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The effects of dydrogesterone treatment on first-trimester aneuploidy screening markers and nuchal translucency in women with threatened miscarriage

Düşük tehdidi olan gebelerde oral didrogesteron tedavisinin ilk trimester anöploidi tarama belirteçleri ve ense kalınlığı üzerindeki etkileri

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Abstract

Objective: To evaluate the effects of dydrogesterone treatment on first-trimester aneuploidy screening markers and nuchal translucency (NT) in women with threatened miscarriage.

Materials and Methods: This study is an prospective case-control study. One hundred seven pregnant women who applied for the first-trimester screening test at 11-14th weeks of gestation were included in the study. The study group consisted of 53 pregnant women using oral dydrogesterone due to the threat of miscarriage for at least 2 weeks and without vaginal bleeding for the last 72 h at the time of enrollment. The control group was composed of 54 healty pregnant women. Fetal Crown-rump length (CRL), NT, pregnancy-associated plasma protein-A (PAP-A) level, and free beta-human chorionic gonadotropin (free B-hCG) levels of the patients were measured.

Results: One hundred seven patients included in the study, 54 (50.46%) were in the control group, and 53 (49.54%) were in the study group using dydrogesterone. Age, body mass index, gravida, parity and abortion numbers, gestational weeks, and CRL values of the two groups were congruent. In the comparison-free B-hCG, PAPP-A and NT values of both groups, no statistically significant difference was found between the two groups in terms of first-trimester test results and NT ($p<0.05$).

Conclusion: The use of dydrogesterone in first-trimester pregnancies does not affect first-trimester screening tests and nuchal translucency.

Keywords: Dydrogesterone, nuchal translucency, threatened miscarriage, prenatal screening tests

Öz

Amaç: Gebelerde düşük tehdidi nedeniyle kullanılan oral didrogesteron tedavisinin ilk trimester anöploidi tarama testi parametreleri ve ense saydamlığı (NT) üzerine etkisini değerlendirmek.

Gereç ve Yöntemler: Bu çalışma prospektif olgu kontrol çalışmasıdır. Çalışmaya 11-14. gebelik haftalarında birinci trimester tarama testi için başvuran toplam 107 gebe dahil edildi. Çalışma grubunu düşük tehdidi nedeniyle en az 2 hafta süreyle oral didrogesteron kullanan ve tedaviden sonra son 72 saatte vajinal kanaması olmayan 53 gebe, kontrol grubunu ise 54 sağlıklı gebe oluşturdu. Katılımcıların demografik ve obstetrik özellikleri kayıt edildi. Fetal tepe popo uzunluğu (CRL), NT, gebelikle ilişkili plazma protein-A (PAPP-A) ve serbest beta insan koryonik gonadotropin (free B-hCG) düzeyleri ölçüldü.

Bulgular: Çalışmaya dahil edilen toplam 107 hastanın 54'ü (%50,46) kontrol grubunda, 53'ü (%49,54) didrogesteron kullanan çalışma grubundaydı. İki grubun yaş, vücut kitle indeksi, gravida, parite ve abort sayıları, gebelik haftaları, CRL değerleri birbiri ile eşlenikti. Her iki grubun free B-hCG, PAPP-A ve NT değerleri ile yapılan karşılaştırmada iki grup arasında ikili test sonuçları ve NT açısından istatistiksel anlamlı fark tespit edilmedi ($p<0,05$).

PRECIS: Although progesterone itself is known as a pregnancy hormone, the safety of exogenous use during pregnancy and its effect on first trimester screening tests have been the subject of many studies.In our study, the effect of first trimester dydrogesterone use on the screening test was examined and it was shown that the speculative hypothesis that it impaired the test was not correct.

