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DOES THE USE OF LOW MOLECULAR WEIGHT HEPARIN AFFECT PREGNANCY SCREENING TEST RESULTS?

DÜŞÜK MOLEKÜL AĞIRLIKLI HEPARIN KULLANIMI GEBELİK TARAMA TESTİ SONUÇLARINI ETKİLER Mİ?

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ABSTRACT

Objective: Low molecular weight heparin, also known as LMWH, is a drug that is frequently utilized in the treatment of venous thromboembolism risk management as well as the prevention of potential miscarriages in pregnancy. Our study sought to answer the question of whether or not the use of LMWH, which is becoming increasingly popular as a treatment option in clinical settings, has an impact on the outcomes of screening tests administered during the first trimester of pregnancy as well as tests intended to detect birth defects in the neural tube.

Methods: This retrospective case-control study included pregnant women who had a first trimester screening test and a neural tube defect screening test during pregnancy follow-up. A comparison was made between fifty-three pregnant women using LMWH and three hundred twenty-five pregnant women not using LMWH. Serum beta human chorionic gonadotropin (beta-hCG), placenta associated plasma protein-A (PAPP-A), and alpha-fetoprotein (AFP) levels were investigated in this study.

Results: Patients included in the study ranged in age from 20 to 47 years. In terms of first trimester screening test markers PAPP-A, PAPP-A multiples of the media (MoM), beta-hCG, beta-hCG MoM, and neural tube defect markers AFP, AFP MoM ($p > 0.05$), there was no significant difference between the control group and LMWH group ($p > 0.05$).

Conclusion: Our study has shown that the use of LMWH during pregnancy does not cause misinterpretation of first trimester screening test and neural tube defect screening tests. Further studies with larger samples are required to confirm our findings.

Keywords: First Trimester Pregnancy, Low Molecular Weight Heparin, Maternal Serum Screening Tests, Neural Tube Defects

ÖZET

Amaç: Düşük moleküler ağırlıklı heparin (DMAH), venöz tromboembolizm risk yönetiminin tedavisinde ve gebelikte olası düşüklerin önlenmesinde sıklıkla kullanılan bir ilaçtır. Çalışmamızda klinik ortamlarda tedavi seçeneği olarak giderek yaygınlaşan DMAH kullanımının gebeliğin ilk trimesterinde uygulanan tarama testlerinin ve nöral tüp defekti belirteçlerinin sonuçlarına etkisi olup olmadığı araştırılmıştır.

Gereç ve Yöntemler: Bu retrospektif vaka-kontrol çalışmasına, gebelik takibi sırasında ilk trimester tarama testi ve nöral tüp defekti tarama testi yapılan gebeler dahil edildi. DMAH kullanan elli üç gebe ile DMAH kullanmayan üç yüz yirmi beş gebe arasında bir karşılaştırma yapılmıştır. Bu çalışmada serum beta insan koryonik gonadotropin (beta-hCG), plasenta ilişkili plazma protein-A (PAPP-A) ve alfa-fetoprotein (AFP) düzeyleri araştırıldı.

Bulgular: Çalışmaya dâhil edilen hastaların yaşları 20 ile 47 arasındaydı. Birinci trimester tarama testi belirteçleri PAPP-A, PAPP-A ortanca katları (MoM), beta-hCG, beta-hCG MoM ve nöral tüp defekt belirteçleri AFP, AFP MoM ($p > 0.05$), açısından kontrol grubu ile DMAH grubu arasında anlamlı fark saptanmadı ($p > 0.05$).

Sonuç: Çalışmamız gebelikte DMAH kullanımının birinci trimester tarama testi ve nöral tüp defekt tarama testlerinin yanlış yorumlanmasına neden olmadığını göstermiştir. Bulgularımızı doğrulamak için daha büyük örneklemli ileri çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Düşük Moleküler Ağırlıklı Heparin, İlk Trimester Gebelik, Maternal Serum Tarama Testleri, Nöral Tüp Defektleri.

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INTRODUCTION

During pregnancy, the body's hemostatic system shifts toward hypercoagulation. Although these physiological changes reduce blood loss during and after birth, they increase the risk of venous thromboembolism (VTE) during pregnancy (Bremme, 2003). Pregnant women are four to five times more likely than non-pregnant women of similar age to develop VTE (Heit et al., 2005).

