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Original Article

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Randomized controlled study of intradermal sterile water injection and intradermal lidocaine injection in obstetric analgesia

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ABSTRACT

Aims: In today's world, the increasing desire for normal and uninterrupted delivery in pregnant women has brought the need to combat labor pain and non-pharmacological techniques to the agenda again. These methods should be reconsidered in order to increase their analgesia effectiveness and to popularize their use.

Methods: In our study, intradermal sterile water (SW) injection technique, which is one of the non-pharmacological techniques, was used and the effects of intra-injection saline and lidocaine were compared. 128 patients were included in our study, and 64 patients were injected with intradermal SW and 64 patients were injected with intradermal lidocaine to provide analgesia. During labor follow-up, durations of labor phases, dilatation and effacement rates were recorded, along with Visuel analoque scale (VAS) scoring and delivery type, episiotomy application, operative delivery, cesarean section, and apgar data. At the end of the delivery, the patient's satisfaction with the procedure, the degree of pain reduction and her willingness to use this method again were questioned and recorded.

Results: Between groups, statistically significant results such as 1st hour dilatation ($p = 0.02$), 30th minute VAS ($p = 0.02$), were obtained. No maternal and fetal side effects were recorded during the study, and no significant difference was found in terms of cesarean delivery episiotomy and neonatal outcomes.

Conclusion: Lidocaine injection can be considered superior to SW injection because its positive effect on VAS score lasts longer.

Keywords: Obstetric analgesia, intradermal injection, non-pharmacological pain control techniques

INTRODUCTION

Labor pain is one of the most severe causes of pain ever defined and one of the most important components of intrapartum care is to support the pregnant woman in the control of this pain. Although birth pain is physiological, it is considered to be unbearable and has created a fear of labor pain that pregnant women think they cannot tolerate due to its social and social environment, and has led to requests for elective cesarean section.

Muscle hypoxia due to contractions, lactic acidosis, stretching and opening of the lower uterine segment, and stretching of ligaments can be shown as the cause of labor pain. In the second stage of labor, women make mentions of a sharp and continuous abdominal pain.[1] In the late first stage and second stage, the descent of the fetus and the stretching of the vagina and perineum tissues also cause pain.[2]

Ideal analgesia for delivery should be safe for mother and baby, preferably noninvasive, without adverse effects on labor. Many pharmacological and non-pharmacological techniques have been tried with these searches. Pharmacological modern analgesia was first developed in 1947 by Dr. Simpson using ether and chloroform. And then until today, many methods such as epidural, spinal, paracervical pudental have been tried.[3,4] Today, epidural analgesia is used by pregnant women and doctors in many clinics. However, side effects such as nausea, urinary retention, numbness and decreased ability to strain, and prolongation of the labor phases have been reported.[5-9]

In addition, many non-pharmacological methods have been tried until today. Massage, hot and cold compresses, transcutaneous electrical nerve stimulation (TENS) and

intradermal sterile water injections (SWI) are considered to be the main ones. The advantages of these techniques are that they are easily accessible, inexpensive and have a low side-effect profile.[10,11]

Intradermal injection has been reported as a highly effective and easy-to-use method in many studies.[12,13] The effect of intradermal injection on labor pain is explained by Gate control theory (GCT). Intradermal blisters formed by injections reduce pain by activating large-diameter fibers carrying the sense of touch and inhibiting small-diameter fibers carrying the pain message. Theory of melzack and wall on pain percetion mentions that non-painful input closes nerve gates to other painful inputs and prevents pain sensation.[24]

A cochrane study of labor pain control, the effects of intradermal and subdermal sterile water injections were compared with a control group. The results of seven studies with 766 samples were analyzed. Four studies assessed intradermal injection, two studies assessed subdermal injection, and one study assessed both intradermal and subdermal injections of sterile water. Sterile water injection reduced labor pain by at least 50%, while the placebo reduced labor pain by 20%.[14]

In some studies, SWI has been reported to be effective in reducing labor pain as well as reducing cesarean section rates. In a multicenter study conducted on 1.866 women who gave birth in Australia, it was found that intradermal injection of 0.1- 0.3 cc sterile water applied to the sacral region significantly reduced the rate of cesarean section.[25]

Previous studies have reported that the effect of intradermal sterile water injection occurs rapidly, but is short-lived, and needs to be repeated.[12-15]

We have thus designed a study to reevaluate the analgesic efficacy of intradermal injection. We planned to apply intradermal lidocaine injection to our patients in order to eliminate the feeling of discomfort and pain in the injection sites mentioned in the studies in which SWI was applied and to see its effect on the duration of analgesia.

