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Değerli Bilim İnsanları;

Dergimizin 2023 yılına ait ikinci sayısını sizlerle paylaşmaktan mutluluk duyuyoruz. Şubat ayında yaşadığımız deprem felaketine karşı gösterdiğimiz milli birlik ve beraberlik bizlere geleceğe dair umut vermektedir. Acılarımızı paylaşarak bu zor zamanların üzerinden hep beraber geleceğiz.

Dergimiz uluslararası EBSCO indeksinde yer almakta olup bu sayıda toplamda 15 makale yer almaktadır. Özgün araştırmalar içinde yeni doğan enfeksiyonları, emzirme aktivitesi ve plasenta previa ile ilişkin çalışmalar obstetrik pratiğinin zorluklarını ve sonuçlarını yansıtmaktadır. Bununla beraber, reprodüktif endokrinolojide anti-mullerian hormon ve endometrium kanseri hastalarında lenf nodu metastazı ile ilgili çalışmaların ilginizi çekeceğine eminiz.

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Characteristics of Healthcare-Associated Infections in a Neonatal Intensive Care Unit

Türkiye'de Bir Yenidoğan Yoğun Bakım Ünitesinde Sağlık Hizmetlerine Bağlı Enfeksiyonların Özellikleri

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ÖZ

Giriş: Sağlık hizmeti ile ilişkili enfeksiyonlar (SHİE), yenidoğan yoğun bakım ünitelerinde (YYBU) neonatal mortalite, morbidite ve sağlık bakım maliyetini artıran risklerden biridir. SHİE'lerin özellikleri farklı bölgelerde ve zaman içinde önemli ölçüde farklılık gösterdiğinden, sürekli SHİE sürveyansı, enfeksiyon kontrolü için SHİE oranlarını ve sağlık bakımıyla ilişkili patojenleri belirlemek açısından önemlidir.

Gereç ve Yöntemler: Türkiye'de üçüncü basamak bir referans merkezindeki SHİE'nin özelliklerini incelemeyi amaçladık. 2011-2013 yılları arasında YYBU'ye kabul edilen tüm yenidoğanlar bu çalışmaya dahil edildi. SHİE ile ilgili bilgiler "Ulusal Hastane Enfeksiyon Gözetim Ağı" ve Hastalık Kontrol ve Önleme Merkezleri (CDC)'nin standartlarına göre toplanmıştır.

Bulgular: Toplam yatan hasta sayısı 1030 idi. Bunların % 29'unda SHİE gelişti. SHİE'nin genel oranı ve yoğunluğu sırasıyla % 29.0 ve % 24.0 idi. Kan dolaşımı enfeksiyonları, SHİE 'lerin % 36.4'ü idi. En sık izole edilen mikroorganizmalar koagülaz negatif Staphylococci ve Klebsiella pneumonia idi. Ortalama metisilin direnci % 87, ESBL oranı % 79 ve VRE oranı %40 idi.

Sonuçlar: Bu çalışma, SHİE 'nin YYBU'de hala ciddi bir sorun teşkil ettiğini belirlemiştir. Sağlık bakımıyla ilişkili patojenler hakkında zamanında ve doğru epidemiyolojik bilgilerin mevcudiyeti, enfeksiyon kontrolü ve uygun ampirik antibiyotik seçimi için gereklidir.

Anahtar kelimeler: Yenidoğan Yoğun Bakım, Sağlık bakımı ile ilişkili enfeksiyon, yenidoğan.

ABSTRACT

Introduction: HCAI is one of the risks which increase neonatal mortality, morbidity, and health care cost in NICUs. As the characteristics of HCAIs vary considerably in different regions and over time, continual HCAI surveillance is important to determine HCAI rates and healthcare-associated pathogens for infection control.

Material and Methods: We aimed to analyze the characteristics of HCAI in a tertiary referring center in Turkey. All newborns admitted to the NICU between 2011-2013 were included in this study. HCAI related information has been collected according to the "National Hospital Infection Surveillance Network" and the definitions of Centers for Disease Control and Prevention.

Results: The total number of inpatients was 1030. Out of them, 29% have developed HCAI. The overall rate and density of HCAI were 29.0% and 24.0%, respectively. Bloodstream infections were 36.4% of HCAIs. The most frequently isolated organisms were coagulase-negative Staphylococci and Klebsiella pneumoniae. Overall methicillin resistance was 87%, ESBL rate was 79%, and VRE rate was 40%.

Conclusions: This study determined that HCAI still presents a serious problem in NICU. The availability of timely and accurate epidemiological information on healthcare-associated pathogens is necessary for infection control and the appropriate selection of empiric antibiotics.

Keywords: Neonatal Intensive Care, Healthcare-associated infection, neonate.

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INTRODUCTION

The medical and technical advances in neonatology have improved the survival of preterm infants with extremely low birth weight (ELBW) along with some possible risks. One of this risks ishealthcare-associated infections (HCAI). These infections cause a significant increase in neonatal mortality, morbidity, hospitalization days, and health care costs in intensive care units (ICUs) (1).

Healthcare-associated infections is localized or systemic condition resulting from an adverse reaction to the presence of an infectious agent(s) or its toxin(s) that was not present on admission to the acute care facility. It is known as nosocomial or hospital-acquired infection and is observed after the admittance of the patients with no prior infection (2). Healthcare-associated infections in terms of the key term "ICU-acquired infection" is defined as an infection occurring later than 48 hours after admission to an ICU, whereas CDC/NHSN requires that there is no evidence that the infection was present or incubating at the time of admission to the ICU, without time restriction (3). Although this difference, it has been reported an excellent concordance between US and European definitions of HCAIs as means of pneumonia and bloodstream infection (3).

In neonatal intensive care units (NICUs), HCAI rate varies in the range of 7.5-59 per 100 patients depending on environmental factors and differences in clinical practice (4-7). Since the incidence density is the most convenient way to correct for time (8,9), when reported as incidence density, the HCAI rate per 1000 hospital days in NICUs varies from 7.5 to 44.6, as giving the rates of HCAI from 3.9 to 15.1 per patient (4,10).

The frequency of HCAI depends on the birth weight, gestational age, and health care facilities. Neonatal infections in low- and middle-income countries are higher than that observed in industrialized countries. Turkey is a developing, middle-income country, and a wide range of HCAI rates (4.2-47.2 per 100 patients) and HCAI incidence density (9.4-20.9 per patient-days) have been reported in neonates (11-14). The most common types of HCAIs were reported as bloodstream infections, lower respiratory tract infections, and urinary tract infections respectively (6,15,16). Coagulase-negative Staphylococci (CoNS) is the most prevalent pathogen among the agents that cause HCAI (3) while gram-negative rods are major pathogens in developing countries (16-17).

The characteristics of HCAIs vary considerably in different regions, over time and referring to the hospitals. The availability of timely and accurate epidemiological information on healthcare-associated pathogens is essential for infection control and the appropriate selection of empiric antibiotics (18,19).

In this study, we aimed to analyze the characteristics of HCAIs including the clinical features, pathogen distribution, and antimicrobial susceptibility in a tertiary referral center in Turkey.

MATERIALS AND METHODS

This descriptive study was conducted by active search of infection records among newborns in the NICU of Marmara University Hospital with 568 beds (124 pediatric beds) during the period 1 January 2011- 31 December 2013. The neonatal intensive care unit with 16 beds has an occupancy rate of 100% and offers care to critically ill newborns, extremely low birth weight premature infants, neonates requiring pre-or postoperative management, and those who have congenital anomalies that require close observation or intervention. The nurse/baby ratio has been 1/3 in the study period.

HCAI related information has been collected prospectively according to the "National Hospital Infection Surveillance Network "UHESA" of The Turkish Ministry of Health. HCAI was defined using the criteria of the Centers for Disease Control and Prevention (CDC-2008) for children <1 year of age (2). The HCAIs were analyzed according to the birth weight of the babies. Group 1 included infants with a birth weight of 750 g and below, Group 2 between 751-1000 g, Group 3 1001-1500 g, Group 4 1501-2500g and Group 5 included infants with a birth weight of >2500 g.

Total number of inpatients, number of days in the hospital per patient, number of days on the ventilator, number of catheter days, and device utilization (DU) ratio per type of device were recorded. DU ratios were calculated by dividing the total number of device days by the total number of patient-days (20).

The extra length of stay was the difference between the length of stay of patients with HCAI and the length of stay of patients hospitalized in the NICU during that period who did not acquire a device associated (DA)-HCAI (21). Crude excess mortality in the NICU has defined as the difference between the crude overall case-fatality rate of patients with an HCAI and that of patients admitted without an HCAI and who did not acquire a HCAI in the NICU during the same period (22).

The frequency and causes of HCAIs, antibiotic sensitivities,

and resistance patterns among the NICU patients have been recorded. All information was recorded by a certified infection control nurse after clinical findings and culture results have been discussed with the consultant neonatologist and infectious disease specialist.

The study permission was obtained from Marmara university ethical committee (file number: 09.2021.1005)

Data were analyzed with descriptive statistics. The rates were calculated using overall HCAI rate, incidence density, device-specific infection rates.

RESULTS

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Table 1. Distribution of patients with healthcare-associated infection based on birth weight.

Birth weight (g)	Number of in-patients	Number of patient days	Number of infections	No. of HCAI per 1000 patient days
<750	36	1636	59	36.1
751-1000	29	1479	47	31.8
1001-1500	74	2599	76	29.2
1501-2500	224	3089	71	23.0
>2500	729	4580	63	13.7
Total	1092	13383	316	23.6

HCAI: Healthcare-associated infection.

Overall mortality rate (deaths per patient at risk) was 1.3% (14/1092) in this period and the rate of deaths in patients with HCAI (the rate of fatality of HCAI) was 8.0% (14/176). We calculated the crude excess mortality of HCAI as 0.8% (81/916). The total length of stay of 176 patients with HCAI was 9218 days while the total length of stay of 916 patients without HCAI was 4165 days.

The central line-associated bloodstream infection (CLABSI) rate was 0.6 per 1000 catheter days while ventilator-associated

pneumonia (VAP) rate was 13.7 per 1000 ventilator days and catheter-associated urinary tract infection (CAUTI) rate was 7.4 per 1000 catheter days. The patients acquired a total of 39 DA-HCAIs, giving an overall rate of 3.6% or 2.9% DA-HCAIs per 1000 ICU-days or 5.3 DA-HCAIs 1000 device days. The ratios of central line use, ventilator use, and urinary catheter use were 0.18, 0.32, 0.03 respectively.

The distribution of the type of HCAI was shown in Table-2. Of the total number of HCAIs, 115 (36.4%) were bloodstream infections (BSIs) with HCAI rate of 10.5%. Seventy-six (24%) of the bloodstream infections were diagnosed clinically because no growth was detected in the culture.

Table 2. The distribution of healthcare-associated infections.

Type of HCAI	**Number of infections (%)**	**The number of the HCAI per 1000 patient days**
BSI	115 (36.4%)	8.6
-Culture proven sepsis	*36 (11.4%)*	
-CLABSI	*3 (0.9%)*	*0.6 per 1000 catheter days*
-Clinically suspected sepsis	*76(24%)*	*5.7 per 1000 patient days*
Pneumonia	67 (21.2%)	5.0
- VAP	*33 (10.4%)*	*13.7 per 1000 ventilator days*
Eye, Eye, Ear, Nose, Throat or Mouth Infections	39 (12.3%)	2.9
Urinary Tract Infection	35 (11.1%)	2.6
- CAUTI	*3 (0.9%)*	*7.4 per 1000 catheter days*
Gastrointestinal Tract Infection	26 (8.2%)	1.9
- NEC	*14 (4.4%)*	*1.0 per 1000 patient days*
Skin & Soft Tissue Infection	20 (6.3%)	1.5
Central Nervous System Infection	12 (3.8%)	0.9
Surgical Site Infection	1 (0.3%)	0.08
Cardiovascular Infection	1 (0.3%)	0.08
TOTAL	**316**	**23.6**

BSI: Blood Stream Infection, CAUTI: Catheter-associated urinary tract infection, CLABSI: Central line-associated bloodstream infection,

One hundred twenty-seven microorganisms were isolated from 316 infections in 176 patients. The sources of the pathogens were bloodstream infections (33.9%), urinary tract infections (UTIs) (24.4%), conjunctivitis and upper respiratory tract infections (URTIs) (11.8%), pneumonia cases (10.2%), gastrointestinal infections (6.8%), skin and connective tissue infections (6.3%) and central nervous system infections (6.3%). Table-3 shows the distribution of the pathogens isolated from HCAI. The most common microorganisms were CoNS accounting for 23.6% (30/127), Klebsiella pneumoniae 20.5% (26/127), Escherichia coli 6.3% (8/127), influenza virus 5.5% (7/127), and Acinetobacter baumannii 6.3% (8/127).

HCAI: Healthcare-associated infection, NEC: Necrotizing enterocolitis, VAP: Ventilatory Associated Pneumonia.

Table 3. Isolated microorganisms in healthcare-associated infections.

Microorganism	No.	Rate (%)
CoNS	**30**	**23.62**
Klebsiella pneumonia	**26**	**20.47**
Escherichia coli	**8**	**6.3**
Acinetobacter baumannii	**8**	**6.3**
İnfluenza virus	**7**	**5.51**
Stenotrophomonas maltophilia	**5**	**3.94**
Pseudomonas aeruginosa	**5**	**3.94**
Clostridium difficile	**4**	**3.15**
Viridans group streptococcus	**4**	**3.15**
Rotavirus	**4**	**3.15**
Staphylococcus aureus	**3**	**2.36**
Klebsiella oxytoca	**3**	**2.36**
Serratia marcescens	**3**	**2.36**
Enterococcus faecalis	**3**	**2.36**
Enterobacter cloacae	**3**	**2.36**
Enterobacteriaceae	**2**	**1.57**
Enterococcus faecium	**2**	**1.57**
Citrobacter spp.	**2**	**1.57**
Candida glabrata	**1**	**0.79**
Candida lusitaniae	**1**	**0.79**
Other klebsiella strains	**1**	**0.79**
Other streptococci	**1**	**0.79**
Morganella morgagnii	**1**	**0.79**
TOTAL	**127**	**100%**

When the antibiotic resistance of the microorganisms in this study is analyzed, methicillin resistance was detected in 33.33% of Staphylococcus aureus strains (MRSA) (1/3), and 89% of coagulase-negative Staphylococci (24/27). Overall methicillin resistance was 83%. Of 88% of Klebsiella pneumoniae isolates were extended-spectrum β-lactamase (ESBL) producers (23/26), whereas 66.67% of Klebsiella oxytoca isolates produced ESBL(2/3). Of Escherichia coli, 63% were ESBL producers (5/8). All Enterococ-

cus faecium strains were vancomycin-resistant (100%) (2/2) whereas Enterococcus faecalis showed no resistance to glycopeptides (0/3). Overall vancomycin-resistant Enterococci rate was 40%. Of Acinetobacter spp. isolates, 75% were resistant to carbapenems. Overall carbapenem resistance was 23.5%. All Acinetobacter baumannii isolates in our unit were sensitive to colistin.

DISCUSSION

Neonatal infection is an important cause of mortality and morbidity worldwide. Monitoring infection rates is increasingly regarded as an important contributor to high-quality health care. HCAIs usually appear due to multidrug-resistant microorganisms, thus blood culture results and surveillance studies have significant contributions in planning proper antibiotic treatment (9).

HCAI rate in NICUs varies between 17.4-157.7 per 100 patients in the literature (10,16,23). The characteristics of HCAIs vary considerably in different regions, over time and referring to the hospital thus the availability of timely and accurate epidemiological information on healthcare-associated pathogens is crucial. In this study, the HCAI rate and density in our neonatal intensive care unit were determined as 28.9 per patient and 23.6 per 1000 patient days, respectively. Turkey is a middle–income country and HCAI rates and antimicrobial resistance is serious problem in the intensive care units overall. However, there are a limited number of studies reporting HCAIs in NICUs. Among them, only a few studies are following CDC criteria (24-27). In the surveillance study done by our group in 2001, HCAI rates of 11.3 per 100 patients and 16.1 per 1000 patient days were recorded (28). The reasons for the recent increase in HCAI rates in our unit could be due to the relocation of the hospital in a low income-suburban area with inadequate antenatal care, the admittance of high-risk pregnancies, increase in the hospitalization of surgical cases, and survival of premature infants due to the advances in the technology that results in prolonged hospitalization. A similar study on 314 patients in 2007 at the Uludag University School of Medicine in Turkey showed HCAI rates of 42.3 per 100 inpatients and 17.9 per 1000 patient days (13).

Although many previous studies worldwide have been done to identify the epidemiology of the HCAIs among neonates in NICUs, the incidence or prevalence of HCAI differs within different regions in the world because it varies based on birth weight, underlying diseases, medical facilities, and level of care in different centers. Centers for Disease Control and Prevention reported HCAI data of USA as device-related infection rates based on birth weight and but not overall HCAI rates in NICUs during recent years. Spain and Brasil reported their HCAI rate as 74.3 and 157.7 HCAIs per 100 patients respectively (16,29). Taiwan has a much lower HCAI rate (13.6 per 100 patients) (30). Similarly, it has been reported that European countries have an HCAI rate of 7-17.4 per 100 patients (23,31). The rates obtained in our study are significantly higher than the rates in industrialized countries. It has been reported that the rates of neonatal nosocomial infections in low-income and middle-income countries are 3 to 20 times higher than observed in industrialized countries (17). This is mainly because of the lack of proper infection control measures and infrastructure to provide appropriate care to vulnerable infants.

Some investigators believe that reporting overall incidence rates may be misleading, because of the wide variations in practice and patient characteristics in different centers; therefore the NHSN system monitors DA-HCAI rates by using an approach that accounts for variability in device use and length of hospital stay (32). For this reason, it is difficult to compare the data on HCAI rates between different centers in different regions of the world and every hospital should implement its own strategy to prevent HCAIs and compare the results with its previous data. It is necessary that common HCAI monitoring methods, terminologies, and statistics should be implemented worldwide.

In NICUs, the most frequently reported HCAIs are bloodstream infections (25-60%) followed by pneumonia (6.8-32.3%) and urinary tract infections (1,32,33). In our study, bloodstream infection rate was 36.4% followed by pneumonia (21.2%), conjunctivitis, and URTI and UTI, respectively. Contrary to the literature, conjunctivitis, and URTI had the third-highest rates, possibly referring to the 2012 influenza virus epidemics.

Critically ill premature infants are especially vulnerable to HCAIs due to their immature immune systems, poor skin integrity, contact with invasive devices, and contact with multiple careers (15). Birth weight and gestational age are inversely proportional to HCAI (32). It has been reported that in Japan between 2002 and 2003, the HCAI rate was 25.2 per 100 patients among the babies with birth weights less than 1000 g, yet 8.4 per 100 patients among the babies with birth weights between 1000 and 1500 g, and 3.7 per 100 patients with birth weights more than 1500 g (34). According to a study in Italy in 2002, the HCAI rate has been reported as 48 per 100 patients among babies less than 1500 g (31). Similar to the numbers in the lite-

rature, our studyrevealed a HCAI rate of 34.1 per 100 patients among the babies with birth weights less than 1000 g, 25.4 per 100 patients between 1001 and 1500 g. 20.7 per 100 patients between 1501 and 2500 and 19.8 per 100 patients among the babies with birth weights more than 2500 g. Even though our high HCAI rate among ELBW infants showed similarity to other reports, the rate among bigger babies is considerably higher than those reported in the literature for these cases. We believe that the main reason for the high rates in this group is the high rate of surgical cases, each of isolation facilities, staffing numbers. Cases that require surgery, prolonged hospitalization such as babies with a congenital heart defect (CHD), congenital anomalies and congenital diaphragmatic hernia (CDH) increase the rate of infection in these babies. A new detailed program of infection control has been implemented after this study. As a result, the HCAI rate was reduced from 36.2 to 24.9 per 100 patients compared with the rate in the previous year.

Device associated-HCAI has been a primary and serious cause of patient morbidity and attributable mortality in developing countries, and it has shown to be a critical factor, predisposing hospitals to increased healthcare costs. For the year 2012, NHSN facilities reported more than 3957 VAPs and the incidence for various types of hospital units ranged from 0.0-4.4 per 1000 ventilator days (35). This data is quite lower than those presented by other Turkish centers (15.4-28.1 per ventilator days) (12,14). In this study, the VAP rate was 13.7 per ventilator days which is higher than those of developed countries. In our unit, the patient: nurse ratio (3:1) can negatively affect adherence to infection control measures and may have played a role in the higher VAP rate.

The rate of CLABSI is reported as 3.8 -12.8 per 1000 catheter days in the literature (36). However, the rate of CLABSI in this study is 0.6 per 1000 catheter days, which is quite low compared to those reported in the literature. This result however is thought to be deceptive. The main reason is probably the low frequency of obtaining both catheter and peripheral culture from small preterm infants and small amounts of blood culture samples.

The agents that cause HCAI in NICUs vary over the years. While the most isolated agent is CoNS in most developed countries today, it is Klebsiella pneumoniae in developing countries (17). In a study that included 16 centers, Turkish Neonatology Society reported that most of nosocomial sepsis were due to gram-negative bacteria, mainly Klebsiella (37). Our study revealed that the most frequently isolated agent in our unit is CoNS, followed by Klebsiella pneumoniae, which is the most frequently isolated agent overall in neonatal intensive care units in Turkey. Coagulase-negative Staphylococci still remains the most common microorganism associated with catheter-related BSIs including peripheral intravenous (PIV) catheter-related BSIs and CLABSIs (1,32,38). PIVs are the most commonly used device for vascular access in newborns. As the lack of evidence to recommend elective removal of PIVs after 72 hours, these catheters are used until they are occluded or there is any extravasation. Although PIVs might be the main source of CoNS infections as well, a conclusive correlation has not been shown between the higher colonization noted after 72 hours and an increased rate of catheter-related BSI (32).

In the developed world, the increase in CoNS related infections is tied to the increased survival rate of ELBW infants, the common use of intravascular catheters, parenteral nutrition, and the use of intravenous lipid emulsions. On the contrary, inappropriate use of broad-spectrum antibiotics and lack of appropriate infection prevention measures can be shown as the main reasons for Klebsiella pneumoniae or other negative gram-negative bacteria.

Although fungi is one of the common causes for blood-stream infections in NICU (36), we found that the rate of Candida isolates was 1.57% in our group. Furthermore, these fungi isolates were only non-albicans species. We interpret this finding that we have implemented fluconazole prophylaxis in preterm infants (< 1000 g) for last 8 years.

There is a direct association between antibiotic overuse and antibiotic resistance, which is becoming increasingly common in NICUs. It is shown that the microorganisms causing HCAI in developed countries are 70% multi-drug-resistant (36,39). Among these, 28.5% of the enterococci are resistant to vancomycin, 59% of Staphylococcus aureus and 89% of CoNS are resistant to methicillin (36). In the study presented here, it is observed that CoNS is 90% methicillin-resistant, and that Klebsiella pneumoniae produced 82.6% ESBL.

Enterococcus faecalis and Enterococcus faecium are common and important healthcare-associated pathogens worldwide today (40). Most enterococcal infections are due to E. faecalis (80%), although epidemiology is changing, and E. faecium isolates now account for up to 20% concomitantly with the rise of vancomycin-resistant isolates (40) E. faecium isolates are ten-times more likely to be vancomycin-resistant than E. faecalis. In Europe, surveillance data shows a large variability between the various countries and the HCAI rate due to vancomycin-resis-

tant enterococci (VRE) ranges from <2% (Finland, Holland) to >20% (Ireland, Greece, Portugal) (40). According to the culture results in this study, the rate of isolated Enterococci was 4% (5 cases), which consisted of vancomycin-resistant E. faceium (2 cases) and E. faecalis with no resistance to vancomycin. The reason for the minimal VRE infections seen in our NICU is tied to the proper use and control of antibiotics. The education of the hospital staff, cohorting of VRE-exposed babies, active surveillance, hand hygiene, an inspection of infection prevention measures, and proper antibiotic strategies are the most important components in preventing VRE infections (39).

CONCLUSIONS

This study determined that the most frequently seen HCAI bacteria are gram-positive bacteria followed by Klebsiella strains. It is also shown that Klebsiella and ESBL rates are higher than the rates observed in developed countries. HCAI still presents a serious issue in Turkey. It is believed that determining the HCAI rates and agents through widely spread prevalence studies along with the information obtained from these studies will help to reduce the mortality and morbidity rates of HCAI.

Strength and limitations: The tests were performed in an advanced microbiology laboratory, and the study was conducted in a referral center. But the limitation of the study was its retrospective nature.

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Is SARS-CoV-2 a risk factor for hypotension during spinal anesthesia for obstetric patients?

Obstetrik hastalarda, SARS-CoV-2 spinal sonrası hipotansiyon için risk faktörü müdür?

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ÖZ

Amaç: COVID-19 pandemisinin başından itibaren, sezaryen operasyonlarında genel anestezide entübasyon ve ekstübasyon sırasında olası virüs yayılımını önlemek için Nöroaksiyel anestezi uygulanması önerilmektedir. Ancak yapılan bazı çalışmalarda aktif COVID-19 varlığında spinal anestezi güvenliğinin, hipotansiyon nedeniyle tartışmalı olduğu belirtilmektedir. Bu çalışmamızda amacımız COVID-19'lu gebe hastalardaki spinal sonrası hipotansiyon oranını literatürde ki COVID 19 olmayan hastalarla karşılaştırarak, Nöroaksiyel anestezinin güvenirliliğini tespit etmektir.

Gereç ve Yöntem: Pandeminin başından, Aralık 2020 yılına kadar olan COVID-19'lu gebelerin medikal kayıtları retrospektif olarak çalışmaya dahil edilmiştir. Demografik- vital, özellikle sistolik ve diastolik kan basınçları, kullanılan efedrin-atropin dozları, infüzyon volümleri ve bulantı- kusma sıklığı analiz edilmiştir.

Bulgular: Spinal anestezinin neden olduğu hipotansiyon hastaların 54'ünde görülmüştür. (%21,69). Vazopressor (efedrin) tüm hipotansif hastalarda kullanılmıştır. Demografik veriler, kullanılan bupivakain ve spinal anestezi öncesi kullanılan kristaloid volüm miktarı hipotansif olan ve olmayan hastalar arasında farklılık göstermemiştir.

Sonuç: Literatürde ilk defa çalışmamızda tek merkezli 249 COVID 19 (+) hastanın spinal anestezi sonrası hipotansiyon oranları ile literatürde ki spinal anestezi sonrası hipotansiyon oranları arasında istatiksel olarak fark olmadığı gösterilmiştir. COVID-19 hastalarında rejyonel anestezinin güvenle uygulanabileceğini önermekteyiz.

Anahtar kelimeler: Hipotansiyon, obstetrik anestezi, rejyonel anestezi, spinal anestezi, SARS-CoV-2

ABSTRACT

Background: Since the onset of COVID-19, recommendations suggest the use of neuraxial anesthesia, over general anesthesia for cesarian section to avoid the risks of aerosolization associated with intubation and extubation. But the safety of performing spinal anesthesia is unclear especially for post spinal hypotension, during the presence of active COVID-19. According to a few studies there was a controversial discussion about the safety of regional anesthesia. In this study we aimed to compare the incidence of hypotension in COVID-19 pregnant patients between non-COVID 19 pregnant patients in the literature to see if the spinal anesthesia is safe or if it poses an additional risk.

Materials and Methods: Medical records of COVID-19 pregnant women for cesarean section from the beginning of the pandemic up to December 2020 were retrospectively retrieved. All the demographic-vital data, including systolic and diastolic blood pressure (SBP-DBP), ephedrine-atropine doses, infusion volumes, and nausea and vomiting were retrospectively analyzed.

Results: Spinal anesthesia induced hypotension was seen 54 of the patients (21,69%). And vasopressors (Ephedrine) were used to all hypotensive patients. Demographic data's, the amount of bupivacaine and crystalloid volume which used before the spinal anesthesia showed no differences between hypotensive and non-hypotensive patients.

Conclusion: This is the first retrospective study which shows 249 COVID 19 patients' data in one center that no significant difference was seen in the incidence of hypotension associated with spinal anesthesia for COVID-19 cesarean section compared to non-COVID group in literature. We recommend using of regional anesthesia safely for patients and anesthesiologists during active COVID-19 patients.

Keywords: hypotension, obstetrical anesthesia, regional anesthesia, SARS-CoV-2, spinal anesthesia

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INTRODUCTION

The emergence of severe acute respiratory syndrome coronavirus 2 (SARS- CoV-2), which has been defined as coronavirus disease 2019 (COVID-19), has prompted innumerable alterations in the practice of anesthesiology. The nature of the association between COVID-19 and pregnancy outcomes remains unclear, and meta-analyses involving patients with COVID-19 who are pregnant are limited. A 2020 systematic review suggested that people who are pregnant did not have an increased risk of SARS-CoV-2 infection or symptomatic COVID19, but they were at risk of severe COVID-19 when they are infected compared with those who were not. (1) And unlike previous viral pandemics, COVID-19 incidence, prognosis, and maternal and neonatal outcomes do not appear to be worse in pregnant women compared to the general population. (2)

In addition to the suggestion of regional anesthesia for the obstetric population, the higher rate of aerosol transmission to healthcare personnel, The American Society of Regional Anesthesia (ASRA), the European Society of Regional Anesthesia and Pain Medicine (ESRA) and the European Society of Anesthesiology (ESA) published guidance on employing regional anesthesia in patients with COVID-19. (3,4)

With regional anesthesia, the risk of person-to-person transmission, which is 6,6 times higher during the respiratory procedures performed in general anesthesia, is minimalized. (5)

The question is, "is regional anesthesia safe for pregnant COVID-19 patients undergoing cesarean section?". In a retrospective analysis at the beginning of the pandemic, Chen et al. reported a higher rate of hypotension after neuraxial blocks. (7) After this study, some questions about the safety of regional anesthesia appeared in minds. (7, 8). However, the effects of SARS-CoV-2 infection on the hemodynamics of pregnant women who underwent neuraxial anesthesia for cesarean delivery are still unclear.

Is there a higher risk of hypotension in COVID-19 pregnant women during regional anesthesia? The goal of this study was to compare the incidence of hypotension in COVID-19 pregnant patients to the incidence of hypotension in non-COVID 19 pregnant patients in the literature to see if spinal anesthesia is safe for this group of patients or if it poses an additional risk.

MATERIALS AND METHODS

After the approval of the local ethical committee, we retrospectively analyzed the files of COVID 19 patients who underwent cesarean section under spinal anesthesia to determine the incidence of hypotension and management strategies for hypotension. The study was carried out with the principles of the Helsinki Declaration. Medical records of COVID-19 pregnant women who were admitted to our hospital for cesarean section were retrospectively retrieved from the beginning of the pandemic up to December 2020. The diagnosis criteria followed the guidelines of the National Health Commission of Turkey, and the SARS-CoV-2 nucleic acid test positivity.

We accepted neuraxial anesthesia-related hypotension as hypotension from the time of local anesthetic injection until 15 min after delivery of the newborn. Hypotension was defined as a systolic blood pressure below 100 mm Hg or a mean arterial pressure below 70 mmHg. All the demographic-vital data, including systolic and diastolic blood pressure (SBP-DBP), ephedrine-atropine doses, crystalloids and colloid infusion volumes, newborn birth weight, and nausea and vomiting were recorded too.

SPSS 17.0 was used to conduct the statistical analysis (SPSS Inc, Chicago, IL, USA). Continuous variables were represented as mean, standard deviation, and median (min-max), while categorical variables were represented as numbers (percentage). The Kolmogorov- Smirnov test was used to assess conformity to normal distribution. When comparing normally distributed data, the student's t-test was used, when data is normally distributed data, the Mann Whitney U test was used. Pearson's chi-square or Fisher's test was used for comparison of categorical variables. For all tests, $p < 0.05$ was considered statistically significant.

RESULTS

249 confirmed COVID-19 patients were included for this study. 54 of 249 cases were hypotensive (21.69 %) and 195 (78.31 %) were normotensive. Demographic data and baseline hemodynamic values were similar between hypotensive and normotensive patients, and no statistical difference was found. 46 of the hypotensive patients and 126 of the non-hypotensive patients were asymptomatic for COVID-19. 8 of the hypotensive and 39 of the non-hypotensive COVID-19 group patients showed only one of the cough, fever, dyspnea, and tachypnea symptoms, and no statistically significant differences were found. The mean bupivacaine usage was 12,58 ± 0,89 mg (11-15 mg) for the hypotensive group and 12,61 ± 1,08 mg (10-15 mg) for the non-hypotensive group. The difference was insignificant

(p=0,74) (Table 1). There were no statistically significant differences between the groups (p =0,62) when 1154,72 ± 426,78 (500-2500) ml crystalloid was infused in the hypotensive group and 1169,70 ± 338,11 (500-2500) ml crystalloid was infused in the non-hypotensive group (Table 1). Colloid infusion was used for 19 of the non-hypotensive and 15 of the hypotensive patients and no statistically differences were found. (p=0.49).

Ephedrine was used for all the hypotensive patients. Atropine was used 3 of the hypotensive and 1 of the non-hypotensive group patients. Atropine usage was significant between groups (X2=5,53 p=0,019) (Table 1).

Table 1: Demographic properties and total amount of drugs of the groups.

	Mean arterial pressure> 70 mm Hg (n=195)	Mean arterial pressure<70 mm Hg (n=54)	p
Age	29,14 ± 5,21 (16-42)	29,74 ± 5,01 (22-45)	0,66
Weight	83,25 ± 17,83 (52-161)	82,21 ± 12,71 (61-110)	0,91
Hight	163,87 ± 7,47 (150-180)	161,00 ± 8,23 (150-175)	0,34
Bupivacaine dosage (mg)	12,61 ± 1,08 (10-15)	12,58 ± 0,89 (11-15)	0,74
Ephedrine dosage (mg)		14,72 ± 6,89 (5-35)	
Crystalloid amount (ml)	1169,70 ± 338,11 (500-2500)	1154,72 ± 426,78 (500-2500)	0,62

Data are expressed as mean ± SD

Newborn weight was 3030,39 ± 575,10 gr for the hypotensive COVID-19 group and 3064,10 ± 604,84 gr for the non-hypotensive COVID-19 group, and there was no statistical difference between the groups (p=0,59).

Nausea and vomiting were observed in 4 (7.41 %) of the hypotensive patients and 12 (6.15 %) of the non-hypotensive group (X2: 0.001, p=0,97).

DISCUSSION

This is the first retrospective study which shows 249 COVID 19 patients' data in one center that no significant difference was seen in the incidence of hypotension associated with spinal anesthesia for COVID-19 cesarean section compared to non-COVID group in literature.

COVID-19 has presented challenges to healthcare systems around the world and will continue to do so for months and perhaps years. The threats that the disease poses to both patients and healthcare workers have changed medical practice, but these changes can offer opportunity to those with subspecialty interests in areas such as regional anaesthesia.

At the beginning of the COVID-19 pandemic there wasn't enough data about which anesthesia technique must be use or which one is better for mother, newborn, and all health care workers (6-8).

All we know is that virus was transmitted by aerosol and the risk of transmission of acute respiratory infection to health professionals during tracheal intubation is 6,6 times higher in the group exposed (5). However, some of these potential benefits of regional anesthesia for healthcare workers and the institution rather than the patients themselves, and we must not forget that patients are at the center of the shared decision-making process when selecting the safest and most effective anesthetic technique for a surgical procedure.

According to a recent editorial, "it is reasonable to consider administering regional anesthesia to patients at higher risk of complications simply to avoid general anesthesia during the pandemic." But the question is, what complications are we dealing with, and what can we do about them?

At the beginning of the pandemic Chen et all state that they used continuous epidural anesthesia or combined spinal-epidural anesthesia (CSE) technique for COVID 19 cesarian section procedures and hypotension was significantly seen 12 of the 14 women —indeed, a high incidence of hypotension. (6). They didn't explain which technique or drug they used (epidural or combined spinoepidural anesthesia) for the anesthesia. In the correspondence of the article, they state that they didn't prefer spinal anesthesia because of possible virus location in the cerebrospinal fluid and the risk of viral spread and they chose epidural anesthesia (10). Epidural anesthesia, which is nowadays a less common choice for scheduled cases, then the high incidence of hypotension is more concerning. They explained the perioperative hypotension with SARS-CoV-2 binds to the angiotensin converting enzyme-II (ACE2) receptor and the ACE2 receptor is a cardio-cerebrovascular protective factor, which plays an important role in regulating blood pressure, in

addition to have an anti-atherosclerosis mechanism (11).

Zhang and Chen et al compared hypotension after regional anesthesia in COVID 19 and non-COVID 19 pregnant patients in another multicenter study (12). After propensity score matching, they included 286 subjects, 186 SARS-CoV-2-infected parturients, and 101 uninfected parturients. The incidence of neuraxial anesthesia-related hypotension in COVID-19 parturients was 57.4% versus 41.9 % in control parturients, indicating a significant difference between the groups. However, there were a few points that were contentious. The authors gathered all regional anesthesia data (spinal, epidural, and combined-spinal epidural (CSE) technique data), and hypotension was defined as a systolic blood pressure of less than 100 mmHg or a mean arterial blood pressure of less than 80% of the baseline value (the mean of repeated measurements before commencing anesthesia). They used vasopressors and fluids both prophylactically and after hypotension developed. The mean arterial pressure in the hypotensive group was 83,9 mmHg. Furthermore, the description of a mean arterial blood pressure below 80% of the baseline value is debatable (13). We only looked at data from spinal anesthesia patients, and hypotension was defined as a systolic blood pressure of less than 100 mm Hg or a mean arterial pressure of less than 70 mm Hg. Vasoconstrictors were only used to treat hypotension, not to prevent it.

In another study, Karasu et al. looked at the cesarian section practices of 61 COVID-19 patients. For 58 of the patients, spinal anesthesia was used, and the incidence of hypotension was 25,9%, which was similar to our findings. Hypotension was found to be prevalent in 21.69 percent of the participants in our study (14).

Before the COVID19 pandemic, a few studies looked at the effects of spinal anaesthesia on vital parameters in pregnant women. Mercier et al discovered that without pharmacologic prophylactic measures, hypotension can occur in up to 80% of women after spinal anaesthesia for caesarean section (15). Lato et al used Doppler sonography to evaluate 40 women before and after spinal anaesthesia. They discovered that after spinal anaesthesia, blood pressure dropped significantly in 90% of the women, and that 43% of the women experienced severe hypotension (16).

Many theories have been proposed to explain the high incidence and severity of hypotension during spinal anesthesia caesarean deliveries (17-18). Maternal age, BMI, weight gain, gravidity, history of hypotension, baseline heart rate, fluid preloading, and anesthetic adjuvant have all been shown to be predictors of spinal anesthesia-related hypotension in cesarean section (19). Other important factors include the height (T5-T4) and density of the sensory block, the increased sensitivity to local anesthetics combined with the effects of the sympathetic block during pregnancy, the amount of local anesthetic, the aggravating role of aortocaval compression by the gravid uterus-baby weight and experience of the anesthesiologist, ASA physical status, urgency of surgery, and surgical department to be predictive factors for spinal anesthesia related hypotension in cesarean delivery (19-22).

There were no differences between groups in terms of demographic data, baby weight and trimester, amount of local anesthetic, or volume of crystalloid infused in our study. Furthermore, all of the anesthesiologists had at least ten years of experience in obstetric anesthesia.