More than sixty percent of idiopathic thromboembolic events are caused by hereditary thrombophilia. This genetic condition is a coagulation disorder, which is responsible for a number of pregnancy-related complications. It plays an undeniable role in the etiology of complications including recurrent miscarriage, intrauterine fetal growth restriction, prematurity, preeclampsia, and placental decollement (Tan, 2002).

Thrombophilia is a collection of inherited and acquired coagulation disorders linked to an increased risk of thrombosis. Thrombophilia, whether heterozygous or homozygous, is linked to recurrent miscarriages and unsuccessful IVF treatments (Flores-Alatriste et al., 2014). Protein C deficiency, antithrombin deficiency, factor V Leiden mutation, methylene tetra hydro folate-reductase (MTHFR) gene C677T polymorphism, protein S deficiency, prothrombin G20210A mutation, plasminogen activator inhibitor-1 polymorphism, and angiotensin converting enzyme polymorphism are the most common types of hereditary thrombophilia (Aracic et al., 2016).

Other than thrombophilia, many conditions are known to increase the risk of pregnancy-related VTE. The most important of these are a history of thrombosis, antiphospholipid syndrome, systemic lupus erythematosus, being over 35 years old, being nulliparous, multiple pregnancy, obesity, smoking, and sedentary lifestyle (Papadakis et al., 2019; James et al., 2006; Jacobsen et al., 2008).

As assisted reproduction is a risk factor in and of itself, thromboprophylaxis with low-molecular-weight heparin (LMWH) should be administered to every woman with an IVF pregnancy beginning in the first trimester (RCOG Green-top Guideline No. 37a, 2015). LMWHs are effective antithrombotic agents that are commonly used in the prevention of both primary and secondary thromboprophylaxis. Thus, preeclampsia, placental decollement, intrauterine fetal growth restriction, recurrent abortion, and intrauterine deaths caused by these vascular complications can be avoided (Aracic et al., 2016; Middeldorp, 2007; Rai and Regan, 2006).

A combination of human chorionic gonadotropin (beta-hCG) level measurement, pregnancy-related plasma protein-A (PAPP-A) level measurement, and fetal nuchal translucency (NT) measurement is used in the first trimester screening test. Thus, this screening method can detect 90% of major chromosomal anomalies with a 5% false positive rate (Nicolaides, 2005). In addition, during the second trimester, the maternal serum alpha-fetoprotein (AFP) level can be determined to screen for fetal open neural tube defects (Wilson, 2014).

Studies have shown that certain drugs used during pregnancy and certain diseases can affect the results of screening tests (Turkcapar et al., 2013; Heinig et al., 2007; Peeva et al., 2019; Unal et al., 2020). Our study sought to determine whether LMWHs, which are commonly used during pregnancy, have the same impact on screening test values as other drugs. This will be the first study to evaluate the effects of LMWH use during pregnancy on screening test markers from the first trimester and neural tube defect screening test markers.

MATERIAL AND METHODS

This is a retrospective study conducted in our obstetrics and gynecology department from 2017 to 2021. Pregnant women who underwent a first trimester screening test and a neural tube defect screening test during pregnancy follow-up were included in the study. The control group consisted of healthy pregnant women who did not take any medications prior to screening tests. The LMWH group consisted of pregnant women who had used LMWH during the screening period.

Data was gathered from patient file records. PAPP-A levels, beta-hCG levels, AFP levels, PAPP-A multiples of the media (MoM) values, beta-hCG MoM values, and AFP MoM values were all recorded for the patients. Pregnant women with missing information in their files at the end of the screening, those who used any medication during pregnancy, those with multiple pregnancies, those with known chromosomal anomaly, and those with a chromosomal anomaly diagnosis in their previous pregnancies were all excluded from the study. The study included 378 pregnant women who met these criteria. Written informed consent was obtained from participants. The ethics committee approved the study, which was carried out in accordance with the Helsinki Declaration.

Statistical Analysis

Mean, standard deviation, median lowest, highest, frequency, and ratio values were used in the descriptive statistics of the data. While the Kolmogorov-Smirnov test was used to measure variable distribution, the Mann-Whitney u test was used to analyze quantitative independent data. In the analysis, the SPSS 27.0 program was used.

RESULTS

The study included 378 pregnant women, with the LMWH group (n:53) and the control group (n: 325). The pregnant women who were included in the study ranged in age from 20 to 47 years old. The LMWH group had a mean age of 34.6 ± 4.9, while the control group had a mean age of 31.8 ± 4.3. The LMWH group had a significantly higher mean age ($p< 0.05$). Furthermore, the number of pregnancies and abortions was significantly higher in the LMWH group ($p< 0.05$).