METHODS

The study was carried out with the permission of the İstanbul Zeynep Kamil Women and Children Diseases Training and Research Hospital Ethics CommitteeAll procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Our study was planned as a prospective randomized controlled study on pregnant women with 3-5 cm cervical dilatation, who entered the active phase of labor and applied to the Obstetrics Clinic in İstanbul Zeynep Kamil Research and Education Hospital between February 2016 and March 2016. Multiple pregnancies, pregnancies with malpresentation, pregnancies who were not between 37-42 weeks of gestation, who had undergone uterine surgery, and pregnant women with systemic disease and CPD examination were not included in the study. 128 pregnant women were included in our study.

Demographic, clinical and biochemical findings of the cases were recorded. Before the procedure, fetal heart rate monitoring was applied to each patient and it was determined that there was a reactive heart beat pattern. In addition, the amplitude, frequency and duration of uterine contractions were determined. After the hospitalization of our patients, it was decided which group to be included in the computer-based randomization system and included in the study. In our study, our patients were divided into two groups. The first group received intradermal SW injection, and the second group received intradermal lidocaine injection, at the injection site from 1 to 10. Amniotomy with appropriate obstetric indications and induction of labor with oxytocin were applied to the patients whose birth follow-up was performed by the delivery room team in both groups. Patients who entered the active labor phase and stated that they had low back pain, injections were given the special region. The region in the shape of an equilateral quadrangle, which is located among posterior superior iliac spines, gluteal muscles, and spinous process of vertebra L4; 3 cm lower and 1 cm medial from superior iliac spines and spines were marked. Injections were given to both groups simultaneously and at the peak point of contractions by obstetricians. The process was terminated when 4 small bullae were observed on the waist. VAS (visual analogue scale) scoring was performed for low back pain before the procedure was performed on the patient.

Visual analogue scale (VAS): the VAS is a 10 cm (100 mm) ruler on which the patient marks the pain, with painlessness on one end and excruciating pain on the other. The patient is told that there are two endpoints and that he or she should mark anywhere between these points that matches the severity of the pain. The distance between the point where the patient marked the pain and the pain-free interval is measured in cm and recorded. It is stated that the VAS has a high sensitivity and reliability in the measurement of pain severity.[26]

Afterwards, if the patient did not give birth at 15-30-60-120-180 minutes, the VAS score was asked again and the vaginal examination was performed and recorded. The delivery of the patient was done by the team working in the delivery room. Type of delivery, gender, weight, 1st and 5th minute APGAR scores, and effects and complications during delivery were recorded. The postpartum patient was asked to rate her satisfaction with the procedure, whether she would like to use this procedure if she gave birth again, and her discomfort

While evaluating the findings obtained in the study, SPSS version 17 program was used for statistical analysis. While evaluating the study data, in addition to descriptive statistical methods (mean, standard deviation), student's t test was used for comparison of normally distributed parameters between groups in comparison of quantitative data. Paired sample t-test was used for within-group comparisons of normally distributed parameters. chi-square test and fisher's exact chi-square test were used to compare qualitative data. The

results were evaluated at the 95% confidence interval and the significance level of p<0.05.

RESULTS

In this double-blind study, considering the exclusion criteria, intradermal injections of 64 sterile water and 64 lidocaine were applied to 128 pregnant women in total. In the results obtained, there was no difference between the groups in demographic data (Table 1).

Table 1. Demographic characteristics of the groups

	SW n: 64 mean ± SD	Lidocaine n: 64 mean± SD	p
Age	24.5 ±5.3	24.5±5.5	0.9
Length	161.4±5.7	161.03±5.5	0.9
Weight	71.4±8.7	73.5±9.8	0.4
Gravity	1.9±1.1	1.6±1.0	0.3
Parity	0.53±0.9	0.50±0.7	0.9
GW	39.4±1.33	39.4±1.31	0.9
Duration of education	7.2±3.5	6.5±3.6	0.5

GW: Get well soon, SW: Sterile water, n: Number, SD: Standard Devision

During the evaluation, it was determined that there was no statistical difference between the two groups in terms of dilatation (p=0.15) and effacement (p=1) during the application, and in terms of VAS scores before the procedure (p=0.72)

Patients with a training period of <8 years and >8 years were divided into two groups. Our patients, who were divided into two groups according to their education levels, were compared with each other in terms of the scores they gave to VAS scores and their compliance scores during labor and no statistically significant results were found (p>0.05).