For many years, perioperative spinal hypotension was believed to arise primarily because of venous vasodilation. However, studies that have utilized cardiac output monitoring have demonstrated that arterial vasodilation is more likely to be responsible for the decrease in blood pressure following spinal anaesthesia, rather than decreased venous return and cardiac output, at least initially (23). Techniques such as fluid loading, vasopressor administration and lower limb compression have been shown to decrease the incidence of spinal-induced hypotension during cesarean section (17). However, no single regimen has eliminated clinically significant maternal hypotension, and combination of techniques may be beneficial, but vasopressors are now recognized as the most important option in the management of hypotension (23). After spinal anesthesia, there is a fall in the mean arterial pressure and a marked reduction in systemic vascular resistance despite increase in cardiac output, heart rate, and stroke volume in the first 15 min after induction of spinal anesthesia even after fluid therapy can be seen. In this situation best treatment is using vasoconstrictors for treatment (24, 25). In this study crystalloid infusion were coloaded during the spinal anesthesia performing for hypotension prophylaxis and treatment, and if the hypotension was persistent crystalloid- colloid volume replacement and intravenous ephedrine 10 mg were used.

We used ephedrine, which is one of the best choices due to its availability for vasopressor treatment in obstetric anesthesia, with a minimum dose of 5 mg and a maximum dose of 35 mg given to all hypotensive patients. In addition, parasympatholytic atropine was used in this study for three hypotensive and one

non-hypertensive group patients, which was statistically significant.

Several authors have reported that low-dose spinal anesthesia for cesarean delivery, using doses of 5-7 mg intrathecal bupivacaine, results in a lesser degree of sympathectomy, vasodilation, and hemodynamic changes, including hypotension. Although a lower intrathecal bupivacaine dose reduces the risk of hypotension and the associated nausea and vomiting, it increases the need for intraoperative analgesic supplementation. It also leads to a shorter duration of block and a slower onset speed (26). If a low-dose spinal anesthesia is planned, the combined-spinal epidural technique, which allows for the use of an epidural catheter to augment the block, if necessary, should be used. Low-dose CSE anesthesia, on the other hand, is superior to single-shot spinal anesthesia only in "complicated" patients (such as those with cardiovascular disease and compromised babies) and/or when a complicated or prolonged caesarean delivery is expected (27). Otherwise, for the majority of patients, single-shot spinal anesthesia is now an effective, quick, simple, and safe option. Furthermore, obstetric anesthesiologists must keep in mind that low-dose spinal anesthesia may necessitate additional analgesia or mask ventilation. During pandemics, mask ventilation or the need for general anesthesia increase the risk of exposure to patients' respiratory secretions as well as the risk of perioperative viral transmission to healthcare workers and other patients. Already we know that in pregnancy functional residual capacity, end-expiratory volumes and residual volumes decreases. Also decreased total lung capacity and inability to clear secretions can make pregnant women more susceptible to severe respiratory infections (28). We know that COVID-19 causes acute respiratory failure, with a major change in the ventilation- perfusion ratio and pulmonary shunt, leading to hemoglobin desaturation, and signs and symptoms of respiratory discomfort or failure (29). In a recent study showed that 82 (5.4%) of the COVID-19 patients with severe or critical illness during pregnancy, and 10 (0.7%) required mechanical ventilation (30). In light of all available information, general anesthesia poses a risk to both the patient and all medical personnel in the operating room.

There was no failure for regional anesthesia among the 249 patients in our retrospective analyses, and none of them were converted to mask ventilation or general anesthesia. When compared to non-COVID 19 pregnant women, we concluded that using spinal anesthesia in cesarean section is quick, effective, and safe for pregnant women with COVID-19 infection. COVID 19 infection does not appear to be a risk factor for hypotension after spinal anesthesia in infected women.

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Perceived Stress, Breastfeeding Motivation and Breastfeeding Success among Mothers with Newborn Infants' Hospitalization in the Neonatal Unit

Bebeği Yenidoğan Ünitesinde Yatan Annelerin Algıladıkları Stres, Emzirme Motivasyonu ve Emzirme Başarısı

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ÖZ

Amaç: Bu araştırma bebeği yenidoğan ünitesinde yatan annelerin algıladıkları stres, emzirme motivasyonu ve emzirme başarısını belirlemek ve aralarındaki ilişkiyi saptamak amacıyla yapıldı.

Gereç ve Yöntem: Bu kesitsel çalışmanın örneklemini 128 term yenidoğanın annesi oluşturdu. Gerekli izinler alındıktan sonra veriler tanıtıcı özellikler veri formu, algılanan stres ölçeği, emzirme motivasyonu ve LATCH emzirme tanılama ölçeği kullanılarak toplandı. Verilerin değerlendirilmesinde tanımlayıcı istatistiksel analizler, Mann-Whitney U testi, Kruskal-Wallis, Dunn-Bonferroni, Spearman korelasyon analizleri kullanıldı. P< 0.05 istatistiksel olarak anlamlı kabul edildi.

Bulgular: Bu çalışmada bebeği yenidoğan ünitesinde yatan primipar annelerden ileri yaşta, ilköğretim ve lise mezunu olan, çalışmayan, doğum öncesinde emzirme eğitimi almayan ve bebeğini doğumdan hemen sonra emzirmeye başlayanların algıladıkları stresin daha yüksek olduğu belirlendi. Araştırmada genç annelerin, üniversite mezunu, çalışan, gebeliği planlı olan ve doğum öncesi emzirme eğitimi alan primipar annelerin emzirme motivasyonu daha yüksekti. Çalışma sonuçları lise ve üniversite mezunu, gebeliği planlı olan, doğumdan önce emzirme eğitimi alan annelerin LATCH ölçeği puanlarının daha yüksek olduğunu gösterdi (p<0.05). Bu araştırmada algılanan stres azaldıkça, emzirme motivasyonu ve emzirme başarısının arttığı belirlendi. Emzirme motivasyonu ile emzirme başarısı arasında ilişki bulundu (p<0.05).

Sonuç: Bebeği yenidoğan ünitesinde yatan annelerin stres düzeylerinin azaltılması ve emzirme motivasyonlarını artırmaya yönelik yenidoğan hemşirelerince eğitim ve müdahale çalışmalarının planlanması ve uygulanması önerilmektedir.

Anahtar Kelimeler: Yenidoğan, anne, emzirme, stres, motivasyon.

ABSTRACT

Aim: This research aimed to determine perceived stress, breastfeeding motivation, and breastfeeding success and to reveal the relationship between them, among mothers with newborn infants' hospitalization in the neonatal unit.

Materials and Methods: This cross-sectional study sampling consisted of 128 term newborn's mothers. After obtaining the necessary permissions data were collected via introductory characteristics form, perceived stress scale, breastfeeding motivation scale, and LATCH breastfeeding assesment scale. Descriptive statistical analyzes, Mann-Whitney U test, Kruskal-Wallis, Dunn-Bonferroni, and Spearman correlation analysis were used for data analysis. P< 0.05 was considered statistically significant in all analyses.

Results: In this sample, the perceived stress was higher among primiparous mothers with newborn infant in the neonatal unit, who were older age, primary and high school graduates, nonworking, who did not receive prenatal breastfeeding training, and started breastfeeding immediately after birth. Breastfeeding motivation was higher among young mothers, university graduates, working, mothers with a planned pregnancy, and who received prenatal breastfeeding training. The results also showed that mothers who graduated from high school and university, whose pregnancy was planned, and who received prenatal breastfeeding training had higher LATCH scale scores. As perceived stress decreased, breastfeeding motivation and breastfeeding success increased, in this study (p<0.05). A correlation was found between breastfeeding motivation and breastfeeding success (p<0.05).

Conclusion: It is recommended that neonatal nurses plan and implement training and intervention studies to reduce the stress levels of mothers whose newborn infants are hospitalized in the neonatal unit and to increase their breastfeeding motivation.

Keywords: Neonates, mother, breastfeeding, stress, motivation.

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INTRODUCTION

Human milk is the main source of nutrition for the newborn. Successfully initiating and maintaining breastfeeding and supporting breastfeeding mothers is one of the most important health goals in terms of immunological, physiological, psychological, and developmental benefits for the newborn (1,2). An estimated 823,000 child deaths can be prevented each year by increasing breastfeeding rates (2). The first hours after birth are critical for initiating and maintaining breastfeeding. Even if there is no life-threatening situation in this process, the fact that newborn hospitalization in the neonatal unit negatively affects the mother-infant interaction as well as the breastfeeding process (3).

One of the main causes of stress and anxiety for parents whose newborn infants are admitted to the neonatal unit is that they are unable to embrace the healthy infant they dreamed of after the emotional rollercoaster of pregnancy and birth (4). In addition, the chaotic environment of the neonatal unit with the sound, light, and medical devices, the restriction of the caregiver role of the parents, especially the mother, the nurses assuming the major responsibility in the care of the newborn infant, the uncertainties about the newborn's health can be counted as other stressors affecting parents with newborn infants in the neonatal unit (5,6). In a previous study, it was reported that hospitalization in the neonatal unit reduces exclusive breastfeeding rates (7). Although there are many factors that affect the continuity and success of breastfeeding of mothers whose newborn infants are hospitalized in the neonatal unit, the mother's willingness to breastfeed, a feeling of competence, and self-confidence about breastfeeding are factors that positively affect breastfeeding success (8,9).

Breastfeeding motivation is among the factors reported to be effective in initiating and maintaining breastfeeding. According to the Self-Determination Theory, motivation types that affect the continuation of breastfeeding are autonomous and controlled motivation (10,11). According to this theory, individuals are autonomously motivated if they perform a behavior because they have the freedom to do so, feel competent, and receive support from significant others. On the other hand, they are motivated in a controlled manner if they perform a behavior for monetary rewards or not to feel guilty, to get approval, or to be appreciated (12). Mothers in a supportive environment with a high level of autonomous motivation are more likely to continue breastfeeding, while mothers with a high level of controlled motivation are less likely to continue breastfeeding (13). In addition, while a mother with low motivation cannot cope with breastfeeding problems, a mother with high motivation makes the necessary effort to cope with the difficulties during breastfeeding and continues breastfeeding (14). Nurses have a key role in initiating, maintaining breastfeeding, and in controlling the factors affecting breastfeeding (10,14). Although there are studies in the literature investigating the stress levels of mothers whose newborn infants are hospitalized in the neonatal unit, there is no study that examines the relationship between perceived stress, breastfeeding motivation, and breastfeeding success in mothers who experience breastfeeding for the first time. In this regard, this study aimed to determine perceived stress, breastfeeding motivation, and breastfeeding success and to reveal the relationship between them, among mothers with newborn infants' hospitalization in the neonatal unit.

MATERIALS AND METHODS

Design and Participating

This research was designed as a cross-sectional study between November 2019 and April 2020 in the Neonatal Unit of a University hospital. The study population consisted of the mothers of term newborn infants who were hospitalized in this Neonatal Unit and had no sucking and swallowing problems. In this regard, primiparous mothers who had no neurological problems were breastfeeding, spoke Turkish, and agreed to participate in the study were included in the study. The sample of the study consisted of 128 primiparous mothers who met the inclusion criteria.

Data Collection

Institutional and Ethics Committee approval was obtained for the study (Decision no: 2017-KAEK-189_2019.11.13_07). The purpose of the study was explained and written consent was obtained from all participants. Face-to-face interviews were conducted with mothers who met the inclusion criteria in an area free of noise and interruptions before breastfeeding time. A questionnaire was applied and lasted for an average of 20 minutes. Afterward, mothers were observed while breastfeeding their infants and the LATCH breastfeeding assesment scale was filled. Data collection tools are explained in further detail below.

Introductory Characteristics Form: The form consisted of questions about the introductory characteristics of the mothers such as age, working status, income status, receiving prenatal bre-

astfeeding education, etc.

Perceived Stress Scale (PSS): PSS was developed by Cohen et al., and later adapted into Turkish by Eskin et al (2013). PSS is a 5-point Likert-type scale and consists of 14 items. Each item on the scale is scored between 0-4 and PSS scores range from 0 to 56. Seven items are scored in reverse. The scale has two sub-dimensions: perceived insufficient self-efficacy (PIS) and perceived stress/distress (PSD). A high score indicates an excess of one's perception of stress (15). In the present research, Cronbach's alpha value of the scale was found to be 0.888.

Breastfeeding Motivation Scale (BMS): BMS was developed by Kestler-Peleg et al (2015), based on Self-Determination Theory. BMS was adapted into Turkish by Mızrak (2017). BMS for primiparous mothers consists of 5 sub-dimensions. BMS is a 4-point Likert type scale and each item is scored between 1-and 4. The factors of the BMS scale are integrative regulation (BMS-IR), intrinsic motivation and identified regulation (BMS-IMR), introjected regulation-social approval (BMS-ISA), introjected regulation-social pressure (BMS-ISP), and external regulation-instrumental needs (BMS-EIN). The scores of the sub-dimensions are calculated by taking the average of the sub-dimension scores of the scale. Higher scores obtained from each sub-dimension indicate higher motivation representing that sub-dimension (11,16). In the present research, the Cronbach's alpha value of the sub-dimensions was found to be between 0.712 and 0.932.

LATCH Breastfeeding Assessment Tool : LATCH was developed by Jensen et al., to evaluate breastfeeding success and the Turkish validity and reliability study of the scale were carried out by Yenal and Okumuş (2003). LATCH evaluates five basic criteria, and each criterion in the scale is given 0, 1, or 2 points. LATCH scores range between 0 and 10. Breastfeeding success is evaluated over the total score. A low score indicates that the mother needs help with breastfeeding. LATCH is scored while observing breastfeeding (8). The Cronbach's alpha value of the scale was found to be 0.780 in this study.

Data Analysis

IBM SPSS Statistics Standard Concurrent User V 26 (IBM Corp., Armonk, New York, USA) statistical package program was used to analyze the data. Variables were presented using number (n), percentage (%), mean±standard deviation

(m±sd), Median (M), first quartile (Q1) and third quartile (Q3) . Shapiro Wilk test and Q - Q graphs were used to check whether the data were normally distributed. Mann-Whitney U test was to compare binary variables. Kruskal-Wallis test was used to compare variables with more than two categories, and multiple comparisons were evaluated with the Dunn-Bonferroni test. Spearman correlation analysis was used to examine the relationship between numerical variables. $P < 0.05$ was considered statistically significant in all analyses.

RESULTS

In table 1, 51.6% of the primiparous mothers participating in the study were in the 26-33 age group, and 41.4% were primary school graduates. In all, 63.3% of the mothers were not working and 71.9% had income equal to their expenses. In this study group, 56.2% of the mothers had planned pregnancies and 54.7% had a normal vaginal delivery. In all, 70.3% of the mothers received prenatal breastfeeding training and the majority of the mothers received the training from nurses. In this sample, 53.9% of the newborns were female and 42.2% were breastfed within the first half-hour after birth (Table 1).

The mean perceived stress scale total score (PSS-total), perceived insufficient self-efficacy (PSS-PIS), and perceived stress/distress (PSS-PSD) sub-dimension scores were found to be 32.51±10.31, 14.68±5.34, and 17.83±5.99, respectively. For the breastfeeding motivation scale (BMS), integrative regulation (BMS-IR), intrinsic motivation and identified regulation (BMS-IMR), introjected regulation-social approval (BMS-ISA), introjected regulation-social pressure (BMS-ISP), and external regulation-instrumental needs (BMS-EIN) sub-dimension mean scores were 40.20±4.69, 21.71±2.89, 6.55±1.52, 3.43±1.72, and 6.13±2.02, respectively. The mean LATCH score was found to be 7.39±2.11 (Table 1).

Table 1. Introductory characteristics of primiparous mothers (n=128)

Features	n/(%)
Age	
18-25	37(28.9)
26-33	66(51.6)
34-41	25(19.5)
Educational status	
Primary education	53 (41.4)
High school	49 (38.3)
University	26 (20.3)
Working status	
Employed	47 (36.7)
Unemployed	81 (63.3)
Income according to expense	
Income less than the expense	21 (16.4)
Income equals expense	92 (71.9)
Income more than the expense	15 (11.7)
Whether pregnancy is planned or not	
Planned	72 (56.2)
Not planned	56 (43.8)
Type of delivery	
Normal birth	70 (54.7)
Cesarian section	58 (45.3)
Prenatal breastfeeding training	
Received	90 (70.3)
Not received	38 (29.7)
Breastfeeding trainee (n=90)	
Nurse	84 (93.3)
Physician	1 (1.1)
Other	5 (5.6)
Newborn gender	
Female	69 (53.9)
Male	59 (46.1)
Newborn's first breastfeeding time	
Immediately after birth	20 (15.6)
Within 30 minutes	54 (42.2)
Within 30-60 minutes	46 (35.9)
After the first 24 hours	8 (6.3)
Perceived stress scale	m±sd
Total score	32.51±10.31
Perceived insufficient self-efficacy (PSS-PIS)	14.68±5.34
Perceived stress/discomfort (PSS-PSD)	17.83±5.99
Breastfeeding motivation scale	
Integrative regulation (BMS-IR)	40.20±4.69
Intrinsic motivation and identified regulation (BMS-IMR)	21.71±2.89
Introjected regulation-social approval (BMS-ISA)	6.55±1.52
Introjected regulation-social pressure (BMS-ISP)	3.43±1.72
External regulation-instrumental needs (BMS-EIN)	6.13±2.02
LATCH scale	7.39±2.11

Tables 2 and 3 provide a comparison of PSS, BMS, and LATCH scale scores according to introductory characteristics of mothers. Perceived stress scale scores of primiparous mothers in the 26-33 and 34-41 age groups had higher compared to those in the 18-25 age group. University graduates had significantly lower PSS-total and PSS-PIS scores compared to primary and high school graduates ($p<0.05$). Primary and high school graduates had similar PSS-total and PSS-PIS scores. University graduates had lower PSS-PSD scores compared to primary school graduates. PSS-total, PSS-PIS, and PSS-PSD scores of non-working mothers were significantly higher compared to working mothers ($p<0.05$). No difference was found between the PSS scores in terms of a planned pregnancy, income status, type of delivery, and gender of the newborn ($p>0.05$). The PSS total and sub-dimension scores of the mothers who did not receive prenatal breastfeeding training were higher compared to mothers who received the training ($p<0.05$). The PSS-total and PSS-PSD scores of mothers who started breastfeeding immediately after birth were higher ($p < 0.05$) (Tables 2 and 3).

Table 2. Distribution of PSS, BMS, and LATCH scale scores according to introductory characteristics of primiparous mothers

	Perceived Stress Scale M(Q1-Q3)			**Breastfeeding Motivation Scale** M(Q1-Q3)					**LATCH Scale** M(Q1-Q3)
Features	**PSS-Total**	**PSS-PIS**	**PSS-PSD**	**BMS-IR**	**BMS-IMR**	**BMS-ISA**	**BMS-ISP**	**BMS-EIN**	
Age									
18-25	24.00[a] (21.50-33.00)	11.00[a] (7.00-15.00)	15.00[a] (11.00-18.50)	44.00[a] (42.50-44.00)	24.00[a] (23.00-24.00)	8.00[a] (7.00-8.00)	2.00 (2.00-4.00)	8.00[a] (6.00-8.00)	8.00 (7.00-9.00)
26-33	38.50[b] (24.50-41.00)	17.00[b] (11.50-18.75)	20.00[b] (13.50-23.00)	39.00[b] (36.00-44.00)	21.50[b] (19.00-24.00)	6.00[b] (6.00-8.00)	3.00 (2.00-5.00)	6.00[b] (4.00-8.00)	7.00 (6.00-9.00)
34-41	39.00[b] (24.00-42.00)	16.00[b] (11.00-19.00)	20.00 [b](13.00-25.00)	40.00[b] (37.00-44.00)	21.00[b] (20.00-24.00)	6.00[b] (6.00-8.00)	3.00 (2.00-5.00)	6.00[b] (5.00-8.00)	7.00 (5.00-9.00)
KW/p	10.606 **p= 0.005**	10.773 **p= 0.005**	10.474 **p= 0.005**	16.396 **p<0.001**	14.621 **p=0.001**	13.207 **p=0.001**	5.386 p=0.068	13.196 **p= 0.001**	1.601 p=0.449
Educational status									
Primary education	40.00[a] (28.50-43.00)	16.00[a] (12.50-20.50)	20.00[a] (15.00-25.00)	39.00[a] (35.00-44.00)	21.00 (19.00-24.00)	6.00[a] (5.00-8.00)	3.00 (2.00-5.00)	6.00 (3.00-8.00)	7.00[a] (5.00-8.50)
High school	37.00[a] (22.00-40.00)	17.00[a] (11.00-18.00)	18.00[ab] (11.00-21.50)	42.00[ab] (39.00-44.00)	24.00 (21.00-24.00)	7.00[ab] (6.00-8.00)	2.00 (2.00-5.00)	7.00 (5.00-8.00)	8.00[b] (7.00-9.00)
University	22.00[b] (18.75-33.75)	11.00[b] (7.00-14.25)	13.00[b] (11.00-20.00)	44.00[b] (39.00-44.00)	24.00 (21.50-24.00)	8.00[b] (6.00-8.00)	2.00 (2.00-4.00)	8.00 (6.00-8.00)	9.00[b] (7.00-10.00)
KW/p	18.128 **p<0.001**	14.411 **p=0.001**	13.886 **p=0.001**	8.524 **p=0.014**	5.544 p=0.063	7.682 **p=0.021**	4.511 p=0.105	5.199 p=0.074	20.136 **p<0.001**
Working status									
Employed	26.00 (20.00-39.00)	11.00 (7.00-18.00)	15.00 (11.00-20.00)	44.00 (40.00-44.00)	24.00 (21.00-24.00)	7.00 (6.00-8.00)	2.00 (2.00-4.00)	8.00 (6.00-8.00)	8.00 (7.00-9.00)
Unemployed	38.00 (28.00-42.00)	16.00 (11.50-18.50)	20.00 (15.00-24.00)	40.00 (36.00-44.00)	22.00 (20.00-24.00)	6.00 (6.00-8.00)	3.00 (2.00-5.00)	6.00 (4.00-8.00)	7.00 (5.00-9.00)
U/p	3.250 **p=0.001**	2.588 **p=0.010**	3.035 **p=0.002**	2.944 **p=0.003**	1.808 p=0.071	1.396 p=0.163	1.872 p=0.061	2.229 **p=0.026**	1.665 p=0.096
Whether pregnancy is planned or not									
Planned	35.50 (22.00-40.00)	15.00 (10.25-18.75)	18.00 (11.00-22.00)	42.00 (39.00-44.00)	24.00 (21.00-24.00)	7.00 (6.00-8.00)	2.00 (2.00-4.00)	7.00 (6.00-8.00)	8.00 (7.00-9.00)
Not planned	38.00 (24.00-42.00)	15.00 (11.00-18.00)	19.00 (13.50-24.75)	40.50 (35.25-44.00)	21.00 (19.00-24.00)	6.00 (5.00-8.00)	3.50 (2.00-5.00)	6.00 (3.25-8.00)	7.00 (5.00-9.00)
U/p	1.602 p=0.109	0.370 p=0.711	1.694 p=0.090	2.138 **p=0.033**	2.152 **p=0.031**	2.034 **p=0.042**	2.282 **p=0.023**	1.705 p=0.088	2.226 **p=0.026**
Income according to expense									
Less	37.00 (22.00-42.50)	15.00 (8.00-19.50)	18.00 (14.00-24.00)	44.00 (38.00-44.00)	24.00 (21.00-24.00)	7.00 (6.00-8.00)	4.00 (2.00-5.50)	8.00 (5.00-8.00)	8.00 (5.50-9.00)

Equal	38.00 (22.00-41.00)	15.00 (11.00-18.00)	19.00 (12.00-22.00)	42.00 (37.00-44.00)	22.50 (20.00-24.00)	6.00 (6.00-8.00)	3.00 (2.00-4.00)	6.00 (5.00-8.00)	7.00 (6.00-9.00)
More	35.00 (20.00-39.00)	14.00 (10.00-18.00)	16.00 (11.00-22.00)	42.00 (37.00-44.00)	22.00 (19.00-24.00)	7.00 (6.00-8.00)	3.00 (2.00-4.00)	6.00 (3.00-8.00)	9.00 (7.00-10.00)
KW/p	1.275 p=0.529	0.378 p=0.828	0.953 p=0.621	0.482 p=0.786	0.302 p=0.860	0.951 p=0.622	1.090 p=0.580	2.040 p=0.361	3.191 p=0.203

The a and b superscripts show the differences between groups. Scale scores were statistically similar between groups with the same letters.

Table 3. Distribution of PSS, BMS, and LATCH scale scores according to introductory characteristics of primiparous mothers (continues)

Features	Perceived Stress Scale M(Q1-Q3)			Breastfeeding Motivation Scale M(Q1-Q3)					LATCH Scale M(Q1-Q3)
	PSS-Total	PSS-PIS	PSS-PSD	BMS-IR	BMS-IMR	BMS-ISA	BMS-ISP	BMS-EIN	
Type of delivery									
Normal	38.00 (23.50-41.00)	16.00 (10.50-18.25)	20.00 (15.00-23.00)	42.00 (37.00-44.00)	22.00 (20.00-24.00)	6.00 (6.00-8.00)	2.50 (2.00-4.25)	6.00 (4.75-8.00)	7.50 (5.75-9.00)
Cesarian	29.00 (22.00-41.00)	13.50 (11.00-18.00)	15.00 (11.00-23.25)	43.50 (37.00-44.00)	24.00 (20.00-24.00)	7.50 (6.00-8.00)	3.00 (2.00-5.00)	7.50 (5.00-8.00)	7.00 (6.00-9.00)
U/p	1.220 p=0.222	1.147 p=0.251	1.796 p=0.073	0.693 p=0.489	1.252 p=0.210	1.450 p=0.147	0.665 p=0.506	1.499 p=0.134	0.292 p=0.770
Newborn's gender									
Female	33.00 (22.00-41.00)	15.00 (10.50-18.00)	18.00 (12.00-23.00)	42.00 (37.00-44.00)	23.00 (20.00-24.00)	7.00 (6.00-8.00)	2.00 (2.00-4.50)	7.00 (5.00-8.00)	8.00 (7.00-9.00)
Male	38.00 (22.00-41.00)	16.00 (11.00-19.00)	19.00 (13.00-24.00)	42.00 (37.00-44.00)	22.00 (20.00-24.00)	6.00 (6.00-8.00)	3.00 (2.00-5.00)	6.00 (4.00-8.00)	7.00 (5.00-9.00)
U/p	0.709 p=0.479	1.083 p=0.279	0.396 p=0.692	0.311 p=0.756	0.548 p=0.584	0.863 p=0.388	1.279 p=0.201	0.636 p=0.525	1.746 p=0.081
Prenatal breastfeeding training									
Received	27.00 (20.00-39.00)	12.50 (7.00-18.00)	15.00 (11.00-20.00)	44.00 (40.00-44.00)	24.00 (21.00-24.00)	8.00 (6.00-8.00)	2.00 (2.00-5.00)	8.00 (6.00-8.00)	8.00 (7.00-9.25)
Not received	41.00 (39.00-44.00)	18.00 (16.00-21.00)	23.00 (18.00-25.25)	37.00 (34.75-40.00)	20.00 (18.00-21.25)	6.00 (4.00-7.00)	4.00 (3.00-4.25)	4.00 (3.00-6.00)	6.50 (5.00-8.00)
U/p	5.758 **p<0.001**	5.270 **p<0.001**	5.044 **p<0.001**	6.274 **p<0.001**	5.400 **p<0.001**	4.768 **p<0.001**	2.405 **p=0.016**	6.376 **p<0.001**	4.166 **p<0.001**
Newborn's first breastfeeding time									
immediately after birth	40.50[a] (35.75-44.75)	18.00 (15.25-20.75)	23.50[a] (17.25-25.75)	40.00 (37.00-43.75)	22.00 (20.00-24.00)	6.50 (6.00-7.00)	4.00 (3.00-4.75)	6.00 (4.25-7.00)	8.00 (5.25-9.75)
Within 30 minutes	33.50[ab] (21.50-41.25)	15.00 (7.00-18.25)	17.50[ab] (13.00-22.25)	42.00 (37.00-44.00)	22.50 (20.00-24.00)	6.50 (6.00-8.00)	3.00 (2.00-5.00)	6.50 (4.00-8.00)	7.00 (6.00-9.00)
Within30-60 minutes	32.50[b] (22.00-39.00)	14.50 (11.00-18.00)	17.00[b](11.00-20.00)	43.00(36.50-44.00)	24.00(20.00-24.00)	6.50(6.00-8.00)	2.00(2.00-4.00)	7.50(4.75-8.00)	7.00(7.00-9.00)
After the first 24 hours	34.00[ab] (17.75-41.75)	14.50 (8.00-18.25)	17.50[ab] (9.75-25.50)	41.50 (38.25-44.00)	24.00 (22.25-24.00)	7.00 (6.00-8.00)	2.00 (2.00-4.75)	6.00 (6.00-8.00)	6.50 (4.25-7.75)
KW/p	8.694 p=**0.034**	6.894 p=0.075	8.476 p=**0.037**	1.315 p=0.726	2.809 p=0.422	1.516 p=0.678	5.683 p=0.128	1.593 p=0.661	2.638 p=0.451

The a and b superscripts show the differences between groups. Scale scores were statistically similar between groups with the same letters.

According to the comparison of breastfeeding motivation scores to introductory characteristics, primiparous mothers in the 18-25 age group had higher BMS-IR, BMS-IMR, BMS-ISA, and BMS-EIN scores. University graduates had significantly higher BMS-IR and BMS-ISA scores compared to primary school graduates (p<0.05). The scores of high school graduates were statistically similar to the other two groups. BMS-IR and BMS-EIN scores of working mothers were significantly higher compared to non-working mothers (p<0.05). It was determined that the BMS-IR, BMS-IMR, and BMS-ISA scores of the mothers with a planned pregnancy were significantly higher and BMS-ISP scores were significantly lower compared to mothers who did not have a planned pregnancy. There was no difference between BMS sub-dimension scores with respect to income status, type of delivery, and newborn's gender (p>0.05). BMS-IR, BMS-IMR, BMS-ISA, and BMS-EIN scores of mothers who received prenatal breastfeeding training were higher compared to mothers who did not receive breastfeeding training before. In contrast, mothers who did not receive breastfeeding training before delivery had higher BMS-ISP score. There was no difference in BMS sub-dimension scores with respect to the time of first breastfeeding after birth (p>0.05) (Tables 2 and 3).

According to the comparison of LATCH scores to introductory characteristics of primiparous mothers, no difference was found in breastfeeding success with respect to age. High school and university graduate primiparous mothers had similar LATCH scores, while the LATCH scores of primary school graduates were significantly lower than the other two groups (p<0.05). LATCH scores were significantly higher in mothers with planned pregnancies (p<0.05). No difference was found in LATCH scores with respect to working status, income status, type of delivery, and newborn's gender (p>0.05). The LATCH scores of the mothers who received prenatal breastfeeding training were significantly higher compared to those who did not (p<0.05). No difference was found in LATCH scores with respect to the breastfeeding time of the newborn (p > 0.05) (Tables 2 and 3).

The relationship between PSS, BMS, and LATCH is illustrated in table 4. A strong negative correlation was found between PSS total, PSS-PIS and PSS-PSD scores and BMS-IR (rho=-0.739, -0.655; -0.718, p<0.001), BMS-IMR (rho=-0.685, -0.649, -0.663, p<0.001) scores. A moderate negative correlation was found between BMS-ISA scores (rho= -0.565, -0.547, -0.549, p<0.001). Furthermore, a weak positive correlation was found between BMS-ISP scores (rho=0.345, 0.247, 0.361, p<0.001). Lastly, a strong negative correlation was found between BMS-EIN scores (rho=-0.674, -0.659, -0.643, p<0.001).

A moderate negative correlation was found between LATCH and PSS-total and PSS-PSD scores (-0.609, -0.604, p<0.001), and a weak negative correlation was found between LATCH and PSS-PIS scores (-0.489, p<0.001). There was a moderate positive correlation between LATCH and BMS-IR, BMS-IMR, BMS-ISA, BMS- EIN scores (rho=0.557, 0.586, 0.594, 0.492, p<0.001). There was a weak negative correlation between LATCH and BMS-ISP scores (rho=-0.283, p=0.001).

Table 4. Relationship between PSS, BMS, and LATCH scale scores

Scales	PSS total		PSS-PIS		PSS-PSD		LATCH	
	rho	*p*	*rho*	*p*	*rho*	*p*	*rho*	*p*
Integrative Regulation (BMS-IR)	-0.739	<0.001	-0.655	<0.001	-0.718	<0.001	0.557	<0.001
Intrinsic Motivation and Identified Regulation (BMS-IMR)	-0.685	<0.001	-0.649	<0.001	-0.663	<0.001	0.586	<0.001
Introjected Regulation-Social Approval (BMS-ISA)	-0.565	<0.001	-0.547	<0.001	-0.549	<0.001	0.594	<0.001
Introjected Regulation-Social Pressure (BMS-ISP)	0.345	<0.001	0.247	0.005	0.361	<0.001	-0.283	0.001
External Regulation-İnstrumental Needs (BMS-EIN)	-0.674	<0.001	-0.659	<0.001	-0.643	<0.001	0.492	<0.001
LATCH	-0.609	<0.001	-0.489	<0.001	-0.604	<0.001		

DISCUSSION

The aim of the present research was to investigate the relationship between perceived stress and breastfeeding motivation, and breastfeeding success in mothers with newborn infants in the neonatal unit, and the results of the study were discussed in light of the relevant literature. In the present research, 70.3% of the mothers had received breastfeeding training before delivery. Gönenli et al (2019), determined that all primiparous mothers received training on breastfeeding in the prenatal period (17). In their study, Bulut and Küçük Alemdar (2021) reported that 71.0% of the mothers received breastfeeding training (18).

Perceived stress levels were higher in older age groups primiparous mothers in the present study. Contrary to this finding, Erdem (2010) found that there was no significant difference in state and trait anxiety levels of mothers with respect to age (19). The perceived stress levels of primiparous mothers with a university degree were lower compared to primary school and high school graduates. Contrary, Omak et al.(2021) and Özyazıcıoğlu and Güdücü Tüfekci (2010) found no significant difference in state and trait anxiety levels with respect to the education level of mothers whose babies were hospitalized in the neonatal unit (20,21). Musabirema et al. (2015) found that among mothers whose babies were hospitalized in the neonatal unit, perceived stress levels in terms of the appearance and sounds of the neonatal unit were higher in primary school graduates compared to university graduates (22). In the present research, no significant difference was found in perceived stress levels with respect to whether the pregnancy was planned or not. Similarly to this result, Omak et al.(2021) reported that there was no difference between the state of wanting pregnancy and anxiety levels among mothers with their babies in the neonatal unit (20). The results of the present study showed that perceived stress levels were higher among non-working mothers. In contrast, Keklikçi et al (2020), reported that working mothers had higher stress levels compared to non-working mothers (3). The perceived stress of mothers who started breastfeeding immediately after birth was higher, in this study. It was thought that this finding might be related to the limitation of movement and pain experienced in the postoperative period, especially after cesarean delivery.

The breastfeeding motivation scale integrative regulation and introjected regulation -social approval scores of university graduate mothers were significantly higher compared to primary school graduates, in this study ($p<0.05$). The integrative regulation sub-dimension, which is a type of autonomous motivation, reflects the purpose of the mother's life and her own reflections (11,13). This type of motivation may be higher in mothers with a high level of education because they can access information about breastfeeding more easily, they are relatively older, and these factors increase their confidence in breastfeeding (23,24). Similar to these results, Mızrak Şahin et al (2019), reported that mothers with a high level of education had higher breastfeeding motivation (25). Introjected regulation-social approval, which is a type of controlled motivation, is the attitudes and behaviors that the mother exhibit externally to her husband or environment to show that she is a good mother (10). The fact that university graduates received higher scores in the social approval sub-dimension was thought of as a positive finding in terms of ensuring the continuity of breastfeeding.

The study results indicate that autonomous motivation types integrated regulation, intrinsic motivation, and identified regulation, and one of the controlled motivation types external regulation-instrumental needs sub-dimension scores were higher among working mothers. Intrinsic motivation and identified regulation, which are autonomous motivation types, are the sum of the notions that the mother enjoys breastfeeding her baby, breastfeeding provides satisfaction to the mother, breastfeeding is important and beneficial for the mother, and the mother feels better as she breastfeeds (13,26). External regulation- instrumental needs sub-dimension, which is a type of controlled motivation, is where the mother sees breastfeeding as a tool and uses breastfeeding as a means to realize her own ambitions. An example of this is when mothers breastfeed to lose weight and avoid the cost of formula (11,13). The high external regulation- instrumental needs sub-dimension scores among working mothers suggests that breastfeeding can be seen as a source of motivation in terms of additional benefits such as using maternity leave.

In the current research, the introjected regulation-social pressure sub-dimension score was higher among mothers whose pregnancy was not planned. Introjected regulation-social pressure sub-dimension, which is a type of controlled motivation, refers to breastfeeding behavior caused by internal pressures (a sense of guilt and anxiety) to prove that she is a good mother and not to shame her spouse or social environment (10). In contrast, integrative regulation, intrinsic motivation, and identified regulation, and introjected regulation-social approval scores were found to be higher in mothers with a planned pregnancy. This simply suggests that mothers who have

a baby willingly are more motivated to breastfeed. This study's results also showed that mothers who received prenatal breastfeeding training had a higher motivation to breastfeed. Antenatal breastfeeding education can have positive effects on the motivation and competence of the mother in setting achievable breastfeeding goals (27,28). On the other hand, mothers who have insufficient knowledge about breastfeeding problems in the prenatal period are more likely to supplement nutrition with formula in the early postpartum period because they are not self-confident in breastfeeding (29). In this study, no difference was found in breastfeeding motivation with respect to the mode of delivery. Contrary to this result, Lange et al (2017), reported that breastfeeding motivation was higher among mothers who had normal vaginal delivery compared to mothers who gave birth by cesarean section (30).

No difference was found in breastfeeding success with respect to the mother's age in this study. Similarly, Küçükoğlu and Çelebioğlu (2014) found no statistically significant difference in LATCH scores with respect to the mother's age (31). In the present research, LATCH scores were higher among mothers with a planned pregnancy. Contrary, Oksal Güneş and Çetinkaya (2017), reported that mothers whose pregnancy was not planned had higher LATCH scores, but the difference was not statistically significant (32). In this study, there was no difference in LATCH scores with respect to the type of delivery. In contrast, Küçükoğlu and Çelebioğlu (2014) found that the breastfeeding success of mothers was affected by the type of delivery (31). Similarly, Turan and Bozkurt (2020) also found that type of delivery had an effect on breastfeeding success (33). In the current study, LATCH scores of primiparous mothers who received breastfeeding education before delivery were significantly higher. İnce et al (2017), determined that the breastfeeding success of mothers who reported receiving both prenatal and postnatal breastfeeding counseling was significantly higher compared to the mothers who did not (9). In line with the "Ten Steps to Successful Breastfeeding" recommended by UNICEF to promote, support, and encourage breastfeeding, it is recommended to initiate breastfeeding within the first half-hour after birth and that the mother and the baby stay in the same room for 24 hours in order to ensure skin-to-skin contact (1). In the present research, no difference was found in LATCH with respect to breastfeeding initiation time. Contrary to this result, other studies reported that mothers who initiate breastfeeding within an hour after birth had more breastfeeding success and longer breastfeeding times (34,35).