The weight distribution, parity, and number of surviving children were comparable between the two groups ($p> 0.05$). While the birth week in the LMWH group was noticeably lower than in the control group ($p< 0.05$), the birth weight did not differ significantly ($p> 0.05$). (Table 1).

There was no significant difference between the LMWH and control groups in terms of PAPP-A, PAPP-A MoM, beta-hCG, beta-hCG MoM, AFP and AFP MoM values ($p> 0.05$)..

Table 1. Comparison of Maternal and Pregnancy Characteristics of LMWH Group and Control Group

	Control Group		LMWH Group		
	Mean ± S.D.	Median	Mean ± S.D.	Median	p
Maternal age (years)	31,8 ± 4,3	32,0	34,6 ± 4,9	35,0	***0,000*** [m]
Weight (kg)	74,0 ± 11,8	72,0	73,6 ± 13,2	72,5	0,901 [m]
Gravidity	1,8 ± 0,9	2,0	2,9 ± 2,9	2,0	***0,001*** [m]
Parity	0,46 ± 0,62	0,00	0,38 ± 0,58	0,00	0,421 [m]
Abortion	0,27 ± 0,53	0,00	1,50 ± 2,85	1,00	***0,000*** [m]
Living Child	0,46 ± 0,62	0,00	0,36 ± 0,58	0,00	0,302 [m]
Gestation week at birth	38,6 ± 2,1	38,9	37,7 ± 2,0	38,2	***0,000*** [m]
Birthweight (gr)	3269 ± 507	3305	3113 ± 598	3163	0,093 [m]
PAPP-A	3,70 ± 2,31	3,00	4,64 ± 6,82	2,98	0,443 [m]
PAPP-A MoM	1,28 ± 0,75	1,08	1,30 ± 0,95	1,10	0,664 [m]
Beta-hCG	97,1 ± 57,7	83,9	85,1 ± 37,5	75,7	0,353 [m]
Beta-hCG MoM	1,11 ± 0,61	0,97	1,02 ± 0,41	0,97	0,806 [m]
AFP	48,7 ± 18,9	45,5	44,5 ± 12,0	42,1	0,339 [m]
AFP MoM	1,13 ± 0,42	1,04	1,07 ± 0,25	1,05	0,910 [m]

[m] Mann Whitney U Test

DISCUSSION

The potential impact of LMWH use during pregnancy on screening test parameters is the main outcome of our study. Our findings indicate that the use of LMWH during pregnancy has no effect on the investigated parameters.

Thromboembolism is observable during pregnancy and puerperium and is a leading cause of morbidity and mortality. LMWH can be used for both the prevention and treatment of this undesirable condition. It does not cross the placenta and does not cause teratogenic effects. In addition, it is preferred in pregnancy due to its favorable maternal safety profile, as it carries a lower risk of hemorrhage, heparin-induced thrombocytopenia, and heparin-induced osteoporosis when compared to heparin use. Numerous proteins are modulated when LMWH is administered to women undergoing assisted reproductive technology, resulting in an increase in the rate of embryo implantation. In addition, it has

a substantial effect on reducing miscarriage rates (Jacobson et al., 2020; Greer et al., 2005; Akhtar et al., 2013).

Pregnant women in developed countries are typically advised to undergo screening for chromosomal abnormalities in their unborn child as part of standard medical practice. Because it gives the family the opportunity to choose whether or not to continue with the pregnancy, chromosomal abnormality screening and diagnosis have long been considered extremely important. In addition, invasive procedures like amniocentesis or chorionic villus sampling can be planned with a higher degree of reliability if factors that could influence the results of screening methods are excluded.

To improve the success rate of the first trimester screening test, ultrasonographic markers and biochemical markers are evaluated together rather than independently. The first trimester screening test includes NT measurement, crown rump length measurement, PAPP-A level, and beta-hCG level. Multiples of the media (MoM) for gestational age were calculated from maternal PAPP-A, AFP, beta-hCG levels, and NT measurements. This calculation takes into account factors such as maternal weight, maternal age, smoking status, and racial origin (Kagan et al., 2008).