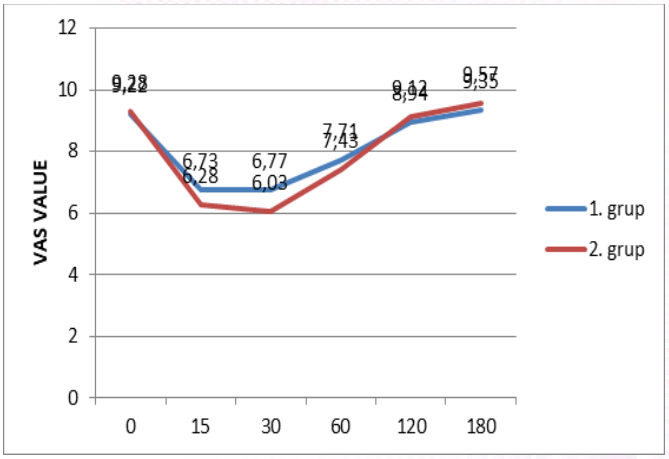

Figure 1. The VAS Score distribution between the groups

87.5% of our study patients mentioned a significant reduction in low back pain within 15 minutes after intradermal injection of lidocaine. While this analgesic effect at a rate of 91.9% reached the 30th minute, 75.4% of the pregnant women felt the analgesia effect in 60 minutes, unlike the 1st group study patients. 14% of pregnant women who did not give birth and continued labor felt the analgesia effect at 180th minute. Our patients stated that their pain started again after an average of 70 minutes. Comprasion of Vas scores between two groups are shown in Table 2 and Figure 1. Also obstetric and neonatal outcomes have been compared for both groups in Table 3.

Table 2. Comparison of VAS scores

	SW n mean ± SD	Lidocaine n mean± SD	p
Application VAS	9.22 ± 1	9.28 ±1	0.72
15.Min VAS	6.73 ±1.88	6.28 ±1.82	0.17
30.Min VAS	6.77±1.74	6.03±1.79	0.02*
1. Hour VAS	7.71±1.64	7.43±1.71	0.35
2. Hour VAS	8.94±1.16	9.12±1.30	0.50
3. Hour VAS	9.35±0.93	9.57±0.73	0.36
Vas Diff. 15. Min.	-2.41±1.92	-2.68±1.78	0.40
Vas Diff. 30. Min.	-2.45±1.79	-3.24±1.78	0.01*
Vas Diff. 60. Min.	-1.53±1.68	-1.83±1.60	0.32
Vas Diff. 120 Min.	-0.37±1.31	0.08±1.60	0.37
Vas Diff. 180 Min.	0.10±1.02	0.45±1.17	0.24

Diff: Difference, n: Number, SD: Standard Devision

Table 3. Comprasion of obstetrical and neonatal outcomes

	SW	Lidocaine	P
Dilation cm during application	4.89	4.69	0.15
1.Hour dilation cm	6.98	6.30	0.02*
2.Hour dilation cm	7.66	7.08	0.13
3.Hour dilation cm	8.25	7.44	0.14
Labor induction	%87.5	%93.8	0.46
Amniotomy	%30.6	%39.1	0.93
Episiotomy	%62.5	%73.4	0.44
Caesarean	%4.7	%4.7	0.55
Operative Birth	%3.1	%7.8	0.06
Baby weight (gr)	3199	3248	0.8
Apgar 1.	7.77	7.86	0.3
Apgar 2.	8.88	8.91	0.6
Total	64	64	

SW: Sterile water

At the end of the birth, a mini-questionnaire was arranged for the patients, and they were asked to score from 1 to 10 on the scales, the degree of satisfaction, the degree of pain relief and the desire to use the same method again, and it was recorded. There was no significant difference between the two groups in these parameters (p>0.05). In the previous studies, for the discomfort and pain sensation at the injection site, 24.7% of the patients in the SW group, whose VAS scoring was performed, described pain at the injection site, while 21.4% of the patients in the lidocaine group described a pain. No significant difference was found between the groups in the analysis.

DISCUSSION

Fear of labor pain increases the rates of elective cesarean section and also creates negative situations on active labor. It has been reported that obstetric analgesia reduces both maternal and perinatal morbidity rates.[27] Ideal analgesia for childbirth should be safe for both mother and baby, preferably noninvasive, without adverse effects on labor. Although the ideal analgesia method with all these features has not been developed yet, the search continues. Today, non-

pharmacological obstetric analgesia techniques have come to the fore again due to the patients' search for natural birth, and the need to develop new techniques has been felt.

Intradermal water block (0.5-.1 ml) consists of 4 small sterile water bubbles into the skin. One is placed on the posterior superior iliac spine, the other two are placed 3 cm below. In the studies, It is mentioned that intradermal SW injection is painful and uncomfortable during the injection and it causes severe pain for 30 seconds.[28,29] The other common problem mentioned is that the analgesia effect is short-lived. We planned this study by considering reducing the feeling of discomfort during the injection and increasing the duration of the analgesia effect with intradermal lidocaine injection instead of intradermal SW injection.