In this research, as perceived stress decreased, breastfeeding motivation and breastfeeding success increased. A high level of stress can affect the mother's motivation to breastfeed and the success of breastfeeding since it means that the mother has difficulty participating in the care of her baby and has more anxiety about breastfeeding. According to these results, an increase in breastfeeding motivation also increases breastfeeding success. These findings demonstrate the importance of supporting breastfeeding motivation to ensure the continuation of breastfeeding in mothers whose babies are in the neonatal unit. Motivation of the mother to breastfeed was evaluated as a positive finding in terms of starting breastfeeding in the early period, and ensuring the continuity of breastfeeding and successful breastfeeding. It was thought that health professionals should determine their motivation levels before giving breastfeeding counseling and support to mothers.

CONCLUSION

The perceived stress was higher among primiparous mothers whose newborn infants received treatment and care in the neonatal unit, who were older age, primary and high school graduates, unemployed, did not receive breastfeeding training before delivery, and started breastfeeding immediately after birth. Breastfeeding motivation was higher among young mothers, university graduates, working mothers, mothers with a planned pregnancy, and mothers who received breastfeeding training before delivery. The results also showed that mothers who graduated from high school and university, whose pregnancy was planned, and who received breastfeeding training before delivery had higher breastfeeding success scores. In the present research, it was found that as perceived stress decreased, breastfeeding motivation and breastfeeding success increased. A correlation was found between breastfeeding motivation and breastfeeding success.

In line with the study findings, it is recommended to plan and implement education and intervention efforts to reduce the stress levels of mothers whose infants are hospitalized in the neonatal unit. Neonatal nurses have the opportunity to observe mothers' breastfeeding behaviors one-on-one, so they have critical importance and role in increasing breastfeeding motivation. Starting from the prenatal period, interventions such as education, and interviews that support autonomous motivation can be implemented, and studies can be carried out to monitor mothers' breastfeeding status and motivation levels. In addition, it is recommended to conduct further evidence-based stu-

dies in the neonatal units to increase breastfeeding motivation and breastfeeding success of primiparous mothers.

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The Effect of Early Neonatal Sepsis on Bronchopulmonary Dysplasia in Very Low Birth Weight Infants

Çok düşük doğum ağırlıklı bebeklerde Erken Neonatal Sepsisin Bronkopulmoner Displazi Üzerine Etkisi

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ÖZ

Amaç: Bronkopulmoner displazi (BPD), çok düşük doğum ağırlıklı bebeklerde en önemli morbiditelerden biridir. BPD multifaktöriyel bir hastalıktır ve patogenezinde inflamasyon önemli bir rol oynamaktadır. Bu çalışmadaki amacımız, preterm bebeklerde erken neonatal sepsis (ENS) varlığının BPD ve diğer preterm morbiditeleri üzerine etkisinin araştırılmasıdır.

Yöntem: Bu retrospektif çalışmaya, gebelik yaşı <30 hafta ve doğum ağırlığı <1500 g olan preterm bebekler dahil edildi. Yeni doğan yoğun bakım ünitemizde 2013-2016 yılları arasında izlenen bebeklerin kayıtları incelendi. ENS tanısı olanlar çalışma grubu olarak belirlenirken, diğer bebekler kontrol grubunu oluşturdu. Majör konjenital anomalisi, perinatal asfiksi olan ve verileri eksik olan bebekler çalışma dışı bırakıldı.

Bulgular: Çalışmamıza toplam 390 bebek dahil edildi. ENS ve kontrol grubunda gebelik yaşı 27,5±1,2 ve 27,6±1,2 hafta, p=0,44)ve doğum ağırlığı (1013±230 ve 1016±217 g,) istatistiksel olarak benzer saptandı. ENS grubunda, orta-ağır BPD (sırasıyla %14,6 ve %9,2, p=0,04) ve mekanik ventilatör gereksinimi istatistiksel olarak daha sık ancak postmenstrüel 36. haftada BPD olmadan sağ kalım (sırasıyla %63,1 ve %73,5, p=0,03) daha düşük oranda saptandı. Lazer tedavisi gereken prematüre retinopatisi ENS grubunda (%16,2 ve %9,6, p=0.03) anlamlı olarak daha sık iken, diğer preterm morbiditeleri açısından iki grup arasında fark saptanmadı. Çok değişkenli lojistik regresyon analizinde ENS'nin orta-ağır BPD gelişimi açısından bağımsız risk faktörü olduğu belirlendi (OR 1,89 % 95 CI 1,10-3,25, p=0,02).

Sonuç: ENS çok düşük doğum ağırlıklı bebeklerde orta-ağır BPD için bağımsız bir risk faktörüdür.

Anahtar kelimeler: Erken sepsis; bronkopulmoner displazi; prematürite; prematüre retinopatisi

ABSTRACT

Objective: Bronchopulmonary dysplasia (BPD) remains a critical morbidity in very low birth weight (VLBW) infants. The etiology is multifactorial, and inflammation plays an essential role in the pathogenesis. We aimed to investigate the effect of early neonatal sepsis (ENS) on BPD and other preterm morbidities in VLBW infants.

Materials and Methods: Preterm infants of <30 weeks of gestation and birth weight <1500 g were incorporated in this retrospective study. We reviewed the records of infants who admitted to the neonatal intensive care unit between 2013 and 2016. Those with ENS diagnosis were assigned to the study group, while the remaining constituted the control group. Babies with major congenital anomalies, perinatal asphyxia, and missing data were excluded from the study.

Results: This study included a total of 390 infants. The gestational ages (27.5±1.2 vs. 27.5±1.2 vs. 27.6±1.2 weeks) and birth weights (1013±230 vs. 1016±217 g, p=0.95) were statistically similar in the groups. Moderate-to-severe BPD (14.6% vs. 9.2% respectively, p=0.04) and requirement for invasive ventilation were more frequent, but survival without BPD at 36 weeks corrected (p=0.03) was lower in the ENS group. While llaser requiring retinopathy of prematurity ROP was significantly more common in the ENS group (16.2% vs. 9.6%, p=0.03), there was no difference between the groups regarding other preterm morbidities. In the multivariate logistic regression analysis, ENS was noted as an independent risk factor for moderate/severe BPD (OR 1.89 95 % CI 1.10-3.25, p=0.02).

Conclusion: ENS was demonstrated as an independent risk factor for moderate-severe BPD.

Keywords: Early sepsis; bronchopulmonary dysplasia; prematurity; retinopathy of prematurity

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INTRODUCTION

Early neonatal sepsis (ENS) remains a significant morbidity with an incidence of 10 per 1000 live births in preterm infants despite the widespread usage of antenatal antibiotic prophylaxis (1). The obstacle concerning ENS in preterm infants is the higher incidence of neonatal morbidity, particularly respiratory and neurological adverse outcomes, and mortality (1). The absence of a universal definition for neonatal sepsis and the variability in diagnostic criteria in the literature hampers the diagnostic process and treatment in neonates, particularly preterm babies (2). On the other hand, the time interval adopted for the diagnosis of ENS varies widely in the literature (3). A considerable percentage of the units put the diagnosis only by the presence of bacteremia, regardless of the clinical findings. Despite the widespread usage of noninvasive ventilation, minimally invasive surfactant implementation, and widespread antenatal steroid use, the incidence of bronchopulmonary dysplasia (BPD) remains stable. Besides the debate regarding the definition, over half of the very preterm infants receive a BPD diagnosis based on current criteria (4). Despite little data regarding the outcomes of very preterm babies with ENS, many etiological factors such as the type of pathogen, timing of infection, presence of chorioamnionitis, and fetal inflammatory response might affect the development and/or the severity of the disease (5). Exposure to bacteria and inflammation during the antenatal and/or postnatal period is known to disrupt alveolarization and causes fibrosis (6).

The relationship between infection and preterm mortality/morbidity has long been a topic of interest to researchers (1). Perinatal inflammation has been linked to BPD, retinopathy of prematurity (ROP), and brain lesions (6-8). Besides, a couple of studies have shown the constellation of preterm morbidities in clusters (9). ELGAN study revealed infection as a risk factor for ROP and BPD in infants < 28 weeks of age, while the diagnosis of sepsis was put by the presence of bacteremia without any clinical criteria (9). Along with variations regarding neonatal sepsis diagnostic criteria, the absence of a universally accepted diagnostic system hinders the comparison of the studies.

Studies have shown that postnatal infection/inflammation was associated with respiratory and neurological morbidity in preterm infants along with the controversy regarding intrauterine infection/inflammation and the BPD relationship (6,7). A couple of these studies investigated the link between neonatal sepsis and preterm morbidity, while others comprised only patients with culture-proven sepsis (10,11). We opted to search the effect of clinical and culture-proven ENS on BPD and other preterm morbidities in very-low birth weight (VLBW) infants.

MATERIALS AND METHODS

We conducted this retrospective cohort study in Zekai Tahir Burak Women's Health Education and Research Hospital between January 2013 and December 2016. Babies who were born alive at $250/^{7}$-$296/^{7}$weeks of gestation were included in the study. Exclusion criteria were major congenital/chromosomal anomalies, perinatal asphyxia, and lack of data.

We reviewed the obstetric and neonatal files. The obstetric and medical history of the mother, mode of delivery, and presence of intervention in the delivery room were recorded from the patient files. Surfactant requirement, BPD (mild-moderate-severe), survival without BPD at 36 weeks corrected, duration of invasive/noninvasive ventilation, patent ductus arteriosus (PDA), grade 3-4 intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), necrotizing enterocolitis (NEC), and the presence of ROP were noted.

All clinical and culture-proven ENS cases were included in the study. Clinical ENS was defined as the presence of clinical findings in keeping with sepsis within the first 72 hours of life, accompanied by elevated acute phase reactant but negative blood culture taken in the first three days. Culture-proven sepsis was defined as blood culture positivity beside clinical findings. While fungal sepsis was included in this analysis, viral infections were not incorporated into the study.

The classification of BPD was made based on the suggestion by Jobe EH and Bancalari E. at the 2001 National Institutes of Health Workshop (12). The definition of ROP was done according to the International Classification of Retinopathy of Prematurity 2 (ICROP-2) system (13). Papile classification was utilized for IVH staging (14). The diagnosis of hemodynamically significant PDA was made by echocardiography performed by a pediatric cardiologist.

The local ethics committee of our hospital approved the study. Verbal or written consent was obtained from the families.

Statistics

Analyzes were performed using SPSS version 21 (IBM SPSS Statistics, Chicago, IL, USA). Chi-square or Fisher exact test was used for the comparison of categorical variables. In the

case of continuous variables, the Student's t-test or Mann-Whitney U test was used for the comparison of groups. The comparison of the dependent groups was performed by the Wilcoxon test. p<0.05 was considered statistically significant.

RESULTS

We performed a retrospective analysis of a total of 390 patients. While 130 were diagnosed with ENS (study group), the remaining 260 constituted the control group. The gestational ages and birth weights were similar in the groups (Table 1). In the study group, 15 patients were diagnosed with culture-proven ENS. E. coli was detected in six, K. pneumoniae in five, and S. agalactiae in four patients. There was no statistically significant difference between the groups regarding demographic and maternal characteristics (Table 1).

Table 1. Demographic characteristics of the groups

	ENS group (n=130)	**Control group (n=260)**	***p***
Gestational age, weeks*	27.5±1.2	27.6±1.2	0.44
Birth weight, g*	1013±230	1016±217	0.95
Small for gestational age, n (%)	19 (14.6)	35 (13.5)	0.75
Male, n (%)	70 (53.8)	128 (49.2)	0.39
caesarean section, n (%)	110 (84.6)	202 (77.7)	0.10
APGAR ^{5}†	7 (6-8)	7 (6-8)	0.52
Multiple pregnancy, n (%)	27 (20.8)	52 (20)	0.85
Antenatal steroid, n (%)	92 (70.8)	171 (65.8)	0.32
Preeclampsia, n (%)	17 (13.1)	46 (17.7)	0.24

* mean±standard deviation †median, interquartile range (IQR)

The gestational weeks (27.5±1.2 vs. 27.6±1.2, p=0.44) and birth weights (1013±230 vs. 1016±217 g, p=0.95) were statistically similar in the groups. The relationship between ENS and preterm morbidities is demonstrated in Tables 2 and 3.

Table 2. Respiratory morbidity of the groups	**ENS group (n=130)**	**Control group (n=260)**	***p***
Requirement for surfactant, n (%)	95 (73.1)	166 (63.8)	0.06
Two doses of surfactant, n (%)	36 (27.7)	48 (18.5)	**0.03**
Mild bronchopulmonary dysplasia, n (%)	45 (34.6)	79 (30.49	0.10
Moderate-severe bronchopulmonary dysplasia, n (%)	19 (14.6)	24 (9.2)	**0.04**
Survival without bronchopulmonary dysplasia at 36 weeks, n (%)	82 (63.1)	191 (73.5)	**0.03**
Duration of noninvasive ventilation, days†	5 (2-12.5)	5 (2-13)	0.81
Duration of invasive ventilation, days†	2 (0-6)	1 (0-4)	**0.03**
Duration of supplemental O2, days†	12.5 (2-24.5)	11 (4-24)	0.75
Air leak, n (%)	2 (1.5)	3 (1.2)	0.74

†median, interquartilerange (IQR)

Table 3. Other preterm morbidities and clinical features of the groups

	ENS group (n=130)	Control group (n=260)	*p*
Proven late-onset sepsis, n (%)	35 (26.9)	61 (23.5)	0.45
Number of proven late-onset sepsis episodes†	0 (0-1)	0 (0-0)	0.59
Patent ductus arteriosus, n (%)	56 (43.1)	105 (40.4)	0.61
Grade III-IV Intraventricular hemorrhage, n (%)	21 (16.2)	26 (10)	0.12
Periventricular leukomalacia, n (%)	14 (10.8)	16 (6.2)	0.09
Necrotizing enterocolitis grade ≥IIb, n (%)	1 (0.8)	7 (2.7)	0.27
Spontaneous intestinal perforation, n (%)	2 (1.5)	3 (1.2)	1
Retinopathy of prematurity requiring laser treatment, n (%)	21 (16.2)	25 (9.6)	**0.03**
Mortality, n (%)	28 (21.5)	39 (15)	0.10
Length of hospital stay, days†	64 (52-839)	66 (51-81)	0.70
Postmenstrual age at discharge, weeks*	37.4±2.7	37.2±2.4	0.82

* mean±standard deviation †median, interquartile range (IQR)

Although the requirement for surfactant was statistically similar in the groups (p=0.06), the need for ≥two doses of surfactant was higher in the ENS group (p=0.03). The incidence of moderate-severe BPD (p=0.04) was higher, and the duration of invasive ventilation (p=0.03) was significantly longer in the ENS group. Besides, the study group was less likely to survive without BPD at postmenstrual 36 weeks (p=0.03). While ROP requiring laser therapy was significantly more common in the ENS group (p=0.03), no difference was found between the groups concerning other preterm morbidities. In the multivariate logistic regression analysis, ENS was noted as an independent risk factor for moderate/severe BPD (OR 1.89 95 % CI 1.10-3.25, p=0.02).

DİSCUSSION

We revealed a longer duration of invasive ventilation, and higher incidence of ROP requiring laser treatment, and lower survival without BPD at 36 weeks corrected in VLBW infants who experienced ENS.

Klinger et al. investigated the outcomes of VLBW infants with ENS in a wide-scale prospective observational study including 15,839 infants from 28 neonatal intensive care units (15). The incidence of severe ROP and BPD was noted to be higher in extremely low birth weight infants with ENS, like our study (15). Although no data was available regarding the duration of mechanical ventilation, researchers hypothesized that the higher BPD risk was most likely related to prolonged exposure to assisted ventilation. ROP and unfavorable neurological outcomes were assumed to be associated with the inflammatory response. On the other hand, only babies with culture-proven ENS were incorporated in that trial as opposed to our study.

Neonatal sepsis was shown to be a strong risk factor for BPD in a single-center, large series from Australia that comprised 798 infants <30 weeks (16). Patients with blood culture positivity before the 36 weeks corrected were included in the study with the diagnosis of sepsis. Unlike the literature and our study, bacterial growth in the blood cultures taken before the 48th hour of life was defined as ENS (16). However, a separate analysis was not performed based on the timing of onset. Besides, the definition of sepsis as the documentation of bacteremia without taking clinical findings into account was the limitation of the study. A significant percentage of these growths might be contamination or bacteremia that was not accompanied by an illness state.

Ohlin et al. showed that 66% of the entire cohort had at least one episode of sepsis in a national prospective study comprising 497 infants of <27 weeks' gestation (17). While proven sepsis was shown as a risk factor for severe BPD, there was no significant association between clinical sepsis and BPD. The strength of this study was the large sample size with the comparison of the groups as clinical and proven sepsis. The difference between the groups regarding BPD might be indicating a more severe disease pattern in case of culture growth in the newborn. One should assess the results with caution given that the study incorporated only live babies.

ELGAN study showed a relationship between early/late bacteremia and ROP in 1223 infants <28 weeks of gestation (9). However, late bacteremia minimally increased the risk of

BPD, not early bacteremia in that study. On the other hand, the authors revealed the coexistence of severe ROP and BPD in extremely low birth weight infants (9). Besides, the definition of early bacteremia was made as culture growth in the first week of life, while the authors defined late bacteremia as growth in blood cultures taken between postnatal weeks 2-4. That classification is not in keeping with the neonatal sepsis guidelines. In addition , clinical findings were not considered in putting the diagnosis of sepsis. Even if a link was demonstrated between severe ROP and ENS in our study, it remains compelling to compare our results with the ELGAN study due to the diversity in the terminology.

There are a couple of strengths and limitations of our study. Both clinical and culture-proven ENS cases constituted the study group and were compared with the infants who never experienced an ENS episode. The results should be evaluated with caution given the predominance of clinical sepsis cases in the study group. A subgroup comparison could not be performed because of the insufficient number of culture-proven patients. However, the exclusion of the patients with contamination was an important strength of our study. Besides, similar rates of late-onset sepsis presumably prevented any confounding effect on the results.

To conclude, ENS was shown as an independent risk factor for moderate-severe BPD in VLBW infants. Further large-scale prospective studies are warranted to reveal further impact of ENS on neonatal morbidity.

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The effectiveness of obstetric gel application in shortening labor duration and preserving vaginal perineal integrity: Prospective observational study

Doğum eylemi süresini kısaltmada ve vajinal perine bütünlüğünü korumada obstetrik jel uygulamasının etkinliği: prospektif gözlemsel çalışma

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ÖZ

Amaç: Bu çalışmanın amacı, obstetrik jel uygulamasının doğum eylemi sonuçlarına etkisini belirlemektir.

Gereç ve Yöntem: Bu randomize olmayan kontrollü çalışma, Ocak 2019 ile Haziran 2019 tarihleri arasında üçüncü basamak bir hastanede gerçekleştirildi. Düşük riskli, verteks pozisyonunda, 16-40 yaş arası, tahmini fetal ağırlığı 2500-4000 gram, gebelik haftası 37-41 hafta arasında olan nullipar gebeler çalışmaya dahil edildi. Çalışma grubunun (n=142) vajinal kanalına, doğumun ilk aşamasında (5 cm servikal açılmadan önce) 3-5 ml hidroksietil selüloz jel aplikatör ile uygulandı. İşlem bebeğin doğumuna kadar her iki saatte bir tekrarlandı. Kontrol grubu (n=191) standart antenatal bakım aldı.

Bulgular: Epizyotomi ihtiyacı çalışma grubunda kontrol grubuna göre anlamlı olarak daha düşüktü (n=72 (%50.7) ve n=175 (%91.6)) (Z=18.902, p<0.001). Ayrıca, çalışma grubundaki kadınların vajinal perineal bütünlüğün korunması açısından anlamlı derecede daha iyi sonuçlara sahip oldukları bulundu (n=53 (%37,3) ve n=160 (%83,7)) (Z=134,893, P<0,001) . Ayrıca çalışma grubunda doğumun ikinci evresinde kontrol grubuna göre (36.68~34.37 dk ve 58.03~30.35 dk) anlamlı kısalma gözlendi (p<0.001).

Sonuç: Obstetrik jel kullanımı doğumun birinci ve ikinci aşamalarını kısaltmakta, epizyotomi ihtiyacını azaltmakta ve perine bütünlüğünün korunmasına yardımcı olmaktadır. Bu nedenle nullipar normal vajinal doğumlarda uygulandığında maliyet etkin olabilir ve yaşam kalitesine olumlu katkı sağlayabilir.

Anahtar Kelimeler: Doğum; İkinci Aşama; Obstetrik Jel; Perine Bütünlüğü

ABSTRACT

Aim: The aim of this study to determine the effects of obstetric gel application on labor outcomes.

Materials and Method: This nonrandomized controlled study was carried out between January 2019 and June 2019 in a tertiary-care hospital. Nulliparous pregnant women with low risk, vertex position, between the ages of 16-40 years, with an estimated fetal weight of 2500-4000 grams and a gestational week between 37-41 weeks were included in the study. Using an applicator, 3-5 ml of a hydroxyethyl cellulose gel was applied to the vaginal canal of the study group (n=142) at the first stage of labor (before 5 cm cervical opening). The procedure was repeated every two hours until the birth of the baby. The control group (n=191) received standard antenatal care.

Results: The need for episiotomy was significantly lower in the study group compared to the control group (n=72 (50.7%) vs. n=175 (91.6%)) (Z=18.902, p<0.001). Moreover, it was found that women in the study group had significantly better outcomes concerning the preservation of the vaginal perineal integrity (n=53 (37.3%) vs. n=160 (83.7%)) (Z=134.893, P<0.001). Also, significant shortening was observed in the second stage of labor in the study group compared to the control group (36.68□34.37 min vs. 58.03□30.35 min) (p<0.001).

Conclusion: The use of obstetric gel shortens the first and second stages of labor, reduces the need for episiotomy, and helps preserve perineal integrity. Thus, it can be cost-effective and contribute positively to life quality if administered in nulliparous normal vaginal deliveries.

Keywords: Labor, Second Stage; Obstetric Gel; Perineal Integrity

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INTRODUCTION

Genital trauma is a frequently encountered complication of vaginal deliveries in nulliparous women (1). Additionally, birth trauma in vaginal delivery may cause postpartum pelvic floor dysfunction and increase the risk of pelvic organ prolapse and stress urinary incontinence (2).

Perineal trauma during vaginal delivery may deteriorate the quality of life and sexual function of women and cause difficulties in newborn care and breastfeeding (3,4). Furthermore, postpartum perineal pain, dyspareunia, and aesthetic concerns may cause women to avoid normal vaginal delivery and prefer to undergo elective cesarean section (5).

On the other hand, prolongation of the second stage of labor may cause negative consequences, such as perineal lacerations, puerperal infection, and postpartum hemorrhage (6). For this reason, efforts have been made to prevent perineal injury and shorten the duration of the labor after full dilatation of the cervix (1,7,8).

There are conflicting reports regarding the use of obstetric gels during vaginal deliveries. Although studies show that obstetric gels reduce the duration of the second phase of labor and have a protective effect on the pelvic floor, there are also studies reporting that they do not shorten the second stage of delivery (6,9,10).

This study aimed to determine the effects of an obstetric gel on labor outcomes, focusing on the length of the second stage of the labor, protection of perineal integrity, and episiotomy proportions.

MATERIALS AND METHODS

Study design

This non-randomized controlled study was conducted in Etlik Zübeyde Hanım Training and Research Hospital. Participants were selected from nulliparous pregnant women admitted to the department of obstetrics for delivery.

Ethical approval (numbered 343, dated 17.12.2018) was received from the Etlik Zübeyde Hanım Training and Research Hospital Clinical Research Ethics Committee. The reporting of the study was done per the CONSORT guideline (11). Informed consent form was obtained from all patients. Consent forms were also obtained from the parents of pregnant women under the age of 18.

Setting

The study was carried out in Etlik Zübeyde Hanım Training and Research Hospital between January 2019 and June 2019. The research hospital has a total of 420 inpatient bed capacity, including nine pregnancy outpatient clinics divided into early pregnancy, normal pregnancy, and risky pregnancy according to the gestational week. The study lasted 6 months. In Etlik Zübeyde Hanım Training and Research Hospital, an average of 12000 to 16000 births take place annually. However, there are limited studies in the literature on obstetric gel application and it was concluded that 453 patients would be sufficient in the power analysis made with reference to the studies titled "use of obstetric gel in nulliparous pregnant women" by Aydıner et al. in 2017 (10).

Participants

Nulliparous pregnant women with low risk, vertex presentation, aged between 16-40 years, having an estimated fetal weight of 2500-4000 grams, and a gestational week between 37-41 weeks, were included in the study.

Patients who underwent cesarean section (42 in control and 47 in the study group) were excluded from the study. Pregnant women with additional diseases such as diabetes, hypertension, or findings of cephalopelvic incompatibility, chorioamnionitis, macrosomia, prolonged rupture of amniotic membrane, fetal anomaly, dead fetus, and high-risk pregnancy were excluded from the study.

During the study period, 453 pregnant women applied to give birth. Patients in the control group were enrolled first. All eligible women who applied between January and March 2019 were invited to participate. After finishing the enrollment process of the control group, applicants between April and June 2019 were invited to join the study group. Data for 191 and 142 participants were analyzed in the control and study groups, respectively (Figure 1).

Interventions

Ultrasonography was performed in all pregnant women in the delivery room, and fetal gestational age was calculated from first-trimester ultrasonography findings. Standard antepartum care was given to all women in the delivery room. All interventions related to the study protocol were implemented by a physician trained for the study. Hourly vaginal pelvic examination was performed to all pregnant women until the end of the first stage of the labor. Later, pelvic examination frequency was adjusted according to the requirement of the second stage of delivery. All vaginal evaluations were done under hygienic conditions to minimize any risk of vaginal infection. Fetal monitoring was performed intermittently until the baby was born. Maternal and fetal parameters were recorded on the partograph during labor.

The obstetric gel used in the study (GynoTAL®, Turkuaz Inc., Istanbul, Turkey) contains deionized water, propylene glycol, carbomer, hydroxyethyl cellulose, and sodium hydroxide. GynoTAL is not allergenic, has high mucoadhesive activity, high viscosity, and high electrical conductivity. This obstetric gel was applied by a trained physician with 3-5 ml special applicator into the vaginal canal at the first stage of labor (before 5 cm opening) and every two hours until the birth of the baby. No perineal massage was implemented during the delivery.

Outcomes

The primary outcome variable of the study was "the duration of the second stage of labor". Other variables were age, body mass index (BMI), education of the mother, pregnancy week, estimated fetal weight (g), presentation (vertex/breech), episiotomy (vacuum or forceps delivery (Kristeller maneuver), estimated fetal weight (g), first and fifth-minute APGAR scores, head circumference (cm), vaginal-perineal lacerations, degree of vaginal tears (operative delivery, shoulder dystocia, episiotomy, macrosomia (induction), epidural anesthesia (prolonged

(>3 hours) second stage of labor (duration of the first stage of labor (minutes), duration of the second stage of labor (minutes).

Study Size

The sample size calculation was based on the primary outcome variable 'duration of the second stage of the labor. To compare the dependent variable between the study and control groups using the independent sample t-test with an effect size of 0.35 (small to medium) and an α error of 0.05, 333 participants (191 controls + 142 study) provides a power of 88.2% (12). This sample size is sufficient to compare a mean difference of 10.5 minutes, given a standard deviation of 30.

The patients were asked whether they wanted to apply the vaginal gel. Those who did not accept the application were included in the control group, and those who accepted were included in the study group.

Statistical Analysis

Statistical analysis was performed via the Statistical Package for the Social Sciences (SPSS) (SPSS for Windows, Version 25.0, Chicago, IL, USA) program. The mean and standard deviations were presented if the variables were numerical, while frequency and percentages were used for presenting categorical data. Normal distribution was evaluated by the Kolmogorov-Smirnov test, while scale variables were compared using the Mann-Whitney U test. The Chi-square (or Fisher's exact) test was used to compare categorical variables. Linear regression analysis was used to check for factors independently affecting the primary outcome variable after correcting for potential confounders. A p-value of less than 0.05 was considered sufficient for statistical significance.

RESULTS

Participants

The mean age of the participants was 24.77 ± 5.33 years (rang=16-40) While 19.2% of the participants (n=64) did not have any education, 18.3% (n=61) were university graduates. Additionally, while shoulder dystocia developed in 2 patients (0.5%), vacuum was required in 7 patients (2.1%) (Table 1).

Table 1: Descriptive characteristics of participants

		Number	Percent
Education	No education	64	19.2
	Primary and secondary school	101	30.3
	High school	107	32.1
	University	61	18.3
Profession	Housewife	274	82.3
	State employee	38	11.4
	Other occupation	21	6.3
Presentation	Occiput anterior	331	99.4
	Occiput posterior	2	0.6
Vacuum		6	1,8
Fetal gender	Female	165	49.5
	Male	168	50.5
Shoulder dystocia		2	0,6
Macrosomia		6	1,8

Outcomes

The need for episiotomy was significantly lower in the gel-applied group compared to the control group (Z=18.902, p<0.001). Moreover, it was found that pregnant women in the study group were significantly more advantageous concerning the preservation of vaginal perineal integrity (Z=134.893, p<0.001) (Table 2).

Table 2: Comparison of categorical variables according to the study groups

		Group			
		Control	Study		
		n (%)	n (%)	χ^2	p
Episiotomy		153(80,1)	15(10,5)		<0.001
Vacuum		5(2.6)	1(0,7)	1.686	0.245*
Kristeller maneuver		83 (43.5)	17(12,0)	38.422	<0.001
Vaginal-perineal tear		164 (85.99)	32 (22.5)	134.893	<0.001
Induction		104(54,5)	41(28,9)	21.674	<0.001
Prolonged second stage of labor		98 (51.4)	89 (62.7)	3.293	0.070
Macrosomia		5 (2.6)	1 (0.7)	1.686	0.245*
Degree of vaginal tear	1st	114 (59,68)	14 (9,85)	7.178	0.028
	2nd	40 (20,94)	18 (12,67)		
	3rd	10 (5,23)	2 (1,40)		

Significant shortening was observed in the first and second stages of labor in the study group compared to the control group (p=0.015 and p<0.001, respectively) (Table 3).

Table 3: Comparison of numerical variables between the study groups As mentioned in the limitations section, the study was not blinded. Since the experiment is completed, it is no more possible to establish blinding. Hence, we suffice by mentioning this as a limitation.

	Group	Mean	SD	Z	p
Age (year)	Control	25.63	5.80	2.793	0.005
	Study	23.63	4.40		
BMI (kg/m^2)	Control	27.58	3.24	2.987	0.546
	Study	27.67	3.83		
Gestational week	Control	39.30	1.30	0.902	0.367
	Study	39.15	1.24		
Estimated fetal weight (g)	Control	3353.57	301.07	0.570	0.569
	Study	3329.75	270.97		
Baby weight (g)	Control	3245.20	345.64	0.314	0.753
	Study	3239.82	359.01		
APGAR 1	Control	8.63	0.55	7.523	<0.001
	Study	8.99	0.08		
APGAR 2	Control	9.94	0.24	3.038	0.002
	Study	10.00	0.00		
Head circumference (cm)	Control	34.71	1.19	2.531	0.011
	Study	34.45	1.19		
First stage of labour (hour)	Control	6.26	3.46	2.444	0.015
	Study	5.49	3.61		
Second stage of labor (min)	Control	58.03	30.35	6.822	<0.001
	Study	36.68	34.37		

BMI: Body mass index. Z: Mann-Whitney U test value. SD: Standard deviation.

As mentioned in the limitations section, the study was not blinded. Since the experiment is completed, it is no more possible to establish blinding. Hence, we suffice by mentioning this as a limitation.

As to our knowledge, there is no rational explanation for the high Kristaller maneuver proportions in the study group. Higher proportions of Kristaller maneuvers in the study group were discussed in the discussion section by indicating that further studies are required to explain this apparent discrepancy. The following sentences were added to the discussion: We applied the Kristaller maneuver individually in patients with decreased maternal pushing pressure and fetal bradycardia only one time per patient. Although we observed higher proportions of Kristaller maneuvers in the study group, as to our current knowledge, there is no rational explanation of this difference. Further studies are needed to enlighten this apparent discrepancy.

Gel use was the only significant variable affecting the duration of the second stage of labor after the correction for age, BMI, Kristeller maneuver (dummy variable), induction (dummy variable), and head circumference (Table 4).

Table 4: Computer data for linear regression analysis

	Unstandardized				95.0% CI for B	
	B	SE	t	p	Lower	Upper
(Constant)	41.083	53.007	0.775	0.439	-63.195	145.362
Gel use	-20.445	4.004	-5.106	**<0.001**	-28.322	-12.567
Age (year)	-0.217	0.353	-0.616	0.539	-0.911	0.477
BMI (kg/m2)	-0.755	0.509	-1.485	0.138	-1.756	0.245
Kristeller	0.826	4.118	0.201	0.841	-7.275	8.927
Induction	-0.237	3.777	-0.063	0.950	-7.668	7.194
Head circumference (cm)	1.220	1.527	0.799	0.425	-1.784	4.224

BMI; Body mass index

DISCUSSION

The episiotomy is a technique applied to prevent severe perineal tears during delivery (13). In 2006, the American College of Obstetricians and Gynecologists (ACOG) recommended that episiotomy should not be used routinely (14). However, in selected cases, if there is a maternal or fetal indication, it is appropriate to perform an episiotomy.

In this study, there was a need for episiotomy of 91.6% in the control group, while in the study group, this figure was 50.7%.

Reducing the need for episiotomy not only provides economic benefits, but also reduces the side effects that may occur due to episiotomies, such as bleeding, infection, dyspareunia, delay in wound healing, urinary fistula, and pelvic floor dysfunction (14-17). Not to be forgotten that these complications have economic burdens beyond decreasing the personal quality of life.

We consider the economic analysis included in our manuscript as an important approach to analyze burden of episiotomy. However, we agree with the reviewer that the economic analysis was not included as an objective of the study. Thus, we modified the objectives as follows: “This study aimed to determine the effects of an obstetric gel on labor outcomes, focusing on the length of the second stage of the labor, protection of perineal integrity, episiotomy proportions, and economic burden.” Furthermore, the paragraphs about economic burden were moved further down in the discussion.

It has been reported that episiotomy is still used at high rates in some countries due to the belief that it prevents severe perineal tears, especially in primiparas (4,18,19). Shortening the second stage of labor can help preserve the vaginal perineal integrity and reduce advanced perineal tears. This study demonstrated that the use of obstetric gel is effective in preserving vaginal perineal integrity in primiparas. It was thought that the shortening of the second phase might play a role in the emergence of these effects. As a matter of fact, various procedures have been studied to reduce the effect of perineal trauma during labor, reduce postpartum blood loss, and shorten labor time to improve obstetric outcomes (1,20). Besides, the decrease in the incidence of spontaneous perineal tears due to the widespread use of gels may decrease the tendency to apply episiotomy over time.

Labor can be handled in three stages (21). The first stage, which is associated with visceral pain, is provoked by contractions of the uterus and lasts till full dilation (approximately 10 cm) of the cervix. The second stage of birth is the stage from the full dilation of the cervix to the baby’s birth. At this stage, the descent of the fetus in the birth canal may cause tension and tears in the tissues of the vagina and perineum (22). The third stage of labor is related to the postpartum period.

It has been reported that the prolongation of the second stage of labor is associated with increased maternal morbidity and operative delivery rates (23). Obstetric lubricant gels were investigated with the prediction that they could reduce the second stage of labor. In addition to researches stating that these gels shorten the second stage of labor and increase perineal integrity (9,24), there are also studies reporting that they are not effective in this regard (6).

This study yielded similar results to articles claiming that obstetric gels are beneficial. Additionally, the degree of vaginal tears was significantly lower in the gel-used group. However, it should be kept in mind that the difference between the groups

in terms of the prolonged second stage of labor does not reach a statistically significant level. The reason for this difference between studies may be the demographic differences of pregnant women included in the studies. It was concluded that the rate of multiparous pregnant women included in the examination may be a factor affecting the results.

A recent study using a gel containing hydroxyl ethyl cellulose found a reduction in the first and second stages of labor, similar to our study. However, no difference was reported in need of episiotomy and APGAR scores (10). Hence, it was thought that the differences in patient selection between the two studies may have influenced the results. As a matter of fact, pregnant women under 18 with a BMI above 30 were not included in the study by Aydıner et al. However, in our study, the rate of those with BMI> 30 was 15.9% (n= 53) and the proportion of pregnant women under the age of 18 was 2.4% (n= 8). It should also be noted that the statistical difference in APGAR scores may not be significant at the clinical level.

In conclusion, the use of an obstetric gel containing deionized water, propylene glycol, carbomer, hydroxyl ethyl cellulose, and sodium hydroxide shortens the first and second stages of labor, reduces the need for episiotomy, and helps to preserve perineal integrity. Due to these features, it has been concluded that the use of obstetric gel in hospital deliveries can be cost-effective and contribute positively to the quality of life of nulliparous pregnant women.

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None

Figure Lagent

Figure 1: Participant flow chart

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Plasenta Previa Tanılı Hastalarda Peripartum Histerektominin Depresyon Düzeylerine Etkisi

The Effect of Peripartum Hysterectomy on Depression Levels in Patients have diagnosis of Placenta Previa

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ÖZ

Amaç: İnsan doğası gereği birçok gereksinimi olan bir varlıktır. İhtiyaçları karşılandığında fiziksel ve ruhsal anlamda sağlıklı bir birey olmaktadır. Doğurabilme potansiyeli de bu ihtiyaçlardan bir tanesi olup, kaybedildiğinde ruhsal sıkıntılara sebep olabilmektedir. Bu çalışmada plasenta previa tanılı hastaların, operasyonlarından sonraki dönemde depresif belirti şiddetleri araştırıldı ve uteruslarını kaybetmenin sonucunda duygu durumlarındaki değişim incelendi.

Gereçler ve Yöntem: Çalışmaya Mart 2012-Kasım 2014 tarihleri arasında plasenta previa tanısı nedeniyle peripartum histerektomi ve sezaryen operasyonları yapılan hastalar dahil edildi. Hastalarda depresyon varlığı araştırıldı ve Beck Depresyon Ölçeği (BDÖ) ile depresif belirti şiddeti değerlendirildi. İstatistiksel analizler NCSS 2007 (NCSS LLC, UT, ABD) programı ile yapıldı.

Bulgular: Çalışmaya toplamda 119 hasta dahil edildi. Peripartum histerektomi yapılan hasta grubu 59 kişi (%49,5) olup ve ortalama BDÖ puanı 11±6 idi. Sezaryen operasyonu yapılan grup ise 60 hasta (%50,5) olup ve ortalama BDÖ puanı 4±2 idi. Peripartum histerektomi yapılan grupta sezaryen operasyonu yapılan gruba kıyasla ortalama BDÖ puanları istatistiksel olarak anlamlı yüksek bulundu (p<0.001).

Sonuç: Çalışma bulguları, peripartum histerektomi yapılan plasenta previa tanılı hastalarda depresif belirti şiddetinin daha yüksek olduğunu ve bu durumun depresyona zemin hazırladığını göstermektedir. Sonuç olarak plasenta previa tanısı nedeniyle takip edilen olgulara histerektomi öncesi ve sonrası dönemde psikolojik destek vermenin önemli olduğu kanaati oluşmaktadır.

Anahtar Kelimeler: Histerektomi, Plasenta Previa, Postpartum Depresyon

ABSTRACT

Aim: Human nature is a creature with many needs. When they need are met, they become a physically and mentally healthy individual. The potential to give birth is one of these needs, and when it is lost, it can cause mental problems. The aim of this study was to investigate the depressive symptom severity of patients diagnosed with placenta previa after surgery and to evaluate mood changes as a result of losing the uterus.

Materials and Method: Patients who underwent peripartum hysterectomy and cesarean section operations due to the diagnosis of placenta previa between March 2012 and November 2014 were included in the study. Presence of depression was investigated in the patients and the severity of depressive symptoms was evaluated with the Beck Depression Scale (BDI). Statistical analyzes were performed using the NCSS 2007 (NCSS LLC, UT, USA) program.