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Sonuç: İlk trimester gebelerde didrogesteron kulanılması ilk trimester tarama testi parametrelerini ve ense saydamlığını etkilememektedir.
Anahtar Kelimeler: Didrogesteron, ense saydamlığı, düşük tehdidi, doğum öncesi tarama testi

Introduction

Threatened miscarriage is the most common complication of pregnancy, manifested by vaginal bleeding, while the cervix are closed before 20 weeks of gestation, occurring in approximately one-fifth of pregnant women[1-3]. In addition to its negative social and economic effects, it has an important effect on physical and psychological well-being. Research showed that the level of distress associated with miscarriage can be equivalent to the stillbirth of a full-term baby and causes post-traumatic stress disorder[4]. This situation forces physclinicians to take more stringent prevention measures. Empirically, it is attempted to be treated and prevented using progesterone supplementation, anticoagulation, and/or immunomodulatory therapies[5]. The most common practice is to prescribe progesterone[6,7]. It is now understood that progesterone is necessary for the initiation and maintenance of pregnancy at all stages[8,9]. It has been reported that progesterone deficiency causes miscarriage[10].

From the late 1900s to the present, first-trimester screening tests remain important for fetal chromosomal anomaly evaluation[11,12]. Nuchal translucency (NT) is a hypoechoic region located between the skin and soft tissues behind the cervical spine. This hypoechoic area is presumed to represent mesenchymal edema and is frequently associated with distended jugular lymphatics. In some studies, it has been stated that progesterone may cause abnormal blood flow patterns and therefore an increase in NT, but it does not change the result of the screening test[13,14]. It has been demonstrated that progesterone could cause both rapid dose-dependent relaxation of the placental vascular smooth muscle and the proliferation of cultured human vascular smooth muscle cells of the umbilical vein.

Incorrect evaluation of NT, which is a sensitive marker in Down syndrome screening and is accepted as a component of first-trimester screening tests, may lead to false-positive results. Therefore, the parameters affecting NT measurements should be thoroughly investigated.

Although there are many publications on dydrogesterone, which is structurally and pharmacologically similar to microgenized progesterone, in the prophylaxis of threatened miscarriage and its use in early pregnancy[15], as far as we know, there is no study on its effect on first-trimester screening test components. In our study, we evaluated the effect of dydrogesterone use in the first-trimester on NT, pregnancy-associated plasma protein-A (PAPP-A), and free beta-human chorionic gonadotropin (B-hCG) values, which are the components of the first-trimester aneuploidy screening test[16].

Materials and Methods

Our study is a prospective observational case-control study conducted at University Health Sciences Turkey, Gaziosmanpaşa Training and Research Hospital on first-trimester pregnant women who presented to our pregnant outpatient clinic between November 2022 and January 2023 for first-trimester screening tests. Participants were included in the study by invitation. Written informed consent was obtained from all pants who agreed to participate. The inclusion criteria were age 18-39 years, between 11-13.6 weeks of gestation, and confirmation of a crown-rump length (CRL) of 45 mm to 84 mm in ultrasonographic evaluation. Pregnant women with multiple pregnancies, high blood pressure, gestational diabetes, metabolic disease with vascular involvement, renal failure, and chronic drug use during pregnancy were excluded from the study.

In the gynecological evaluation, pregnancies with closed cervix and vaginal bleeding were diagnosed as a threatened miscarriage. All participating pregnant women were questioned about whether they experienced the threat of miscarriage and vaginal bleeding and therefore used oral dydrogesterone. Participants who used oral dydrogesterone for at least 2 weeks and no-bleeding for the last 72 h were included in the case group. Pregnant women who used dydrogesterone for less than two weeks or whose bleeding still continued after treatment were excluded from the study. The control group was composed of 54 healthy pregnant women with the same criteria as the study group but who did not take exogenous dydrogesterone and without bleeding.

The reason for taking the 2-week period as a criterion is in almost all the studies that can be compared in the literature, oral microgenized progesterone was used and the duration of use was taken as 2 weeks. To make an accurate comparison with other studies in the literature, it was sought to use at least two weeks to ensure that the duration was constant. The reason for seeking a condition of 72 h without bleeding after treatment was to eliminate the possible effect of bleeding on the test. Pregnant women who used any progesterone other than dydrogesterone were excluded from the study.