In randomized studies, the effects of intradermal water blocks application and alternative non-pharmacological methods (TENS, activity massage, bath) on pain in the lumbar region at birth were compared. In all studies, intradermal water block application was found to significantly reduce low back pain.[23] It was found that the relief in pain continued for 120 minutes when the application was not repeated, and most of the women wanted the application to be repeated.[30] In Fogarty's (2008) review, it was found that sterile water for intradermal injection had a strong analgesic effect on low back pain at birth and its use did not cause any side effects.[23] In addition, the same study found the effect of the application on fetal rotation, pelvic floor muscles and cervical dilatation. Similar results were found in our study. In both groups, over 80% of the patients were relieved at the 15th minute, and a significant decrease in VAS scores was observed. It was found that the patient who was injected with lidocaine in the 2nd group at 30 minutes was statistically superior to the 1st group in terms of pain relief (p=0.01). While 91% of the 2nd group patients described a decrease in VAS scores compared to the first minute, 83% of the 1st group patients mentioned a decrease in their VAS scores. Intradermal SW injection also contributed to cervical dilatation in our study. The 1st group 1st hour cervical dilatation was found to be higher than the 2nd group and it was statistically significant (p=0,02).

In a similar randomized study of 272 cases, Trolle, Moller, Kronberg, and Thomsen (1991) reported that a remarkable analgesic effect was noted in the experimental group administered sterile water injection, even 1 and 2 hours after administration, compared to the placebo control group.[19] In the same study, it was stated that no side effects of the technique were observed, and that the mothers were satisfied with the application and that they would like to use the method again in case they give birth again.[19] Similar results were obtained in our study. While the analgesic effect was still continuing in 66% of the patients in the 60th minute VAS scoring, and lower VAS values were recorded in the group using SW, 75% of the patients in the 2nd group still mentioned analgesia effectiveness at the 60th minute. No maternal-fetal side effects were recorded during our study, and no difference was found between Apgar scores, operative delivery rates and cesarean delivery rates. In the satisfaction scales, the results were recorded as follows: 68.8% of the patients in the 1st group stated that they were satisfied with the procedure by giving a score of 6 and above on the satisfaction scale, and 64.2% of them gave a score of 6 or higher for the question of whether they would like this procedure if they gave birth again. 71.9% of the patients in the 2nd group stated that they were satisfied with the procedure by giving a score of 6 and above on the satisfaction scale, and 64.1% of them gave a score of 6 or above to the question of whether they would like this procedure if they gave birth again.

Martensson and Wallin, in their review of eight randomized controlled trials on 828 women, found that SWI administration was associated with significantly reduced cesarean rates.[18] In our study, the cesarean rates for both groups were the same, and they were similar to the primary cesarean rates in our hospital. Birth patterns according to hours between two groups are shown in Figure 2. While there are no studies on intradermal lidocaine injection, it can be considered superior to SW injection because its positive effect on VAS score lasts longer and its analgesia efficiency is more pronounced.

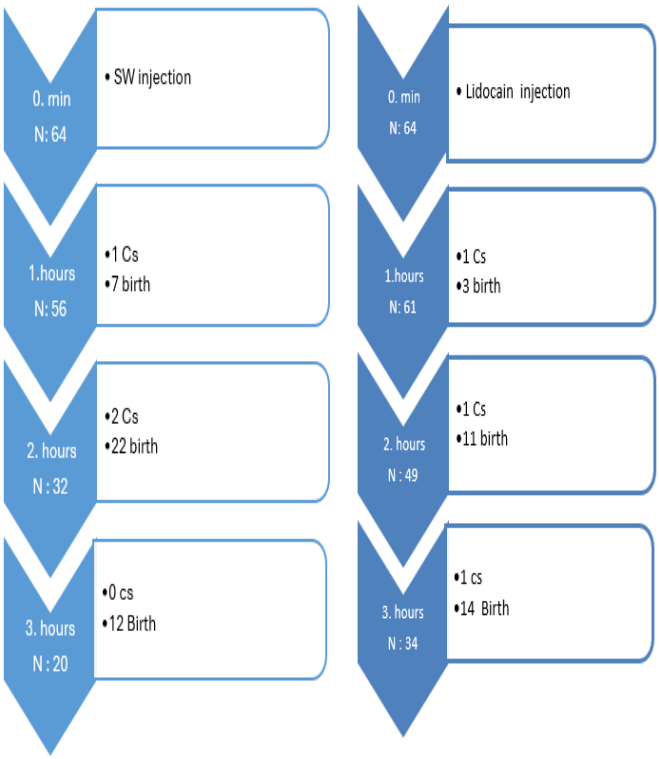

Figure 2. Birth patterns according to hours between two groups

CONCLUSION

Although there are many studies in the literature investigating non-pharmacological applications for the control of labor pain, no study has been found on pain control with intradermal lidocaine injection. As a result of the present study, both SWI application and intradermal lidocaine injection cause a significant decrease in pain scores, it is preferred by women, and most of them will use it again if necessary. The most important thing is that it significantly reduces the low back pain experienced at birth without any side effects on the fetus and mother. For these reasons, SWI or intradermal lidocaine injection may be preferred more as a non-pharmacological pain control method used to reduce low back pain during labor. It was concluded that more studies could be designed for pain control related to intradermal lidocaine injection.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the İatanbul Zeynep Kamil Women and Children Diseases Training and Research Hospital Ethics Committee

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

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Is vitamin D level important in pregnant women with COVID-19?

