using commercially available kits manufactured by DSL (Diagnostic Systems Laboratory, Webster, TX).

Participant selection criteria for the study was as follows: female, premenopausal, between the ages of 18 and 40, not on birth control or any other steroid hormone medication, and healthy. Samples were drawn between the 10th and 14th day of the menstrual cycle. The timing of the cycle was chosen because estradiol and estrone are known to peak between the 10th and 14th day of the cycle and

Table 1. Serum Estrogen Levels and Estrogen Quotients.

Subject number	Day of cycle	Estriol pg/mL	Estradiol pg/mL	Estrone pg/mL	Estrogen quotient (Estriol)/[(Estradiol)+(Estrone)]
1	10	233	52.5	21.2	3.2
2	10	186	43.4	14.4	3.2
3	10	1254	188.8	55.0	5.1
4	10	329	40.4	23.4	5.2
5	10	369	43.9	20.4	5.7
6	10	700	30.9	68.0	7.1
7	10	374	35.9	15.1	7.3
8	10	429	25.3	33.1	7.3
9	10	941	86.7	32.5	7.9
10	10	736	21.5	70.6	8.0
11	10	1616	61.2	127.4	8.6
12	10	726	61.7	52.5	6.4
13	10	826	22.6	39.1	13.4
14	10	1614	57.9	144.4	8.0
15	10	771	11.3	35.4	16.5
16	10	1700	30.7	58.6	19.0
17	11	595	15.1	35.9	11.7
18	11	2408	156.8	121.9	8.6
19	12	961	32.8	71.6	9.2
20	12	1161	71.2	27.3	11.8
21	12	1271	22.2	72.0	13.5
22	14	685	24.6	43.4	10.1
23	14	988	31.1	65.8	10.2
24	14	212	23.7	12.5	5.9
25	14	1412	183.4	54.7	5.9
26	14	1146	17.4	68.6	13.3
				Average	8.9
				Standard deviance	3.9

the date for the estriol peak is yet unknown. The serum of the 26 participants that met the study criteria was analyzed to determine the concentration of estriol, estrone, and estradiol.

The Estrogen Quotient (EQ), a calculated value illustrating the proportionately large quantity of estriol compared to the sum of estrone and estradiol, was determined by taking the ratio of the total estriol concentration to the sum of the total estrone and estradiol concentrations using RIA.

Five women had samples drawn on different days of the cycle to explore the values of estriol and the EQ throughout several times in the cycle. Because it was unknown when the estriol peak occurred during the cycle, each woman was tested at different times of the cycle.

Results

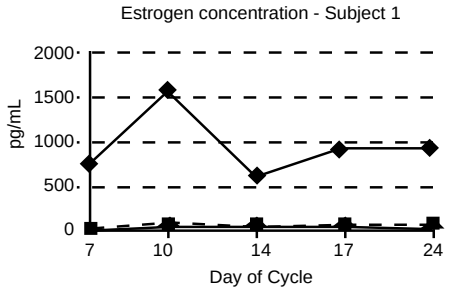
The results of the 26 serum estrogen concentrations in pg/mL are outlined in Table 1. A wide variation in estriol concentrations was observed in our study population. A low estriol value of 186 pg/mL and a high value of 2408 pg/mL were measured in this study. The average serum estriol of the 26 women was 909 ± 554 pg/mL. The estrogen quotient also displayed a relatively large degree of variation with a low of 3.2 and a high of 19.0. The average EQ was 8.9 with a standard deviation of 3.9.

Table 2. Serum Estrogen Concentrations on Various Days of the Cycle.

Subject 1

Day of Cycle	Estriol pg/mL	Estradiol pg/mL	Estrone pg/mL	Eq E3/(E2+E1)
7	700	68	31	7.1
10	1616	127	61	8.6
14	685	43	25	10.1
17	944	52	31	11.4
24	897	40	22	14.5

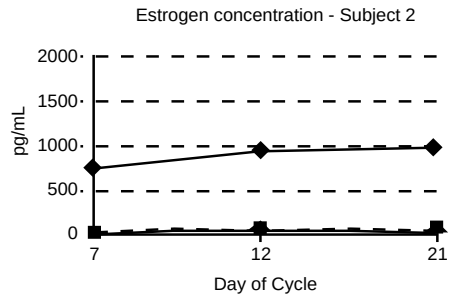
Eq Average 10.3



Subject 2

Day of Cycle	Estriol pg/mL	Estradiol pg/mL	Estrone pg/mL	Eq E3/(E2+E1)
7	689	36	17	13.0
12	961	72	33	9.2
21	1018	51	18	14.8