In the group using dydrogesterone, it was required to have received treatment at a standard dose for at least 2 weeks. The dose recommended by the pharmaceutical company for dydrogesterone treatment was accepted as the standard dose. To standardize the study, daily use of 10 mg orally every 8 h up to 30 mg was accepted as the standard; doses higher than this were considered high doses and excluded from the study. Only oral preparations were included in the study.

The pregnancy histories, medical histories, smoking habits, age, and height information of the patients were questioned, and the information was recorded. Then, measurements of all participants were made using the same ultrasonography (USG) scanner by the same single physician. Gestational age was calculated using the fetal CRL. All ultrasound examinations

were performed with a 4.5-16.5 MHz transabdominal probe or with a 5-9 MHz transvaginal trans-ducer (Mindray DC8 Expert, Wauwatosa). In cases where it was difficult to visualize the fetus [such as with high body mass index (BMI)], the was examined 2-dimensionally (5-9 MHz). Scans were performed transvaginally using a transvaginal probe. Patients with a CRL less than 45 mm and more than 84 mm, the presence of a non-viable fetus, multiple pregnancies, the presence of major serious fetal anomalies such as anencephaly, the presence of spina bifida, and cardiac anomalies were excluded from the study. NT measurements were performed thrice for each patient and the highest value was recorded[15]. Measurements were made in the sagittal plane, whereas the fetus was in a neutral position, with clear separation of the amnion membrane, and after magnification on the USG screen to cover the fetal head and upper thorax. Patients NT values greater than 2.5 mm were excluded (which is roughly equivalent to the 95th percentile[15]. Immediately after USG evaluations, blood samples for PAPP-A and free B-hCG were taken from the patients.

Ethical approval was obtained from the Ethics Committee of University Health Sciences Turkey, Gaziosmanpaşa Training and Research Hospital before starting the study (date: 23/11/2022, no: 145) and was carried out in accordance with the Declaration of Helsinki.

Statistical Analysis

In the power analysis performed before starting the study, it was found appropriate to detect a difference of at least 0.25 (medium level) effect size between the groups, with 80% power and 5% type error, with a total of 106 people, and a minimum of 53 people in each group. The calculation was made using the G*Power 3.1.9.7 program. It was aimed to reach the numbers specified as the study endpoint. The normality of the distribution of continuous variables was evaluated using the Shapiro-Wilk test. Student's t-test was used to compare normally distributed variables, and the Mann-Whitney U test was used for non-normally distributed variables. Spearman Rho correlation coefficients were calculated to examine the linear relationship between continuous variables. Fisher's Exact test was used in the analysis of categorical data. The analysis of the data was performed using the IBM SPSS 21 program.

Results

Of the 107 patients included in the study, 54 (50.46) were in the control group and 53 (49.54%) were in the dydrogesterone group. The demographic characteristics of the participants in the groups are presented in Table 1. There was no statistically significant difference between the two groups in terms of

Table 1. Demographic parameters of groups

	No medication			Medication			
	Mean ± SD	Median (IQR)	Min-max	Mean ± SD	Median (IQR)	Min-max	p
Age (years)	27.93±5.69	27 (23.75-32.25)	18-39	28.21±6.06	26 (24-33.5)	18-40	0.893
BMI (kg/m^2)	25.53±5.89	25.25 (20.91-28.4)	16.73-47.67	25.19±5.03	25.28 (22.48-27.55)	18.34-47.67	0.810
Gravidity	2.43±1.31	2 (1-3)	1-8	2.32±1.31	2 (1-3)	1-8	0.575
Parity	1.07±0.99	1 (0-2)	0-4	1.04±1.04	1 (0-2)	0-4	0.738
Abortion	0.28±0.66	0 (0-0)	0-3	0.21±0.53	0 (0-0)	0-3	0.632
Curettage	0.02±0.14	0 (0-0)	0-1	0.02±0.14	0 (0-0)	0-1	0.989
Ectopic pregnancy	0.06±0.23	0 (0-0)	0-1	0.06±0.23	0 (0-0)	0-1	0.981
Vaginal birth	0.54±0.77	0 (0-1)	0-3	0.42±0.63	0 (0-1)	0-2	0.494
Cesarean	0.52±0.79	0 (0-1)	0-3	0.58±0.89	0 (0-1)	0-3	0.822