Results: A total of 119 patients were included in the study. The patient group who underwent peripartum hysterectomy was 59 (49.5%) and the mean BDI score was 11±6. The group that underwent cesarean section was 60 patients (50.5%) and the mean BDI score was 4±2. Mean BDI scores were statistically significantly higher in the peripartum hysterectomy group compared to the cesarean section group (p<0.001).

Conclusion: The study results are suggested that depressive symptom severity is higher in placenta previa patients undergoing peripartum hysterectomy, providing a basis for depression. Finally, psychological support is necessary for patients who are followed for placenta previa before and after hysterectomy.

Keywords: Hysterectomy, Placenta Previa, Postpartum Depression

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GİRİŞ

İnsan entelektüel, sosyal, duygusal ve fiziksel birçok gereksinimleri olan bir varlıktır. Tüm bu gereksinimleri karşılandığında fiziksel ve ruhsal olarak sağlıklı bir birey olabilmektedir (1).

Canlı türlerinde meydana gelen evrim sayesinde daha karmaşık türlerin ortaya çıkması da beraberinde gelmiştir. Türlerdeki bu gelişim aynı zamanda embriyoların da daha korunaklı ortamlarda saklanmalarını zorunlu kılar. Plasenta, bu anlamda fertilize olmuş yumurtanın gelişimini ve olgunlaşmasını sağlayan ana organdır. Plasentanın tamamen ya da kısmi olarak, alt uterin segmente yerleşmesi ve servikal osun üzerini kaplaması plasenta previa olarak tanımlanır (2). Plasenta previanın dünyada genel prevalansı %0.4'tür (3). Başlıca risk faktörleri plasenta previa öyküsü, geçirilmiş sezaryen ve çoğul gebeliktir (4). Diğer risk faktörleri artmış parite, ileri anne yaşı, infertilite tedavisi, geçirilmiş abort ve uterin cerrahi öyküsü, maternal kokain ve sigara kullanımı, beyaz olmayan ırk ve erkek fetüs olarak sıralanabilir (5-7). Plasenta previa olgularında sezaryen mutlaka deneyimli uzmanlar tarafından veya onların gözetiminde yapılmalıdır. Amerikan Obstetri ve Jinekoloji Derneği ve Maternal Fetal Tıp Derneği'nin önerileri doğrultusunda komplike olmayan plasenta previa tanılı gebelikler 36+0 ile 37+6 haftalar arasında sezaryen ile doğurtulmaktadır (8). Plasentanın yapıştığı alt segmentten kaynaklanabilecek aşırı kanama halinde, uterotonikler, mesane sondasının balonu veya Bacri balon ile kompresyon, aort basısı gibi konservatif yöntemler zaman kazandırabilir (9). Konservatif yaklaşımların yetersiz kalması durumunda, kanama kontrolüne yönelik B-Lynch sütürü, bilateral uterin veya hipogastrik arter ligasyonu ve tüm yöntemlerin çaresiz kalması halinde histerektomi uygulanabilir (10).

Depresyon umutsuzluk, kaygı, üzüntü ile birlikte fizyolojik işlevlerde, konuşma ve düşüncede yavaşlama ve durgunlaşma belirtilerinin bir araya gelmesiyle oluşan bir sendromdur. Ek olarak değersizlik, güçsüzlük, karamsarlık, isteksizlik gibi duygu ve düşünceler de eşlik edebilmektedir. Depresyon çeşitli ruhsal veya ruhsal olmayan hastalıklarda görülebilir (11). Bu çalışmada amacımız günümüzde gittikçe artan sıklıkla görülen plasenta previa tanılı hastalarda, yapılan histerektominin depresyon düzeylerine etkisini incelemektir.

GEREÇ VE YÖNTEMLER

Bu çalışma, prospektif olarak planlandı ve döneminde yıllık doğum sayısı yaklaşık 15000 olan, tersiyer bir merkez, Kanuni Sultan Süleyman Eğitim ve Araştırma Hastanesi'nde Mart 2012-Kasım 2014 tarihleri arasında yapıldı. 18-45 yaş arası antenatal dönemde çalışma merkezinde plasenta previa tanısı alıp takip edilen veya diğer kurumlardan bu tanıyı alarak doğum için yönlendirilen hastalardan viabilite sınırının üzerinde doğum yapanlar çalışmaya dahil edildi. 18 yaşın altı adölesan gebeler, çalışmadan taşınma vb gibi nedenlerden ötürü geri çekilmek isteyenler, öncesinde bilinen psikiyatrik rahatsızlığı olan hastalar çalışmadan devre dışı bırakıldı. Plasenta previa nedeniyle sezaryen olan hastalar Grup 1, histerektomi olan hastalar Grup 2 olarak adlandırıldı. Çalışmanın yapıldığı süre zarfında hastaneye başvuran toplam 133 plasenta previa tanılı gebe çalışmaya davet edildi. Grup 1 (n:60) plasenta previa nedeniyle sezaryen operasyonu olan hastalar ile Grup 2 (n:73) peripartum histerektomi yapılan hastalar olarak oluşturuldu. Histerektomi olan hasta grubundan 12 tanesi uygun kriterleri karşılamadığından çalışma dışı bırakıldı. Tüm hastalar postpartum 6. ayda bir psikiyatri uzmanı tarafından DSM IV-TR'ye göre depresyon yönünden muayene edildi. Tedavi gerekliliği görülen Grup 2'den 2 hasta daha çalışma dışı bırakıldı (n:59). Sonuç olarak kalan 119 hasta, Beck Depresyon Ölçeği (BDÖ) ile değerlendirildi. Çalışmaya alınan tüm hastalarda yaş, obstetrik, psikiyatrik ve jinekolojik hastalık öyküsü, doğum anındaki gebelik haftası, ve BDÖ puanları değerlendirildi. Hastaların psikiyatrik muayeneleri sonrası uygulanan BDÖ puanları psikiyatri uzmanı tarafından değerlendirildi. Çalışma öncesinde hastalardan yazılı onam alındı. Çalışma protokolü Kanuni Sultan Süleyman Eğitim ve Araştırma Hastanesi Etik Kurulu tarafından onaylandı (Sayı:2015/9-173, Konu No: KAEK/2015.10.9) ve Helsinki Bildirgesi ilkeleri uyarınca yürütüldü.

Beck Depresyon Ölçeği: Depresyonda mevcut olan somatik, bilişsel, duygusal ve motivasyonel belirtileri ölçmeye yaramaktadır. On beş yaşın üzerinde ergen ve yetişkinlere uygulanabilmektedir. Ölçeğin uygulanması, yaklaşık 10 ila 15 dakika sürmektedir. Toplam 21 belirti kategorisini içermektedir. Her madde 0 ile 3 puan arasında puanlanmaktadır ve toplanmaları ile depresyon puanı elde edilmektedir. Alınabilecek en yüksek puan 63'tür. Ölçeğin Türkçe geçerlik ve güvenirlik çalışması Hisli tarafından yapılmış ve ölçeğin kesme puanı 17 olarak belirlenmiştir (12). On yedi ve üzerinde alınan puanlar depresyon olduğunu göstermektedir.

İstatistiksel analiz: Bu çalışmada istatistiksel analizler NCSS 2007 (NCSS LLC, UT, ABD) paket programı ile yapıldı. Verilerin değerlendirilmesinde tanımlayıcı istatistiksel yöntemlerin (ortalama ± standart sapma, medyan, interkartil aralık) yanı sıra, normal dağılım gösteren ikili grupların karşılaştırmasında bağımsız t testi, normal dağılım göstermeyen ikili grupların karşılaştırmasında Mann-Whitney U testi kullanıldı. Nitel verilerin karşılaştırılmasında ise, ki-kare testi kullanıldı. Sonuçlar, $p<0.05$ istatistiksel anlamlılık düzeyinde değerlendirildi.

BULGULAR

Toplam 119 hasta çalışmaya dahil edildi. Yaş ortalamaları Grup 1(n:60)'in 31,6±5,7 ve Grup 2 (n:59)'nin 32,8±4,71 idi. Gravide (p=0,002) ve parite (p=0,001) değerleri histerektomi olan grupta anlamlı olarak daha yüksek görüldü. Geçirilmiş sezaryen sayısı histerektomi olan grupta daha yüksek izlendi (p=0,0001). Gruplar arası eğitim düzeyinde, normal doğum, abort ve küretaj sayılarında anlamlı fark izlenmedi (p>0,05). Grup 2'nin BDÖ puan ortalaması Grup 1'den istatistiksel olarak anlamlı yüksek bulundu (p=0,0001) (Tablo 1).

Tablo 1. Hasta gruplarının karşılaştırılması-1

	Grup I Histerektomi (-) n:60	Grup II Histerektomi (+) N:59	p değeri
Yaş	31,6±5,76	32,8±4,71	0,28
Gravida	2,85±1,53 3 (2-3,75)*	3,71±1,39 3 (3-5)*	**0,002**
Parite	1,33±1,19 1 (0-2)*	1,98±0,88 2 (1-3)*	**0,001**
Geçirilmiş Sezaryen Sayısı	1,15±0,99 1 (0-2)*	1,9±0,76 2 (1-2)*	**0,0001**
Normal Doğum Sayısı	0,18±0,93 0 (0-0)*	0,1±0,36 0 (0-0)*	0,530
Abort	0,42±0,65 0 (0-1)*	0,51±1,01 0 (0-1)*	0,554
Küretaj	0,1±0,3 0 (0-0)*	0,2±0,52 0 (0-0)*	0,185
Eğitim Yılı	5,97±3,74	5,27±3,63	0,306
BDÖ † Puanı	3,43±1,97	10,27±5,68	**0,0001**

* Median (IQR) İnterquartil range

† Beck Depresyon Ölçeği

BDÖ puanı 17 üzeri olanların sayısı, Grup 2'de anlamlı olarak daha yüksek bulundu (p=0,0001) (Tablo 2).

Tablo 2. Hasta gruplarının karşılaştırılması-2

		Grup I Histerektomi (-) n %	Grup II Histerektomi (+) n %	p değeri
Eğitim Durumu	Okur-Yazar Değil	12 20,00%	13 22,03%	0,985
	İlköğretim	42 70,00%	41 69,49%	
	Lise	5 8,33%	4 6,78%	
	Üniversite	1 1,67%	1 1,69%	
BDÖ*	<17 BDÖ	60 100,00%	47 79,66%	**0,0001**
	≥17 BDÖ	0 0,00%	12 20,34%	

*Beck Depresyon Ölçeği

TARTIŞMA

Günümüzde, geçirilmiş sezaryen sayılarının artması ve bununla beraber anne yaşının daha ileriye taşınması, plasenta previa (plasenta akretanın eşlik ettiği veya etmediği) görülme sıklığını belirgin şekilde arttırmıştır (3). Peripartum histerektomi, doğum sırasında annenin ölüm ya da ciddi morbidite riski nedeniyle yapılan bir operasyondur (13). Doğum eylemine hazırlanan ya da

yeni anne olmuş bir kadına yaşamsal risk nedeni ile doğurganlık organının bebeği ile birlikte alınabileceği ya da alınmış olduğu bilgisi verilmesi doğum eylemine, anneliğe ve bebeğe verilen anlamı değiştirebilir. Literatürde bu konuda yapılmış çalışmalar az sayıda olup, postpartum depresyonu araştıran çalışmalar ile sınırlı görünmektedir (14). Çalışmamızdaki gruplar arasında BDÖ puanındaki anlamlı farkın nedeni; kadınların reprodüktif çağda üreme organlarını kaybetmeleri, bir kez daha anne olma şanslarının ellerinden alınması ve toplumdaki kadınlık kimliğini kaybetmiş olarak hissetmeleri olabilmektedir.

Kadınlar depresyon için risk altındadır. Bunun sebebi daha çok sosyokültürel faktörlerle ilintilidir. Sosyalleşme süreci içinde kadına ve erkeğe yüklenen roller birbirinden farklıdır. Sunulmuş olan doyum yolları, beklentiler ve çare arama davranışları erkeğe daha fazla özgürlük tanımaktadır. Tüm bunlar kadını birtakım yönlerden kısıtlamaktadır (15). Literatüre bakıldığında, 24'ü histerektomi olan 41 hastanın dahil olduğu Şentürk ve ark.'ın yaptığı bir çalışmada, Edinburgh Doğum Sonrası Depresyon Ölçeği puanları histerektomi grubunda, bizim çalışmamıza benzer şekilde, yüksek bulunmuştur (16). Bir başka çalışmada da, benign nedenlerle histerektomi yapılan hastalarda cinsel fonksiyon bozukluğu ve depresyon araştırılmış ve istatistiksel olarak anlamlı olmasa da, depresyon puanlarında artış bulunmuştur (17).

BDÖ bir tanı ölçeği değildir; yalnızca belirti şiddetini gösteren bir ölçektir. Çalışmamızda peripartum histerektomi geçiren hasta grubunda BDÖ için kesme puanı ≥17 olan 12 hasta görülmektedir. Psikiyatri uzmanı tarafından depresyon tanısı konmamış olan bu grupta, belirti şiddetlerinde histerektomi olmayan gruba kıyasla meydana gelen artış istatistiksel olarak anlamlıdır. Yapılan değerlendirmede hastaların en çok cinsel konulara olan ilgileriyle alakalı soruda yüksek puan verdikleri tespit edilmiştir. Çoğu kadın için çocuk doğurabilmek hayatının en önemli rolüdür. Histerektomi ile bu yeteneğini istemeden kaybetmesi nedeniyle, kadınlık kimliğinin zedelenmiş olarak görmesi ve kendini değersiz hissetmesi olasıdır (18). Çalışmamızdaki hasta grubu annelik rolü henüz bitmeden histerektomi olması nedeniyle, bu durumdan daha da kötü etkilenmiştir. Ancak mesane invazyonu olan plasenta perkrata olgularında maternal mortalite oranının %6 olduğu göz önüne alındığında hastalığın ciddiyeti tekrar düşünülmeli ve histerektomi gerekliliği doğan bu hastalara uygun psikolojik desteğin verilmesi ile birlikte depresyon açısından daha az başvurunun olabileceği görüşündeyiz (19). Kadının histerektomiye bakış açısı partnerinin histerektomiye verdiği tepki ile de ilişkili bulunmuştur. Şu da unutulmamalıdır ki; kadının partneri empati sahibi ve destekleyici ise, histerektomi sonrası kadındaki olumsuz tepkilerin azalma ihtimali mevcuttur (20).

Eğitim seviyesi azaldıkça depresyon, şizofreni, anksiyete bozuklukları ve post-travmatik stres bozukluğu gibi psikiyatrik rahatsızlıkların arttığı bilinmektedir (21). Postpartum ve antenatal depresyon ile ilgili çalışmalarda ise sonuçlar değişkendir (22, 23). Çalışmamızda eğitim seviyesi ile BDÖ puanları arasında anlamlı bir farklılık izlenmedi. Bundan sorumlu en önemli iki etken, kadınların anne olma içgüdüsünün eğitim seviyesinden bağımsız olması ve mortalitesi %6'lara varan bir hastalığın tedavisinde histerektominin kabul edilebilir olmasıdır.

Hastaların doğum öncesinde ruhsal olarak ve BDÖ ile değerlendirilmemiş olması çalışmamızın başlıca kısıtlılığıdır. Gelecekte beden algısı, cinsel doyum ölçeği gibi ek ölçekler de kullanılarak peripartum histerektominin depresyon, cinsel yaşam ve beden algısına olan etkilerinin incelenmesine yönelik çalışmalar yapılabilir.

SONUÇ

Peripartum histerektomi geçiren gebelerde postpartum 6.ayda değerlendirilen Beck Depresyon Ölçeklerinde histerektomi geçirmeyen gebelere göre depresyon düzeylerinin anlamlı olarak daha yüksek olduğu sonucu bulundu. Kadınların peripartum histerektomiden psikolojik açıdan etkilendiği görüşünü benimseyerek, bu gibi riskli gebelik geçiren annelere antenatal ve postnatal dönemde uygun psikolojik desteğin verilmesi gerektiğini düşünmekteyiz.

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Serum anti-Mullerian hormon seviyesi ve antral follikül sayısının stimüle edilmemiş menstruel siklustaki değişiminin saptanması

Variability of serum anti-Mullerian hormone level and antral follicle count in an unstimulated menstrual cycle.

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ÖZ

Amaç: Çalışmada düzenli menstruel siklusu olan sağlıklı hastalarda, doğal siklusta serum anti-Mullerian hormon değerlerinin ve antral follikül sayımının, intra-menstruel değişiminin saptanması amaçlanmıştır.

Gereç ve Yöntemler: Çalışmaya menstruel siklusu düzenli olan, sistemik hastalık ve geçirilmiş over cerrahi öyküsü olmayan, son iki ay içinde hormonal kontraseptif preparat kullanmamış olan 50 sağlıklı kadın dahil edilmiştir. Serum anti-Mullerian hormon seviyeleri ve antral follikül sayısı stimüle edilmemiş aynı siklus içerisinde erken folliküler faz, geç folliküler faz ve luteal fazda olmak üzere üç kez değerlendirilmiştir. Yaş gruplarına göre serum anti-Mullerian hormon seviyelerinin karşılaştırılması amacıyla da hastalar genç (<35 yaş) ve ileri yaş (≥35 yaş) olmak üzere iki gruba ayrılmıştır.

Bulgular: Hastaların yaş ortalaması 30.8, vücut kitle indeksi ortalaması 23.4 kg/m2 ve ortalama siklus uzunluğu 28.5 gün olarak bulunmuştur. Aynı menstruel siklusta erken folliküler faz, geç folliküler faz ve luteal faz olmak üzere üç kez değerlendirilen serum anti-Mullerian hormon seviyesi ortalaması 2.66 ng/dl ve ortalama antral follikül sayısı 17.4 olarak saptanmıştır. En yüksek serum anti-Mullerian hormon seviyesi ve antral follikül sayısı geç folliküler fazda bulunmuştur ve bu fark antral follikül sayısında olmasa da serum anti-Mullerian hormon seviyesi karşılaştırmasında istatistiksel olarak anlamlı bulunmuştur. (p = 0.307, p = 0.044). Serum anti-Mullerian hormon variabilitesi genç grupta, ileri yaş gruba kıyasla daha fazla olarak saptanmış olup istatistiksel olarak anlamlı bulunmuştur. (0.241 vs 0.132, p = 0.011)

Sonuç: Serum anti-Mullerian hormon seviyeleri menstruel siklus içinde dalgalanmalar göstermekte olup, en yüksek serum anti-Mullerian hormon seviyesi geç folliküler fazda saptanmıştır. Antral follikül sayımı menstruel siklus boyunca sabit kalmıştır.

Anahtar Kelimeler: Anti-Mullerian hormon, menstruel siklus, over rezervi, antral follikül sayısı, intra-siklik variabilite

ABSTRACT

Aim: To evaluate the variability of anti-Mullerian hormone (AMH) and antral follicle count (AFC) in an unstimulated menstrual cycle.

Materials and Method: The study was designed on 50 women who had regular menstrual cycles and did not have any systemic disease or previous ovarian surgery. Serum AMH levels and antral follicle counts of all participants were evaluated three times in the same menstrual cycle in the early and late follicular phase and luteal phase. To evaluate the intracyclic AMH fluctuation according to age, participants were divided into two groups; younger (<35 years) and older (≥35 years old).

Results: The mean age of the participants was 30.8, the mean BMI was 23.4 kg/m2, and the mean menstrual cycle duration was 28.5 days. Mean AMH values evaluated at three different times in the menstrual cycle, early follicular, late follicular, and luteal phase, were 2.66 ng/dl and mean AFC 17.4. The highest mean AMH level and AFC were detected in the late follicular phase and this was statistically significant for AMH level but not for AFC (p = 0.044, p = 0.307, respectively). The intracyclic fluctuation of AMH was greater in the younger patient group. The coefficient of variation was 0.241 in the younger patient group, and 0.132 in the older patient group. (p = 0.011)

Conclusion: Serum AMH levels fluctuate throughout the menstrual cycle and the highest serum AMH level was detected in the late follicular phase. AFC remained stable throughout the cycle.

Keywords: Anti-Mullerian hormone, menstrual cycle, ovarian reserve, antral follicle count, intra-cycle variability

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INTRODUCTION

Due to the increasing tendency of women to postpone their pregnancy plans for various reasons in the modern world, the evaluation of ovarian reserve has gained great importance in recent years (1). Also, diseases that reduce ovarian reserve such as premature ovarian failure or endometriosis, in individuals without children, lead them to assisted reproductive techniques such as oocyte or embryo freezing (2). In addition, especially in young women diagnosed with malignancy, the possibility of ovarian failure after radiotherapy or chemotherapy brings future fertility concerns and creates extra stress on patients (3). Due to the reasons mentioned above, the interest and need for assisted reproductive treatments (ART) have increased in recent years.

For many years, anti-Mullerian hormone (AMH) and antral follicle count (AFC) have been routinely used to evaluate ovarian reserve. It is known that AMH secretion is independent of gonadotropins and therefore can be evaluated on any day of the menstrual cycle (4). AFC, on the other hand, is usually evaluated in the first days of the cycle before ART (5).

Individualization of the therapies in IVF depends on the prediction of ovarian response to controlled ovarian stimulation. Two sensitive ovarian reserve markers AMH and AFC are being used to foresee the poor and high responders to optimize stimulation protocol and gonadotropin dosage (6). Among ART, protocols in which ovarian stimulation is started randomly at any time of the cycle have been frequently used before chemotherapy or radiotherapy in patients with malignancy who desire fertility (7). In a study that evaluated the ovarian response to hyperstimulation in random start stimulation protocols, no detrimental effect of the presence of corpus luteum or dominant follicle was shown, supporting the applicability of random start protocols (8). In addition, dual stimulation in the same cycle has become a frequently used method as an assisted reproductive treatment method in patients with poor ovarian response in recent years (9). Considering these new ovarian stimulation protocols, we aimed to determine the variability of AMH and AFC in an unstimulated menstrual cycle in this study.I

MATERIAL AND METHODS

The participants included in this prospective study were randomly selected among the patients who applied to the gynecology outpatient clinic of the University of Health Sciences, Umraniye Training and Research Hospital, Istanbul, between July and September 2019, and they all provided written informed consent for participation.

We estimated the required sample size to test a moderate intracycle variability (effect size d: 0.4, two-tailed) between matched pairs with 80% power and 5% type I error rate. A total sample size of 52 patients was needed to show effect sizes 0.4 with adequate power. The effect size was estimated by assuming a mean change equivalent to 40-50% of the standard deviation for each parameter would be clinically significant.

Regular menstrual cycle is defined as a 25 to 35 days cycle and maximum 5 days difference between consecutive cycles. In light of this information, this study was designed on 50 women with regular menstrual cycles without any known history of infertility. Detailed reproductive history was taken. Age, BMI, chronic illness, medications, previous surgeries, and smoking details were recorded. Moreover, dysmenorrhea, dyspareunia, and dyschezia were questioned.

Exclusion criteria were irregular menstrual cycles, BMI >30 kg/m2. and <18 kg/m2., polycystic ovary syndrome, hormonal medicine use in the last 2 months, suspected or known endometriosis patients, previous ovarian surgery, any known chronic diseases, breastfeeding, ovarian mass, and malignancies.

Three evaluations for AMH level and AFC were performed for each woman in the same cycle. The first evaluation was done between days 2-4 and defined as early follicular phase. The second evaluation was done between days 8-10 and recorded as late follicular phase. Finally, the third evaluation was done between days 16-18 as a luteal phase evaluation. The third evaluation was confirmed to be in the luteal phase, with corpus luteum and/or free fluid in the pelvis as an indication of ovulation in the ultrasound examination. AFC was performed by the same gynecologist using a Voluson E6 device with the Sonography-based Automatic Volume Calculation (Sono AVC) technique which provides a 3-dimensional ovarian image and an automated antral follicle count. It saves time for both the patient and the sonographer, standardizes the measurements and allows quality control (10) (Figure 1).

Figure 1. Antral follicle counting - SonoAVC

Following the analysis of 150 serum samples for AMH; 50 participants were divided into two groups based on their ages as follows; younger patient group (<35 years) and older patient group (35 years).

The same kit, using Snibe Co. LTD Maglumi 4000+ AMH immunoassay device evaluated all samples. The kit used was a sandwich chemiluminescence immunoassay wherein one

antibody binds to the AMH mature-region and the other antibody binds to the AMH pro-region. The measuring range was indicated as 0.02-25 ng/ml.

Statistical Analysis

Statistics were performed with the SPSS 25.0 package program. The distribution of the data was found to be normal with the Kolmogorov Smirnov test. Variations through phases were evaluated with Anova. P-value < 0.05 was accepted as statistically significant. Every individual's AMH level coefficient of variation and the mean values were calculated. Spearman correlation coefficient was used to evaluate which of the two age subgroups has the greatest variation. The coefficient of variation (Cv), calculated as standard deviation (SD)/mean, was used as a measure to describe and compare variations between groups.

The study was conducted in accordance with Declaration of Helsinki Ethical Principles and Good Clinical Practices and approved by the ethics committee of Umraniye Training and Research Hospital (B.10.1.TKH.4.34.H.GP.0.01/129) (Date of approval: 26.06.2019)

RESULTS

The age of the women included in the study ranged from 18 to 44 years, with an average of 30.8 years. The mean BMI was 23.4 kg/m2 and the mean menstrual cycle duration was 28.5 days.

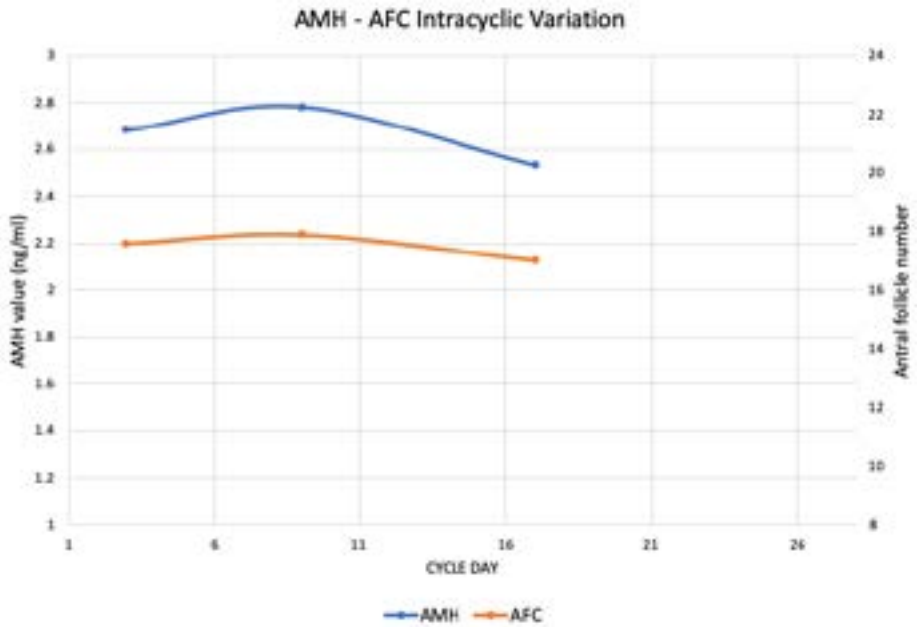
Mean AMH values evaluated at three different times in the menstrual cycle, early follicular, late follicular, and luteal phase, were 2.66 ng/dl and mean AFC 17.4. The mean AMH was 2.68 ng/dl in the early follicular phase, 2.78 ng/dl in the late follicular phase, and 2.53 ng/dl in the luteal phase. The highest mean AMH level was detected in the late follicular phase, which was statistically significant (p = 0.044) (Table 1).

Table 1 Mean AMH levels and AFC detected in early follicular phase, late follicular phase and luteal phase.

	Early Follicular Phase	Late Follicular Phase	Luteal Phase	p-value
AMH (ng/ml)	2.68 ± 1.97	2.78 ±2.02	2.53 ± 1.89	**0.044**
AFC	17.6 ±11.1	17.9 ±12.4	17 ± 11.2	0.307

*Values are shown as mean (± standard deviation)

The mean AFC was 17.6 in the early follicular phase, 17.9 in the late follicular phase, and 17.0 in the luteal phase (Figure 2).



The highest AFC was detected in the late follicular phase however the intra-cyclic difference was not statistically significant (p = 0.307) (Table 1). Variation of AMH levels between menstrual phases was greatest between late follicular phase and luteal phase (p=0.019, 95% CI (0.033, 0.464)) (Table 2).

Table 2 Comparison of mean AMH levels according to menstrual cycle phases

AMH (ng/ml)	Absolute difference	p-value	95% CI
Early Follicular vs Late Follicular Phase	-0.099	0.880	(-0.329, 0.132)
Early Follicular vs Luteal Phase	0.150	0.531	(-0.121, 0.421)
Late Follicular vs Luteal Phase	0.248	**0.019**	(0.033, 0.464)

Evaluation according to age subgroups revealed that the highest mean AMH level was detected in the late follicular phase in both the younger and older groups (Table 3).

Table 3 Mean AMH levels throughout the cycle according to age subgroups

	Age groups			
	18-34 years n=36	**35-45 years** n=14	**Total** n=50	**p-value**
AMH Cv	0.241	0.132	0.162	**0.011**
St. Dev	0.158	0.085	0.119	

*AMH Cv: AMH coefficient of variation. St. Dev: Standard Deviation

The intracyclic fluctuation of AMH was greater in the younger patient group. The coefficient of variation was 0.241 in the younger patient group, and 0.132 in the older patient group (p = 0.011) (Table 4).

Table 4 AMH- Coefficient of variation between age subgroups

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DİSCUSSION

In this study, we found that the AMH values in the late follicular phase of the menstrual cycle were significantly higher than in the early follicular and luteal phases, and the intracyclic variation was greater in the young age group whereas AFC was similar throughout the cycle.

In the literature, there are numerous studies about intracyclic variation of plasma AMH levels in different patient groups. In a study that focused on the AMH level variation in the follicular phase of 24 healthy regularly menstruating women; the blood samples were taken every other day until the LH peak in two consecutive cycles of the patients: one untreated and one FSH treated cycle. In the untreated cycle, AMH levels remained the same during the follicular phase (11). La Marca et al investigated day-to-day fluctuations in AMH levels in a study of 12 healthy, regularly menstruating women; they demonstrated no significant change in intracyclic AMH levels throughout the menstrual cycle (12). In contrast, various studies found a significant increase in AMH levels in the late follicular phase and pre-ovulatory phase compared to post-ovulatory phase and luteal phase. Hadlow et al conducted a study on 12 regularly menstruating, relatively old aged women (mean 36 years) and took 6 blood samples in the same menstrual cycle. They found AMH levels to be statistically significantly higher in the early follicular phase than the luteal phase. In addition, they evaluated AMH results against common cut-offs for definition of reduced ovarian reserve, and they determined that a minimum of 4 women out of 12 crossed the cutoff or not depending on which day the blood sample was taken (13). In a study including 36 regularly menstruating women, blood samples to evaluate serum AMH, FSH, E2, inhibin B, and free testosterone levels were taken every other day and every day periovulatory. Median AMH levels were significantly higher in the late follicular phase compared to the ovulatory and early luteal phase (14). In parallel to these studies we also found that AMH levels were significantly higher in late follicular phase compared to luteal phase.

In a study published in 2017, the intra-cyclic AMH variation was examined in 171 infertile women aged 18-42 years. In this study, in which the participants were divided into three groups as adequate, high and diminished according to their ovarian reserves, serum AMH levels were higher in all three groups during the follicular phase than the luteal phase (15). In 2019, Gorkem et al. searched the AMH fluctuations during the follicular and luteal phases of the menstrual cycle in 257 infertile women. In this study, in which the participants were divided into three groups as hypo-response, normo-response, and hyper-response, serum AMH levels in the follicular phase were found to be higher than those in the luteal phase in all three groups (16). Consistent with these studies, we also found that mean AMH level in the late follicular phase was significantly higher in the early follicular and luteal phases.

Sowers et al. evaluated the AMH fluctuations in the cycle in 20 women aged 30-40 years and stated that AMH has two cycle patterns. The first is “Aging ovary”, which is observed in women with AMH levels below 1 ng/mL, which includes shorter cycle lengths with little intra-cycle AMH changes, while the second, “Younger ovary” pattern included higher levels of AMH with significant changes during the cycle (17). In another study from Hehenkamp et al, periovulatory AMH increase in the young patient group is present but it is not statistically significant (18). Overbeek et al. reported in their study that the amplitude of fluctuations in serum AMH level was greater in young women than in older women (19). In a review published in 2013, La Marca et al evaluated the variability of AMH levels by age, BMI, ethnicity, and smoking. According to this review, ethnicity may affect AMH levels, smoking negatively affects AMH levels, there is a negative relationship between BMI and AMH levels, and younger women had significantly more intra-cycle fluctuations in AMH levels than older women (20). In line with these studies, we also found that the AMH fluctuation in the younger group was greater than the older patient group.

In addition to AMH, there are also studies in the literature on intra-cyclic variability of AFC, another indicator of ovarian reserve. In 2010, van Disseldorp et al. evaluated the inter and intra-cycle stability of AFC and AMH and demonstrated that serum AMH had less individual intra- and inter-cycle variation than AFC. They stated that serum AMH level is a more reliable and robust way of assessing ovarian reserve in subfertile women compared to AFC (21). Depmann et al. evaluated AMH and AFC fluctuations in the cycle of 44 women in a wide age range, including 25-46 years old. In this study, in which the median AMH level was 0.48 and the median AFC was five, they did not detect a statistical significance in the fluctuations of neither AMH nor AFC within the cycle (22). Deb et al. conducted a study on 36 healthy regularly menstruating women and they performed ultrasonographic examinations using SonoAVC on four different days in the same menstrual cycle. They found no significant intracyclic variation in small AFC(6mm) (23). In a study published by Mavrelos et al. in 2016, they investigated the variation of AFC in the early and late follicular phase and its clinical effect in infertile women. In this study, the authors stated that although the AFC in the early follicular phase was statistically significantly higher than the AFC in the late follicular phase, this did not significantly affect the ovarian stimulation protocol design and the prediction of excessive ovarian response in patients (24). In this study, in which AFC was evaluated 3 times during the cycle as early follicular, late follicular, and luteal phases, the highest number of antral follicles was detected in the late follicular phase, nevertheless it was not statistically significant. We think that these different results found in studies on intra-cycle fluctuations of AFC are related to the number of patients included in the study, the mean age of the patients, and ovarian reserves.

The strengths of this study are that the population studied were regularly menstruating women around 30 years old women and the variability of AMH in this population is of clinical interest in the era of women postponing the childbearing age. To these women, it is important to give comprehensive counseling on their fertility aspects (1). Also, it is important, especially in random start protocols and oncofertility patient populations to know whether an intracyclic fluctuation of AMH or AFC exists since the treatment protocol is determined on a cycle-independent measurement of AMH or AFC (25).

In this prospective study, all ultrasonographic evaluations were performed on the same ultrasound device by the same gynecologist to avoid interobserver variability. In addition, AMH values were determined accordingly on the same day of antral follicle count via the SonoAVC technique. However, the limited

number of participants for subgroup analyses and the fact that AFC and AMH evaluations were performed on only three different days representing the entire menstrual cycle are limiting factors.

CONCLUSION

We found that serum AMH levels fluctuate throughout the menstrual cycle and the highest mean AMH levels were detected in the late follicular phase. This fluctuation was much more significant in the younger patient group. AFC remains stable throughout the cycle. Despite statistically significant fluctuations in AMH levels, its clinical significance is still open to debate. We think that randomized controlled studies with larger series are needed to clarify the effect of serum AMH evaluation timing in the menstrual cycle on protocol selection and treatment success in ART.

Declarations

Ethics approval and consent to participate

All participants signed informed written consent before being enrolled in the study. The study was reviewed and approved by the ethics committee of the University of Health Sciences, Umraniye Training and Research Hospital. (Ethics approval reference number: B.10.1.TKH.4.34.H.GP.0.01/12 Date: 26.06.2019) All procedures were performed according to the Declaration of Helsinki Ethical Principles and Good Clinical Practices.

Availability of data and materialsThe data supporting this study is available through the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Concept & Design (MD, RNB) Data acquisition (MD), Analysis (MD, IE), Drafting (MD, IK), Critical revision (MD, RNB, IK, IE) Final approval ((MD, RNB, IK, IE,)

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This manuscript is the result of the MD thesis of the corresponding author.

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Özgün Araştırma / Original Article

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Factors Affecting The Success Of Vaginitis Treatment In Pregnant Women; A Prospective Cohort Study

Gebelerde Vajinit Tedavisinin Başarısını Etkileyen Faktörler; Prospektif Kohort Çalışması

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ÖZ

Amaç: Kadın genital sisteminin anatomisi, fizyolojisi ve florası gebeliğe bağlı hormonal, metabolik, endokrinolojik ve immünolojik nedenlerle değişir. Disbiyoz, fetoplasental ünitede asendan veya hematojen yolla enfeksiyonlara neden olarak kronik inflamatuar süreçlerle spontan erken doğum riskini artırır. Çalışmamızın amacı vajinitli gebelerde vajinite zemin hazırlayan, tedaviye direnç oluşturan ve nükslere neden olan kötü kişisel alışkanlık ve uygulamaları ortaya çıkarmaktır.

Gereçler ve Yöntem: Tanımlayıcı çalışmamız etik kurul onayı ile Aralık 2021 - Nisan 2022 tarihleri arasında Kadın Hastalıkları ve Doğum Kliniğine başvuran hasta gurubu ile yapılmıştır. Çalışma grubumuz, okuma yazma bilen, işbirlikçi, anketteki tüm soruları yanıtlamaya gönüllü 18 yaş üstü 178 gebeden oluşmaktadır.

Bulgular: Katılımcıların %71,9'unda (128 kişi) vajinal duş, %67,4'ünde (120 kişi) iç çamaşırını hiç ütülememekte, %66,9'unda (119 kişi) perineyi arkadan öne doğru temizleme, %41,2'sinde günlük ped kullanımı (73 kişi), %41'inin (73 kişi) sentetik çamaşır kullanımı, %16,3'ünün (29 kişi) genital temizlik ürünü kullanımı, %7,3'ünün (13 kişi) iç çamaşırını elde yıkama , %5,6'sı (10 kişi) sık cinsel ilişki davranışı sergilemiştir. Genital bölge temizliği ile ilgili olarak hastaların %11,2'si (20 kişi) beyaz sirke kullanmayı, %3,4'ü (6 kişi) asidik karışım kullanmayı biliyordu. Katılımcıların %6.7'si (12 kişi) vajinal probiyotik kullanımını biliyordu.

Sonuç: Çalışmamızın sonuçları dikkate alındığında özellikle sosyo-ekonomik ve kültürel düzeyi düşük olan kadınlarda genital hijyen konusunda yanlış uygulamaların alışkanlık vasfı kazandığı söylenebilir.Bu doğrultuda kadınların genital hijyenle ilgili uygulamada yaptıkları hatalar ve tekrarlayan enfeksiyon olasılığı nedeniyle önleyici tedbir olarak genital hijyen konusunda eğitime ihtiyaç duydukları sonucuna varılmıştır.Çalışmamız ile kadınlarda genital enfeksiyonların ortaya çıkmasındaki en önemli eksikliğin eğitim eksikliği olduğu sonucu ile birinci basamakta çalışan tüm sağlık profesyonellerinin bunu önlemeye yönelik bir eğitim planı geliştirmeleri önerilmektedir.

