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The Effect of Estrogen and Progesterone Levels on Uterine Contractions in Term and Postterm Pregnancy

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Abstract

Aim and Background: In our study, it is aimed to determine the estrogen and progesterone levels in term and postterm pregnancies, to investigate the effects of these levels on labor and to contribute to the understanding of the mechanism that causes postterm labor, to predict this situation or to pioneer the development of possible strategies to prevent its negative effects.

Material and Methods: Our study consist of pregnant women that they were between 37-41 weeks of age, which correlated with the last menstrual period and the ultrasonography results performed in the first trimester of 100 people who applied to Health Sciences University Istanbul Training and Research Hospital, and the fetal development was found to be compatible with the calculated gestational age in the third trimester examinations. It consists of two main groups, namely the term pregnant (TG) group of 50 people, and the postterm pregnant (PTG) group of 50 people, who were confirmed to have passed the 41st gestational week with the same method. Both groups were divided into two subgroups of 25 each, each with and without pain; A total of 4 study groups were formed as painful TG, painless TG, painful PTG, and painless PTG. The serum progesterone and estrogen levels of the patients were measured and compared statistically before labor.

Results: The comparisons made in our study shows that there are no statistically significant differences observed between the term and postterm pregnant groups, except for the gestational week. The comparisons of pregnant women with pain; Similarly, in the comparison of term and postterm groups in terms of estrogen and progesterone values, it is seen that there is no statistically significant difference in parameters other than gestational week.

Conclusion: As a result of our study, no statistically significant difference was found in terms of estrogen and progesterone levels between term and postterm pregnant women and between those

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with and without pain. Based on this, we can conclude that estrogen and progesterone levels cannot be used as an indicator of the onset of labor between term and postterm pregnancies.

Keywords: Term pregnancy, Postterm pregnancy, Estrogen, Progesterone

1. Introduction and Purpose

Based on this particular literature, we can list the main properties of estrogen on myometrium as follows: hypertrophy and hyperplasia of myometrial cells, increase in contractile protein levels, increase in usable biologic energy, increase in membrane potential increase; increase in spontaneous activity, increase in myometrial sensitivity (1).

Estrogen plays a critical role from the beginning of pregnancy. It evolves endometrial tissue in benefit of implantation of embryo. In the process of gestation estrogen plays a role in myometrium proliferation and contractions during labor. Csapo and Schofield had already proved the importance of the role of estrogen in the 1950s. *Diethylstilbestrol*(DES) had been an estrogen agonist used in order to prevent spontaneous abortus until the late 1940. The search for the effects of DES has been a very important step in the effects of estrogen in pregnant myometrium but DES has been removed due to increased risk of clear cell carcinoma in vagen and cervix. (1)

Indicating absolute effects of progesterone on myometrium is not as easy as indicating estrogens. Base effect of progesterone is maintaining pregnancy and keeping it. In this context, its base effect is from two fundamental capacities: Preparing endometrium for implantation and continuation of progression of desidua; suppressing Myometrial activity and sensitivity (1).

The effects of estrogen and its counterpart, progesterone, have long been demonstrated, especially when it comes to the pregnant myometrium (2). A functional withdrawal of progesterone appears to be the signal that puts the myometrium in a reproductive state. Through its receptors in the endometrium, it provides decidualization, implantation and uterine receptivity in the pregnant uterus with the effect of estrogen. Estrogens are known to be effective both in the segmental expansion of the myometrium and in the formation of the contractile response before and during delivery (3).

In our study, it is aimed to determine the estrogen and progesterone levels in term and postterm pregnancies, to investigate the effects of these levels on labor and to contribute to the understanding of the mechanism that causes postterm labor, to predict this situation or to pioneer the development of possible strategies to prevent its negative effects.

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2. Materials and Methods

Establishment of Working Groups

We evaluated 100 patients who admitted to Istanbul Education and Research Hospital, Obstetrics and Gynecology, who has correlation between last menstrual cycle and first trimester fetal ultrasonography.