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ABSTRACT

Aim: The COVID-19 pandemic started in Wuhan City, Hubei Province, China in late December 2019. In our study, we aimed to evaluate the effectiveness of vitamin D levels on the clinic of the disease, laboratory findings, severity of the disease and, length of hospital stay by grouping pregnant patients with a diagnosis of COVID-19 according to their vitamin D levels.

Methods: A total of 125 patients were included. According to the vitamin D levels of the patients at the time of hospitalization, two groups were determined as below and above 20ng/ml, which is the limit of vitamin D deficiency. The patients in these two groups were compared in terms of demographic features, clinical findings, laboratory findings, imaging findings, hospitalization times and need for intensive care.

Results: When evaluated according to serum 25 hydroxyvitamin D level, patients' fever, pulse, oxygen saturation, the severity of lung involvement in computed tomography, hospitalization there was no statistically significant difference between the groups in terms of duration and need for intensive care. When the laboratory parameters of the patients at hospitalization were compared according to serum 25 hydroxyvitamin D levels, there was no statistically significant difference between the two groups in terms of any laboratory parameter. As a result of the analysis, only lymphocyte count was determined as the independent variable affecting the severity of lung involvement in thorax CT (Computed tomography). As the lymphocyte count decreased, the severity of involvement in thorax CT increased.

Conclusion: Our study showed that vitamin D level did not have a significant relationship with any of the parameters related to COVID-19 such as clinical and laboratory findings, severity of the disease and duration of hospitalisation. It is also supported by our study that the decrease in lymphocyte counts is associated with severe COVID-19 disease.

Keywords: Vitamin D, pregnancy, COVID-19

INTRODUCTION

Cases of pneumonia of unknown etiology were reported in Wuhan city, Hubei Province, China in December 2019 and it was observed that the disease spread rapidly. Fever, shortness of breath and cough were the common features of the cases. It was determined that those who died from the disease were mostly elderly patients with comorbidities. As a result of the studies carried out to identify the agent, it was observed that the disease agent was a new type of coronavirus similar to Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV), and its name was determined as 'Severe Acute Respiratory Syndrome coronavirus 2' (SARS-CoV-2), and the disease was called 'COVID-19' as an abbreviation of the words 'Coronavirus disease 2019.[1] The disease spread all over the world in a short time and was declared a pandemic by the World Health organization (WHO) on 11 March 2020.[2]

According to WHO data, more than 263 million cases and more than 5 million deaths were reported until December 2021, and it is estimated that the actual number of cases and deaths is much higher than reported.

SARS-COV-2 is a single-stranded, enveloped RNA virus. It is a zoonotic virus and is transmitted by droplet. It binds to the cells it will infect with angiotensin converting enzyme-2 (ACE-2) receptor.[3] The most common symptoms of the disease are fever, cough and malaise. The most common laboratory findings are lymphopenia, elevated C-reactive protein (CRP) and elevated erythrocyte sedimentation rate. The clinical presentation of patients varies as asymptomatic, mild disease, severe disease and critical disease. The severity of the disease is associated with advanced age, comorbidities

(diabetes, hypertension, obesity, chronic kidney disease, chronic respiratory diseases, malignancies) and male gender.[4,5] So far, there is no antiviral treatment with proven efficacy. Physiological changes that occur during pregnancy make pregnant women more vulnerable to viral infections. Although it was thought that pregnant women survived the COVID-19 disease more mildly at the beginning of the pandemic, as a result of extensive studies conducted in the following periods, it was stated that the disease had a more severe course in pregnant women compared to non-pregnant women and caused more deaths.[6,7]

Immunomodulatory activity of vitamin D is known. It decreases proinflammatory cytokines (T helper 1, Interleukin-2, TNF alpha and Interferon gamma) and increases antiinflammatory cytokines (Interleukin 4, Interleukin 5 and Interleukin 10). This has been thought to be preventive and therapeutic against the hyperinflammation state called 'cytokine storm', a complication of COVID-19 disease. Vitamin D also increases the production of antimicrobial peptides such as cathelicidin and defensin. Especially cathelicidin shows antiviral activity by acting on the envelopes of viruses. This feature has shown that vitamin D is protective against respiratory tract viruses.[8-12]

In our study, we aimed to evaluate the effects of vitamin D levels of pregnant patients diagnosed with COVID-19, who were grouped according to vitamin D levels, on the clinic, laboratory findings, severity of the disease and duration of hospitalisation.