ABSTRACT

Introduction: Anatomy, physiology, and flora of the female genital system change due to pregnancy-related hormonal, metabolic, endocrinological, and immunological reasons. Dysbiosis increases the risk of spontaneous preterm birth with chronic inflammatory processes by causing infections in the fetoplacental unit by the ascending or hematogenous route. Our study aimed to reveal the bad personal habits and practices predispose to vaginitis, create resistance to treatment, and cause recurrences in pregnant women with vaginitis.

Material-Methods: Our descriptive study was conducted on a group of patients who applied to the Department of Obstetrics and Gynecology, between December 2021 and April 2022, with the ethics committee's approval. Our study group consists of 178 pregnant women over 18 who are literate, cooperative, and volunteered to answer all the questions in the questionnaire.

Results: Vaginal douching in 71.9% (128 people) of the participants, not ironing their underwear at all in 67.4% (120 people), cleaning the perineum from back to front in 66.9% (119 people), 61.2% daily pad use in 61.2% (109 people), synthetic laundry use in 41% (73 people), use of genital cleaning products in 16.3% (29 people), hand washing underwear in 7.3% (13 people) and 5.6% (10 people) had frequent sexual intercourse behavior. Regarding genital area cleaning, 11.2% (20 people) of the patients knew about using white vinegar, and 3.4% (6 people) used the acidic mixture. 6.7% (12 people) of the participants knew the use of vaginal probiotics.

Conclusion: Considering the results of our study, it can be said that wrong practices regarding genital hygiene continue, especially in women from low socio-economic and cultural levels. In this respect, the women need training on genital hygiene as a preventive measure due to the mistakes they make in practice related to genital hygiene and the possibility of experiencing a genital infection in a significant part of them. In conclusion, considering that the most significant deficiency in the occurrence of genital infections in women is the lack of education, it is recommended that all health professionals develop a training plan to prevent genital infections and apply it to women in the regions they work.

Keywords: Vaignitis, probiotics, pregnancy, life modification, recurrence, Treatment failure

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INTRODUCTION

Vaginitis is a general expression given secondary to infection, inflammation, or changes in the normal vaginal flora in the vagina. The most common underlying pathology is nonspecific vaginitis, with a 40-50% rate. While 20-30% of candidiasis is detected, Trichomoniasis is observed in the remaining patient group1. Symptoms include vaginal discharge, odor, itching, burning, dysuria, dyspareunia, and irritation-discomfort. Along with these complaints, vaginitis is among the most common reasons women apply to the gynecology outpatient clinic.

Bacterial vaginosis (BV) is a polymicrobial clinical condition that occurs when anaerobic bacteria in the vaginal tissue replace lactobacilli. Clinical diagnosis can be made with the Nugent microbiological scoring method. The Nugent Score is gram stain scoring system for vaginal swabs to diagnose bacterial vaginosis. The Nugent score is calculated by assessing the decrease in Lactobacillus scoring as 0 to 4, Gardnerella vaginalis morphotypes scoring as 0 to 4 and Mobiluncus spp. morphotypes scoring as 0 to 2. A total score of 7 is consistent with bacterial vaginosis without culture. The Nugent score is not preferred in todays clinical practice because of it's time-consuming nature and the necessity of expert microscopist*.

In addition, the diagnosis can be made by at least three Amsel criteria, including a sticky, milky white appearance in vaginal discharge, pH greater than 4.5, positive Whiff test (amine) with 10% KOH, and 'clue cell' evaluations in microscopic examination 2.

The community located on the skin and mucous membranes of the human body and creates a critical defense mechanism by preventing the proliferation of pathogenic microorganisms under normal conditions is called flora. Maintaining the vaginal floral balance will prevent infections in the feto-maternal compartment and vaginal infections. It will help in the process of maintaining the pregnancy to a sufficient week.

Anatomy, physiology, and flora of the female genital system change due to pregnancy-related hormonal, metabolic, endocrinological, and immunological reasons3. The microbiome, differentiated by these changes during pregnancy, facilitates the emergence of urogenital infections. Dysbiosis increases the risk of spontaneous preterm birth with chronic inflammatory processes by causing infections in the fetoplacental unit by the ascending or hematogenous route. Preterm labor is associated with vaginal dysbiosis 29.

Repetetive treatment requirement in pregnant patients with vaginitis is due to the restrictions on drug therapy. There are several important factors why we are unable to releive symptoms in some pregnant women such as frequent sexual activity, systemic disease (such as diabetes mellitus), sexually transmitted diseases, antibiotic use, as well as vaginal douching habits, irritant and wrong personal practices such as the use of allergen products (genital washing products) and hygiene disorders.

The aim of our study was for pregnant women with vaginitis who applied to our obstetrics clinic in Kars province; It is to reveal the bad personal habits and practices that predispose to vaginitis, create resistance to treatment and cause recurrences. With our study, we aim to report our experiences about the results by conducting a survey that will raise awareness about perineal health.

MATERIAL AND METHODS

Our descriptive study was conducted on a group of patients who applied to the Department of Obstetrics and Gynecology, between December 2021 and April 2022, with the ethics committee's approval. Our study group consists of 178 pregnant women over 18 years old who are literate, cooperative, and volunteered to answer all the questions in the questionnaire. The questionnaire method was used as a data collection tool. Patients under 18 years old who could not cooperate or had a disease that limited self-care were excluded from the study. In addition, the study did not include patients with severe systemic diseases like cancer or immundefiency, a history of immunosuppressive drug use, or those who received prior vaginitis treatment for the last three months. The patients filled out the questionnaire on their own in the waiting room after filling out their informed consent under the physician's supervision after the diagnosis was made and their prescriptions were prepared. With the delivery of the questionnaires, the patient was informed in detail about their wrong attitudes. Our questionnaire consisted of 25 questions in five groups in which socio-demographic characteristics, complaints, risk factors, risky behaviors, and knowledge about treatment practices were questioned. While creating our survey questions in our study, we have benefited from Dalbudak et. Al (13), Yağmur Y. et al (19), Hacialioğlu N. et al (23), Karaer A. et al (25), and Ünsal A. et al's (27) studies as well as developing the quetions in line with our current observations and experiences in our practice.

Our study complies with the Declaration of Helsinki, the principles of Good Clinic Practice, and does not conflict with the ethical rules of the subject research.

Statistical analyzes of the study were carried out in the SPSS 21.0 package program. Categorical variables were represented by number and percentage, and continuous numerical variables were represented by center and prevalence measures such as mean, standard deviation, minimum and maximum values. The conformity of the variables to the normal distribution was checked with Kolmogorov Smirnov and Shapiro Wilk tests. Pearson Chi-square test was used to compare categorical variables between groups. As the statistical significance level, a p-value below 0.05 was accepted as the limit.

RESULTS

178 pregnant women were included in the study, and the mean age was 26.13 ± 4.47 years.

51.1% (91 people) of the participants were 26 years old, and over, 34.3% (61 people) had primary school or lower education level, and 87.1% (155 people) were not working.

Table 1. Socio-demographic characteristics of the patients

	n	%
Age		
18-25	87	48,9
26 and above	91	51,1
Education Status		
Primary school and below	61	34,3
Middle school	52	29,2
High school	58	32,6
University	7	3,9
Working Status		
Working	23	12,9
Not working	155	87,1
Total	**178**	**100,0**

89.9% (160 persons) of the pregnant women had discharge complaints; this discharge was described as white cheese cut by 58.4% (104 persons). 59.6% of the patients (106 people) had similar complaints before.

There was a systemic disease in 9.6% (17 individuals) of the pregnant women. 39.3% (70 people) of the patients had used antibiotics last month, and 28.1% (50 people) had genital complaints in their spouses.

Table 2. Complaints and characteristics of patients

	n	%
Complaints		
Vaginal discharge	160	89,9
Itching	118	66,3
Combustion	105	59,0
Bad smell	100	56,2
Dyspareunia	80	44,9
Features of vaginal discharge		
In the form of cuts of white cheese	104	58,4
Yellow	46	25,8
Transparent	17	9,6
Sparkling green	11	6,2
Similar complaints before		
Yes	106	59,6
No	72	40,4

There was no significant difference between the presence of systemic disease and age, education and employment status of the patient (p>0.05). There was no significant difference between antibiotic use of pregnant women education and age,employment status (p>0.05).

Table 3a. Risk factors in patients

	n	%
Systemic disease	17	9,6
Antibiotic use	70	39,3
The genital complaint in spouse	50	28,1

Regarding genital area cleaning, 11.2% (20 people) of the patients knew about using white vinegar, and 3.4% (6 people) used the acidic mixture. 6.7% (12 people) of the participants knew the use of vaginal probiotics.

A significant difference was found between the education status of the patients and the behavior of not using any iron (p=0.003). It was determined that the non-ironing behavior of those with high school or higher education was lower than the other groups.

A significant difference was found between the working status of the pregnant women and the behaviors of cleaning the perineum from back to front and using daily pads (p=0.028) (p=0.005). While cleaning the perineum from the back to the front was more common in the working group, daily pad use was more in the non-working group.

A significant difference was found between the age groups of the participants and the behavior of using genital cleaning products and washing underwear by hand (p=0.036) (p=0.001). While the behavior of using genital cleaning products is higher in the group aged 26 and over, the behavior of washing underwear by hand is lower than the other group.

DISCUSSION

Every year, approximately one million women worldwide are exposed to urogenital tract infections such as non-sexually transmitted urinary tract infections and bacterial vaginosis, and at least 75% of women have a history of genital infection 4. The most common clinical form of genital tract infections in women is vulvovaginitis. Vaginal discharge is the most common reason for women to apply to gynecology outpatient clinics, and almost all women face discharge from time to time throughout their lives 5 6 7. Vaginitis, an inflammation of the vagina, is characterized by a foul odor, burning, painful sexual intercourse, dysuria, and itching, most commonly causing vaginal discharge 5. Vaginal infections; cause problems such as negative body image effects, increased vaginal symptoms or odor, fear of sexually transmitted disease or cancer, avoidance of sexual activity due to pain, physical exhaustion, and psychological problems. At the same time, it causes economic loss, time, and loss of workforce 5 7 8. Patients may be isolated from society, their self-confidence may decrease, and their social and quality of life may be adversely affected.

During pregnancy, especially in the early stages, the vaginal microbiome changes. Shifts in Lactobacillus subtypes can only stabilize the vaginal microbiome. The immune system of the pregnant is weakened to prevent the rejection of the fetus. However, the abundance of lactobacilli, especially in early pregnancy, will cause an increase in acidic secretions, which is a natural barrier against pathogenic microorganisms, with low vaginal Ph. while lactobacilli diversity increases in the following

weeks of gestation and postpartum, a numerical return to the baseline and enrichment of other bacterial associations will be observed.

Bacteria have been shown to cross intact maternal-fetal membranes in pregnant women and isolated in the amniotic fluid and placenta of healthy pregnant women 9. Studies have suggested that genital system dysbiosis results from asymptomatic infections such as chronic endometritis before pregnancy, and some obstetric and neonatal complications are associated with maternal reproductive system dysbiosis 10 11.

Dysbiosis or microbiome changes can be caused by many physiological and pathological conditions, diet, weight gain, hormonal environment, and environmental conditions 3. Immunological, endocrinological, and metabolic changes can thus cause significant changes in the microbiome 12, and in this way, it can cause infections in the fetoplacental unit by the ascending or hematogenous route. The low virulence infection state here may initiate chronic inflammatory processes that may cause adverse maternal or neonatal outcomes. Although it should be sterile, the isolation of microorganisms in the amniotic fluid or placenta of women who gave birth preterm excludes the concept of 'contamination is unlikely.'

While the most common factors among the reasons why vaginitis symptoms cannot be alleviated are misdiagnoses and re-contamination with frequent sexual intercourse, non-sexual relapses such as immune depression, drug resistance, and bad personal habits can be observed.

Incorrect and inadequate genital hygiene practices increase the risk of vaginal infection. During pregnancy, people often make treatment difficult, delay or cause disease recurrence with wrong personal attitudes. Despite successful antibiotic treatments today, it is clear that these bad personal habits will reduce the effectiveness of the treatment applied.

Dalbudak et al. 13 reported that some wrong and inadequate genital hygiene behaviors, such as vaginal douching, increase the risk of vaginal infection. Researchers have stated that the most critical risk factor for bacterial vaginosis is vaginal douching for cleansing 14, 15. In our country, 16, 17, 18, 19, 20, and abroad, 15,21,22 studies have shown that vaginal douching is widespread among women. Studies have shown that women who douche have a higher rate of genital tract infections than those who do not 18,23. In the study of Nansel et al. 24, it was reported that the incidence of bacterial vaginosis is 1.80 times higher in women who douche more than once a week. In Karaer et al. 25's study, it has been reported that approximately 60% of the participants do vaginal douching, and more than 90% apply this application weekly or more frequently. In their study, Karaer et al. 25 reported that vaginal douching is a strong etiological reason for preterm labor, and it was noted that it might cause many secondary effects such as pelvic inflammatory disease, ectopic pregnancy, and sexually transmitted diseases, as well as causing an increase in the risk of BV.

Considering the hygiene behaviors of the participants in our study, we found vaginal douching habits in 71.9% of them. Although the result we obtained supports the literature, considering the socio-demographic characteristics of Kars province, we have determined that although it is compatible with the education level and socio-economic level, it is higher than the literature data rates.

Dalbudak et al. 13 reported daily pad use at 52% in the case group and 45% in the control group. In addition, it was determined that women who use daily pads have a 1.3 times higher risk of getting a vaginal infection than those who do not ($p>0.05$). In the study of Patel et al. 26, two times more in women who use daily pads, in the study of Kısa and Taşkın 18, it is stated that the risk of getting a vaginal infection is 2.34 times more in those who use daily pads. In her study of Flood, she said that about half of the women use daily pads and emphasized that this issue should be noted. In our study, we interpreted the fact that we determined the rate of using daily pads as 61.2%, which is higher than the literature, as the more widespread use of social media and advertising tools, making it accessible to more people and making daily pads attractive with marketing techniques such as using smart slogans as 'organic products'. We attributed the use rate of genital cleansing products to 16.3%, contrary to daily pads, to the fact that these products were not popular enough and did not find enough space in the advertising sector.

Karatay et al. 16 determined that 79.2% used cotton underwear, and the remaining 15.5% used synthetic underwear. Synthetic underwear keeps the perineal area moist, increasing the possibility of genital infection. With the introduction of technology into homes, the frequency of washing clothes with washing machines at high temperatures has increased. Although the studies do not make enough determinations about the underwear choices of the patients and the underwear cleaning methods, they agree that the underwear selection and the ways of cleaning the laundry are factors in the development of vaginal infections. In our study, the rate of using synthetic underwear was determined as 41% with our survey questions, and 7.3% of the participants stated that they washed their underwear by hand, while 67.4% indicated that they used underwear without ironing.

Karatay et al. 16 also found that 36.9% of the participants cleaned the genital area from front to back, and the vast majority did this inaccurately. When the genital area is cleaned from back to front rather than from front to back, or when it is cleaned randomly, microorganisms such as E.coli are transported from the anal region to the vagina and urethra, causing infections. In our study results, this rate was much higher with 66.9% compared to Karatay et al.

Yagmur et al. 19 applied a questionnaire to 914 pregnant women in their study to reveal the relationship between genital hygiene and practices of pregnant women and genital tract infections. While 57.2% of the participants took a vaginal shower every other day, 48.1% achieved results by changing their underwear every other day. They determined that there were inadequacies and mistakes in pregnant women's hygiene habits in developing genital infections, which they defined as 17.4% in their study. As a result, it was emphasized that the attention of health personnel working in primary health care institutions and women's health and obstetrics units should be drawn to this issue. They also pointed out that health professionals should inform women about the importance of hygiene during preconception or pregnancy and the negative situations that may arise from lack of hygiene.

One of the most important components of preventive health services is health education given to women. Prevention of genital tract infections and early diagnosis and treatment are pos-

sible with planned and effective health education. In the study of Ünsal et al. 27, it was determined that 40.1% of women had received information about genital hygiene before, while 59.9% of them did not. Karatay et al. 16, in their studies, stated that only 13.2% of women received information about genital hygiene. These results show that the rate of informing women about protection from genital tract infections, genital hygiene, and what to do in case of genital tract infection is low in our country.

It has been revealed that the wrong and inadequate genital hygiene behaviors of women who do not receive adequate information increase the risk of vaginal infection. In our study, the knowledge levels of pregnant women about protective behaviors and attitudes were found to be low in line with the literature. Those who knew about white vinegar were 11.2%, and those who knew about vaginal probiotics were 6.7%. When genital infections are not treated, they can progress and cause pelvic inflammatory disease and even female genital organ cancers, affecting women's fertility. At the same time, it negatively affects women's sexual and family life, reducing their quality of life 28. From these perspectives, knowing the risk factors that cause genital infections in women is crucial.

The factors that cause genital infection in women are very diverse; Since these risks can be partially controlled with personal practices, personal factors gain more importance when we look at the dangers individually in terms of genital infection. It is seen that there are risks such as lack of hygiene, improper cleaning of the genital area after the toilet, lack of hand washing habits, not using appropriate underwear, and not paying enough attention to menstrual hygiene 18. It is clear that women need education on this subject, but health care providers often neglect this education.

In the literature review, changing underwear every day, wearing cotton underwear, changing pads frequently enough during periods when the amount of bleeding is low and heavy during menstruation, not using daily pads, avoiding vaginal douche, carefully monitoring the genital area for signs of disease, paying attention to genital hygiene is commonly suggested. Among the common suggestions of all literature reviews; are providing education and counseling to women on these issues, having information brochures prepared on correct genital hygiene practices and protection from genital infections for every woman who applies to health institutions, and supporting women with audio-visual means on the subjects they are conscious of, and informing them about their inadequacy.

Vaginitis is the most frequently detected disease among obstetrics outpatient clinic applications, and its recurrences can force the physicians. The medical treatment agents which can be used in pregnant women are limited. Although pregnancy is predisposed to vaginitis, it may accompany pregnancy complications if not treated. Maintaining the vaginal floral balance will prevent infections in the feto-maternal compartment as well as vaginal infections and will help in the process of maintaining the pregnancy to a sufficient week.

Genital hygiene is the most crucial step in preventing genital infections. In addition to the limited prescription treatments, especially in recurrent cases, genital cleansing with white vinegar instead of vaginal douching, recommending mixtures prepared with acidic fruit juices into fermented yogurt cost-effectively provide the acidic pH and flora of the vagina, or promoting the use of oral/vaginal probiotics. We foresee that it will be helpful.

Patients should be advised to use cotton underwear instead of synthetic underwear, to wash their clothes separately from the underwear of the people they live within a high temperature and washing machine, to dry the washed laundry in a home environment, and to wear it by ironing, not to remove clean the pubic hair thoroughly, that the genital hair is necessary for the health of the genital area. We have a prediction that not wearing underwear at some time intervals during the day will be beneficial for it will provide aeration, reduce humidity, the patients' complaints will decrease, recurrence rates will decrease, and positive results can be obtained without the need for serious medical treatments.

Not preferring genital cleaning products, avoiding vaginal douching, avoiding alkaline soap-like cleaning products, choosing the right and correct perineal cleaning methods, and avoiding daily pads are among the suggestions that we believe will yield successful results. In order to support our claim, comparing the results of randomized controlled studies with known and accepted treatment methods and the recommendations we mentioned may be the subject of future studies.

CONCLUSION

Despite the limited number of patients, we believe that our study will help with the general hygiene understanding of the population, the determination of the general mistakes accepted as accurate in their daily lives, and the factors that can increase the success of treatment in a clinic, as well as emphasizing the importance of primary care preventive medicine studies.

Limitations of medical treatment in pregnant patients can cause repetitive infections that can be hard to take under control. So, as a result, correcting the wrong personal practices and hygiene habits can help prevent such genital infections disease and facilitate treatment.

Considering the results of our study, wrong attitudes regarding genital hygiene appear to be common, especially in women from low socio-economic and cultural levels. In this respect, it has been concluded that women need training on genital hygiene as a preventive measure due to the mistakes they make in daily practice related to genital hygiene and the possibility of experiencing a genital infection in a significant part of them.

At the end of this study, considering that the most significant deficiency in the occurrence of genital infections in women is the lack of education, it is recommended that all health professionals, especially the ones working in primary care, should develop a training plan to prevent genital infections and apply it to women in the regions they work. Hoping our study will contribute to the literature, we believe that studies on feedback on life, behavior, and attitude changes in forwarding planning will complement the existing literature.

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Evre IIIC Endometrium Kanserinde Paraaortik Lenf Nodu Metastazı Varlığına Göre Klinik, Cerrahi ve Patolojik Faktörlerin Dağılımı

Distribution of Clinical, Surgical, and Pathological Factors in Stage IIIC Endometrial Cancer Patients with Paraaortic Lymph Node Metastasis

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ÖZ

Amaç: Bu çalışmada Evre IIIC1 ve evre IIIC2 endometrium kanserinde, hasta grupları arasında klinik, cerrahi ve patolojik risk faktörlerinin dağılımını incelemek ve farklılığı tanımlamak amaçlanmıştır.

Gereçler ve Yöntem: Kliniğimizde FIGO 2009 kriterlerine göre evre IIIC1-2 endometrium kanseri tanısı alan 115 hasta çalışmaya dâhil edildi. Hastaların demografik, klinik, cerrahi ve patolojik özellikleri hasta dosyalarından ve patoloji raporlarından retrospektif olarak elde edildi.

Bulgular: Hastaların 39'unda (%33.9) sadece pelvik lenf nodu metastazı, 14'ünde (%12.2) sadece paraaortik lenf nodu metastazı, 62'sinde (%53.9) ise hem pelvik hem paraaortik lenf nodu metastazı mevcuttu. Otuz dokuz (%33.9) hasta FIGO IIIC1, 76 (%66.1) hasta FIGO IIIC2 evredeydi. Evre IIIC2 hasta grubunda evre IIIC1'e göre derin myometrial invazyon ve malign peritoneal sitoloji istatistiksel olarak anlamlı yüksekti. Buna karşın yaş, tümör boyutu, çıkarılan lenf nodu sayısı, preoperatif CA 125 değeri, FIGO grade derecesi, lenfovasküler alan invazyonu, servikal tutulum durumu ve adneksal metastaz durumu ile hastalığın paraaortik bölgeye yayılıp yayılmaması arasında anlamlı farklılık gözlenmedi.

Sonuç: Evre IIIC endometrium kanserinde paraaortik lenf nodu metastazı varlığında derin myometrial invazyon ve malign peritoneal sitoloji görülme olasılığı artmaktadır.

Anahtar kelimeler: Endometrium kanseri, evre IIIC, paraaortik lenf nodu metastazı

ABSTRACT

Aim: To analyze the distribution of clinical, surgical, and pathological risk variables among patient groups in stage IIIC1 and stage IIIC2 endometrium cancer, and to identify the differences.

Materials and Method: The study comprised 115 endometrial cancer patients identified as stage IIIC1-2 in our clinic, according to FIGO 2009 criteria. Patients' demographic, clinical, surgical, and pathological features were retrospectively extracted from patient files and pathology reports.

Results: Thirty-nine (33.9%) patients had only pelvic lymph node metastasis, 14 (12.2%) patients had only paraaortic lymph node metastasis, and 62 (53.9%) patients had both pelvic and paraaortic lymph node metastasis. The stages of 39 (33.9%) patients were FIGO IIIC1 and 76 (66.1%) were FIGO IIIC2. Deep myometrial invasion and malignant peritoneal cytology were statistically higher in stage IIIC2 patients than in stage IIIC1 patients. However, age, tumor size, number of lymph nodes excised, preoperative CA 125 value, FIGO grade, lymphovascular space invasion, cervical involvement, and adnexal metastasis did not found to be associated with the disease dissemination to the paraaortic area.

Conclusion: Deep myometrial invasion and malignant peritoneal cytology is higher in stage IIIC endometrial cancer patients with paraaortic lymph node metastasis.

Keywords: Endometrial cancer, stage IIIC, paraaortic lymph node metastasis

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GİRİŞ

Endometrium kanseri gelişmiş ülkelerde kadın genital sistemin en sık görülen kanseridir (12.9/100.000) (1). Evrelenlendirilme 1988 yılından beri Uluslararası Jinekoloji ve Obstetri Federasyonu (The International Federation of Gynecology and Obstetrics; FIGO) kriterlerine göre cerrahi olarak yapılmaktadır. Buna göre pelvik ve/veya paraaortik lenf nodu metastazı varlığı evre IIIC olarak tanımlanmaktadır. Ancak 2009 yılındaki evreleme sisteminde evre IIIC; evre IIIC1 ve evre IIIC2 olarak ikiye ayrılmıştır (2, 3). Evre IIIC1 sadece pelvik lenf nodu metastazı varlığı olması, evre IIIC2 ise pelvik lenf nodu durumundan bağımsız olarak paraortik lenf nodu metastazı olması şeklinde tanımlanmıştır (3).

Erken evre düşük grade düzeyli endometrium kanserli hastalar iyi prognoza sahiptir ve 5 yıllık sağ kalım oranları %90'nın üzerindedir. Lenfadenektominin bu hasta grubunda sağ kalımı iyileştirmediği gösterilmiştir (4). Lenfatik metastaz varlığındaysa prognoz kötüdür (5). Tanı anında endometrium kanserlerinin yaklaşık %15-20'si ileri evrededir (evre III veya IV) ve ileri evre hastalıkta 5 yıllık sağ kalım %40'lara kadar düşmektedir (6, 7). Doğru cerrahi kararı vermek ve gereksiz lenfadenektomiyi önlemek için risk faktörlerini belirlemek ve buna göre lenfadenektomiyi cerrahi prosedüre eklemek doğru yaklaşımdır. Tümör histolojisi, tümör boyutu, servikal invazyon varlığı, tümör grade derecesi ve myometrial invazyon derinliği endometrium kanserli hastalarda lenf nodu diseksiyonu için kullanılan iyi tanımlanmış uterin risk faktörleridir (8-10).

Her iki evrede sağ kalım farklılığının yanında metastazı belirleyen prognostik faktörlerin dağılımı da farklılık gösterebilmektedir (11). Ancak evre IIIC1 ve evre IIIC2 hastalıkta prognostik faktörlerin dağılımı konusunda yeterli bilgi bulunmamaktadır. Bu çalışmada amacımız bu iki hasta grubu arasında klinik, cerrahi ve patolojik risk faktörlerinin dağılımını incelemek ve farklılığı tanımlamaktır.

GEREÇ VE YÖNTEMLER

Ocak 2008 ile Ocak 2022 arasında kliniğimizde FIGO 2009 kriterlerine göre evre IIIC1-2 tanısı alan endometrium kanseri hastaları çalışmaya dâhil edildi. Tüm hastalara standart olarak total histerektomi, bilateral salpingo-oforektomi ve sistematik pelvik ve paraortik lenfadenektomi uygulandı. İnkomplet cerrahi uygulananlar, tümör tipi non-epitelyal olanlar, neoadjuvant kemoterapi alanlar ve evresi IIIC dışı olanlar çalışma dışında bırakıldı. Çalışma için Etik Kurul'dan onay alındı (E2-22-2040).

Çalışmaya gerekli şartları sağlayan 115 hasta dahil edildi. Hastaların yaşı, preoperatif CA 125 değeri (IU/ml), tümör tipi ve boyutu, çıkarılan lenf nodu sayısı, metastatik lenf nodu bölgesi, myometrial invazyon derinliği, lenfovasküler invazyon olup olmadığı, servikal ve adneksal yayılımı ve peritoneal sitoloji sonucu hasta dosyalarından ve patoloji raporlarından retrospektif olarak elde edildi.

Tüm istatistiksel analizler, "Statistical Package for the Social Sciences (SPSS) for Windows 22.0" sürümü kullanılarak yapıldı. Tanımlayıcı değerler aritmetik ortalama ± standart sapma, medyan ve yüzde olarak ifade edildi. Kategorik değişkenler ki-kare testi ile, devamlı değişkenler Anova Table Test ile analiz edildi. P değerinin 0.05 ve altında olması istatistiksel olarak anlamlı kabul edildi.

BULGULAR

Hastaların median yaşı 60 yıldı (aralık, 42-86 yıl). Median preoperatif CA 125 değeri 55.5 IU/ml (aralık, 2-432) ve median tümör boyutu 45 mm'ydi (aralık, 3-130 mm). Tümör tipi 67 (%58.3) hastada endometrioid tipti. Total çıkarılan lenf nodu sayısının median değeri 55'ti (aralık, 23-167). Hastaların 39'unda (%33.9) sadece pelvik lenf nodu metastazı, 14'ünde (%12.2) sadece paraaortik lenf nodu metastazı, 62'sinde (%53.9) ise hem pelvik hem paraaortik lenf nodu metastazı mevcuttu. Evre 39 (%33.9) hastada FIGO IIIC1 ve 76 (%66.1) hasta FIGO IIIC2'ydi. Myometrial invazyon bir hastada (%0.9) yokken 15'inde (%13) serozal invazyon mevcuttu. Ek olarak 18'inde (%15.7) peritoneal sitoloji ve 93'ünde (%80.9) lenfovasküler alan invazyonu pozitifti (Tablo 1).

Tablo 1. Genel özellikler

Özellikler		Ortalama±SD	Ortanca (Aralık)
Tanı anında yaş		60.4±7.871	60 (42-86)
Tümör boyutu (mm)		44.2±20.896	45 (3-130)
Total çıkarılan lenf nodu sayısı		60.5±25.218	55 (23-167)
Preoperatif CA 125 değeri (IU/ml)		55.5±105.406	18 (2-432)
		n	**%**
Tümör tipi	Endometrioid	67	58.3
	Seröz	15	13
	Berrak hücreli	9	7.8
	Müsinöz	1	0.9
	Andiferansiye	1	0.9
	Mikst tip	22	19.1

FIGO 2014 Evre	IIIC1	39	33.9
	IIIC2	76	66.1
Metastatik lenf nodu bölgesi	Sadece pelvik	39	33.9
	Sadece paraaortik	14	12.2
	Pelvik ve paraaortik	62	53.9
Myometrial invazyon derinliği	Myometrial invazyon yok	1	0.9
	<1/2	28	24.3
	≥1/2 [1]	71	61.7
	Serozal invazyon	15	13
Lenfovasküler alan invazyonu	Negatif	18	15.7
	Pozitif	93	80.9
	Rapor edilmemiş	4	3.5
Servikal tutulum	Negatif	77	67
	Glandüler	2	1.7
	Stromal	36	31.3
Peritoneal sitoloji	Negatif	94	81.7
	Pozitif	18	15.7
	Rapor edilmemiş	3	2.6
Adneksal yayılım	Negatif	97	84.3
	Pozitif	18	15.7

[1]: Serozal tulum yok

Evre IIIC1'e göre IIIC2'de derin myometrial invazyon ve malign peritoneal sitoloji istatistiksel olarak anlamlı yüksekti. Evre IIIC2'de derin miyometrial invazyon hastaların %82.9'unda gözlenirken bu oran evre IIIC1'de %58.9'du (p=0.017). Malign peritoneal sitoloji için bu oranlar sırasıyla %21.3 ve %5.4'tü (p=0.031) (Tablo 2). Buna karşın yaş, tümör boyutu, çıkarılan lenf nodu sayısı, preoperatif CA 125 değeri, FIGO grade derecesi, lenfovasküler alan invazyonu, servikal tutulum durumu ve adneksal metastaz durumu ile hastalığın paraaortik bölgeye yayılıp yayılmamasına göre anlamlı farklılık göstermemekteydi.

Tablo 2. Paraaortik lenf nodu metastazı varlığına göre klinik, patolojik ve cerrahi faktörlerin dağılımı

Parametre		**Paraaortik Lenf Nodu Metastazı**				**P değeri**
		Negatif		**Pozitif**		
	Ortalama±SD	**Ortanca (Aralık)**	**Ortalama±SD**	**Ortanca (Aralık)**		
Yaş (yıl)		59.5±7.563	59 (42-76)	61±8.034	61 (45-86)	*0.340*
Tümör boyutu (mm)		41.7±28.05	45 (5-120)	59.7±19,06	45 (3-130)	*0.654*
Toplam çıkarılan lenf nodu sayısı		61.9±28,05	54 (25-167)	59.7±23.796	55 (23-162)	*0.358*
Preopratif CA125 değeri (IU/ml)		28.8±12.9	26 (17-51)	74±135.742	14 (2-432)	*0.335*
		n	**%**	**n**	**%**	
FIGO grade	1	11	35.5	9	20.9	*0.251*
	2	11	35.5	23	53.5	
	3	9	29	11	25.5	
Myometrial invazyon derinliği	Yok	1	2.6	-	-	***0.017***
	<1/2	15	38.5	13	17.1	
	≥1/2 [1]	23	58.9	63	82.9	
Lenfovasküler alan invazyonu	Negatif	7	19.4	11	14.7	*0.523*
	Pozitif	29	80.6	64	85.3	

Servikal tutulum	Negatif	25	64.1	52	68.4	*0,641*
	Pozitif	14	35.9	24	31.6	
Peritoneal sitoloji	Negatif	35	94.6	59	78.7	***0.031***
	Pozitif	2	5.4	16	21.3	
Adneksal metastaz	Negatif	35	89.7	62	81.6	*0.254*
	Pozitif	4	10.3	14	18.4	

[1]: Serozal invazyon dahil

TARTIŞMA

Endometrium kanseri FIGO evre IIIC hasta grubunun değerlendirildiği bu çalışmada paraaortik lenf nodu tutulumunda derin myometrial invazyonun ve malign peritoneal sitolojinin anlamlı olarak yüksek olduğu görüldü. Ancak diğer klinik, cerrahi ve patolojik faktörler açısından FIGO evre IIIC1 ve IIIC2 hasta grupları benzerdi.

Endometrium kanserinde sadece evre IIIC hastalığın değerlendirildiği az sayıda çalışma bulunmaktadır. Bizden farklı olarak Fujimoto ve ark.'larının (12) 63, Şahin ve ark.'larının (13) ise 47 evre IIIC endometrium kanseri hastasıyla yaptığı çalışmada, evre IIIC1 ve evre IIIC2 hasta grupları arasında klinik, cerrahi ve patolojik faktörler açısından anlamlı fark gösterilmemiştir.

Evre IIIC1 ve evre IIIC2 toplam 2359 hastanın incelendiği Surveillance, Epidemiology and End Results (SEER) data çalışmasında yüksek tümör grade düzeyinin, ekstrauterin yayılımın ve metastatik lenf nodu sayısının evre IIIC2 hasta grubunda anlamlı olarak fazla olduğu gösterilmiştir (14), fakat derin myometrial invazyon hakkında bilgi verilmemiştir. Kikuchi ve ark.'larının (15) çalışmasında evre IIIC2 hasta grubunda evre IIIC1 hasta grubuna göre yüksek grade düzeyli endometrioid tümör anlamlı olarak yüksek bulunurken, derin miyometrial invazyon ve malign peritoneal sitoloji açısından fark saptanmamıştır.

Malign peritoneal sitoloji önceden endometrium kanserinin cerrahi evrelemesinin bir parçası iken FIGO 2009 kriterleri ile evrelemeden çıkarılmıştır. Ancak malign peritoneal sitoloji varlığında negatif sitolojiye sahip olanlara göre prognozun daha kötü olduğu ve bu hasta grubunda sistemik adjuvan tedavinin tedaviye eklenmesi gerekliliği gösterilmiştir (16, 17). Sunduğumuz çalışmamızda evre IIIC hastalıkta paraaortik lenf nodu metastazı varlığında malign peritoneal sitolojinin sadece pelvik lenf nodu metastazı olanlara göre 4 kat daha sık olduğu ve paraaortik metastazı olanların %21'inde malign peritoneal sitoloji olduğu gösterildi.

FIGO evre IIIC1 ve IIIC2 hastalık grubunun değerlendirildiği ve iki hasta grubu arasında klinik, cerrahi ve patolojik faktörlerin dağılımının incelendiği çalışmalar oldukça sınırlı sayıdadır. Çoğunlukla bu çalışmalar onkolojik sonuçları tanımlamaya yöneliktir. Bizim çalışmamızda sadece evre IIIC endometrium kanseri olgularının değerlendirilmiş olması çalışmanın güçlü yanını oluşturmaktadır. Ancak retrospektif yapısı sunulan çalışmamızın önemli limitasyonudur.

SONUÇ

Sonuç olarak evre IIIC'de hastalığın paraaortik bölgeye yayılmasının yanında prognozu kötüleştirecek diğer faktörlerin varlığı artmaktadır. Sunulan çalışmada evre IIIC hasta grubunda paraaortik lenf nodu metastazında derin myometrial invazyon ve malign peritoneal sitoloji görülme olasılığının arttığı gösterilmiştir. Daha geniş hasta serileri ve çok merkezli çalışmalar ile bu bulgular desteklenmelidir.

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Özgün Araştırma / Original Article

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Disseminated intravascular coagulation in obstetric patients: maternal and fetal results

Obstetrik hastalarda dissemine intravasküler koagulasyon: maternal ve fetal sonuçları

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ÖZ

Amaç: Çalışmamızda obstetrik nedenlerle dissemine intravasküler koagulasyon (DİK) gelişen hastaların, antepartum değerlendirilmesi ile gelişebilecek komplikasyonların önceden önlenmesi ve maternal ve fetal morbidite ve mortalitenin azaltılması yönünde yol gösterici bilgilerin elde edilmesi amaçlanmıştır.

Gereçler ve Yöntem: Obstetri ve perinatoloji kliniklerine yatan ve DİK gelişen obstetrik hastalar retrospektif olarak incelendi. Hastaların DİK skorlaması International Society on Thrombosis and Haemostasis (ISTH) kriterlerine göre yapıldı. Hastaların maternal ve fetal sonuçları dökümante edildi.

Bulgular: Verilerin incelendiği 6 yıllık süre içerisinde 108281 doğumda 57 gebede DİK geliştiği tespit edildi ve DİK insidansı %0,052 olarak bulundu. DİK öncülü gebelik komplikasyonu kategorileri: plasenta invazyon ve implantasyon anomalileri, postpartum kanama (atoni), plasenta dekolmanı, gebeliğin hipertansif hastalığı ve diğer olarak bulundu. Maternal morbidite oranı %38.6, maternal mortalite oranı 1 hastayla %1.75 olarak bulundu. Hastaların %35'ine laparotomi/re-laparotomi ve bu hastalardan %21'ne histerektomi yapıldı. Yenidoğan doğum ağırlığı ortalaması 2341.3 gramdır. Yenidoğan yoğun bakım ihtiyacı %34.5, ölü doğum oranı %25,5'tir. Neonatal ölüm oranı %3,6 olarak tespit edilmiştir .

Sonuç: Doğumda yönetim şemasının anahtar bir rolü vardır çünkü gebeliğin terminasyonu genellikle altta yatan obstetrik bozukluğu ortadan kaldırır. Erken tanı ve aktif tedavi protokolleri, mortalite ve morbiditeyi azaltır. Gebelikteki koagulasyon kaskadında görülen fizyolojik değişikliklerden dolayı, gebe olmayan erişkinler için geliştirilen ISTH DİK skorlaması yerine gebeliğe spesifik bir DİK skorlamasının geliştirilmesi tanı koymayı kolaylaştırabilir.

Anahtar kelimeler: Dik, postpartum kanama, obstetrik bozukluklar, skorlama sistemi, kan transfüzyonu

ABSTRACT

Aim: In our study, it was aimed to obtain guiding information to prevent complications that may develop in advance and to decrease maternal and fetal morbidity and mortality by evaluating the antepartum of patients who developed DIC due to obstetric reasons.