Our study confirmed that they were between 37-41 weeks of age, which correlated with the last menstrual period and the ultrasonography results performed in the first trimester of 100 people who applied to Health Sciences University Istanbul Training and Research Hospital, and the fetal development was found to be compatible with the calculated gestational age in the third trimester examinations. It consists of two main groups, namely the term pregnant (TG) group of 50 people, and the postterm pregnant (PTG) group of 50 people, who were confirmed to have passed the 41st gestational week with the same method. Both groups were divided into two subgroups of 25 each, each with and without pain; A total of 4 study groups were formed as painful TG, painless TG, painful PTG, and painless PTG.

This study was carried out in accordance with the decision of the ethics committee number 2949 to Istanbul Education and Research Hospital.

In this study serum estrogen and progesterone levels were measured from pregnant patients from all 4 groups who started labor and came to outpatient clinic routine control before delivery. Serum E2, PR levels of pregnant women who participated in the study were checked. After 10-12 hours of fasting, the serum sample taken into the S-Monovette (without anticoagulant) tube was centrifuged at 4000 rpm for 10 minutes. After centrifugation, serum samples were studied in the ROCHE COBAS 411 device with E2, PR electrochemiluminescence immunologic (ECLIA) method. Inappropriate or suspicious results were studied by resampling.

Exclusion Criteria

Pregnant women who were not sure of their last menstrual period, who did not undergo ultrasonography in the first trimester, who did not approve to be included in the study, who had a history of preeclampsia, gestational diabetes, cholestasis, who had multiple pregnancies, who had fetal oligo/polyhydramnios, and who had additional obstetric pathology were not included in the study.

3. Statistical Analysis

Statistical analyzes were performed with the help of SPSS version 23 program. Conformity of variables to normal distribution histogram graphs and Kolmogorov-Examined with the Smirnov/Shapiro-Wilk test. Mean, standard deviation, median, minimum and maximum values were used while descriptive analyzes were presented. The Mann Whitney-U Test was used when evaluating the nonparametric variables between the two groups. While presenting the categorical variables, the frequency and percentage values of the variables were used. Cases with a P-value below 0.05 were considered as statistically significant results.

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4. Results

Table 1. Descriptive Statistics by Term and Postterm Groups

	Group									
	Term					Postterm				
	Mean	S.D	Median	Min.	Max.	Mean	S.D.	Median	Min.	Max.
Age	27,54	±6,18	27,00	16,00	41,00	27,26	±5,49	27,00	16,00	37,00
BMI	30,34	±8,69	28,00	21,00	71,00	28,93	±3,97	28,50	22,00	42,00
Week	38,58	±,97	39,00	37,00	40,00	41,13	±,34	41,00	41,00	42,00
Progesterone usage?	175,36	±77,86	169,00	30,00	366,00	178,78	±87,87	200,50	11,00	359,00
Estrogen	20524,34	±7994,18	20309,50	1722,00	37038,00	29511,61	±39649,80	23389,00	64,00	274459,00
Period After Pregnancy	2,42	±2,38	2,00	,00	9,00	2,24	±3,00	2,00	,00	13,00
Chronic Disease	,00	±,00	,00	,00	,00	,00	±,00	,00	,00	,00
Gravida	2,88	±2,45	2,00	1,00	14,00	2,37	±1,51	2,00	1,00	6,00
Parity	1,48	±2,11	1,00	,00	11,00	1,15	±1,37	1,00	,00	5,00
Contraction, n (%)										
(-)	25 (50,00)					22 (47,83)				
(+)	25 (50,00)					24 (52,17)				

Descriptive Statistics

As seen above, the descriptive statistics of the demographic data of the study participants are given in Table 1.