p: Mann-Whitney U test, BMI: Body mass index, SD: Standard deviation, IQR: Interquartile range, Min-max: Minimum-maximum

Table 2. NT, PAPP-A, free B-hCG MoM levels of groups

	No medication			Medication			
	Mean ± SD	Median (IQR)	Min-max	Mean ± SD	Median (IQR)	Min-max	p
Free B-hCG MoM	0.9±0.5	0.81 (0.54-1.11)	0.25-3.02	0.83±0.39	0.76 (0.55-1.1)	0.28-2.17	0.654
PAPP-A MoM	1.04±0.66	0.88 (0.62-1.34)	0.3-4.15	0.99±0.78	0.74 (0.61-1.08)	0.35-4.15	0.299
NT MoM	0.91±0.22	0.92 (0.79-1.02)	0.19-1.45	0.95±0.17	0.93 (0.83-1.04)	0.58-1.45	0.241*

p: Mann-Whitney U test, *Student's t-test, NT: Nuchal translucency, MoM: Multiple of the median, PAPP-A: Pregnancy-associated plasma protein-A, SD: Standard deviation, IQR: Interquartile range, Min-max: Minimum-maximum

Table 3. Change of NT, PAPP-A, free B-hCG MoM levels of the groups according to CRL

	No medication			Medication			p
	Mean ± SD	Median (IQR)	Min-max	Mean ± SD	Median (IQR)	Min-max	
Free B-hCG MoM							
45-54 (n=23/17)	0.86±0.4	0.76 (0.51-1.25)	0.25-1.73	0.79±0.41	0.56 (0.49-1.27)	0.29-1.43	0.665
55-64 (n=17/16)	0.74±0.27	0.7 (0.52-0.96)	0.28-1.18	0.77±0.3	0.71 (0.56-0.94)	0.28-1.51	0.723*
65-74 (n=7/7)	1.07±0.5	0.94 (0.74-1.06)	0.72-2.17	0.94±0.57	0.72 (0.62-1.02)	0.43-2.17	0.259
75-84 (n=7/13)	1.28±0.94	1.31 (0.35-1.73)	0.32-3.02	0.89±0.37	0.8 (0.65-1.28)	0.32-1.44	0.438
PAPP-A MoM							
45-54 (n=23/17)	1.2±0.86	1.03 (0.62-1.43)	0.36-4.15	1.4±1.22	0.84 (0.62-1.54)	0.36-4.15	0.935
55-64 (n=17/16)	0.83±0.45	0.65 (0.45-1.18)	0.3-1.65	0.66±0.21	0.73 (0.44-0.74)	0.35-1.04	0.790
65-74 (n=7/7)	0.99±0.19	0.99 (0.82-1.06)	0.76-1.33	0.89±0.37	0.92 (0.46-1.28)	0.39-1.33	0.545*
75-84 (n=7/13)	1.11±0.56	1 (0.6-1.48)	0.57-2.06	0.93±0.34	1.07 (0.61-1.2)	0.43-1.48	0.387*
NT MoM							
45-54 (n=23/17)	1.01±0.15	1.02 (0.91-1.05)	0.76-1.3	1.04±0.14	1.03 (0.92-1.13)	0.89-1.3	0.607
55-64 (n=17/16)	0.83±0.24	0.83 (0.76-0.92)	0.19-1.45	0.93±0.22	0.86 (0.78-1.1)	0.65-1.45	0.326
65-74 (n=7/7)	0.88±0.3	0.92 (0.58-1.02)	0.47-1.38	0.88±0.17	0.92 (0.77-1.02)	0.58-1.05	0.983*
75-84 (n=7/13)	0.77±0.14	0.73 (0.66-0.83)	0.6-1.03	0.89±0.11	0.84 (0.82-1.01)	0.66-1.06	0.943*