METHODS

The study was carried out with the permission of the Gazi Yaşargil Training and Research Hospital Non-Interventional Clinical Researches Ethics Committee (Date: 27/07/2021 Decision No: E-58146266) and Dicle University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee (Date: 27/05/2021 Decision No: 339). All procedures were carried out in accordance with the ethical rules and principles of the Declaration of Helsinki.

Our study was conducted between March 2020 and January 2021 on pregnant patients hospitalised due to COVID-19 disease in Dicle University Faculty of Medicine Pandemic Hospital and Diyarbakır Health Sciences University Gazi Yaşargil Training and Research Hospital Gynecology and Obstetrics Clinic (ward or intensive care unit).

Our study was a retrospective study and patient data were obtained from patient files obtained from the archives of the hospitals. A total of 125 patients from Dicle University Faculty of Medicine and Diyarbakır Health Sciences University Gazi Yaşargil Training and Research Hospital were included in our study.In our study, according to the vitamin D levels of pregnant patients hospitalised due to COVID-19 in both hospitals at the time of hospitalisation, two groups were determined as below and above the vitamin D deficiency limit of 20ng/ml. Age (years), trimester of pregnancy, gravidity and parity, body mass index (BMI) (kg/m^2), vital signs; fever, pulse rate, arterial blood pressure (mm/hg), oxygen saturation, severity of involvement on thorax CT (mild, moderate, severe), whether they needed intensive care, which treatment was given, duration of hospitalisation (days), laboratory values during hospitalisation and discharge; CRP, D-dimer, INR, ferritin, troponin I, procalcitonin, MPV, PLT, WBC, lymphocyte, monocyte, eosinophil, haemoglobin and platelecrit were compared.

Inclusion Criteria For Our Study;

- Having a live, intrauterine pregnancy confirmed definitively by ultrasonography.
- Having a positive COVID-19 RT-PCR test result or a negative test result but diagnosed as COVID-19 with thorax CT, clinical and laboratory findings.
- Patients do not have other chronic diseases that may affect their clinical course and vitamin D levels (hypertensive diseases, diabetes mellitus, heart diseases).

Vitamin D levels of our patients were determined by measuring 25 hydroxyvitamin D level in blood. A 2cc blood sample was collected in a biochemistry tube. Vitamin D was measured with Shimadzu's HPLC 20AT device. Results were given as ng/ml. All laboratory variables except serum 25 hydroxyvitamin D were measured both at admission and discharge, 25 hydroxyvitamin D was measured only at hospitalization. Laboratory values at hospitalization and discharge were compared. Pregnancy and gestational age of our patients were determined by last menstrual period (LMP), previous ultrasonography (USG) data and fetal USG measurements with GE Voluson E8 Ultrasound device (year of manufacture 2015). The lung involvement of COVID-19 in the thorax CT scans of our patients was divided into 3 categories as mild, moderate, and severe involvement as determined by radiology units. The clinical course of our patients was evaluated according to the follow-up of vital signs, duration of hospitalization and the need for intensive care. The classification of the disease as mild or severe was not done due to the fact that the physicians working in our clinics were constantly changing due to the pandemic working order and that a standardization could not be achieved due to the two different hospitals.

COVID-19 diagnoses of our patients were determined according to the COVID-19 RT-PCR test results of Dicle University Faculty of Medicine Microbiology Laboratory and Diyarbakır Provincial Health Directorate Public Health Laboratory. 115 patients with positive test results and 10 patients with negative test results but whose thorax CT, clinical symptoms and laboratory findings were compatible with COVID-19 disease were included in the study.

Statistical Analysis

The conformity of continuous variables to normal distribution was analysed by Shapiro-Wilk test. Continuous variables were expressed using mean ± standard deviation or median (minimum-maximum) values. According to the results of the normality test, mann whitney U test and Independent Paired sample t test were used for comparisons between groups. Categorical variables were analysed using chi-square test, fisher's exact chi-square and fisher-freeman-halton tests. The difference score value was calculated in order to examine the change in the final measurements compared to the initial measurements, and intergroup comparisons of these

measurements were made using the mann-whitney U test and the independent paired sample t test. Wilcoxon signed ranks test and dependent sample t test were used to compare laboratory values at hospitalisation and discharge. Linear regression analysis was performed to investigate the factors that may be effective on length of hospitalisation. As a result of the univariate linear analysis, those with a p value less than 0.250 were included in the multiple linear analysis test. Among the correlated values, those with clinical significance were included in the analysis. An ordinal regression analysis was performed to investigate the factors that may be effective on the severity of lung involvement in thorax computed tomography. Among the highly correlated values, only those with clinical significance were included in the analysis.For statistical analyses, SPSS (IBM corp. released 2012. IBM SPSS statistics for windows, version 21.0. armonk, NY: IBM Corp.) programme was used and type I error level was accepted as 5% in statistical analyses.