Table 2. Comparison of Demographic and Progesterone Values of Pregnants Between 37-41 Weeks in terms of Painful and Painless Groups

TERM	Contraction										p
	-					+					
	Mean	s.d.	Median	Min.	Max.	Mean	s.d.	Median	Min.	Max.	
Age	28,88	±6,44	28,00	16,00	41,00	26,20	±5,72	25,00	20,00	41,00	0,094
BMI	31,88	±10,94	28,00	21,00	71,00	28,80	±5,44	28,00	21,00	42,00	0,502
Week	38,48	±1,05	38,00	37,00	40,00	38,68	±,90	39,00	37,00	40,00	0,389
Progesterone	189,56	±67,74	182,00	86,00	366,00	161,16	±85,84	161,00	30,00	326,00	0,237
Estrogen	22222,08	±5643,43	21372,00	11916,00	36569,00	18826,60	±9624,10	18352,00	1722,00	37038,00	0,154
Elapsed Time	2,43	±2,59	2,00	,00	9,00	2,40	±2,19	2,00	,00	7,00	0,803
Gravida	2,92	±2,71	2,00	1,00	14,00	2,83	±2,22	2,00	1,00	9,00	0,975
Parity	1,48	±2,37	1,00	,00	11,00	1,48	±1,87	1,00	,00	8,00	0,634

Mann Whitney U Test

Table 3. Comparison of Demographic and Progesterone Values of Pregnant Over 41 Weeks with and without Pain Groups

POSTTERM	Contraction										p
	-					+					
	Mean	s.d.	Median	Min.	Max.	Mean	s.d.	Median	Min.	Max.	
Age	27,82	±5,46	27,00	18,00	37,00	26,75	±5,59	27,00	16,00	37,00	0,643
BMI	29,05	±4,40	28,00	24,00	42,00	28,83	±3,62	29,00	22,00	38,00	0,477
Week	41,18	±,39	41,00	41,00	42,00	41,08	±,28	41,00	41,00	42,00	0,327
Progesterone	185,59	±87,16	195,50	16,00	359,00	172,54	±89,92	200,50	11,00	336,00	0,792
Estrogen	35643,36	±55030,57	23595,00	230,00	274459,00	23890,83	±15553,25	22864,00	64,00	58172,00	0,652
Elapsed time	1,95	±2,75	,50	,00	8,00	2,50	±3,24	2,00	,00	13,00	0,413
Gravida	2,36	±1,65	1,50	1,00	6,00	2,38	±1,41	2,00	1,00	5,00	0,712
Parity	1,00	±1,48	,00	,00	5,00	1,29	±1,27	1,00	,00	3,00	0,250

Mann Whitney U Test

Demographic data (Age, BMI, Week, Gravida, Parity, Elapsed time), estrogen and progesterone values of pregnant women between 37-41 weeks are given in Table 2. When these values are compared, it is striking that there is no statistically significant difference between the two groups in any of the parameters. Similarly, demographic data, estrogen and progesterone values of pregnant women over 41 weeks are shown in Table 3. When the values of the 41 week and older pregnant women are compared, it is seen that there is no statistically significant difference between the parameters. This proves that the study groups were formed equally.

Table 4. Comparison of Demographic and Progesterone Values in terms of Term and Postterm Groups with Pain

Contraction (+)	Group										p
	Term					Postterm					
	Mean	s.d.	Median	Min.	Max.	Mean	s.d.	Median	Min.	Max.	
Age	26,20	±5,72	25,00	20,00	41,00	26,75	±5,59	27,00	16,00	37,00	0,521
BMI	28,80	±5,44	28,00	21,00	42,00	28,83	±3,62	29,00	22,00	38,00	0,451
Week	38,68	±,90	39,00	37,00	40,00	41,08	±,28	41,00	41,00	42,00	**<0,001**
Progesteron	161,16	±85,84	161,00	30,00	326,00	172,54	±89,92	200,50	11,00	336,00	0,496
Estrogene	18826,60	±9624,10	18352,00	1722,00	37038,00	23890,83	±15553,25	22864,00	64,00	58172,00	0,358
Elapsed Time	2,40	±2,19	2,00	,00	7,00	2,50	±3,24	2,00	,00	13,00	0,644
Gravida	2,83	±2,22	2,00	1,00	9,00	2,38	±1,41	2,00	1,00	5,00	0,694
Parity	1,48	±1,87	1,00	,00	8,00	1,29	±1,27	1,00	,00	3,00	0,992