Materials and methods: Obstetric patients who were hospitalized in obstetrics and perinatology clinics and developed disseminated intravascular coagulation (DIC) were retrospectively analyzed. DIC scoring of the patients was made according to the International Society on Thrombosis and Haemostasis (ISTH) criteria. Maternal and fetal outcomes from the patients were documented.

Results: During the 6-year period in which the data were analyzed, DIC was detected in 57 pregnants out of 108281 deliveries, and the incidence of DIC was found to be 0.052%. The categories of pregnancy complication preceding DIC: placental invasion and implantation anomalies, postpartum hemorrhage (atonia), placental abruption, hypertensive disease of pregnancy and others were found. Its rate in maternal morbidity was 38.6% and maternal mortality rate was 1.75% with 1 patient. 35% of the patients had laparotomy / re-laparotomy and 21% of these patients had hysterectomy. The average birth weight of the newborn is 2341.3 grams. Neonatal intensive care need is 34.5%, stillbirth rate is 25.5%. Neonatal mortality rate was determined as 3.6%.

Conclusion: The management scheme plays a key role in delivery because termination of pregnancy often eliminates the underlying obstetric disorder. Early diagnosis and active treatment protocols reduce mortality and morbidity. Because of the physiological changes seen in the coagulation cascade during pregnancy, using a pregnancy-specific DIC score instead of the ISTH DIC score developed for non-pregnant adults may facilitate diagnosis.

Keywords Dic, postpartum hemorrhage, obstetric disorder, scoring system, blood transfusion

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INTRODUCTION

Disseminated intravascular coagulation (DIC) is an acquired hemostasis disorder. It develops due to uncontrollable activation of coagulation, insufficiency of natural anticoagulant mechanisms and out of control of fibrinolysis(1). DIC is not a disease on its own, but always develops secondary to an underlying disease. It occurs especially after sepsis, infections, malignancy, obstetric complications, trauma, toxic and immunological reactions(2). Uncontrolled peripartum hemorrhage, resulting in consumption coagulopathy and disseminated intravascular coagulation (DIC), is one of the leading causes for maternal mortality worldwide(3). Tissue factor secreted from monocytes triggers the coagulation system(4). It is known that the placenta plays the greatest role in the release of tissue factor into the blood in obstetric patients(5). There is no laboratory test that alone confirms or excludes the diagnosis of DIC. The International Society on Thrombosis and Haemostasis (ISTH) proposed a diagnostic scoring system for DIC in 2001(6). The parameters evaluated in this scoring system are platelet count, D-dimer and fibrin degradation products, prolongation of prothrombin time and fibrinogen. Patients with a high probability of DIC based on their ISTH score are categorized as overt DIC and there is a good correlation between these patients and the development of DIC.

Although DIC due to obstetric causes is rare, its morbidity and mortality are quite high(7). It is often associated with adverse maternal outcomes, which can result in massive blood transfusion, hysterectomy and even death(8). Obstetric causes associated with DIC include amniotic fluid embolism, placental abruption, placenta previa, severe preeclampsia/eclampsia, HELLP syndrome, dead fetus, delayed abortion, septicemia, and acute fatty liver of pregnancy(9). The prevalence of DIC was found to be between 0.03% and 0.35% in obstetric patients(10,11). In one study, DIC was found to be the second most common cause of serious maternal morbidity after blood transfusion, with a rate of 32 cases per 10,000 births in the United States(12). The most important steps in the effective treatment of DIC are early diagnosis and treatment of the underlying disease.

In this study, it was aimed to retrospectively examine obstetric patients who developed DIC, to predict the complications that may develop and to emphasize the key points in the treatment for reducing maternal/fetal morbidity and mortality.

MATERIAL AND METHODS

In our study, the files of obstetric patients who were admitted to the perinatology and obstetrics clinics of Dr Zekai Tahir Burak Women's Health Training and Research Hospital, Ankara, between 01/01/2010 and 31/12/2015 and who developed disseminated intravascular coagulation (DIC) were retrospectively analyzed. The files of 251 patients who were likely to have DIC were reviewed, 132 patients were excluded from the study due to deficiencies in laboratory values. DIC scoring of the patients was performed according to the International Society on Thrombosis and Haemostasis (ISTH) criteria. Patients with a score of 5 and above in the ISTH scoring were considered to be overt DIC. Sixty-two patients with a DIC score of less than 5 were excluded from the study, and 57 patients with a DIC score of 5 and above were included in the study. Obstetric complications leading to DIC were divided into 5 categories: hypertensive diseases of pregnancy, postpartum hemorrhages (atonia), placental abruption, placental invasion and implantation anomalies, and others.

Demographic data of patients (age, gravida, parity, abortions, previous D/C, gestational week, presence of chronic disease), hospitalization duration, diagnoses, ultrasonographic measurements, mode of delivery (cesarean section or normal vaginal delivery), intraoperative complications, additional surgical methods (bakri balloon, hemostatic sutures, uterine artery ligation, hypogastric artery ligation), hysterectomy, laparotomy, pregnancy complication categories, laboratory values, transfusions (erythrocyte suspension, fresh frozen plasma, whole blood, platelet suspension, fibrinogen, albumin), disseminated intravascular coagulation (DIC) score, developing maternal complications, maternal death and referral rates, infant birth weight, 1st and 5th minute APGAR scores, and newborn intensive care admission need data were obtained.

Statistical Analysis

The conformity of the variables in the study to the normal distribution was evaluated graphically and using the Shapiro-Wilks test. The mean ± standard deviation values were given for the age variable, which was determined to have a normal distribution. IBM SPSS Statistics 21.0 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) and MS-Excel 2007 programs were used for statistical analysis and calculations. Statistical significance level was accepted as $p<0.05$.

RESULTS

In this study, the files of 119 patients were reviewed, and 57 patients with an ISTH DIC score of 5 and above and diagnosed with overt DIC were included in the study. The mean age of the patients was 29.4±6.3 years (min=18.0; max= 41.0). The mean hospitalization was 8.8±8.8 days. Hospitalization diagnoses of the patients are listed. It was observed that 14 (24.6%) of the 57 patients included in the study had a diagnosis of placenta previa totalis as a hospitalization diagnosis.

Gestational weeks were calculated according to the last menstrual period and the median week of gestation was 35.0 (min= 17.0; max= 40.0), and the median of gravida was 3.0 (min= 1.0; max= 12.0). Demographic characteristics and laboratory parameters of the patients were analyzed (Table 1). The ISTH DIC score parameters were evaluated and the mean platelet value was 63175/µL, the mean Inr value was 1.55 INR, the mean D-Dimer was 29.6 g/L, and the mean fibrinogen was 102.1 mg/dL. The mean creatinine of kidney function tests was 0.9 mg/dL. The creatinine value of 14 patients was found to be higher than the reference value of 1.2 mg/dL, and 4 of these patients were referred to tertiary care centers with a preliminary diagnosis of acute renal failure (ARF). The mean AST of liver function tests was 217.5 U/L. The AST value of 25 patients was found to be higher than the reference value of 35 U/L. The mean LDH value was 1249.2 U/L (Table 1).

Table 1. Demographic characteristics and laboratory parameters

	n	median (min; max)	mean±SD
Gestational week	55	35.0 (17.0; 40.0)	33.5±5.1
Gravidity	57	3.0 (1.0; 12.0)	2.9±1.9
Minimum Hemoglobin	57	6.0 (3.1; 13.2)	6.5±2.1
Total Hemoglobin loss	56	5.0 (0.0; 9.9)	5.0±2.3
Minimum thrombocyte	57	57000.0 (24000.0; 258000.0)	63175.4±34063.6
INR	57	1.52 (0.87; 4.84)	1.55±0.53
D-dimer	57	34.4 (2.1; 87.0)	29.6±17.7
Fibrinogen	57	81.0 (23.0; 506.0)	102.1±77.8
LDH	56	825.0 (318.0; 5479.0)	1249.2±1242.7
Creatin	57	0.6 (0.2; 4.1)	0.9±0.8
AST	57	25.0 (10.0; 3351.0)	217.5±553.3

The median DIC score was 6.0 (min= 5; max=8). There were 23 (40.4%) patients with DIC score of 5 and 5 (8.8%) patients with 8. According to the analysis of pregnancy complication categories; placental invasion and implantation abnormalities in 15 patients (26.3%), postpartum hemorrhage (atony) in 13 patients (22.8%), placental abruption in 11 patients (19.3%), hypertensive disease of pregnancy in 11 patients (19.3%) and 7 patients (12.3%) were in the other category (Table 2). In the other category, there were 2 uterine ruptures and 1 each episiotomy site hematoma, HELLP syndrome, hemolytic anemia, sepsis and idiopathic DIC. While 47 (83.9%) of the patients delivered by cesarean section, 9 (16.1%) patients had normal vaginal delivery. Laparotomy was performed in 20 (35%) of the patients who developed postpartum hemorrhage, and hysterectomy was performed in 12 of these patients whose bleeding could not be stopped. The uterine bleeding of the other 8 patients was controlled with hypogastric artery ligation, B-Lynch suture or application of Bakri balloon.

Table 2. DIC causes and maternal outcomes

Causes number	Hypertensive Disease of Pregnancy (11)	Postpartum Hemorrhage (atony) (13)	Placental abruption (11)	Placental invasion and implantation abnormalities (15)	Other (7)	Total (57)-(%)
Case, %	19.3	22.8	19.3	26.3	12.3	100
Type of delivery						
Vaginal delivery	1	5	0	0	3	9 - 16.1
Cesarean delivery	10	8	10	15	4	47 - 83.9
Massive transfusion	1	3	0	7	0	11 - 19.2
Hysterectomy	0	8	0	4	0	12 - 21
Complication	9	4	4	2	3	22 - 38.6
Refer	5	1	2	1	1	10 - 17.5
Maternal death	0	0	0	0	1	1 - 1.75

Red blood cell suspension (RBCs), fresh frozen plasma (FFP) and fibrinogen were mostly used in blood and blood products transfusion. The median number of units of 51 patients who received RBCs was 6.0 units (min=1; max=18.0), the median amount of 53 patients who received fibrinogen was 2.0 grams (min= 1.0; max= 5.0), the median unit of 55 patients who received FFP was 5.0 (min= 1; max= 15.0) units. In addition, there were 30 patients who received platelets (min=1; max=9), 33 patients who received whole blood (min=1; max= 9), and 2 patients who received cryoprecipitate (min= 10; max= 11). The number of patients who received massive blood transfusion (≥10 U RBCs in 24 hours) was 11 (Table 2). There was 1 patient who was not transfused, and

the patient's ISTH DIC score was 5.There were 22 (38.6%) patients with maternal complications. These complications are: HELLP syndrome, ARF, pleural effusion, retinopathy, hemolytic uremic syndrome (HUS), acute respiratory distress syndrome (ARDS), pulmonary thromboembolism, hepatorenal syndrome, hemolytic anemia and thrombophlebitis (more than one complication can be found in a patient). The mean DIC score of the patients who developed complications was 6.3 (there were 7 patients with DIC score of 5; 5 patients with 6; 6 patients with 7; and 4 patients with 8). There was 1 patient with a DIC score of 8 and no complication, and 1 of the patients with a DIC score of 8 died. Maternal mortality rate was 1.75%. Ten (17.5%) patients who developed complications were referred to a tertiary center and none of these patients died.

Pregnancy complication categories leading to DIC and neonatal outcomes were compared. Neonatal outcomes of pregnant women with abruptio placentae showed that 7 out of 9 (77.7%) newborns were stillborn, and 1 out of 2 live-borns died in the neonatal period. Due to the high rate of cesarean section performed in the early weeks of pregnancy in patients diagnosed with hypertensive disease of pregnancy, the birth weights of the newborns in this group were found to be lower than the other groups (mean week of birth=31.6; min=25; max39). The mean newborn birth weight was 2341.3±1043.3 grams (median= 2455.0; min= 380.0; max= 4650). The birth weight of newborns were evaluated and 13 (24.1%) had a very low birth weight, 13 (24.1%) had a low birth weight and 28 (50.9%) had normal birth weight and there was a 1 (1.8%) non viable fetus (Table 3). Nineteen of these newborns were transferred to newborn intensive care unit (NICU), 13 newborns' Apgar scores were less than 7 at 5 minutes. Apgar score information at the 5 minute of 16 newborns could not be reached. The live birth rate was 74.5% (41/55), stillbirth rate was 25.5% (14/55) and the neonatal mortality was 4.8% (2/41).

Table 3. Neonatal outcomes

	n (%)		n (%)
Neonatal outcome (n= 55)		**Admission to the NICU (n= 19)**	
Live	41 (74.5)	No	36 (65.5)
Stillbirth	14 (25.5)	Yes	19 (34.5)
Weight grup (n= 54)		**Apgar score at 5 minutes (n= 41)**	
Very low birth weight (500 – 1499)	13 (24.1)	≤ 7	13 (31.7)
Low birth weight (1500 – 2499)	13 (24.1)	> 7	28 (68.3)
Normal birth weight (≥ 2500)	28 (50.9)		
Non-viable	1 (1.8)		

Between 2010 and 2015, 229 patients (0.21%) were diagnosed with placental abruption with ICD 10 code "O45" out of 108281 deliveries in our hospital. DIC occurred in 11 of these patients and the incidence of DIC in placental abruption was found to be 4.8%. In 108281 deliveries that occurred during this 6-year period, a total of 57 patients were found to have overt DIC, and the calculated incidence of DIC for the six-year study was found to be 0.052%.

DISCUSSION

In this study, we retrospectively analyzed the maternal and fetal outcomes of 57 patients who developed DIC due to obstetric reasons. Since the total number of births in our hospital during this 6-year period was 108281, we found the incidence of DIC in our hospital as 0.052% (57/108281), and this value was similar to other rates in the literature(10,12). Since there is no specific method to diagnose DIC, we tried to gain objectivity in the diagnosis by using the DIC scoring system recommended by ISTH. The ISTH scoring system was originally designed for non-pregnant patients and its use in pregnancy is still controversial due to the physiological changes seen in the coagulation cascade during pregnancy. It is known that fibrinogen increases throughout pregnancy, especially in the third trimester(13). It has been suggested that serum fibrinogen may not be as important as other laboratory parameters in the diagnosis of DIC because only 5% of patients showed a decrease in serum fibrinogen in the validation study of the ISTH scoring system(14). However, this system has good predictive value for the diagnosis of DIC and the identification of critically ill patients. This score can be used not only for diagnostic purposes but also prognostically, therefore it is important to use a DIC score in the diagnosis of patients with DIC(11). Erez et al developed a modified DIC score in pregnancy using only three components of the ISTH DIC score (platelet count, fibrinogen concentrations, and PT difference), suggesting that physiological hemostatic changes in pregnancy limit the applicability of this scoring system(11). They stated that this scoring system had 88% sensitivity and 96% specificity when the cutoff value was ≥26. When we designed our study, we did not use the modified DIC scoring suggested by Erez et al., as the ISTH scoring system is more widely used.

In our study, obstetric precursors causing DIC were placental invasion and implantation anomalies (26.3%), postpartum atony bleeding (22.8%), placental abruption (19.3%), hypertensive

disease of pregnancy (19.3%) and other (unclassified) (12.3%) and this distribution was different from similar studies in the literature(9,11). Placental anomaly is a major risk factor for peripartum hemorrhage and can lead to morbidity and mortality of the mother and neonate(15). Uncontrolled postpartum bleeding from placenta previa can lead to overt DIC in patients and can result in blood transfusion, hysterectomy, admission to the ICU, and even death(16). Considering the hospitalization diagnoses of the patients who developed DIC in our study, the diagnosis of placenta previa totalis was prominent in 14 (24.6%) patients. All of the 15 pregnant women in our study with placental invasion and implantation anomaly delivered by cesarean section. All of these patients underwent blood transfusion due to acute postpartum hemorrhage (min=6 ES, max=18 ES), 7 of them underwent massive transfusion, and 4 of them underwent hysterectomy due to unceasing uterine bleeding, and no patient died. Similarly, in a study by Goksever et al., it was seen that 35% of 279 patients with overt DIC received more than 4 units of blood transfusion(17). As seen in our study, due to the risk of postpartum hemorrhage, in order to stabilize blood loss during delivery and reduce morbidity and mortality rates, deliveries must be planned electively in the presence of an experienced team and adequate blood preparation must be done before the operation. Since DIC occurs with uncontrollable activation of coagulation and insufficiency of anticoagulant mechanisms, supportive treatment and blood transfusion to these patients are of critical importance. Early recognition of patients with DIC and initiation of treatment are very important. In DIC secondary to obstetric causes, the diagnosis may sometimes be delayed because pregnancy itself predisposes to coagulation. Laboratory tests should be repeated every 30 minutes and transfusion should be started with a minimum of 6 U Erythrocyte, 6 U FFP and 4-6 U Platelet suspension in pregnant women with severe bleeding. Massive transfusion protocols generally recommend 1/1/1 red blood cell/FTP/platelet transfusion(18). The goal in massive obstetric hemorrhage is to keep the hemoglobin concentration above 10 g/dL because pregnant women who develop DIC continue to lose blood and this blood loss reaches its maximum at the time of delivery.

When maternal complications were evaluated, we found that the most frequently affected organ associated with obstetric DIC was the kidney. Elevated creatinine levels were detected in 14 patients (higher than the reference value of 1.2), and ARF developed in 4 (7%) patients and were referred to multidisciplinary centers. In a study by Zhao et al, ARF (16.5%) was stated as the most common type of organ failure(19). The overall ARF rate in our study (7%, 4/57) was lower than in other studies (24.1% to 61%) in developing countries(20,21). Although DIC is not directly related to morphological changes in the kidney, it is thought that DIC potentially triggers ARF by stimulating cytokine release from the endothelium, which is one of the important mechanisms of kidney damage(22).

We observed that the worst results among newborn outcomes were in the ablatio placenta group. In 9 patients, 7 of the newborns resulted in stillbirth, 2 of them resulted in live birth, while 1 of the live-borns died in the early neonatal period. While placental abruption alone can cause severe bleeding that threatens maternal and fetal life, additional DIC in these patients complicates the situation. In these patients, termination of pregnancy as soon as possible and initiation of blood transfusion reduces maternal morbidity and mortality. In hypertensive diseases of pregnancy, emergency cesarean section rates are high in the early weeks due to preeclampsia or eclampsia. Since these patients are classified in the risk group for postpartum bleeding(23), it is important to keep the amount of intraoperative bleeding to a minimum. In cases of acute bleeding, the necessary blood and blood products should be transfused immediately before the coagulation factors in the serum are depleted.

CONCLUSION

DIC secondary to obstetric complications is a life-threatening condition(7). As we mentioned in our study, identification of the antecedent causes, early diagnosis and active treatment protocols are of critical importance in reducing maternal and fetal morbidity and mortality rates. The most important point in the treatment of DIC is the rapid elimination of the underlying disease, because delayed treatment is often associated with a poor prognosis. Delivery also plays a key role in the management scheme because termination of pregnancy usually eliminates the underlying obstetrical disorder.

Since obstetric patients who develop DIC usually have severe peripartum hemorrhage, transfusion of blood and blood products to these patients is very important in the treatment. If the hospital where the patient is located does not have sufficient blood bank reserves, if the team that can do this is inexperienced when surgical intervention is required, or if there is no neonatal intensive care unit, the patient should be referred to a multidisciplinary center quickly.

Although the ISTH DIC scoring system gives good results in non-pregnant patients, physiological changes in the coagulation cascade during pregnancy may delay the diagnosis. Although modified DIC scoring for pregnant women has been developed in some studies, there is still a need for an internationally accepted pregnancy-specific DIC scoring.

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Disclosure statement

The authors have no conflicts of interest to report.

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COVID-19 Pozitif Gebelerin Hastaneye İlk Başvurularındaki Demografik, Klinik ve Laboratuvar Verilerinin Değerlendirilmesi

Evaluation of Demographic, Clinic and Laboratory data of COVID-19 (+) Pregnants in their First Admission to Hospital

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ÖZ

Amaç: Acil Servise başvuran gebelerin demografik, klinik ve laboratuvar verilerini değerlendirerek, gebeliğin farklı trimesterlerinde COVİD-19 hastalığının klinik seyrini araştırmak.

Gereç ve Yöntemler: Olgular semptomlara ve oksijen saturasyon (Sat O2) değerine göre asemptomatik, hafif semptomatik ve şiddetli hastalık olarak 3 grupta incelendi. Laboratuvar testlerinde lenfopeni, yüksek CRP, ferritin ve D-dimer seviyeleri kötü prognostik faktörler olarak kabul edildi.

Bulgular: COVİD-19'lu 678 gebenin 118'i (%17.4) birinci trimesterde, 261'i (%38.5) ikinci trimesterde ve 299'u (%44.1) üçüncü trimesterdeydi. 120'si sadece COVİD-19 enfeksiyonuna bağlı olmak üzere toplam 257 (%37,9) COVİD-19 (+) gebe hastaneye yatırıldı. Olguların 57'sinde (%8.4) ağır hastalık saptandı, bunların 29'u (%50.9) 2. trimesterde, 26'sı (%45.6) 3. trimesterdeydi. Ağır hastalık insidansı gebeliğin sonraki haftalarında ilk trimestere göre anlamlı derecede yüksekti (p=0.004). Kötü prognostik laboratuvar kriterlerinin trimesterlere göre dağılımı incelendiğinde, COVİD-19'lu gebelerin %22,9'u ilk trimesterde en az 1 kötü prognostik laboratuvar kriterine sahipken, bu oran ikinci ve üçüncü trimesterlerde sırasıyla %41,7 ve %63 idi (p<0.001).

Sonuç: Bu çalışmada, COVİD-19 pozitif gebelerde hastalığın seyrinin gebeliğin ileri haftalarında ilk trimestere göre daha şiddetli olduğunu gözlemledik.

Anahtar Kelimeler: COVİD-19, gebelik, trimester

ABSTRACT

Aim: To investigate the clinical course of COVID-19 in different trimesters of pregnancy by evaluating the demographic, clinical and laboratory data of pregnant women who applied to the Emergency Service.

Materials and method: Cases were examined in 3 groups as asymptomatic, mild symptomatic and severe disease according to symptoms and oxygen saturation (Sat O2). High levels of CRP, ferritin, D-dimer and lymphopenia in blood tests were considered as poor prognostic factors.

Results: Of 678 pregnant women with COVİD-19, 118 (17.4%) were in the first trimester, 261 (38.5%) were in the second trimester and 299 (44.1%) were in the third trimester. A total of 257 (37.9%) COVID-19 (+) pregnant women were hospitalized and 120 of them were due to COVID-19 infection without any obstetric indications. Severe disease was detected in 57 (8.4%) of the cases; 29 of them (50.9%) in the 2nd trimester and 26 (45.6%) in the 3rd trimester. The incidence of severe disease was significantly higher in the later weeks of pregnancy compa-red to the first trimester (p=0.004). When the distribution of the poor prognostic laboratory crite-ria according to trimesters was examined, 22.9% of pregnant women with COVID-19 had at least one poor prognostic laboratory criterion in the first trimester, while this rate was 41.7% and 63.9% in the second and third trimesters, respectively (p<0.001).

Conclusion: In this study, we observed that the course of the disease in COVID-19 positive pregnant women was more severe in the later weeks of pregnancy compared to the first trimester.

Key Words: COVID-19, pregnancy, trimester

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INTRODUCTION

The pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has led to an unprecedented global health crisis. While many infected people are asymptomatic or have mild symptoms, some develop serious disease that can lead to pneumonia, acute respiratory distress syndrome, multisystemic dysfunction, and death. The virus appears to be more dangerous in some high-risk individuals, especially the elderly or those affected by multiple diseases (1). Pregnant women are a particularly vulnerable group to critical illnesses related to COVID-19 due to immunologic, physiological, and anatomical changes during pregnancy (2). Since the onset of the pandemic, many systematic reviews and large observational cohorts have reported a higher risk of severe disease in pregnant women (3). In addition, it was observed that the risk of serious illness and need for intensive care unit were highest in pregnant women in the third trimester (4).

In this study, we aimed to compare the clinical course of COVID-19 in the first, second, and third trimesters of pregnancy by evaluating the data of infected pregnant women who applied to the emergency department of one of the main national pandemic centers.

MATERIAL AND METHODS

This cross-sectional survey study was conducted on 678 pregnant women who were diagnosed with COVID-19 by RT-PCR analysis between October 1, 2020 and May 1, 2021 in Ankara City Hospital. Demographic features, clinical signs and laboratory test results were obtained from hospital records. The study protocol was approved by both the Institutional Ethics Committee (E2-21-581) and the Turkish Ministry of Health.

Vital signs were checked (heart rate, rhythm, respiratory rate, blood pressure, body temperature and Sat O2) and obstetric evaluation was performed after taking the history of each patient. Then thorough physical examination was done by an infectious disease specialist. Basic laboratory tests including complete blood count, C-reactive protein (CRP), procalcitonin, clinical biochemistry parameters, cardiac enzymes, coagulation parameters, fibrinogen, D-dimer, ferritin were carried out. Chest X-ray and chest CT examination were not performed on any of the pregnant women.

Cases were divided into 3 groups as asymptomatic, mild symptomatic (uncomplicated) and severe disease according to the definitions in the national COVID-19 guideline (https://covid19bilgi.saglik.gov.tr/depo/rehberler/COVID-19_Rehberi.pdf?type=file) (Table 1).

Table 1: Definitions of COVID-19 disease severity according to the national COVID-19 guide

Mild symptomatic (=uncomplicated)	Fever and/or muscle/joint pain and/or cough and/or sore throat are present, BUT No respiratory distress (no dyspnea, respiratory rate <24/min and SatO2 >93% in room air)
Severe Disease	Fever and/or muscle/joint pain and/or cough and/or sore throat are present AND Respiratory distress present (dyspnea or air hunger and/or respiratory rate >24/min and/or SatO2 <93%

As defined in the national COVID-19 guide, poor prognostic factors in blood tests (lymphocyte count<800 mg/ml, ferritin>500ng/ml, D-Dimer>1700ng/ml, CRP greater than 10 times the upper limit of normal value) are indicative of severe disease. In this study, we investigated the correlation between poor prognostic factors and disease severity.

Statistical analysis

Statistical analyses were performed by using SPSS (version 21.0; IBM Corporation, NY, USA). Descriptive data were expressed as number (n) and percentage (%), mean ±SD, median (minimum - maximum). Chi-square test was used for intergroup comparisons of categorical data. p-values ≤.0.05 were considered statistically significant.

RESULTS

In total, 257 (37.9%) of 678 COVID-19 (+) pregnant women were hospitalized; 137 for obstetric reasons, and 120 only for COVID-19 infection. Despite being asymptomatic, 28 were hospitalized because of mutant virus detection, 24 with poor laboratory prognostic factors and 11 for social reasons. The number of patients with severe disease at admission was 57.

The number of asymptomatic pregnant women was 284 (41.9%). At least one symptom was present in 394 (58.1%) cases (Table 2). Oxygen saturation (SatO2) in room air was found to be below 90% in 10 (1.5%) and between 90-93% in 47 (6.9%) pregnant women. In 91.6% of cases, SatO2 was ≥94%.

Severe disease was present in 57 (8.4%) cases; 29 (50.9%) of them were in the 2nd trimester and 26 (45.6%) were in the 3rd trimester. It was observed that the rate of severe disease was statistically significantly higher in the advanced weeks of gestation than in the first trimester (p=0.004).

Table 2: Symptoms of COVID-19 positive pregnant patients

Symptoms	
Cough	n=172 (25.4%)
Dyspnea	n=94 (13.9%)
Myalgia/artralgia	n=64 (9.4%)
Taste/smell loss	n=60 (8.8%)
Headache	n=59 (8.7%)
Fever (>38)	n=54 (8.0%)
Fatigue	n =50 (7.4%)
Sore throat	n =43 (6.3%)
Flu like symptoms	n =21 (3.1%)
Low back/back pain	n =13 (1.9%)
Diarrhea	n =12 (1.8%)

In laboratory findings lymphocyte count was <800 mg/dl in 123 patients, D-Dimer level was>1700 ng/ml in 205 patients, ferritin level was>500 ng/ml in 35 patients, CRP value more than 10 times the upper limit in 76 patients.

At least one poor prognostic criterion was found in 48.2% (n=327) of cases. When the distribution of the presence of poor prognostic laboratory criteria according to trimesters was examined, 22.9% of the patients with COVID-19 had at least one poor prognostic laboratory criterion in the first trimester, while this rate was 41.7% and 63.9% in the second and third trimesters, respectively (p<0.001) (Table 3).

Table 3: Presence of poor prognostic factors in laboratory tests in pregnant women with COVID-19 (+) according to their gestational age

	I.Trimester (n=118) %17.4	II.Trimester (n=261) %38.5	III.Trimester (n=299) %44.1	p
Asymptomatic (n=284)	52 (25.5%)	53 (26%)	179 (48.5%)	
Mild symptomatic (n=337)	64 (19%)	179 (53.1%)	94 (27.9%)	
Severe illness (n=57)	2 (3,5%)	29 (50.9%)	26 (45.6%)	
Rate of severe illness	1,6%	11.1%	8.7%	(p=0.004).
Rate of the patients had at least one poor prognostic laboratory finding (n=327)	22.9% (27/118)	41.7% (109/261)	63.9% (191/305)	(p<0.001)
Intensive Care Unit (n=12)	1	5	6	
Mechanical Ventilation (n=6)	1	1	4	
Mortality (n=4)	1	1	2	

Among 12 critically ill pregnant women who required admission to the intensive care during hospitalization, only 1 was in 1st trimester, 5 were in 2nd trimester and 6 were in 3rd trimester. Six patients were intubated in intensive care unit (ICU); one patient was in first trimester, one patient was in second trimester and four patients were in third trimester. Maternal mortality was observed in 4 (0.59%) cases. As shown in Table 3, we observed that in the 2nd and 3rd trimesters, especially in the 3rd trimester, the severity of the disease and the possibility of having poor prognostic laboratory findings were significantly higher than the first trimester.

DISCUSSION

Pregnant women are more susceptible to develop severe illness after respiratory viral infection due to physiological changes of the immune and cardiopulmonary systems during pregnancy (5). During the 2009 pandemic outbreak, 5% of all Influenza A subtype H1N1-related deaths belonged to pregnant women (8). Also both SARS-CoV and MERS-CoV have been associated with higher case fatality rates and more severe complications during pregnancy (6, 7). Compared with SARS and MERS, COVID-19 appears to be less lethal and most of the pregnant women with COVID-19 in literature were asymptomatic or only had mild symptoms (7). However, as noted in many reports, special attention should be paid to this vulnerable group, as pregnant women are at higher risk of hospitalization and admission to the ICU compared to non-pregnant women (8, 9).

In the vast majority of cases, the course of COVID-19 during pregnancy had been reported as asymptomatic (10). The symptomatology was similar with other populations and also no specific pregnancy-related COVID-19 symptoms were known (11). In our study 284 (41.9%) of cases were asymptomatic and 394 (58.1%) cases were symptomatic. We observed mild symptoms in 337 (49.7%) symptomatic patients and respiratory distress in 57 (8.4%) patients. Among severely symptomatic women, 12 (1.76%) were critical and admitted to ICU. Six (0.73%) patients required invasive mechanical ventilation and maternal mortality was 4 (%0.58).

The observed rates of disease severity and mortality is in line with recent analyses in literature. Delahoy et al. reported that 54.5% of 598 pregnant women with COVID-19 were asymptomatic and 45% symptomatic at admission. Of these, 7.3% required an ICU, 3.8% were intubated and 0.33% died (12). According to the findings of a recent systematic review, 6 % of 367 pregnant patients developed severe pneumonia, 2.8% required mechanical ventilation and maternal mortality was 0.54% (13). It was reported in another study that 14 of 43 (32.6 %) COVID-19 (+) pregnant women had no symptom at the time of admission to hospital. Of 29 (67.4%) symptomatic patients, 86% were mild, 9.3% were severe and 4.7% were critical (14). Similar results were found in our study, with 85.6% mild, 11.4% severe and 3% critical of 394 (58.1%) symptomatic patients.

Mullins et al. evaluated the outcomes of 4,005 pregnant women with SARS-CoV-2 infection using data from the 2020 UK PAN-COVID study and the US AAP-SONPM National Perinatal COVID-19 registries and reported the maternal mortality rate of 0.2–0.5% (15).

Studies during the COVID-19 pandemic have shown that the vast majority of cases occur in the third trimester of pregnancy (16-19). Also in this study, 18.6% (n=126) of COVID-19 (+) pregnant women were in the 1st trimester, 36.4% (n=247) were in the 2nd trimester and 45.0% (n=305) were in the 3rd trimester.

Of 57 cases with severe disease, 29 (50.9%) were in the 2nd trimester and 26 (45.6%) were in the 3rd trimester. When the severity of the disease was examined according to trimesters, it was observed that the rate of severe disease was higher in the advanced weeks of gestation than in the first trimester (p=0.004). This finding is in line with previous studies on pregnant women with COVID-19 (4, 20, 21).

When we analyzed the literature on the immunology of SARS-CoV-2 infection, pregnant women had lymphopenia, elevated C-reactive protein and D-dimer levels and an altered immune response that predisposed them to severe or critical COVID-19 (22, 23). In this study these laboratory findings are accepted as poor prognostic factors according to the guidance of the National COVID-19 guideline.

At least one poor prognostic criterion was found in 327 (48.2%) cases. When the distribution of the presence of poor prognostic laboratory criteria according to trimesters was examined, 22.9% of the patients had at least one poor prognostic laboratory criterion in the first trimester, while this rate was 41.7% and 63.9% in the second and third trimesters, respectively (p<0.001).

Due to the significant physiological changes that occur in the respiratory system and altered cell mediated immunity during pregnancy, susceptibility to respiratory pathogens and the risk of complications of respiratory tract infectious increa-

se (24, 25). With the enlargement of the uterus and the structural changes of the ribcage, the diaphram is elevated, chest wall compliance is decreased, the functional residual capacity (FRC) and expiratory reserve volume (ERV) are reduced. A decrease in FRC with an increase in oxygen consumption lowers the mother's oxygen reserve (26). These physiologic changes including congestion and increased secretions, reduce the tolerance to hypoxia and lead to physiological dyspnea as well as increased susceptibility to respiratory pathogens. The greatest changes occur in advanced weeks of pregnancy and majority of pregnant women complain about breathlessness in the third trimester. In addition to physiological dyspne; shortness of breath due to pneumonia in COVID-19 can increase the risk of hypoxemia and exacerbate the clinical presentation (27). Especially in the third trimester, significant fluid exchanges between interstitial, intracellular and intravascular compartments, maximum maternal cardiac output, catecholamine fluctuation and release of inflammatory mediators may put the patient at risk of endothelial dysfunction, pulmonary edema, myocardial edema and cardiac dysfunction (28).

Also, the physiological hypercoagulation state, which occurs when coagulation factors such as fibrinogen and D-dimer rise above the initial value of 50% in the third trimester, increases the risk of coagulation disorders seen in COVID-19 (29).

CONCLUSION

This study on pregnant women with COVID-19 found a significant relationship between the severity of the disease and the trimester of pregnancy. The incidence of severe disease and poor prognostic laboratory findings in advanced weeks of gestation was significantly higher than in the first trimester. In early pregnancies with COVID-19, the disease has a milder course in terms of both clinical and laboratory findings.

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Özgün Araştırma / Original Article

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Hipoksik İskemik Ensefalopatide Umblikal Kord Ph ve İzlemde Alınan Kardiyak Belirteçlerin Yenidoğan ve Bebeklik Dönemi Nörogelişimsel Sonuçlara Etkisi

Effect Of Umblical Cord Ph And Follow-Up Cardiac Markers on Neurodevelopmental Results in Hypoxic Ischemic Encephalopathy

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ÖZ

Amaç: Hipoksik iskemik ensefalopati (HİE); anormal bilinç durumu, nöbetler, çoklu organ yetmezliği ile seyredebilen klinik bir durumdur. Bu retrospektif çalışma ile terapötik hipotermi (TH) uygulanan HİE tanılı yenidoğanların kord kan gazı pH değeri ve kardiyak belirteçleri ile difüzyon Manyetik rezonans görüntüleme (MRG), nörolojik muayeneleri ve gelişimsel sonuçlarının değerlendirilmesi amaçlanmıştır.

Gereç- Yöntem: Ocak 2015- Ocak 2021 tarihleri arasında Hacettepe Üniversitesi İhsan Doğramacı Çocuk Hastanesi Yenidoğan Yoğun Bakım Ünitesi'ne yatırılarak HİE evre 2-3 tanısı ile TH tedavisi almış ve poliklinik izlemine gelen hastalar çalışmaya dahil edildi. Umblikal kord kan gazı pH, Troponin-I, CK-MB değerleri, diffüzyon MRG bulguları ile Bayley Bebekler ve Küçük Çocuklar için Gelişimi Değerlendirme Ölçeği-III (BSID-III) sonuçları karşılaştırıldı.

Bulgular: Çalışmaya alınan 17 hastanın ortalama gebelik haftası 39 hafta (37-41), doğum ağırlıkları ortalama 3360 ± 325 g, 13'ü (%59) erkekti. Hastaların aEEG/EEG izleminde 10 (%59)'unda nöbet tespit edilmedi. Kordon kan gazı pH değeri ortancası ile anormal difüzyon MRG sonuçları arasında istatistiksel olarak fark saptanmadı. BSID-III skorları ile kord kan gazı pH değerinin ortancası arasında; kalp belirteçleri ile difüzyon MRG ve BSID-III sonuçları arasında istatistiksel fark saptanmadı.

Sonuç: Hipoksik iskemik ensefalopati olan bebeklerde TH endikasyonu için kullanılan kord kan gazı değerleri uzun dönem nörolojik-gelişimsel prognozun öngörülmesinde yeterli değildir. Hasta sayısı arttırıldığı takdirde bu hastalarda kalp kasının hipoksiden etkilendiğini gösteren kardiyak enzimlerdeki artış, uzun dönem izlemde bebeğin karşılaşabileceği nörolojik-gelişimsel sorunları öngörmede yararlı olabilecektir.

Anahtar kelimeler: Hipoksik iskemik ensefalopati, terapötik hipotermi, kardiyak belirteçler, nörogelişimsel izlem

ABSTRACT

Aim: Hypoxic ischemic encephalopathy (HIE); It is a clinical condition that can progress with abnormal consciousness, seizures, and multi-organ failure. In this retrospective study, it was aimed to evaluate the cord blood gas pH value and cardiac markers, as well as diffusion magnetic resonance imaging (MRI), neurological examinations and developmental results of newborns diagnosed with HIE who underwent therapeutic hypothermia (TH).

Materıals-Methods: Patients who were hospitalized in the Neonatal Intensive Care Unit of Hacettepe University İhsan Doğramacı Children's Hospital between January 2015 and January 2021 and received TH treatment with the diagnosis of HIE stage 2-3 and were followed up in the outpatient clinic were included in the study. Umbilical cord blood gas pH, Troponin-I, CK-MB values, diffusion MRI findings and Bayley Developmental Assessment Scale for Infants and Young Children-III (BSID-III) results were compared.

Results: Mean gestational week of 17 patients included in the study was 39 weeks (37-41), mean birth weight was 3360 ± 325 g, 13 (59%) were male. Seizures were not detected in 10 (59%) of the patients in aEEG/EEG follow-up. There was no statistical difference between the median cord blood gas pH value and abnormal diffusion MRI results. Between the BSID-III scores and the median of the cord blood gas pH; There was no statistical difference between heart markers and diffusion MRI and BSID-III results.