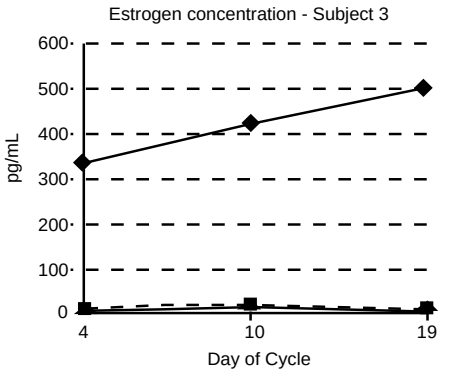
Eq Average 12.3



Subject 3

Day of Cycle	Estriol pg/mL	Estradiol pg/mL	Estrone pg/mL	Eq E3/(E2+E1)
4	343	24	17	8.4
10	429	33	25	7.4
19	512	12	17	17.7

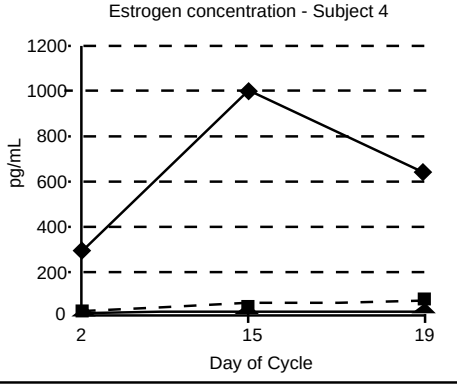
Eq Average 11.1



Subject 4

Day of Cycle	Estriol pg/mL	Estradiol pg/mL	Estrone pg/mL	Eq E3/(E2+E1)
2	303	7	1	37.9
15	988	66	31	10.2
19	653	86	23	6.0

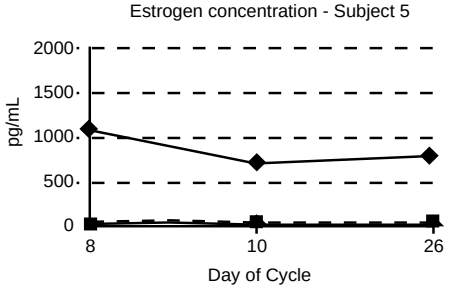
Eq Average 18.0



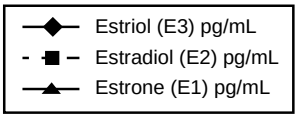
Subject 5

Day of Cycle	Estriol pg/mL	Estradiol pg/mL	Estrone pg/mL	Eq E3/(E2+E1)
8	1104	68	11	14.0
10	736	71	22	7.9
26	786	17	10	29.1

Eq Average 17.0



Legend



The second data set presents the estrogen levels of five women on different days of their menstrual cycles (Table 2). Because this was a preliminary study and the date of the estriol peak was unknown, the five subjects were tested at different times of the cycle. Subject 1 had blood drawn on the 7th, 10th, 14th, 17th and 24th days of the cycle. The estrogen quotient was lowest (EQ 7.1) on day 7 and increased to a high of 14.5 on day 24. Subject 2 was tested on the 7th, 12th and 21st days of the cycle. The estriol concentration followed a slight upward slope, but due to a peak in the estrone and estradiol concentrations, the EQ reached a minimum of 9.2 on the 12th day of the cycle. Subject 3 also exhibited an increase in estriol level as the cycle progressed; however, the EQ was nearly the same on the 4th and 10th day (8.4 and 7.4 respectively), but due to a drop in estradiol and estrone on the 19th day, the EQ rose sharply to 17.7. Subject 4 had the earliest data point — the 2nd day of the cycle. The estrone and estradiol were both very low which was to be expected (1 pg/mL and 7 pg/mL respectively), but interestingly the estriol remained fairly high at 303 pg/mL, yielding a very high EQ of 37.9. Subject 5 had samples drawn on the 8th, 10th and 26th day of the cycle. The EQ regressed from 14.0 on day 8 down to 7.9 on day 10 and soared to 29.1 on day 26 (the latest day of the cycle in our study).

Conclusion

The fractionated estrogen concentration data from the population of 26 women shows that the estriol in every case was at least three times as great as the concentration of estradiol and estrone combined. In fact, the average EQ for the population was 8.9. With estriol circulating at nearly 10 times the concentration of estrone and estradiol, it appears at least a possibility that there must be unknown significant biological activity for this "weaker" hormone. (One might draw a parallel with the history of DHEA research).

The conclusion that may be obtained from the five-women research project investigating fractionated estrogen concentrations at different times of the menstrual cycle is that estriol is in higher concentration than both estrone and estradiol every day of the cycle that this study tested. It was observed that very early in the cycle (day 2) and very late in the cycle (day 26) the two subjects had very high Estrogen Quotients. As we know, estrone and estradiol are very low both late and early in the cycle, but it is very interesting to see that estriol does not seem to display the same proportionate drop in concentration.

The findings of this study necessitate additional research including more patients, more data points over the span of the cycle, and urine fractionated estrogen studies.

For more information on therapeutic applications of estriol see: Estriol: Safety and Efficacy. *Altern Med Rev* 1998;3(2):101-113.