RESULTS

Of the 125 pregnant patients included in the study, the median age was 29 years. 15-43 C ovid-19 virus PCR test positivity was detected in 115 (92%) of a total of 125 patients. The results of computerised thorax tomography were graded as mild, moderate and severe according to the severity of the findings. Demographic data and clinical features of the patients are shown in Table 1.

Patients were divided into two groups as lower than 20 ng/ml and higher than 20 ng/ml according to serum 25 hydroxyvitamin D level. There was no statistically significant difference between these groups in terms of age, BMI, trimester of pregnancy, number of gravities and parities, fever, pulse rate, oxygen saturation, COVID-19 virus PCR test positivity, severity of lung involvement on computerised thoracic tomography (Figure 1), lenght of hospitalisation (Figure 2) and need for intensive care (Table 2).

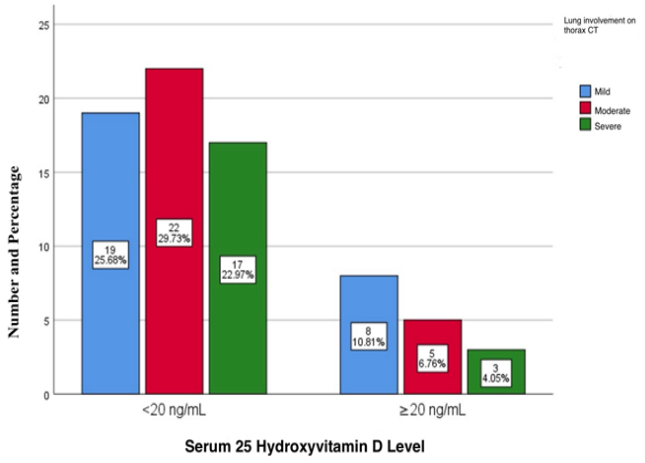

Figure 1. Severity of lung involvement on thorax CT according to serum 25 hydroxyvitamin D level grouping

When the laboratory parameters of the patients at the time of hospitalisation were compared according to serum 25 hydroxyvitamin D level grouping, there was no statistically significant difference between the two groups in terms of any laboratory parameter.

Table 1. Age, BMI averages, trimester of pregnancy, parity and clinical characteristics of the patients

Parameter	Values (n=125)
Age (years)	29.3±6.0
BMI (kg/m2)	22.1 (18.3-34)
Pregnancy trimester (n=124)	
I	18 (%14.4)
II	17 (%13.6)
III	89 (%71.2)
Gravidity (n=116)	
1	11 (%8.8)
2	19 (%15.2)
≥3	86 (%68.8)
Median value	3 (1-8)
Parity (n=116)	
0	16 (%12.8)
1	29 (%23.2)
2	36 (%28.8)
≥3	35 (%28)
Median value	2 (0-7)
Fever (°C) (n=123)	36.5 (36-39)
Pulse rate (/dk) (n=120)	88 (70-135)
Oxygen saturation (%) (n=123)	98 (78-100)
PCR positivity	115 (%92)
Severity of lung involvement on thorax CT (n=74)	
Mild	27 (%21.6)
Moderate	27 (%21.6)
Severe	20 (%16)
Lenght of hospitalisation (days) (n=123)	5 (0-35)
Intensive care needs	18 (%14.4)

Non-normally distributed data are expressed as median (minimum-maximum). normally distributed data are expressed as mean±st deviation and n (%). BMI: Body mass index

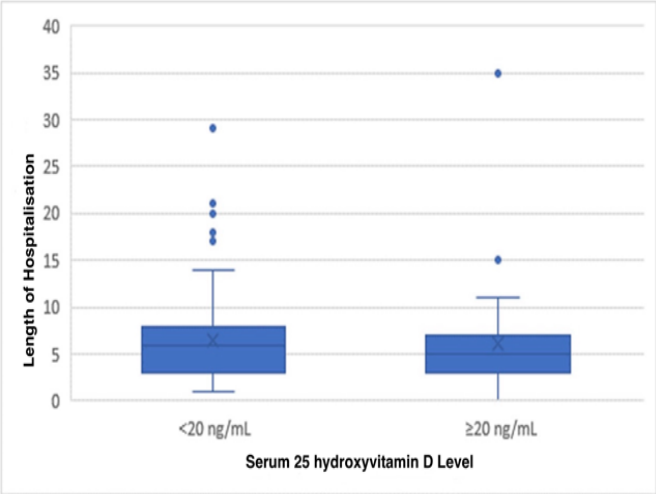

Figure 2. Lenght of hospitalisation according to serum 25 hydroxyvitamin D level grouping