Conclusıon: Cord blood gas values used for TH indication in infants with hypoxic ischemic encephalopathy are not sufficient to predict long-term neurodevelopmental prognosis. If the number of patients is increased, we can say that cardiac enzymes, which show that the heart muscle is affected by hypoxia in these patients, may be useful in predicting the neurological-developmental problems that the baby may presence in long-term follow-up.

Keywords: Hypoxic ischemic encephalopathy, therapeutic hypothermia, cardiac markers, neurodevelopmental follow-up

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GİRİŞ

Hipoksik iskemik ensefalopati (HİE); anormal bilinç durumu, nöbetler ile seyredebilen ve sıklıkla solunum güçlüğü, tonus değişiklikleri ve refleks kaybının eşlik ettiği, bazen de multiorgan yetmezliği gelişebilen klinik bir durumdur. (1) Dünyada 1000 canlı doğumda 1,5 sıklığında gözlenirken, Türkiye'deki HİE sıklığı 2008 yılında yapılan bir araştırmaya göre binde 2,6 olarak tespit edilmiştir. (2,3) Ayrıca, HİE'nin dünya çapındaki bebek ölümlerinin %23'ünden sorumlu olduğu bildirilmiştir. (4)

Klinik ve deneysel çalışmalar HİE oluşumunda nöronal zedelenmenin iki fazda olduğunu göstermektedir. Birincil zedelenme hipoksi sırasında ortaya çıkar ve nekrotik hücre ölümüne neden olur. İkincil zedelenme reperfüzyon sonrasında ortaya çıkar. Birincil zedelenme ile ikincil zedelenmenin ortaya çıkışı arasındaki altı saatlik sürede (tedavi penceresi) uygulanacak tedaviler hipoksik-iskemiye bağlı nöron hasarını azaltır. Günümüzde doğum asfiksisi sonrası gelişen reperfüzyon hasarını önlemede, ilk altı saatlik sürede uygulandığında, yararı kanıtlanmış olan tek tedavi terapötik hipotermi (TH) tedavisidir. (5-7) Sarnat & Sarnat sınıflamasına göre HİE; hafif (evre 1), orta (evre 2) ve ağır (evre 3) HİE olarak sınıflandırılmakta olup; orta ve ağır HİE tanısı alan yenidoğanlara TH tedavisi uygulanması önerilmektedir. (8)

Hipoksik iskemik ensefalopatiden sadece beyin dokusu değil, aynı zamanda tüm organlar etkilenir. Bu nedenle bebeğin solunum sistemi, kan gazları, kalp, böbrek ve karaciğer fonksiyonları değerlendirilir. Kalp fonksiyonlarının değerlendirilmesinde, biyokimyasal belirteçlerin (CK-MB, Troponin-I gibi) term bebeklerde asfiksi için değerli olduğu bildirilmiştir. Plasental kan akımındaki herhangi bir kesinti, fetüste yaşamsal organları korumak için 'dalış refleksi' oluşmasına neden olur. Miyokard dokusu yetersiz rezerve sahip olduğu için hipoksi durumunda zedelenebilir ve serum troponin I, CK-MB değerleri artabilir. Bu belirteçlerin artması, HİE sırasında miyokard hasarının bir göstergesidir. (1,5) Kalpte oluşan zedelenme ile nöronal hasarın ve nörogelişimsel sonuçların ilişkisini araştıran az sayıda çalışma bulunmaktadır. (6)

Bu retrospektif çalışma ile hastanemizde TH uygulanan HİE tanılı yenidoğanların umblikal kord kan gazı pH değerleri, kardiyak belirteçleri, difüzyon manyetik rezonans görüntüleme (MRG), nörolojik muayene ve gelişimsel sonuçlarının birbirleriyle olan ilişkilerinin değerlendirilmesi amaçlanmıştır.

GEREÇ VE YÖNTEMLER

Etik kurul onayı (2020/17-09) alındıktan sonra, hastane kayıtları tarandı, Ocak 2015- Ocak 2021 tarihleri arasında Hacettepe Üniversitesi İhsan Doğramacı Çocuk Hastanesi Yenidoğan Yoğun Bakım Ünitesi'ne yatırılarak HİE evre 2-3 tanısı ile TH tedavisi alan ve poliklinik izlemlerine gelen 30 hasta belirlendi. Bu hastalardan biri Down sendromlu olduğu için, iki hasta exitus olmaları nedeniyle çalışmadan çıkarıldı. Difüzyon MRG bulgusu olan 24 hasta içerisinden çalışmaya gelişimsel izlemleri yapılabilen 17 hasta alındı.

Türk Neonatoloji Derneği'nin Neonatal Ensefalopati Tanı ve Tedavi Rehberi'nde belirtilen HİE tanı kriterlerini (gebelik yaşı 36 haftadan büyük ve postnatal 6 saatten küçük olan yenidoğanlardan, kord kan gazında veya doğumdan sonraki ilk bir saat içerisinde bakılan pH ≤ 7.00 veya BE ≤ -16 mmol/L olan, 10. dakika Apgar skoru <5 veya devam eden resüsitasyon ihtiyacı olan, klinik değerlendirmede Sarnat & Sarnat tanı kriterleri ve Thompson skorlarına göre orta veya ağır ensefalopati bulguları) karşılayan ve TH verilen bebeklerin hastane dosya kayıtları incelendi, izlem sonuçları değerlendirildi. (5,8,9) Sarnat & Sarnat tanı kriterleri ve Thompson skorları ile HİE'nin şiddeti, amplitüd entegre elektroensefalografi (aEEG) veya elektroensefalografi (EEG) bulguları (trase, nöbet aktivitesi, düşük zemin aktivitesi) kaydedildi. (8,9) Ayrıca demografik veriler, anne öyküsü, Apgar skorları, neonatal-klinik bulgular, fizik muayene, nörolojik muayene bulguları, kord kan gazı değerleri, TH sırasında Troponin I, CK-MB değerleri (postnatal 1.,2.,3. gün), konvansiyonel ve diffüzyon MRG (postnatal 3- 5. gün) sonuçları kaydedildi.

Merkezimizde tüm orta ve yüksek riskli bebekler taburculuk sonrasında Yenidoğan, Gelişimsel Pediatri polikliniklerinde ve Gelişimsel Fizyoterapi Ünitesinde belirli aralıklarla değerlendirilmektedir. Gelişimsel izlem sırasında ailelerin sosyoekonomik-sosyokültürel düzeyleri; anne- baba eğitim ve mesleki durumuna göre oluşturulmuş olan Hollingshead-Redlich ölçeği kullanılarak sınıflandırılmaktadır. (10) Ölçekte en yüksek sosyoekonomik düzey 1, en düşük olan ise 5 olarak belirtilmiştir. Bebekler ve Küçük Çocuklar için Gelişimi Değerlendirme Ölçeği-III (Bayley- III ölçeği), düzeltilmiş yaşı 0-42 ay arasında olan bebek ve çocukların, bilişsel, dil ve hareket alanlarında gelişimini değerlendirmek amacıyla uygulanmaktadır. Elde edilen bilişsel bileşik, dil bileşik ve hareket bileşik puanları 70'in altı, 71- 85 ve 86 puan üzeri olarak sınıflandırılmış olup; 86 puan ve üzeri ayrıca normal olarak gruplandırılmaktadır. (11) Bu çalışmada da Bayley- III ölçeği uygulanarak puanlama yapıldı.

İstatistiksel analiz için "Statistical Package for Social Sciences version 28 (SPSS, Chicago, IL, USA)" kullanıldı. Veriler ortalama ± standart sapma, ortanca (en düşük-en yüksek değer), yüzde ve oran ile ifade edildi. Değişkenler için Shapiro-Wilk testi ile normal dağılım analizi yapıldı. Normal dağılıma uyan veriler için ortalama ve standart sapma, uymayan veriler için ortanca ve en düşük- en yüksek değerleri yazıldı. Grup karşılaştırmaları için değişkenlerin ortanca değerlerinin üstündeki ve altındaki değere göre sınıflama yapılarak, nonparametrik Mann Whitney U testi uygulandı. Elde edilen sonuçlarda 0,05'den küçük p değeri anlamlı olarak kabul edildi.

Çalışma uluslararası klinik çalışmalar ağına (ClinicalTrials.gov/NCT04766541) da kaydedildi.

BULGULAR

Çalışmaya alınan hastaların klinik ve demografik özellikleri Tablo I'de gösterilmiştir.

Sosyodemografik verisi elde edilmiş olan 17 ailede anne yaşı ortalama 29 ± 5,3, baba yaşı ortalama 35 ± 7 yıl; anne eğitim yılı ortancası 12 (3-18), baba eğitim yılı ortancası 12 (5- 22) yıl idi. Ailelerin sosyodemografik ve sosyokültürel düzeyi Hollingshead-Redlich ölçeğine göre ailelerin 5'i (%31,3) seviye II; 4'ü (%25) seviye III; 6'sı (%37,5) seviye IV; 1'i seviye V olarak sınıflandırıldı.

Tablo I: Klinik ve demografik özellikler (n=17)	
Gestasyon Yaşı (hafta) †	39 (37-41)
Doğum ağırlığı (gram)*	3360± 325
Erkek cinsiyet, n (%)	13 (59)
Sezaryen ile doğum, n (%)	12 (55)
Apgar (1.- 5.- 10. Dakika) †	4 (0-8) – 6 (1-9) – 8 (4-9)
Yatış süresi†	8 (4- 28)
Anne yaşı†	28 (21- 38)
1. ay nörolojik muayene normal	15 (%88)
3. ay nörolojik muayene normal	15 (%88)
aEEG/ EEGde nöbet aktivitesi yok	10 (%59)
*ortalama± SD † ortanca (min- max)	

Hastalardan 4'ünün (%13,8) 6. Ay; 6'sının (%20,7) 12. Ay; 6'snın (%20,7) 18. Ay; 1'inin (%3,5) 24. ayda yapılmış Bayley-III ölçeği değerlendirmesi mevcuttu.

Hastaların Bayley-III'e göre bilişsel bileşik puanı ortanca 95 (90-97,5); dil bileşik puanı ortanca 89 (84,5-98,5); hareket bileşik puanı ortanca 94 (92,5-100) olup sınıflandırma detayları tablo 2'de verilmiştir. Çalışmamızdaki tüm hastalar taburculuk sonrası izlenmiş ve gelişimleri desteklenmiş olup hastalardan ikisinin Çocuklar için Özel Gereksinim Raporu (ÇÖZGER) mevcuttu ve bu çocuklar özel eğitim desteği almaktaydı.

Bayley Bebek ve Çocuklar İçin Gelişimi Değerlendirme Ölçeği-III (Bayley-III) Sonuçlarına göre 17 hastadan, bilişsel bileşik puanı 70'in altında olan 1 (%5,9), 71- 85 puan arası olan 1 (%5,9), 86 puan ve üzeri ise 15 (%88,2) hasta saptanmıştır. Dil bileşik puanına göre ise 70'in altında olan 1 (%5,9), 71- 85 puan arası olan 3 (%17,6), 86 puan ve üzeri ise 13 (%76,5) hasta saptanmıştır. Hareket bileşik puanı değerlendirildiğinde ise, 70'in altında olan 2 (%11,8), 71- 85 puan arası olan 0, 86 puan ve üzeri ise 15 (%88,2) hasta saptanmıştır.

Hollingshead-Redlich ölçeğine göre seviye II-III; ve seviye IV-V sınıflandırılarak ele alındığında Bayley-III'e göre herhangi bir alanda anormal sonucu olan 5 hastadan 4'ü (%80); normal olan 11 hastadan 3'ü (%27.27) daha düşük seviye olan IV-V sınıfındaydı (p: 0.106).

TH yapılan hastaların kord kan gazı pH ortanca 6,9 mmHg (6,7-7,1), laktat ortanca 13,9 mmol/L (1-19), baz açığı ortanca -18 mmol/L (16- 39) bulundu. Bulunan ortanca değerlerin üzerindeki ve altındaki sayılar iki alt gruba ayrılarak değerlendirmeye alınmıştır.

17 hasta içerisinde ulaşılabilen 14 hastanın Diffüzyon MRG sonuçlarının normal veya anormal olması ile kord pH'sının ortanca değeri arasında nonparametrik Mann Whitney U karşılaştırılması yapıldığında istatistiksel anlamlı ilişki saptanmadı (p: 0,122). 6- 24 ay arası yapılan Bayley-III değerlendirmesindeki bilişsel, dil, hareket ölçekleri ile kord pH ortanca değeri arasında istatistiksel fark saptanmadı (sırasıyla; 0,143; 0,602; 0,143). (Tablo II)

Diffüzyon MRG ve 6- 24 aylar arası Bayley III değerlendirme sonuçlarının Troponin I ve CK- MB değerine göre değerlendirilmesine göre istatistiksel fark saptanmamıştır (Tablo II).

	Tablo II: Diffüzyon MRG ve Nörogelişimsel sonuçlarının kord pH, Troponin I ve CK- MB ortanca değerine göre değerlendirilmesi								
		n (%)	*P Kord pH‡*	*P 1.gün (TnI)**	*P 1.gün (CK-MB) †*	*P 2.gün (TnI)**	*P 2.gün (CK-MB) †*	*P 3.gün (TnI)**	*P 3.gün (CK-MB) †*

Diffüzyon MRG Anormal	Normal	7 (50)	0,122	0,661	0,442	0,681	0,442	0,534	0,833
	7 (50)								
Bayley-III Hareket bileşik puanı Anormal	Normal	15 (88)	0,143	0,591	0,963	0,515	0,408	1,00	0,445
	2 (12)								
Bayley-III Dil bileşik puanı Anormal	Normal	13 (76)	0,602	0,884	0,963	0,897	0,897	1,000	0,445
	4 (24)								
Bayley III bilişsel bileşik puanı Anormal	Normal	15 (88)	0,143	0,591	0,963	0,515	0,408	1,000	0,445
	2 (12)								
	ǂ Anormal grup Kord pH'sının ortanca değeri 6,9 (6,7-7,1)'e göre *Anormal grup Troponin I (TnI) ortanca değerlerine (0,047; 0,05; 0,031, sırasıyla) göre † Anormal grup CK-MB ortanca değerlerine (42,40; 99,00; 69,20; sırasıyla) göre								

TARTIŞMA

Bu çalışmada göbek kordon kan gazındaki pH değeri ile TH tedavisi sırasında (postnatal 1.,2.,3.gün) ölçülen troponin-I ve CK-MB belirteçlerinin yenidoğan dönemindeki MR difüzyon, 1. ve 3. aylıkken yapılan nörolojik muayeneleri ve 6 - 24 aylar arasında yapılan Bayley III sonuçlarıyla ilişkisi değerlendirilmiştir.

Hipoksik iskemik ensefalopati tanısı alan bebeklerde göbek kordon kan gazı parametrelerinde pH değeri, TH tedavisi endikasyonlarından birini oluşturur. Çünkü göbek kordon kanı (arteriyel) pH değerinin 7.00'nin altında olmasının nörolojik-motor gelişim geriliği ile ilişkili olduğu saptanmıştır. (12,13,14) Çalışmamızda ise hasta göbek kordonu pH değerinin ortancasına göre bakıldığında, difüzyon MRG ile arasında anlamlı ilişki saptanamadı. Bu durumun hasta sayısı yetersizliğine bağlı olduğunu düşünmekteyiz.

Çalışmamızda hastalara 6-24 aylar arasında yapılmış olan Bayley III skorları ve kordon pH ortanca değerine göre alt grup değerlendirmesi yapıldığında motor, dil, bilişsel değerlendirmeler arasında anlamlı fark saptanmadı. Çalışmamızdaki tüm hastalara TH tedavisi uygulandığı için, nörogelişimsel sonuçlarda fark saptanmamasının nedeni TH tedavisinin olumlu etkisi olabilir. Bir Cochrane metaanalizinde, TH tedavisi ile yenidoğanların 18. aylarında nöromotor gelişimlerinde iyileşme gözlendiği bildirilmektedir. (15)

Al Amrani ve arkadaşlarının TH tedavisi alan 33 yenidoğan ile yaptığı bir çalışmada; postnatal 2. günde yapılan difüzyon MRG'deki belirgin olan difüzyon değişiklikleri, daha sonraki anormal nörogelişimsel sonuçlarla ilişkilendirilmiştir. (16) Hunt ve arkadaşlarının 2004 yılında yaptığı çalışmada ise, difüzyon MRG'da internal kapsülde meydana gelen difüzyon kısıtlılığının uzun dönemde nörogelişimsel prognozu tahminde oldukça değerli olduğu ortaya konmuştur. (17) Bir çalışmada, perinatal asfiksiye maruz kalmış bebeklerde ilk 48 saatte yapılan difüzyon MRG sonuçları normal olan bebeklerin 24. ay nöromotor gelişim izlemleri de normal bulunmuştur. (18) Başka bir çalışmada perinatal asfiksi nedeniyle TH tedavisi uygulanan bebeklerin postnatal 4-5. günlerinde çekilen difüzyon MRG ile 24. ay nörogelişimsel prognoz arasında korelasyon olduğu tespit edilmiştir. (19)

Çalışmamızda hipoksinin kalp üzerine olan etkileri nedeniyle kardiyak belirteçleri kısa ve uzun dönem izlemde prognoz tahmini açısından değerlendirildi. Troponin I, CK-MB ortanca değerleri ile anormal difüzyon MRG ve uzun dönem Bayley III skorları arasında yapılan alt grup değerlendirmesine göre istatistiksel olarak fark saptanmadı. Sweetman ve arkadaşlarının 54 hasta ile yaptığı çalışmada 3. gün bakılan troponin T değerinin difüzyon MRG ile tespit edilen beyin hasarı arasında anlamlı korelasyon gösterdiği saptanmıştır. (6) Bizim çalışmamızda fark saptanmama nedenini ise hasta sayımızın yetersiz olması olarak düşündük. Montaldo ve arkadaşlarının çalışmasında ise, 178 bebeğin postnatal ilk 12 saatindeki kardiyak belirteçleri ile Bayley II skoru değerlendirilmiş, troponin I değeri ile Bayley II arasında korelasyon saptanmış, CK-MB ile anlamlı korelasyon saptanmamıştır. (20) Çalışmamızda troponin I ve CK-MB ortanca değerleri ile Bayley III skoru arasındaki değerlendirmede anlamlı bir fark saptanmamıştır.

Çalışmamızın en önemli kısıtlılığı, nörogelişimsel değerlendirmenin geniş bir aralığı (6 ila 24 ay arasını) kapsamasıdır. Li-

teratürde 22-24 ay arası değerlendirmeler göz önüne alınırken bizim çalışmamızda hasta sayısı azlığı nedeniyle 6-24 ay arası tüm BAYLEY III değerlendirmeleri alınmıştır. Gelişimsel Pediatri izlemleri sırasında bebeklere en erken dönemden itibaren de gelişimsel destek sunulmuştur. Sadece gelişimsel izlem yapılan değil aynı zamanda TH tedavisi alan hasta sayısı azlığı da bir diğer kısıtlılıktır. Daha uzun yıllar alınarak daha kapsamlı bir çalışma planlanabilir.

Ayrıca bu hastaların gelişimsel değerlendirmeleri 6 ila 24 ay arasında yapılmış olması ve daha uzun dönemde izlenememesi de çalışmanın bir diğer önemli kısıtlılığıdır.

SONUÇ

Hipoksik iskemik ensefalopati olan bebeklerde TH endikasyonu için kullanılan kord kan gazı değerleri uzun dönem nörolojik-gelişimsel prognozun öngörülmesinde yeterli değildir. Hasta sayısı arttırıldığı takdirde bu hastalarda kalp kasının hipoksiden etkilendiğini gösteren kardiyak enzimleri uzun dönem izlemde bebeğin karşılaşabileceği nörolojik-gelişimsel sorunları öngörmede yararlı olabileceğini söyleyebiliriz. Ancak halen prognoz öngörüsünde kullanılabilecek kanıt değeri yüksek belirteçler bulunmamakta, bu konuda klinik ve gözlemsel çalışmalara ihtiyaç bulunmaktadır.

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The Role of Systemic Inflammatory Response Markers in Differential Diagnosis of Ovarian Tumors

Over Tümörlerinin Ayırıcı Tanısında Sistemik İnflamatuar Belirteçlerin Rolü

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ÖZ

Amaç: Çalışmamızda preoperatif inflamatuar kan parametrelerinin benign seröz kistadenom, seröz borderline ovarian tümör (BOT) ve high grade over karsinomu (HGSOC) ayırıcı tanısındaki yerini analiz etmek amaçlandı.

Gereçler ve Yöntemler: Ovaryan tümöre sahip 370 hasta retrospektif olarak 3 grup olarak değerlendirildi. Hastalar benign seröz kistadenom, seröz BOT ve HGSOC olarak gruplandırıldı. Preoperatif kan inflamatuar parametreleri: Hemoglobin (Hb), kırmızı hücre dağılım genişliği (RDW), Hb/RDW, Nötrofil / Lenfosit(N/L) ve Platelet/ Lenfosit (P/L) oranları analiz edildi.

Bulgular: P/L and N/L oranlarının benign seröz kist adenomda, seröz BOT'e ve HGSOC 'e göre anlamlı derecede düşük olduğu bulundu (p<0.001 and p<0.001). Benign seröz kistadenom, seröz BOT ve HGSOC ile karşılaştırıldığında daha düşük RDW median değere sahip olduğu saptandı. (p<0.001). Hb/RDW oranı HGSOC'lu hastalarda istatiksel olarak anlamlı olarak en düşük, benign seröz kistadenomlu hastalarda anlamlı olarak en yüksekti (p<0.001).

Sonuç: Preoperatif Hb/RDW, benign seröz kistadenom, seröz BOT ve HGSOC'nin ayırt edilmesinde belirleyici olarak kullanılabilir olduğunu düşünmekteyiz. N/L ve P/L, benign seröz kistadenom ve seröz BOT'ı HGSOC'den ayırt etmek için kullanılabilir .

Anahtar Kelimeler: Over kanseri, inflamatuar kan belirteçleri, kırmızı hücre dağılım genişliği(RDW)

ABSTRACT

Aim: The aim of this study is evaluating the predictive value of preoperative inflammatory blood parameters for differential of serous cystadenoma, serous borderline ovarian tumor (BOT) and high-grade serous ovarian (HGSOC) carcinoma.

Materials and Method: In this single-center study, we retrospectively enrolled 370 patients with ovarian tumors were divided into three groups. The groups were classified as serous cystadenoma, serous BOT and HGSOC. The potential association of preoperative hemoglobin (Hb), red cell distribution width (RDW), Hb/RDW ratio, ratio of neutrophils to lymphocytes (N/L) and ratio of platelets to lymphocytes (P/L) were analyzed.

Results: P/L and N/L were significantly lower in benign serous cystadenoma or serous BOT than HGSOC (p<0.001 and p<0.001). Benign serous cystadenoma was significantly associated with lower median RDW compared to serous BOT and HGSOC (p<0.001). Hb/RDW ratio was significantly lowest in patients with HGSOC and significantly highest in patients with benign serous cystadenoma (p<0.001).

Conclusion: Preoperative Hb/RDW can be used as predictor for discrimination of benign serous cystadenoma, serous BOT and HGSOC. N/L and P/L may be considered to distinguish the benign serous cystadenoma and serous BOT from HGSOC.

Keywords: Ovarian cancer, inflammatory blood markers, red cell distribution width (RDW)

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INTRODUCTION

Epithelial ovarian cancer is one of the most common tumors and has the highest mortality rate among malignancy in the women worldwide (1). Most cases of epithelial ovarian cancer are diagnosed as advanced stage due to the definition of the identifications diagnosis techniques and the absence of obvious clinical symptoms in the early stages (2). Borderline ovarian tumors (BOT) have the good prognosis due to low recurrence and metastasis rates, and surgical cure rates are high in most cases (3). Clinical symptoms, tumoral markers and imaging are still not enough in differential diagnosis among benign cases, BOT and early stage ovarian cancer. Several inflammatory markers have been evaluated by researchers for discrimination of benign, borderline and ovarian cancers (3).

Inflammatory response plays a crucial role in carcinogenesis, tumor progression and metastasis(4). Therefore, preoperative inflammatory ratio and their rates have recently evaluating of many different cancers(5,6). Additionally, blood inflammatory markers seem simple, reproducible and cost-effective for differential diagnosis of ovarian mass. Ratios of neutrophils to lymphocytes (N/L) and platelets to lymphocytes (P/L) can be predictive for diagnosis of ovarian malign tumors(7,8).

Red cell distribution width (RDW) is used to determine red blood volume size variation and the etiology of anemia (9). It has been demonstrated that elevated RDW levels associated with diagnosing ovarian cancer and distinguishing it from benign ovarian tumors. Qin et al. demonstrated that High RDW levels have been shown to be associated with diagnosing ovarian cancer and distinguishing it from benign ovarian tumors(10). Fank et al. reported that hemoglobin-to-red cell distribution width low ratio (Hb/ RDW) ratio poor prognosis hepatocellular cancer. According to our knowledge, value of Hb/ RDW ratio is still not investigated for ovarian masses(11).

The aim of this study was to evaluate the predictive value of preoperative parameters including Hb/RDW, N/L and P/L in discrimination of benign serous cyst adenoma, serous borderline and high-grade serous ovarian cancer.

MATERIALS AND METHODS

This retrospective study enrolled in of 370 adult female patients who underwent primary surgery in the gynecological oncology department between February 2018 and January 2023. Data were collected from the institution's electronic database and patients' file. Having diagnosis of benign serous cystadenoma, serous BOT or high grade serous ovarian cancer (HGSOC) in the final pathologic report, patients older than 18 years old and non-pregnancy were inclusion criteria. The exclusion criteria were the presence history of secondary malignancy, histological types other than serous epithelial tumors such as non-serous epithelial tumors, germ cell tumors, sex-cords cell tumors, patients who received neoadjuvant therapy, having local or systemic infection diseases, receiving preoperative transfusion, history of splenectomy, using anticoagulant drugs, history of comorbidity for renal disease and heart failure. Informed consent was obtained for use of the medical records for research purposes from patients. This study was approved by the Institution Ethics Committee (approval number: E2-23-3188)

The preoperative counts of monocytes, neutrophils, lymphocytes, platelets, Hb, RDW, albumin and CA125 were analyzed within the 9 days before the operation. The cut off value of was CA125:35 U/ml. The International Federation of Gynecology and Obstetrics (FIGO) ovarian cancer staging was revised according to 2021(12). The blood cell ratios were analyzed as follows: Hb/RDW, N/L and P/L.

Statistical Analysis

Continuous variables were evaluated as mean ± standard deviation and median, categorical variables were evaluated frequencies. Statistical analyses were used The Student's t-test or Mann-Whitney U-test for two group comparisons. The differences between more than two groups were evaluated by One-way ANOVA test or Kruskal-Wallis test as appropriate. The differences between three groups were evaluated by Kruskal-Wallis test, and post hoc analysis was performed using Dunn test. P <0.05 was accepted as statistical significance. Data was analyzed using the SPSS 11.5 for Windows (SPSS Inc., Chicago, IL, USA). Post-hoc test analysis was performed using the "dunn test" package.

RESULTS

All cohort included a total of 320 patients with ovarian tumors. The rate of the groups was benign serous cystadenoma in 104 (28.1%), serous BOT 82 (22.2%) and 184 (49.7%) HGSOC. Age was statistically difference among groups. The median age was 52 years, 43.5 years and 58 years for benign, serous BOT and HGSOC; respectively (p<0.001). The median ve mean values of the cohorts were shown in Table 1.

Table 1: Complete blood counts.

	Mean±SD	Median (Min-Max)
Hb (mg/dl)	12.42±1.62	12.50 (1.60-20.60)
PLT	349.84±127.68	320.00 (2.11-826.00)
RDW (%)	14.20±1.62	13.80 (11.50-24.80)
P/L	222.57±153.18	172.75 (0.98-1376.00)
N/L	3.32±2.48	2.56 (0.86-24.95)
Hb/RDW	0.89±0.16	0.90 (0.12-1.44)
Albumin (g/dL)	43.25±4.60	44.00 (15.10-52.00)
Ca125 (U/ml)	708.06±1565.21	91.50 (2.00-12000.00)

The clinical characteristics and results of the blood cell ratios of cohorts are shown in Table 2. The median Hb and albumin were significantly higher in HGSOC than benign serous cystadenoma or borderline serous ovarian tumors (p<0.001 and p<0.001). PLR and NLR were significantly lower in benign serous cystadenoma or serous BOT than HGSOC (p<0.001 and p<0.001). Benign serous cystadenoma was significantly associated with lower median RDW compared to serous BOT and HGSOC (p<0.001). Median CA125 had statistically significance among groups. Median ca125 was 11 U/ml, 44 U/ml and 457 U/ml for benign serous cystadenoma, serous BOT and HG-

SOC, respectively (p<0.001). Hb/RDW ratio was statistically difference among groups. HB/RDW ratio was significantly lowest in patients with HGSOC and significantly highest in patients with benign cystadenoma (p<0.001).

Table 2: Comparison of clinical characteristics and complete blood count among study groups.

Variables	Benign (n=104)		Borderline (n=82)		Over Ca (n=184)		p value
	Mean±SD	Median (Min-Max)	Mean±SD	Median (Min-Max)	Mean±SD	Median (Min-Max)	
Age (years)	52.74±12.36	52.00[a] (18.00-80.00)	45.17±15.89	43.50[b] (21.00-88.00)	59.26±10.25	58.00[c] (37.00-85.00)	<0.001
Hb (mg/dl)	12.86±1.60	13.10[a] (1.60-15.30)	12.76±1.27	12.95[a] (9.10-15.60)	12.03±1.67	12.10[b] (5.61-20.60)	<0.001
PLT	1.02±0.29	1.00[a] (0.00-3.60)	284.38±64.16	279.00[a] (125.00-474.00)	307.67±70.77	309.50[b] (157.00-481.00)	<0.001
RDW (%)	13.53±0.90	13.40[a] (11.60-15.90)	14.10±1.09	14.00[b] (12.10-19.10)	14.62±1.97	14.00[b] (11.50-24.80)	<0.001
P/L	136.48±44.11	131.35[a] (61.48-245.26)	152.81±46.47	151.18[a] (60.13-302.72)	302.31±180.22	270.45[b] (0.98-1376.00)	<0.001
N/L	1.96±0.58	1.87[a] (1.02-3.82)	2.24±0.77	2.13[a] (0.94-5.20)	4.57±2.96	3.84[b] (0.86-24.95)	<0.001

Malignant ovarian tumors aggressive tumors due to diagnosis advanced stage and the deadliest female genital system cancers (1). Therefore, it is pivotal to establish distinguishing diagnosis among ovarian masses and predicting the prognosis of ovarian cancers (3). In recent years, the differential diagnosis of ovarian tumors has been evaluated by focusing on inflammatory parameters (3). Our study aimed to investigate the predictive value of preoperative blood cell markers and ratios among ovarian benign serous cystadenoma, serous BOT and HGSOC.

Chronic inflammation microenvironment is hallmarks for tumor initiation, development and metastasis (13). Lymphocytes play role in anti-tumoral immune function. Stimulated lymphocytes leads to increase apoptosis and inhibit tumor cell proliferation (14). Kiss et al demonstrated that monocytes increase tumor progression and metastasis (15). Neutrophilia can increase tumor cell proliferation, invasion and vascularization due to an inflammatory microenvironment (16).

Yun et al. showed that N/L and P/L were significantly higher in ovarian cancers compared to benign and borderline tumors (3). In addition to, they reported that N/L and P/L ratio were not significantly difference between benign and borderline ovarian tumors (3). Bakacak et al. reported that N/L and P/L ratio were significantly higher in patients with ovarian cancer than in patients with benign ovarian tumors(17). We found that P/L and N/L significantly higher in HGSOC than in benign serous cystadenoma or serous BOT (p<0.001 and p<0.001).

RDW is a measure of the size heterogenenity of red blood cells. RDW is closely related to patients with non-hemotologic diseases such as endometrial cancer and ovarian cancer (8, 9). Low hemoglobin reflects the body's level of anemia and causes tumor hypoxia (18). Hypoxia in tumor tissue increases angiogenesis and, accelerates tumor aggression and spread (19). Qin et al. reported that there was statistically significant higher RDW in patients with ovarian cancer compared to benign ovarian tumors (p < 0.001)(10). In addition, they reported that high RDW was significantly related to late stage in ovarian cancer(10). We found that the median RDW was significantly higher in HGSOC and BOT than benign serous cystadenoma (p<0.001). Median RDW may be used to distinguish the benign serous cystadenoma from HGSOC and BOT.

Hb/RDW is a novel marker of blood inflammatory markers and reflects the body's systemic inflammatory levels(20). There are scarce studies in the literature on Hb/RDW in oncologic diseases (11,21). Chi at al demonstrated a meta-analysis which reported that low Hb/RDW was predictor of poor prognosis for 2985 cancer patients (21). They reported that low Hb/RDW was associated with two-fold risk for poor disease free survival and overall survival (p < 0.0001). Sun et al reported a study that analyzed Hb/RDW levels in 362 patients with esophageal cancers (22). They demonstrated that low Hb/RDW ratio was significantly associated with metastatic lymph node status and advanced stage. On multivariant analysis, low Hb/RDW was an independent poor prognostic factor for overall survival(22). The median Hb/RDW ratio was reported as 977.68 ± 168.79 and 1121.41 ± 78.68 in patients with nasopharengeal malignancy and benign, retrospectively(20). The Hb/RDW was significantly lower in nasopharengeal cancers groups compared to healthy group (20). In the present study, Hb/RDW ratio was statistically difference among groups. HB/RDW ratio was significantly lowest in patients with HGSOC and significantly highest in patients with benign cystadenoma. Therefore, preoperative Hb/RDW can be useful predictor in differential diagnosis of benign serous cystadenoma, serous BOT and HGSOC.

This study has some limitations, such as its retrospective nature, single center institution and its small sample size. In addition, we did not study other relevant inflammatory markers such as C-reactive protein (CRP), procalcitonin and erythrocyte sedimentation rate (ESR). These indicators may also benefit Hb/RDW to distinguish among ovarian tumors. Despite these limitations, to our knowledge, this is the first study that evaluated the relationship between Hb/RDW and pure serous ovarian masses including benign serous cystadenoma, serous BOT and HGSOC.

CONCLUSION

Because of the importance of early diagnosis in ovarian cancer, preoperative differential diagnosis among ovarian masses is very crucial. Both imaging methods and CA-125 can be insufficient for diagnosis, therefore median RDW, Hb / RDW, N/L and P/L can help to differentiate ovarian masses preoperatively. Preoperative RDW may be used to differential diagnosis the benign serous cystadenoma from HGSOC and BOT. Preoperative Hb/RDW can be useful predictor in differential diagnosis of benign serous cystadenoma, serous BOT and HGSOC. Nevertheless, more prospective clinical trials are necessary to accurate these results.

Conflict of interest

The authors have declared that they have no conflict of interest relevant to this article.

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Olgu Sunumu / Case Report

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Gebelikte intrauterin exitusla sonuçlanan şiddetli trombositopeni ve literatürün gözden geçirilmesi

Severe thrombocytopenia resulting in intrauterine exitus in pregnancy and review of the literature.

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ÖZ

Şiddetli trombositopeni ve intrauterin exitus fetusun eşlik ettiği bir gebeliği ve bunun yönetimini literatürü gözden geçirerek sunmayı amaçladık.

21 yaşında, 24 hafta tekil gebeliği olan hasta, bulantı, kusma, burun kanaması şikayeti ile başvurdu. Hastada, şiddetli trombositopeni (plt:6000/uL) saptandı; fetal kalp atımı izlenmemesi üzerine, terminasyon kararı verildi. Hb:6,7 g/dl, ALT:28 U/L, AST:70 U/L, LDH:2297 U/L, Haptoglobin<10 mg/dl, Albumin:2,47 g/dl, kreatinin:0,83 mg/dl, direk coombs: negatif, indirek coombs: negatif, TİT:protein 4+ idi. Periferik yaymada fragmente eritrositler mevcuttu. Hastaya mikroanjioptik hemolitik anemi tanısıyla, 4 Ü aferez trombosit, 3 Ü ES, 30 gr İVİG, 120 mg prednol uygulandı. Plt:59000 /uL olduğunda, doğum indüksiyonuna başlandı. İndüksiyon sırasında, plazmaferez uygulandı ve 6 saat sonra vajinal yolla doğum gerçekleşti.

Gebelikte şiddetli trombositopeni saptanan hastaların, nedene yönelik ayırıcı tanısı en kısa sürede yapılmalıdır. Ayırıcı tanı için, ADAMTS 13 gibi ileri tetkik sonuçlarını beklemek için, hayati riskler nedeniyle vakit yoktur ve hızlı davranmak gerekir.

Anahtar kelimeler: trombositopeni, TTP, gebelik, ADAMTS13

ABSTRACT

We aimed to present a pregnancy with severe thrombocytopenia and intrauterine exitus fetus and its management by reviewing the literature.

A 21-year-old patient with a 24-week singleton pregnancy was admitted with complaints of nausea, vomiting and epistaxis. Severe thrombocytopenia (plt: 6000/uL) was detected in the patient and fetal heartbeat were not observed, so termination was decided. Hb: 6.7 g/dl, ALT: 28 U/L, AST:70 U/L, LDH:2297 U/L, Haptoglobin<10 mg/ dl, Albumin:2.47 g/dl, creatinine: 0.83 mg/dl, direct coombs: negative, indirect coombs: negative, TIT: protein 4+. Fragmented erythrocytes were found in peripheral blood smear. With the diagnosis of microangioptic hemolytic anemia, the patient was administered 4 U apheresis platelets, 3 U ES, 30 g IVIG, 120 mg prednol. When plt:59000 /uL, labor induction was started. During induction, plasmapheresis was applied and vaginal delivery occurred 6 hours later.

The differential diagnosis of patients with severe thrombocytopenia during pregnancy should be made as soon as possible. For differential diagnosis, there is no time to wait for further examination results such as ADAMTS 13, due to life-threatening risks, and it is necessary to act quickly.

Keywords: thrombocytopenia, TTP, pregnancy, ADAMTS13

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GİRİŞ

Trombotik mikroanjiyopati bozuklukları, mikroanjiyopatik hemolitik anemi, trombositopeni ve uç organ hasarı ile karakterizedir (1). Gebelik sırasında ve doğum sonrasında, en sık neden, HELLP Sendromu (hemoliz, karaciğer enzimlerinde yükselme, düşük trombosit sayısı) veya preeklampsi olsa da (2), nadiren, trombotik trombositopenik purpura (TTP) ve atipik hemolitik üremik sendroma (HUS) bağlı olarak da gelişebilir. Pekçok klinik ve laboratuvar bulgusu örtüştüğü için, TTP ve HUS, sıklıkla preeklampsi veya HELLP Sendromu ile karıştırılır. Ancak bu noktada ayırıcı tanının acil olarak yapılması gerekir. Her iki durumda da, tanıda gecikme yaşamı tehdit eden komplikasyonlara yolaçabilir. Bu komplikasyonlar arasında, böbrek yetmezliği, nöbet, stroke, akciğer ödemi, yaygın damar içi pıhtılaşma (DIC), kan transfüzyonu, yoğun bakım ünitesine kabul ve ölüm sayılabilir (3). Ayrıca, HELLP Sendromu ve preeklampsi hastalarında, gebeliğin sonlandırılması ile beraber aşikar bir şekilde klinik iyileşme izlenirken, TTP için plazma değişimi, HUS içinse, ekulizumab tedavisi gerekecektir (4).