Mann Whitney U Test

Table 5. Comparison of Demographic and Progesterone Values in terms of Term and Postterm Groups Without Pain

Contraction (-)	Group										p
	Term					Postterm					
	Mean	s.d.	Median	Min.	Max.	Mean	s.d.	Median	Min.	Max.	
Age	28,88	±6,44	28,00	16,00	41,00	27,82	±5,46	27,00	18,00	37,00	0,481
BMI	31,88	±10,94	28,00	21,00	71,00	29,05	±4,40	28,00	24,00	42,00	0,830
Week	38,48	±1,05	38,00	37,00	40,00	41,18	±,39	41,00	41,00	42,00	**<0,001**

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Progesteron	189,56	±67,74	182,00	86,00	366,00	185,59	±87,16	195,50	16,00	359,00	0,983
Estrogene	22222,08	±5643,43	21372,00	11916,00	36569,00	35643,36	±55030,57	23595,00	230,00	274459,00	0,348
Elapsed time	2,43	±2,59	2,00	,00	9,00	1,95	±2,75	,50	,00	8,00	0,288
Gravida	2,92	±2,71	2,00	1,00	14,00	2,36	±1,65	1,50	1,00	6,00	0,444
Parity	1,48	±2,37	1,00	,00	11,00	1,00	±1,48	,00	,00	5,00	0,441

Mann Whitney U Test

Pregnant women with contraction; Comparisons of term and postterm groups in terms of estrogen and progesterone values are shown in Table 4. When these comparisons are examined, it is understood that no statistically significant difference was observed except for the gestational week. Pregnant women with pain; The comparisons of term and postterm groups in terms of estrogen and progesterone values are given in Table 5. When the results of these comparisons are examined, it is seen that there is no statistically significant difference in the parameters other than the gestational week.

5. Discussion

Preterm birth (below 37 weeks of gestation) occurs in approximately 15 million births each year and is one of the most important causes of death in the first postnatal month. (4) The highest rates of preterm births (about 15% of all live births) occur in countries such as Sub-Saharan Africa, Pakistan, and Indonesia. However, even in the United States, this rate is still 10% of all live births. (5) Surprisingly, approaches to preventing and treating preterm labor have changed little over the past 50 years. This is due, on the one hand, to the fact that the mechanism underlying myometrial contractions is not fully understood, and on the other hand, pharmaceutical companies have made little effort to develop drugs in this area. The quiescence of the myometrium throughout pregnancy is controlled by increased progesterone (P4) levels. The source of this progesterone in pregnancy; placenta or ovarian corpus luteum. There are two progesterone receptor (PR) isoforms in humans. (PR-A and PR-B) (6, 7). Due to its structure, PR-A is more transcribed than PR-B, and in addition, it inhibits the transcription of PR-B in myometrial cells (8,9, 10). The ratio of PR-A to PR-B in pregnant women who experienced term labor, compared to those who did not start labor despite being term. was found to be significantly increased (11).

In rodents and most mammals, maternal P4 levels remain high throughout pregnancy and drop sharply before birth (12). Based on this, it was thought that P4 withdrawal was associated with labor. However, in humans, blood and myometrial levels of P4 do not show such a decrease

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during late pregnancy and labor. However, progesterone antagonists increase myometrial contractility and cervical ripening in humans. (13, 14)
Term and preterm labor begins with an enhanced inflammatory response. An increase in the levels of proinflammatory cytokines is observed in the amniotic fluid (15). In addition, neutrophil and macrophage invasion is observed in fetal membranes, cervix and myometrium(16, 17). Invasion of these cells and secretion of cytokines and chemokines cause activation of inflammation-related transcription factors. With this activation, myometrial proinflammatory and contractile oxytocin receptor and cyclooxygenase-2 genes are activated and labor begins (18, 19). Similarly, intraamniotic infection-associated chorioamnionitis may cause a similar inflammatory response and thus initiate preterm labor (20). Critical inflammatory signals from both mother and fetus can trigger term labor. The tension created by the growing fetus on the uterine wall in the near-term period may trigger the labor (21, 22). The increased incidence of preterm birth in twin and multiple pregnancies suggests that uterine ovarian distension is a causal factor for preterm labor (23).