p: Mann-Whitney U test, *Student's t-test, NT: Nuchal translucency, MoM: Multiple of the median, CRL: Crown-rump length, PAPP-A: Pregnancy-associated plasma protein-A, SD: Standard deviation, IQR: Interquartile range, Min-max: Minimum-maximum

demographic characteristics, and the groups were conjugate with each other.

The NT, PAPP-A, and free B-hCG multiple of the median (MoM) levels of the groups are shown in Table 2. There were no significant differences in NT MoM levels, maternal serum PAPP-A, and free B-hCG MoM levels between the study and control groups.

Both groups were divided into four subgroups to determine the relationship between NT and dydrogesterone use for specific CRL measurements. CRL in the first, second, third, and fourth groups were 45-54 mm, 55-64 mm, 65-74 mm, and 75-84 mm, respectively. The NT, PAPP-A, and free B-hCG MoM levels of the groups are shown in Table 3. There were no significant differences in NT levels, maternal serum PAPP-A, and free B-hCG levels between the study and control groups for all subgroups of CRL measurements.

When examining whether fetal NT measurements were related to maternal and fetal parameters, no significant relationship was found between these parameters and NT MoM values. A negative significant relationship was found between NT MoM and CRL mm only in drug users and non-users ($p<0.05$). This means that as CRL measurements increase, regardless of drug use, the NT MoM value decreases (Table 4).

Table 4. The relationship between fetal nuchal translucency measurements and maternal and fetal parameters

NT MoM		No medication	Medication
Age (years)	r	-0.102	0.061
	p	0.464	0.663
BMI (kg/m^2)	r	-0.086	0.081
	p	0.538	0.562
Gravidity	r	-0.102	0.136
	p	0.463	0.332
Parity	r	-0.192	0.056
	p	0.165	0.693
Abortion	r	0.176	-0.042
	p	0.204	0.767
Vaginal birth	r	-0.016	0.029
	p	0.906	0.837
Cesarean	r	-0.183	0.091
	p	0.184	0.515
CRL (mm)	r	-0.519	-0.418
	p	<0.001	0.002
Free B-hCG MoM	r	-0.077	-0.206
	p	0.578	0.139
PAPP-A MoM	r	0.081	0.048
	p	0.560	0.732

p: Spearman Rho correlation, MoM: Multiple of the median, BMI: Body mass index, PAPP-A: Pregnancy-associated plasma protein-A, NT: Nuchal translucency

Discussion

In our study, we investigated the effects of dydrogesterone treatment on first-trimester aneuploidy screening markers and NT in women with threatened miscarriage. We found similar NT levels in patients who used dydrogesterone because of the

threat of miscarriage and in the control group that did not. We also found similar levels of PAPP-A and free B-hCG between the groups. The use of dydrogesterone in first-trimester pregnancies does not affect first-trimester screening tests and nuchal translucency.