Syncytiotrophoblasts secrete PAPP-A. It is an insulin-like growth factor binding metalloproteinase. It is essential for placental growth and development (Poon et al., 2019). PAPP-A levels were found to be lower in sickle cell anemia and Familial Mediterranean Fever patients (Turkcapar et al., 2013; Peeva et al., 2019). No correlation between LMWH use and PAPP-A levels in pregnant women was determined in our study.

HCG is a heterodimer made up of 237 amino acids. It is made up of two subunits: beta (145 amino acids) and alpha (93 amino acids). There are eight carbohydrate side chains in it. HCG is a member of the same glycoprotein hormone family as follicle stimulating hormone (FSH), thyroid stimulating hormone (TSH), and luteinizing hormone (LH). This explains why their alpha subunits are similar (Nwabuobi et al., 2017). HCG levels typically rise between 8 and 10 gestational weeks before declining to a plateau between 18 and 20 weeks (Shiefa et al., 2013). Since Bogart et al. discovered that beta-hCG levels increase in Down syndrome pregnancies, it has been used routinely in screening programs (Bogart et al., 1987). In a study of patients with systemic lupus erythematosus, beta-hCG levels were found to be higher in first trimester screening tests, while beta-hCG MoM levels were significantly higher in pregnant women taking epileptic drugs (Heinig et al., 2007; Heinig et al., 2007). Our study determined that the use of LMWH had no effect on the level of beta-hCG in pregnant women.

The first trimester screening test is a program that detects the possibility of a fetus with chromosomal aneuploidies such as trisomy 13, trisomy 18, or trisomy 21. This test is performed during the first trimester of pregnancy. Down syndrome is a genetic condition that can result in mild to severe mental, behavioral, and developmental issues in affected individuals. When trisomy 21 pregnancies are contrasted with normal pregnancies, the maternal level of free beta-hCG is found to be higher, the NT measurement is found to be thicker, and the PAPP-A level is found to be lower (Heinig et al., 2007). Fetal growth restriction, exomphalos, and a single umbilical artery are the defining characteristics of Edwards syndrome, also known as trisomy 18. Patau syndrome is characterized by a collection of symptoms that include megacystis, fetal tachycardia, fetal growth restriction, and holoprosencephaly (Trisomy 13). In cases of Edwards syndrome and Patau syndrome, the levels of maternal beta-hCG and maternal PAPP-A are lower (Nicolaides, 2004).

In the first trimester, the screening test is carried out by utilizing both serum markers and NT measurement in conjunction with one another. The fetal nuchal translucency (NT) can be measured most accurately between weeks 11 and 14 of gestation. When taking the measurement, you should employ as much magnification as is practically possible. When determining the maximum thickness of the subcutaneous translucency, it is recommended that the measurement be taken sagittally while the patient is in a neutral position (Nicolaides, 2005). As only serum markers were measured for this study, NT measurement was not taken into account.

AFP is a 69 kDa glycoprotein derived from the fetal liver and yolk sac (Mizejewski, 2004). Increased maternal serum alpha-fetoprotein levels during pregnancy are associated with open neural tube defect and chromosomal aneuploidy (Wilson, 2014). Instances of open spina bifida and anencephaly are referred to as open neural tube defects. Due to the incomplete closure of the neural tube, they appear around 4 weeks into pregnancy (Palomaki et al., 2020). The AFP test is only used as a screening tool for neural tube defects. When it is found to be elevated, diagnostic fetal ultrasonography, as well as AFP and acetylcholinesterase measurements in the amniotic fluid, are required to be

performed (Wilson, 2014). AFP levels are found to be elevated in pregnant women with systemic lupus erythematosus (Petri et al., 1995), despite the fact that the incidence of neural tube defects is not found to be increased. In the course of our study, it was determined that the consumption of LMWH did not result in an increase or decrease in AFP and AFP MoM levels. The primary limitations of this study were the use of a retrospective methodology and the limited sample size. Our study is unique in that it is the first article to look into this topic, which is one of its strengths.

CONCLUSION

The screening test parameters for the group using LMWH during pregnancy were comparable to those of the control group. Our study demonstrated that LMWH use during pregnancy has no effect on either the first trimester screening test or tests for neural tube defects. Further studies with larger sample sizes are required to confirm our findings.

Conflict of Interest

The authors declare that they have no conflict of interest.

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Author contributions

Plan, design: AG; Material, methods and data collection: AG; Data analysis and comments: AG; Writing and corrections: AG

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