Increased estrogen level in the blood and/or increased myometrial estrogen receptor activity increases uterine contractility near term (24, 25, 26, 27). In addition, the effect of estrogen increasing the migration of immune cells causes uterine inflammation and has a labor initiating effect. (27) As a feature unique to the human placenta, corticotropin-releasing hormone (CRH) is produced from the placenta (28). As the delivery approaches, the placenta secretes CRH at increasing rates. This increased production of CRH is thought to act as an initiating signal for labor. (29, 30)

If we take a look at the studies in the literature that measure the levels of estrogen and progesterone hormones during and after pregnancy; Boroditsky RS et al.(31) looked at E1, E2, E3 and Progesterone levels in pregnant women in their study. They observed that hormone levels did not change before and during birth. Keresztes P et al. (32), on the other hand, showed that E2 levels increased but there was no change in progesterone levels in a study in which they compared prenatal and postnatal hormone levels in pregnant women. Wu BT. et al. (33) similarly, they measured E2, E3 and Progesterone levels in serum and amniotic fluid in term pregnant women before and during delivery. While no difference was observed in serum E2, E3 and Progesterone levels, E2, E3 were found to be high in amniotic fluid, but no change was found in progesterone levels. There was no statistically significant difference in hormone levels between the groups.

Marek B, et al. (34) also examined the relationship between estrogen and progesterone in blood and saliva in both normal and pathological pregnancies in their study. They argued that the hormone concentration in saliva reflects the free hormone circulating in the blood, which is not bound to proteins and whose labeling provides more reliable clinical information. Perry LA et al. (35) examined the levels of steroid hormones in the blood and saliva in their study. With this; Marek et al. in contrast, they found only a weak correlation between free hormone concentrations in the blood and levels measured in saliva. In our study, only the hormone levels in the serum were measured and compared (34).

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Konopka CK et al.(36) evaluated serum levels of E2 and E3 progesterone hormones in pregnant women who had labor induction with dinoprostone. While a decrease in progesterone hormone is observed in pregnant women with successful labor induction; No change was detected in E2, E3 hormone levels.

Goharkhay N et al. (37) measured plasma progesterone, E2 and DHEAS levels in pregnant women induced by prostaglandin E2 in their study. While a decrease was observed in the progesterone level, an increase was observed in the E2 and DHEAS levels. Pregnant women who underwent induction were not included in our study, only those who were followed up spontaneously were included in the study. However, as mentioned above, no significant difference was found in the serum estrogen and progesterone levels of pregnant women.

In our study, we compared estrogen and progesterone levels between term and postterm pregnancies between painful and non-painful groups. As a result of our statistical analysis, we saw that these hormone levels did not make a statistically significant difference regardless of pain. When we look at the literature, it is seen that the effects of different factors such as withdrawal of progesterone as the initiator of labor or the use of progesterone antagonists, proinflammatory signals, increase in estrogen levels, increase in uterine CRH secretion. We compared estrogen and progesterone hormone levels, which are thought to play the strongest role among these, in term and postterm pregnancies. Despite the differences in estrogen-progesterone levels found in the literature between preterm and term pregnancies, no similar difference was found in term and postterm pregnancies, as we revealed in our study. Interestingly, the pain that indicates the onset of labor did not show any difference between these hormone levels.

6. Conclusion

As a result of our study, no statistically significant difference was found in terms of estrogen and progesterone levels between term and postterm pregnants, and between those with and without pain. Based on this, we can conclude that estrogen and progesterone levels cannot be used as an indicator of the onset of labor between term and postterm pregnancies.

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