The use of first-trimester screening tests is very common because it is non-invasive. It does not require special training other than NT measurement, it can be performed as soon as the patient is seen in outpatient clinics, and it is still one of our powerful weapons as a screening test. It is of great importance that it is performed meticulously and its accuracy has increased. Therefore, the factors that may affect the parameters should be investigated thoroughly. In the study that was the starting point of our study, Giorlandino et al.[13] were the first to examine the relationship between first-trimester progesterone therapy and the fetus in a total of 3.716 pregnant women and they found that the use of exogenous progesterone increased NT. Moreover, they showed that this increase was independent of maternal age, BMI, smoking, and gestational age. They stated that this increase did not change the results of first-trimester screening tests. However, although they evaluated many progesterone formulations in their studies, dydrogesterone was excluded. Additionally, in the correspondence with Bellver et al.[17] on the subject after these studies, it was stated that the NT increase was only in the 11th week, and it did not occur in the following weeks. Again, in the same correspondence, it was emphasized that different formulations might change the fetal circulation differently and thus affect NT. Based on this criticism, we included pregnant women who used a single preparation for the same period in our study.

In the study by Namlı Kalem et al.[18] in 2018, 121 pregnant women using intravaginal progesterone for assisted reproduction treatment (ART) and 124 healthy pregnant women who did not use progesterone were compared and it was found that NT increased in the progesterone group and this increase was statistically significant. However, in this study, the women who became pregnant spontaneously and who did not use drugs were chosen as the control group and compared with the case group, which became pregnant with assisted reproduction. Whether assisted reproduction pregnancy itself affects NT is unknown. To exclude this factor from our study, we included pregnant women who became pregnant spontaneously and excluded the ART group from the study. In a study by Keçecioğlu et al.[14] that was designed retrospectively in 2016, groups that did and did not receive micronized progesterone were compared and it was shown that oral progesterone treatment increased only NT and free B-hCG values without causing abnormal results in the test result. In their ROC analysis, the area under the curve for NT was found as 0.634, which was distinctive, and a correlation was found between treatment time and NT[14].

In a study conducted in 2021, Karadağ et al.[19] divided case and control groups by dividing women who did and did not use progesterone into subgroups according to their CR, not according to their gestational week. As a result, they found no differences in MoM levels of NT, PAPP-A, and free B-hCG in all CRL groups[19].

In the study of Karaca et al.[20] in 2022, which we found as the most recent in the literature, the participants were divided into three groups according to bleeding and progesterone use, and they found that free B-hCG increased in the group that used progesterone regardless of whether the women had bled, compared with the group that did not use progesterone.

Study Limitations

The main limitation of our study is The small number of patients and not being compared with other progesterone types. New works with other types of progesterone can be detailed. There are no detailed studies on the duration of progesterone use in the literature. New studies can be performed by comparing the duration of use. The other limitation is the dose regimen of dydrogesterone; we gaved all patients orally 30 mg/day dydrogesterone, but the patient weight was different. Although we excluded in the study the patients >30 kg/m^2 BMI, different weights of patients could obtain different dose regimens.

Conclusion

The strength of our study is that the speculative hypothesis that the use of progesterone affects fetal circulation and increases nuchal translucency, thus increasing the risk in first-trimester screening tests, is not true.However, all of these studies were performed either with micronized progesterone or with other progesterone preparations that excluded dydrogesterone. There is no other study in the literature comparing NT, PAPP-A, and free B-hCG levels with the use of dydrogesterone. Oral use is very convenient and preferred compared with vaginal use in women with bleeding. Additionally, because it did not change any parameters, it had no negative effect on the reliability of the first-trimester screening test and the objectivity of the NT value, which provides an advantage in terms of use in first-trimester pregnancies. If our study is supported by studies involving larger numbers of participants, we think that dydrogesterone will come to the forefront during pregnancy because it does not affect first-trimester tests.

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Ethics

Ethics Committee Approval: Ethical approval was obtained from the Ethics Committee of University Health Sciences Turkey, Gaziosmanpaşa Training and Research Hospital before starting the study (date: 23/11/2022, no: 145) and was carried out in accordance with the Declaration of Helsinki.

Informed Consent: Written informed consent was obtained from all pants who agreed to participate.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.Y., Concept: E.Y., Design: E.Y., Data Collection or Processing: E.Y., Analysis or Interpretation: E.Y., B.T., Literature Search: E.Y., B.T., Writing: E.Y., B.T.

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