OLGU SUNUMU

21 yaşında, takipsiz, bilinen sistemik hastalık öyküsü bulunmayan, ultrasonografi (USG) muayenesine göre, 24 hafta tekil gebeliği olan hasta, bulantı, kusma, burun kanaması şikayeti ile başvurdu. TA: 110/ 70, nabız: 85/ dk idi. Herhangi bir obstetrik patoloji saptanmayan ancak şiddetli trombositopenisi (plt: 9000/ uL) olan hastanın, Hb: 13 g/ dl, plt: 9000/ uL, ALT: 12 U/ L, AST: 40 U/ L, Albumin: 2,47 g/dl, total protein: 4,62 g/ dl, kreatinin: 0,83 mg/dl, total biluribin: 0,27 mg/dl idi. Hematoloji tarafından immün trombositopeni ön tanısı ile, 1 ünite (Ü) aferez ve 1 Ü havuzlanmış trombosit transfüzyonu ve 32 mg/ gün prednol tedavisi uygulandıktan sonra, plt: 36000/ uL idi. Hematoloji tarafından, idame prednol tedavisi verilerek, 10 gün sonra kontrol önerisiyle taburcu edildi. Hasta hematoloji kliniğine kontrole geldiğinde, plt: 6000/ uL idi ve obstetrik kontrolü de istenen hastada, fetal kalp atımı izlenmemesi üzerine, kadın doğum kliniğine terminasyon için yatırıldı. Hastanın öyküsünde 1 haftadır makroskopik hematürisi olduğu ancak bunun için doktora başvuruda bulunmadığı öğrenildi. Vital bulgular: TA: 130/ 80, nabız: 98/ dk, ateş: 36 0C idi. Fizik muayenesi sırasında vücudunda peteşi ve purpura izlenmedi. Hb:6,7 g/ dl, plt: 6000/ uL, total biluribin 0,88 mg/ dl, ALT: 28 U/ L, AST: 70 U/ L, LDH: 2297 U/L, haptoglobin <10 mg/dl, INR: 0,94, albumin: 2,47 g/dl, kreatinin: 0,83 mg/dl, direct coombs: negatif, indirect coombs: negatif, TİT: protein 4+, lökosit: 11, eritrosit> 400 idi. Periferik yaymada fragmente eritrositler mevcuttu. Hastaya mikroanjioptik hemolitik anemi tanısıyla, 4 Ü aferez trombosit, 3 Ü ES, 30gr İVİG, 120 mg prednol uygulandı. Plt 59000/uL olduğunda vakit kaybedilmeden doğum indüksiyonuna (Foley sonda ile intrauterin balon takılması, oral misoprostol, IV oksitosin) başlandı. İndüksiyon sırasında, hasta başında plazmaferez işlemi yapıldı ve 6 saat sonra vajinal yolla doğum gerçekleşti. Postpartum 3 saatlik takip sonrasında herhangi bir komplikasyon izlenmeyen hasta, ileri tetkik ve araştırma için hematoloji kliniğine devredildi. Hastaya hematoloji kliniğinde, TTP tanısıyla, 19 kez plazmaferez ve IV steroid tedavisi verildi; tedaviye cevap alınan hasta, şifa ile taburcu edildi. Yatışı sırasında, dış laboratuvara gönderilen ADAMTS 13 numune sonucunun, 10 gün sonra, uygunsuz numune olarak raporlandığı öğrenildi.

TARTIŞMA

Amerikan Obstetrisyen ve Jinekologlar Koleji' nin (ACOG), 2013 yılında, preeklampsi için tanı kriterlerini revize ettiğinden beri, şiddetli preeklampsi tanısı için, proteinürinin bulunması gerekli değildir. Şiddetli preeklampsi sırasında, endotel hasarı ilerledikçe, mikroanjiopatik hemolitik anemi ve trombositopeni ortaya çıkabilir (2). Yine ilk kez 1982' de Dr. Louis Weinstein, tarafından tanımlanan HELLP Sendromu' nda da, yüksek karaciğer enzimleri, aspartat transaminaz (AST) ve alanin transaminazın (ALT) normalin üst sınırının iki katından fazla yükselmesi ve trombositopeninin (< 10000 /µl) yanısıra mikroanjiyopatik hemolitik anemi görülmektedir (5). Günümüzde HELLP vakalarının %15-20' sinin hipertansiyon veya proteinüri olmaksızın meydana geldiği tahmin edilmektedir ve genellikle, hastalarda, bulantı/ kusma, sağ üst kadranda veya epigastrik bölgede karın ağrısı gibi ek belirti ve semptomlar vardır (6). İlk tanımlanan HELLP vakalarında dissemine intravasküler koagülasyon sık bir bulgu değilken, günümüzde, doğum sonu kanama, plasenta dekolmanı veya fetal ölüm durumlarının eşlik etmesiyle oldukça sık rastlanan bir durumdur (7). HELLP Sendromu' na eşlik eden hemoliz için aşağıdakilerden bir veya daha fazlasının olması gerekir: 1. mikroanjiyopatik hemolitik anemiyi düşündüren anormal periferik yayma (örn., şistositler); 2. toplam bilirubin > 1,2 mg/dl; 3. laktat dehidrogenaz (LDH) > 600 U/L; 4. haptoglobin < normalin alt sınırı(8). Hemolizin tespit edilmesi, HELLP Sendromunu' nu teşhis etmek veya ekarte etmek için gerekli ve önemlidir. Hemoliz olmayan kadınlarda, trombotik mikroanjiopati beklenmez ve böyle durumlarda, ayırıcı tanıda, gebeliğin akut yağlı karaciğeri düşünülebilir (9). Coombs pozitif hemoli-

zi olanlarda da otoimmün hemolitik anemi düşünülebilir (10). Hastamızda tansiyon arteryel ölçümleri, klinik takibi boyunca normaldi. Yine karaciğer fonksiyon testlerinde iki kat yükselme izlenmedi. İndirect ve direct coombs testleri de negatif idi. Bu nedenle, hastanın hastaneye yatırılarak izlendiği tüm takiplerinde, preeklampsi veya HELLP Sendromu ile uyumlu klinik ve laboratuvar bulgusu izlenmemiştir.

Hemolitik üremik sendrom (HÜS), mikroanjiyopatik hemolitik anemi, trombositopeni ve akut böbrek hasarı ile karakterizedir. Kanlı diyare öyküsü, tipik HÜS tanısı için, önemli bir semptomdur ve hastalığa Shiga toksin üreten Escherichia coli neden olur. Ancak atipik HÜS varlığında da, diyare, bulantı, kusma olabilir (11). Atipik HÜS vakalarında, akut böbrek hasarı hemen her zaman mevcuttur ve yüksek serum kreatinin, atipik HÜS tanısı için en önemli kriterdir (12). Atipik HÜS' ü ortaya çıkaran neden olarak, kompleman aktivasyonunu düzenleyen genlerdeki mutasyonlar ve buna bağlı kontrolsüz kompleman aktivasyonu suçlanmaktadır. Kompleman düzenleyicilere karşı inhibitör antikorlar da tanımlanmıştır (13, 14). HÜS tanısı için bu mutasyonların veya kompleman inhibisyon antikorlarının (anti-CFH) tanımlanması gerekli değildir. Yine bazı durumlarda da aşırı kompleman aktivasyonu tetiklenebilir. Bunlar arasında en önemli nedenler, gebelik, organ nakli, sistemik lupus eritematozus veya malignite sayılabilir. Eğer gebelikte veya doğum sonrasında ortaya çıkarsa, gebelikle ilişkili atipik HÜS (p-aHÜS) olarak adlandırılır. Literatür incelendiğinde, p-aHÜS sıklıkla preeklampsi, plasenta dekolmanı, fetal ölüm veya doğum sonu kanama gibi obstetrik komplikasyonlar sonrasında ortaya çıkan vaka sunumları şeklindedir. Ancak komplike olmayan doğumlardan sonra da ortaya çıkabilir (15). Hastalığın kliniğinde göze çarpan en belirgin durum, özellikle en çok karıştırılan HELLP Sendromu ve şiddetli preeklampsi ile karşılaştırıldığında, HÜS'da, çok daha şiddetli izlenen, akut böbrek hasarını işaret eden laboratuvar bulgularıdır (hiperkreatininemi, oligüri veya anüri) (16). Bu nedenle, özellikle serum kreatinin> 1.1 mg/dl ve serum LDH> 1000 U/L ise, atipik HÜS tanısı düşünülmelidir. HÜS tanısını destekleyen diğer faktörler hastanın özgeçmiş veya soygeçmişinde HÜS öyküsü, yüksek LDH: AST oranı (>10:1) veya düşük hemoglobin (<8.0 g/dl) olmasıdır. Yüksek bir LDH: AST oranı, karaciğer tutulumu ile orantısız eritroist hemolizini gösterir. Hemoglobin düzeyi, hemokonsantrasyon nedeniyle şiddetli preeklampsi ve HELLP Sendromu' nda normal izlenebilirken, HÜS' de tipik olarak çok düşüktür. Ayrıca 1000 U/L' nin üzerindeki LDH değerleri de atipik HÜS' te sık görülürken, HELLP Sendromu' nda daha az sıklıkta görülür (6, 17). Atipik HÜS klasik olarak karaciğer enzim yüksekliği ile ilişkili olmasa da gebelikle ilişkili atipik HÜS ile ilgili çok sayıda vakada, HELLP' e benzer AST veya ALT yükselmeleri tanımlanmıştır (18, 19). Bu nedenle, AST veya ALT yüksekliği, HUS veya TTP için tanısal incelemeyi engellememelidir. Vakamızda karaciğer fonksiyon testlerinde yükselme izlenmedi. HELLP ve şiddetli preeklampsili hastalarda, obstetrik komplikasyonlar olmadığı sürece, doğum sonrasında hızlı iyileşme gözlenirken, HÜS' da serum kreatininde, sıklıkla, 4 mg/dl üzerinde, dramatik ve hızlı artışlar ve hastada açıklanamayan hızlı kötüleşme ortaya çıkar. Nedene yönelik tedavi mümkün olmadığında veya dirençli vakalarda, komplemen blokajı yapan ekulizumab verilmelidir. Ekulizumabın, uzun süreli prognoza olumlu etkisi vardır (12). Bu nedenle, her ne kadar ilk basamak tedavide, tanı kesinleşene kadar sıklıkla, plazmaferez ve/ veya kortikosteroidler denense de tanının daha fazla geciktirilmeden, ekulizumab tedavisine geçilmesi, anne morbiditesini azaltabilir (20). Vakamızda, hemoglobin düzeyi çok düşse de oligüri izlenmedi; kreatinin, üre, AST ve GFR normal sınırlar içinde kaldı. LDH: AST oranı da düşük idi. Özellikle renal hasar bulgusunun ve HÜS öyküsünün bulunmaması ve diyare semptomu olmaması nedeniyle, HÜS tanısından uzaklaşıldı.

TTP, mikroanjiyopatik hemolitik anemi, trombositopeni, ilişkili purpura veya kanama, nörolojik anormallikler, ateş ve böbrek fonksiyon bozukluğu (hematüri ve/ veya proteinüri veya yüksek kan üre azotu) beşlisi ile karakterize olmakla beraber, gerçekte, hastaların sadece %20-30' u, bu klasik beşli ile başvurur. Hematolojik olmayan bulguların tutarsızlığı nedeniyle, mikroanjiopatik hemolitik anemi ve trombositopeninin varlığı, TTP şüphesini artırmalı ve tedaviye başlamak için gecikilmemelidir. Günümüzde, trombositopeni ve mikroanjiyopatik hemolitik aneminin varlığı (artmış LDH, azalmış hemoglobin ve haptoglobin vb.) TTP' nin olası teşhisi için yeterlidir. Ayrıca renal replasman gerektiren böbrek yetmezliği, TTP' nin tipik bir özelliği değildir. Oysa, ayırıcı tanıda en çok karıştırılan, HUS mikroanjiopatik hemolitik anemi, plazma disintegrin- metalloproteinaz-trombospondin tip1- 13 (ADAMTS13) >10 IU/dL ve baskın böbrek hasarı olan trombositopeni kliniği ile tanımlanır. HUS' de, trombositopeni TTP' deki kadar şiddetli olmayabilir ve başvuru anında anemi değişken olabilir (21). TTP ile ilişkili maternal mortalite, plazma değişiminin hemen başlatılmasıyla, %90' dan, hızlıca, %10' un altına düşürülebilir(22). Bu nedenle ayırıcı tanı vakit kaybedilmeden, hızla yapılmalı ve plazmaferez tedavisine bir an önce başlanmalıdır.

Trombositopeni şiddetli preeklampsi, HELLP, TTP ve atipik

HÜS için ortak bir bulgudur. Ancak çok derin trombositopeni, özellikle trombosit sayısı <30.000/µl olduğunda, TTP için şüphe uyandırmalıdır(23). Hemolitik anemi ve trombositopeni ile beraber anormal ADAMTS13 aktivitesi (<%10) olan kadınlarda, mutlaka TTP düşünülmeli ve geç kalmadan plazmafereze başlanmalıdır.

SONUÇ

Gebelikte trombositopeni ve hemoliz için en sık nedenler HELLP sendromu ve şiddetli preeklampsi iken, diğer nedenlerden, TTP ve HÜS, daha nadir ortaya çıkar ve bu da bu durumların tanısında ve spesifik tedavide gecikmeye yolaçabilir. Klinik tablo beklenmedik bir şekilde, yaşamı tehdit eden komplikasyonların ortaya çıkmasına doğru evrilebilir. Bu nedenle, gebe takibi yapan hekimlerin, gebelikte hemolizin diğer nedenlerinden haberdar olması ve ağır trombositopeni ile hastaneye başvuran gebe hastalarda, ayırıcı tanıda, TTP ve HÜS' u gözönünde bulundurmaları önemlidir.

TTP ve HÜS şüphesi olan hastaların, kadın doğum, hematoloji, neonataloji, nefroloji ve yoğun bakım uzmanlarından oluşan, anne ve bebeğin hayatta kalma şansını artıracakları, multidisipliner yaklaşımla tedaviyi sağlayan üçüncü basamak merkezlere, mümkün olan en hızlı şekilde sevk edilmesi gerekir.

Hastadan bilgilendirilmiş onam alınmıştır.

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Sperm Kryopreservasyonunda Epigenetik Değişiklikler

Epigenetic Changes in Sperm Cryopreservation

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ÖZ

Spermatozoa kriyoprezervasyon teknolojisi, erkek fertilitesi için en çok kullanılan koruma protokolüdür. Erkek doğurganlığının yönetimi, kanser tedavisi, vazektomi veya cerrahi infertilite tedavilerinden önce donör spermlerini depolamak ve korumak için kullanılmaktadır. Epigenetik yeniden programlamanın embriyonik gelişimde hayati bir rol oynadığı bildirilmiştir ve birkaç çalışma, kusurlu epigenetik yeniden programlamanın anormal fetal büyüme, kanser ve diyabet gibi hastalıklar ile ilişkili olduğunu göstermiştir. Yapısal ve fizyolojik değişikliklerin yanı sıra, spermatozoadaki gen ve proteinlerin ekspresyonunun, mRNA stabilitesinin ve epigenetik içeriğin donma-çözme işleminden etkilenebileceği bildirilmektedir. Dondurulmuş-çözülmüş spermatozoadaki bu değişiklikler doğurganlık potansiyelini ve embriyo gelişimini etkileyebilmektedir. Kriyoprezervasyonda toksisite, epigenetik stabilite, mikrobiyal kontaminasyon gibi birden fazla güvenlik sorunu vardır. Bu sorunlardan epigenetik stabilite ve dondurulmuş spermatozoa ile doğan çocukların sağlığı üzerindeki kriyoprezervasyonun etkileri hakkında çok az bilgi vardır. Bu derlemede, kriyoprezervasyon sırasında spermlerdeki değişiklikler ve epigenetik modifikasyonları hakkındaki makaleler özetlenmiştir.

Anahtar kelimeler: Sperm Kryopreservasyonu, Epigenetik, Yardımcı Üreme teknolojileri

ABSTRACT

Spermatozoa cryopreservation technology is the most widely used preservation protocol for male fertility. Cryopreservation of human sperm is used to store and preserve donor sperm prior to male fertility management, cancer treatment, vasectomy or surgical infertility treatments. Epigenetic reprogramming has been reported to play a vital role in embryonic development, and several studies have shown that defective epigenetic reprogramming is associated with diseases such as abnormal fetal growth, cancer, and diabetes. In addition to structural and physiological changes, it has been reported that the expression of genes and proteins in spermatozoa, mRNA stability and epigenetic content may be affected by freeze-thaw process. These changes in frozen-thawed spermatozoa can affect fertility potential and embryo development. There are multiple safety issues in cryopreservation, such as toxicity, epigenetic stability, and microbial contamination. Of these issues, little is known about the effects of cryopreservation on epigenetic stability and the health of children born with frozen spermatozoa. In this review, articles on changes in sperm and their epigenetic modifications during cryopreservation are summarized.

Keywords: Sperm Cryopreservation, Epigenetics, Assisted Reproductive Technologies

GİRİŞ

Spermatozoa kriyoprezervasyon teknolojisi, erkek fertilitesi için en çok kullanılan koruma protokolüdür. Kriyoprezervasyon prosedürlerinde büyük gelişmeler olmasına rağmen bazı olumsuzluklar çözüm beklemektedir. Bunlardan en önemlisi, taze spermatozoa kullanılan siklusa kıyasla donmuş-çözülmüş spermatozoa kullanılan sikluslarda daha düşük doğurganlık hızıdır. Bu nedenle, kriyoprezervasyon altında spermin hayatta kalmasının iyileştirilmesi ve donmuş spermatozoanın güvenliği endişe yaratmaya devam etmektedir (1).

Spermleri ilk olarak 1776'da Lazaro Spallanzani dondurarak saklamıştır. Hamilelik ve canlı doğum sağlayan insan spermlerinin ilk başarılı dondurularak saklanması 1953'te Sherman ve Bunge tarafından bildirilmiştir. Daha sonraki bu alandaki gelişmelerin ardından, donmuş-çözülmüş spermatozoadan, 1984'te in vitro fertilizasyondan (IVF), 1990'da intrauterin inseminasyondan (IUI), 1992'de subzonal inseminasyondan ve 1994'te intrasitoplazmik sperm enjeksiyonundan (ICSI) sonra gebelik elde edilmiştir (2).

İnsan sperminin kryopreservasyonu, erkek doğurganlığının yönetimi, kanser tedavisi, vazektomi veya cerrahi infertilite tedavilerinden önce donör spermlerini depolamak ve korumak için kullanılmaktadır. Kriyoprezervasyon sperm varlığını artırsa da, kriyoprezerve edilmiş spermin fertilizasyon potansiyeli, spermdeki yapısal ve fizyolojik değişiklikler nedeniyle tehlikeye girer. Dondurma işlemi sırasında, sıcaklıktaki ani değişiklikler, ozmotik stres ve buz oluşumu gibi çeşitli faktörlerin, çözüldükten

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sonra düşük sperm kalitesine yol açabileceği öne sürülmektedir. Ayrıca, donma-çözme işlemi sırasında artan reaktif oksijen türleri (ROS) üretimi, spermatozoadaki yapısal ve fonksiyonel değişikliklerin bir başka nedenidir (3). ROS üretimi, epigenetik hatalara yol açabilecek DNA metilasyonunu olumsuz yönde değiştirir (4).

Önceki çalışmalar, gametler ve preimplantasyon embriyolarının hem doğum öncesi hem de doğum sonrası gelecekteki büyüme ve gelişme potansiyelini etkileyebilecek çevresel koşullara duyarlı olduğunu göstermiştir. Böylece in vitro manipülasyonların, preimplantatif embriyoların gelişim potansiyellerini ve epigenetiklerini etkileyebileceği sonucu çıkarılmaktadır (5). Epigenetik yeniden programlamanın embriyonik gelişimde hayati bir rol oynadığı bildirilmiştir ve birkaç çalışma, kusurlu epigenetik yeniden programlamanın anormal fetal büyüme, kanser ve diyabet gibi hastalıklar ile ilişkili olduğunu göstermiştir (6).

Yapısal ve fizyolojik değişikliklerin yanı sıra, spermatozoadaki gen ve proteinlerin ekspresyonunun, mRNA stabilitesinin ve epigenetik içeriğin donma-çözme işleminden etkilenebileceği bildirilmektedir. Dondurulmuş-çözülmüş spermatozoadaki bu değişiklikler doğurganlık potansiyelini ve embriyo gelişimini etkileyebilir (3).

Kriyoprezervasyonda toksisite, epigenetik stabilite, mikrobiyal kontaminasyon gibi birden fazla güvenlik sorunu vardır (1). Bu sorunlardan epigenetik stabilite ve dondurulmuş spermatozoa ile doğan çocukların sağlığı üzerindeki kriyoprezervasyonun etkileri hakkında çok az bilgi vardır. Bu derlemede, kriyoprezervasyon sırasında spermlerdeki değişiklikler ve epigenetik modifikasyonları hakkındaki makaleler özetlenmiştir.

SPERMATOZOANIN YAPISAL ÖZELLİKLERİ

Memeli spermatozoası, temel olarak belirgin şekilde yoğunlaştırılmış bir çekirdek, çok az sitoplazma ve genel bir hidrodinamik şekle sahip son derece uzun bir kamçıdan oluşan en özel hücrelerden biridir (7). Sperm hücresinin temel işlevi, babanın genetik mirasını ve epigenetik bilgiyi embriyoya iletmektir. Daha da önemlisi, sperm kromatinindeki genlerin çoğunluğu protaminler tarafından yüksek oranda yoğunlaştırılırken, gelişimin ilk aşamalarında potansiyel olarak ihtiyaç duyulan genler, bir epigenetik işaretleme biçimini temsil eden histonlarla ilişkilidir (7).

Somatik hücrelerle karşılaştırıldığında, spermatozoa çok farklı bir kromatin yapısı ve organizasyonu barındırır. Spermdeki DNA, histonların büyük çoğunluğunun yerini alan ve altı kat daha yoğun bir DNA paketleme yapısına izin veren, spermatozoal DNA'yı hücre dışı stres faktörlerine karşı koruyan protaminlere bağlıdır. Spermatogenez sırasında protaminasyon, histonlar tarafından taşınan çoğu epigenetik bilginin çıkarılmasıyla sonuçlanır. Yine de kalan histon proteinleri önemlidir ve erken embriyonik gelişim için genleri dengeleyebilir (8).

Erkek gamet fonksiyonunu kontrol etmenin kilit bir unsuru, altta yatan genlerin aktivasyonuna veya baskılanmasına izin veren metilasyon, asetilasyon ve fosforilasyon gibi histonların translasyon sonrası modifikasyonunu (PTM) içerir. Histon PTM'leri, transkripsiyon, DNA onarımı, DNA replikasyonu ve kromozom yoğunlaşması gibi hücresel süreçleri yönetmede esastır (9).

Montjean ve ark. yaptıkları çalışmada global sperm DNA metilasyon seviyesinin sperm konsantrasyonu, sperm motilitesi ve sperm DNA bütünlüğü ile ilişkili olduğunu bildirmiştir. Düşük konsantrasyon ve düşük sperm motilitesinde global DNA metilasyon düzeyi düşük bulunmuştur (4,10).

SPERMATOZOA KRYOPREZERVASYONU

Semen kriyoprezervasyonu, Lazaro Spallanzani'den sonra Polge'nin gliserolün kriyoprotektan özelliklerini keşfetmesiyle ivme kazanmıştır. Bu çalışmalar, doğurganlığın korunması alanında bir dönüm noktası olmuştur. Bununla birlikte, sperm kriyobiyolojisindeki sayısız başarıya rağmen, kriyoprezervasyondan sonra canlı spermatozoayı optimal olarak geri kazanabilen yöntemler için araştırmalar devam etmektedir (11).

Semen kriyoprezervasyonunda, kriyoprotektan ve dondurma prosedüründe farklılık gösterebilen çeşitli protokolleri kullanılır, ancak çoğunlukla sperm koruma süreci nispeten birkaç adım içerir. İlk adım, suyun ozmoz yoluyla hareketiyle hücreyi dehidrate eden yüksek çözünen konsantrasyonları içeren bir kriyoprotektan eklenmesini içerir. Bu hücrelerin içindeki suyun uzaklaştırılması, donma ve çözme sırasında hücre tahribatına neden olan hücre içi buz kristali oluşumunu en aza indirmek için önemlidir. Kriyoprotektanlarla birlikte, buz oluşumuna veya yeniden kristalleşmeye bağlı olarak olası hücre içi su miktarını en aza indirmek için uygun soğutma ve ısıtma oranlarının uygulanması esastır (12).

Donma hasarı ile ilgili iki mekanizma vardır, birincisi hücreyi delip yok eden buz kristallerinin oluşumu, diğeri ise sıvı fazın bileşimindeki değişikliklere olan etkilerdir. Genel olarak, kryprotektanlar (CPA) toplam çözünen madde konsantrasyonunu arttırır ve oluşan buz miktarını azaltır (2).

EPİGENETİK

Epigenetik, genler ve fenotipi meydana getiren ürünleri arasındaki nedensel etkileşimleri inceleyen biyoloji dalıdır. Bugün bildiğimiz şekliyle epigenetik, mitotik ve/veya mayotik olarak kalıtsal olan ve DNA dizisinde bir değişiklik gerektirmeyen gen fonksiyonundaki değişikliklerin incelenmesi olarak tanımlanmıştır (13).

Epigenetik süreçler, DNA metilasyonunu, histon modifikasyonlarını ve kromatin yeniden şekillenmesini içerir. Bu modifikasyonların kısa veya uzun vadeli sonuçları olabilir ve mitotik olarak hücreden hücreye ve germ hattı yoluyla bir sonraki nesle aktarılabilir. Histonların etrafını saran DNA, kromatin modelinin bir parçası olan nükleozom oluşumu ile sonuçlanır. Özel DNA düzeni, bir genin transkripsiyonel olarak aktif mi yoksa sessiz mi olacağını belirler (9).

Embriyogenezin gelişim programı hem genetik hem de epigenetik mekanizmalar tarafından kontrol edilir. Epigenetik işaretler, DNA'nın ve bununla ilişkili kromatin proteinlerinin enzim aracılı kimyasal modifikasyonlarıdır. DNA'nın birincil dizisini değiştirmemelerine rağmen, genom fonksiyonunun düzenlenmesinde ve gelişmesinde önemli roller oynarlar. Genom çapında epigenetik yeniden programlama, döllenmeden hemen sonra zigotta başlayan ve preimplantasyon gelişiminin blastosist aşamasına kadar uzanan erken embriyoda meydana gelir (6).

Epigenetik, hangi genlerin, ne zaman ve hangi dokularda aktif olduğunu düzenlemede hayati bir rol oynayan DNA'nın kompaktlığını ve yeniden programlanmasını kontrol eder. Gametogenez ve erken embriyo gelişimi sırasında, iki terminal olarak farklılaşmış hücre (spermatozoon ve oosit) bir totipotent zigot oluşturmak üzere birleştikçe, hem erkek hem de dişi kalıtsal kromatine kapsamlı epigenetik modifikasyonlar eklenir. Gelişimin bu erken evresinde kromatine yapılan bu tür kapsamlı modifikasyonlar, memeli genomunu, DNA'ya, ilişkili proteinlere, kodlayan ve kodlamayan RNA'lara kovalent modifikasyonlar şeklinde gelebilen, çevresel olarak indüklenen epigenetik değişikliklere duyarlı hale getirir. Ağırlıklı olarak hayvan çalışmalarından elde edilen bulgular, bu tür değişikliklerin, gelişimsel süreçlerde, yetişkinlikte belirli hastalıklara yatkınlıkla birlikte doğuştan anormalliklerle sonuçlanan değişikliklerede yol açabileceğini göstermektedir (9).

Memelilerde DNA metilasyonu, çoğunlukla CpG dinükleotidlerinde sitozin kalıntılarının 5. karbonunda meydana gelir (13). CpG olmayan metilasyon, embriyonik kök hücrelerde ve bölünmeyen hücrelerde saptanır ve hücre tipine özgü fonksiyonları düzenler. CpG bölgeleri, CpG adaları olarak bilinen belirli genomik lokasyonlarda yüksek sıklıkta meydana gelir. Memelilerde, CpG adacıkları sıklıkla promotör bölgelerde bulunur ve genellikle metillenmezken, diğer CpG bölgeleri metillenir (3).

DNA metilasyonu, transkripsiyonel susturma ile ilişkilidir. Bununla birlikte, imprinting, X-kromozomu inaktivasyonu, tekrarlayan ve sentromerik dizilerin susturulması dahil olmak üzere diğer önemli moleküler işlemlerde kritik roller oynar. Kovalent histon translasyon sonrası modifikasyonları gibi diğer epigenetik mekanizmalar, histon proteinleri üzerindeki fonksiyonel grupların (asetil, metil, fosforil, sumoil) eklenmesi veya çıkarılmasıyla kromatin yapısını değiştirir. Histon modifikasyonları, DNA-kromatin bağlanmasını etkiler, böylece DNA stabilitesini ve transkripsiyon faktörlerine uygunluğunu değiştirir. Gen ekspresyon paternleri, kromatin yeniden şekillenmesi ve histon varyantlarının tanıtılması dahil olmak üzere kovalent olmayan histon modifikasyonlarından da etkilenebilir. Kodlamayan RNA'lar, genomik imprinting ve gen susturma, hücre kaderi kararları için gerekli olan diğer önemli epigenetik mekanizma örnekleridir. Bu nedenle epigenetik mekanizmalar, dondurarak saklamanın hücre kaderi kararları üzerindeki bazı etkilerini açıklamak için potansiyel bir mekanizma sağlar (13). DNA metilasyonu, beş DNA metiltransferazdan (DNMT'ler) oluşan bir protein ailesi tarafından kurulur ve korunur. Bunlar arasında, üç de novo DNMT (DNMT3A, 3B ve 3C) ve katalitik olarak aktif olmayan bir kofaktör (DNMT3L), genellikle bir CpG bağlamında sitozin metilasyonunun kurulmasından sorumludur (14).

Genomik damgalama, memeli genlerinin bir alt kümesini etkileyen ve ebeveyn monoalelik ekspresyon paterni ile sonuçlanan epigenetik bir fenomendir. Ebeveyn alellerini farklılaştırmak için, germ hücrelerinde DNA metilasyonu ve histon modifikasyonlarını içeren epigenetik işaretler başlatılır ve embriyonik gelişim ve doğum sonrası yaşam süresi boyunca korunur. Son zamanlarda yapılan çalışmalar, sperm kriyoprezervasyonunun epigenetik bozukluklarla ilişkili olup olmadığı sorusuna cevap vermeye başlamıştır. Ancak kriyoprezervasyonun spermdeki epigenetik modülasyon üzerindeki etkileri ve olası epigenetik değişikliklerin donmuş spermatozoa ile doğan çocukların sağlığı üzerindeki etkileri hakkında sınırlı bilgi mevcuttur. Bazı çalışmalar kriyoprezervasyonun insan sperm genlerinin DNA metilasyon paternini etkileyemeyeceğini bildirmiş olsa da, diğer araştırmaların sonuçları bu çalışmalarla tutarlı değildir (3).

KRYOPRESERVASYONUN SPERMLERDEKİ EPİGENETİK DEĞİŞİKLİKLERİ

Kryopreservasyonun spermler üzerine etkileri serbest oksijen radikallerin artışı, membran hasarı, DNA fragmentasyonu, can-

lılığın azalışı, apoptosis, hücre iskelet hasarı, motilite azalması, fertilizasyon yeteneğinin azalması, mitokondri hasarı ve epigenetik değişiklikler olarak sıralanabilir. Sperm kriyoprezervasyonu, membran geçirgenliği, motilite, metabolizma, apoptoz, kapasitasyon ve fertilizasyon ile ilgili çeşitli hücresel süreçlerde yer alan proteinleri değiştiren fiziksel değişiklikleri indükler (2).

Kriyoprezervasyon, sperm transkriptomu ve proteomiklerinde moleküler bozukluklara yol açabilecek ani ozmotik ve sıcaklık değişikliklerini içerir. Mevcut kriyoprezervasyon protokollerini optimize etmek için kriyoprezervasyon sırasında bu moleküler bozuklukların tam olarak anlaşılması esastır. Epigenetik ile ilgili olarak, daha önceki çalışmalar, dondurarak saklamanın motilite, kapasitasyon, oosit bağlama yeteneği ve akrozom reaksiyonu gibi temel sperm fonksiyonlarında yer alan spesifik genlerin profillerini değiştirdiğini göstermiştir (1).

Spermatozoanın genleri ve protein ekspresyonu, mRNA stabilitesi ve epigenetik içeriğinin donma-çözme işlemi sırasında modüle edildiği düşünülmektedir. Kriyoprezervasyon, doğurganlık potansiyeli ile ilgili anahtar genlerin (SNORD116/PWSAS ve UBE3A) ekspresyonunu etkileyebilir (11).

Son zamanlarda, sperm hücrelerinde dondurma işlemi sırasında meydana gelebilecek bazı epigenetik modifikasyonları açıklamaya başlayan başka çalışmalar da vardır. Flores ve arkadaşları, kriyoprezervasyondan sonra domuz spermatozoası baş kısmında nükleoproteinik yapı değişikliklerini göstermişlerdir. Bunlar histon H1-DNA bağlayıcı proteinler ve protein-DNA disülfit bağlarındaki değişiklikleri içermektedir (17). Zeng ve arkadaşlarının bir çalışmasında, DNMT3A, DNMT3B, JHDM2A, KAT8, PRM1, PRM2 ve IGF2 gibi epigenetik ile ilgili genlerin ekspresyonunun donma öncesi ve sonrasında değişebileceğini ve farklı kriyoprotektif ajanların eklenmesi, domuz spermatozoasındaki epigenetik ile ilgili genlerde donma veya kriyoprezervasyon kaynaklı ekspresyon değişikliklerine karşı daha iyi koruma sağlayabileceği belirtmiştir (16). Başka bir çalışma, kriyoprezervasyonun, anne tarafından transkribe olan LIT1, SNRPN ve MEST gibi insan sperm genlerinin DNA metilasyon modelini ve ayrıca baba tarafından transkribe edilen MEG3 ve H19 genlerini etkilemediğini bildirdi (11).

Spermatozoa, döllenme sırasında oosite paternal mRNA verir ve bu nedenle erken embriyo gelişiminde önemli bir rol oynar. Ayrıca, dondurma işlemi sırasında, spermatozoadaki transkriptler ve mRNA-protein etkileşimleri kaybolabilir ve bu da embriyo gelişimini doğrudan etkileyebilir. Sperm mRNA'sı ile erken gelişim arasındaki korelasyonlar insanlarda ve bazı hayvanlarda bildirilmiştir. Kriyoprezervasyonun insan sperm fertilitesi ile ilgili birkaç anahtar transkript (PRM1, PRM2, PEG1/MEST ve ADD1) ifadesini azalttığı gösterilmiştir (11).

Dondurma ve çözme, sperm mRNA'sının transkripsiyonunu kısmen değiştirebilir ve mRNA'lar ile proteinler arasındaki etkileşimi engelleyerek embriyoların erken gelişimini etkileyebilir. Hayvan deneylerinde, sperm histon modifikasyonu ve metilasyonu gibi birçok epigenetik değişiklik, çözmeden sonra gözlenmiştir (15) . Dondurulmuş hücrelerde histon H3 ve H4 asetilasyonunda önemli azalma tespit edilmiştir. Ayrıca, kriyoprezervasyon, aktif olarak kopyalanan genlerle ilgili bir değişiklik olan H3K4me3 seviyesini azaltır; ve transkripsiyonel baskı ile ilgili bir modifikasyon olan H3K27me3 seviyesini arttırır (3).

Dondurarak saklama sırasında sperm nükleer DNA'sının zarar görmesiyle ilgili endişelere rağmen, donmuş spermle döllenmiş yavrularda genetik veya fenotipik anomalilerde doğrulanmış bir artış tanımlanmamıştır. Spermdeki oksidatif stres, erken embriyonik gelişim sırasında epigenetik yeniden programlamayı etkileyebilir (3).

Mikro-RNA, mRNA translasyonunu etkiler ve miR-22 ve miR-450b-5p, taze spermatozoa ile karşılaştırıldığında kriyoprezervasyondan sonra spermatozoada önemli ölçüde down-regüle edilir. Bu epigenetik değişiklikler, donma-çözme işleminden etkilenen spermatozoa hareketliliği ve doğurganlığındaki düşüşün ana nedeni olabilir (1).

DNA metiltransferazlar (DNMT) tarafından oluşturulan metilasyon işaretlerini bozabilecek kriyoprezervasyon kaynaklı stres ve kriyoprotektan toksisitesi nedeniyle DNA değişiklikleri ve epigenetik mutasyonlar üretilebilir. ROS, DNMT ekspresyonunun up regülasyonuna veya bölgeye özgü hipermetilasyon ile sonuçlanan yeni bir DNMT içeren kompleks oluşumuna neden olabilir (4).

SONUÇLAR

Son yıllarda yapılan çalışmalar IVF/ICSI tedavilerini takiben doğan bebeklerde, anormal plasentasyon, düşük doğum ağırlığı veya yüksek doğum ağırlığı gibi epigenetik düzensizlik ile ilişkili olabilecek, olumsuz perinatal sonuç riskinin arttığını bildirmektedir. Bu çalışmalara rağmen, epigenetik bozuklukların sıklığını arttırmada infertilite nedeninin mi yoksa ICSI, kryopreservasyon gibi yöntemlerin mi rol oynadığını göstermek zordur (9).

Kriyoprezervasyon sırasında aşırı ROS üretiminin sperm kalitesi üzerinde zararlı etkileri vardır. Anormal sperm önemli bir serbest radikal kaynağı olduğundan, kriyoprezervasyon işleminin neden olduğu ROS seviyesi anormal spermde morfolojik olarak

normal spermden daha yüksek olabilir. Oksidatif stresin, DNA, histonlar ve histon değiştiricileri etkileyerek hücrelerin epigenetik durumunu etkileyebileceği düşünülmektedir (3).

DNA metilasyonundaki kriyoprezervasyonla ilgili değişikliklerin, kriyoprezervasyon ve/veya laboratuvar teknikleri ile ilgili protokollerin bir özelliği mi yoksa spermatogenez sırasında spermde neden olan epigenetik kusurlar mı olduğu henüz belirlenmemiştir. Bu tekniğin güvenliğini sağlamak için sperm kriyoprezervasyon protokollerini optimize etmenin, girdi DNA metilasyon hatalarının oluşmasını önlemek için ihtiyati bir yaklaşım olarak kabul edilebileceği görülmektedir. Ayrıca, sperm kriyoprezervasyonunun kullanımı küresel olarak arttığından, kriyoprezervasyon sonuçlarının çok merkezli, uzun vadeli bir takip çalışmasının yürütülmesi ve inprinting hatalarıyla ilgili daha fazla sayıda hastalığın değerlendirilmesi için daha fazla çalışma yapılmalıdır (4).

Kriyoprezervasyonun sperm DNA metilasyonu üzerindeki etkisi hakkında kesin bir sonuca varmak için, kriyoprezervasyon işleminin aynı koşulları altında daha büyük numune boyutlarına sahip multiklinik çalışmalara ve DNA metilasyon analizine ihtiyaç vardır.

Özetle, yardımcı üreme tekniklerinde sperm motilite ve fertilizasyonu tehlikeye atan durumların sperm kriyoprezervasyonu ile ilişkisi giderek artan çalışmalarla gösterilmiştir. Kryopreservasyonun epigenetik modifikasyonlar üzerinde meydana getirdiği değişiklikler açıktır. Bu yüzden sperm kryopreservasyon işleminin standartları belirlenmeli ve olası sonuçları hakkında hastalara danışmanlık verilmelidir.

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