Although CRP and D-dimer levels were lower in pregnant women with serum 25 hydroxyvitamin D levels ≥20ng/ml compared to those with levels below 20 ng/ml, this difference was not statistically significant.When we compared the laboratory values of the patients at hospital discharge according to serum 25 hydroxyvitamin D level grouping, there was no statistically significant difference between the two groups in terms of any laboratory value. Pregnant women with low serum 25 hydroxyvitamin D levels had

higher discharge CRP levels than the others. However, this difference was not statistically significant. In addition, no statistically significant difference was found between the serum 25 hydroxyvitamin D level groups in the change in hospitalisation and discharge laboratory values (Table 3).

Tablo 2. Comparison of age, mean BMI, trimester of pregnancy, parity and clinical findings of the patients according to serum 25 hydroxyvitamin D level grouping

	Serum 25 Hydroxyvitamin D level		p
	<20 ng/ml (n=89)	≥20 ng/ml (n=36)	
Age (years)	28 (15-43)	30 (18-40)	0.776m
BMI (kg/m2)	22.3 (18.3-34)	22.1 (19-29)	0.476m
Pregnancy trimester (n=124)			
I	11 (%12.5)	7 (%19.4)	
II	13 (%14.8)	4 (%11.1)	0.566X²
III	64 (%72.7)	25 (%69.4)	
Gravidity (n=116)			
1	5 (%6)	6 (%18.2)	
2	15(%18.1)	4 (%12.1)	0.116X²
≥3	63 (%75.9)	23 (%69.7)	
Median value	3 (1-8)	3 (1-7)	
Parity (n=116)			
0	8 (%9.6)	8 (%24.2)	
1	23 (%27.7)	6 (%18.2)	
2	29 (%34.9)	7 (%21.2)	0.089X²
≥3	23 (%27.7)	12 (%36.4)	
Median value	2 (0-7)	2 (0-5)	
Fever (°C) (n=123)	36.5 (36-39)	36.5 (36-39)	0.360m
Pulse rate (/dk) (n=120)	88 (70-135)	87 (75-125)	0.146m
Oxygen saturation (%) (n=123)	97 (78-100)	98 (91-100)	0.486m
PCR positivity	81 (%91)	34 (%94.4)	0.723f
Severity of lung involvement on thorax CT (n=74)			
Mild	19 (%32.8)	8 (%50)	0.429X²
Moderate	22 (%37.9)	5 (%31.3)	
Severe	17 (%29.3)	3 (%18.8)	
Lenght of hospitalisation (days) (n=123)	6 (1-29)	5 (0-35)	0.478m
Intensive care needs	15 (%16.9)	3 (%8.3)	0.219X²

Non-normally distributed data are expressed as median (minimum-maximum), normally distributed data as mean±SD and n (%). m Mann-Whitney U test, X² Chi-square test, f Fisher-Freeman-Halton test. CT: Computed tomography

Enoxaparin Sodium was given to 71.2% (n=89), lopinavir/ritonavir combination to 56% (n=70), hydroxychloroquine sulphate to 8% (n=10), oseltamivir to 4% (n=5). When the treatments administered to the patients were compared according to serum 25 hydroxyvitamin D levels, no statistically significant difference was found between the groups in any of the treatments. Enoxaparin sodium was the most frequently given treatment in both groups. EAS a result of the analysis performed for the factors affecting the lenght of hospitalisation, oxygen saturation and severity of lung involvement on thorax CT were determined as independent variables affecting the duration of hospitalisation (Table 4).

As the severity of lung involvement on thorax CT increased and oxygen saturation decreased, the duration of hospitalisation increased. (Y (length of hospitalisation)= 39.427-(0.460x saturation)+(1.071x severity of AC uptake on thorax CT)

Table 3. Comparison of the changes in the laboratory values of the patients at hospitalisation and discharge between serum 25 hydroxyvitamin D level groups.

	Serum 25 hydroxyvitamin D level		p
<20 ng/mL (n=89)		≥20 ng/mL (n=36)	
Hemoglobin (g/dL) (n=118)	-0.5 (-4.30:2.1)	-0.4 (-3.30:1.4)	0.730m
White blood cell count (10^9/L) (n=118)	0.99 (-10.34:23.97)	0.46 (-7.54:15.49)	0.790m
Lymphocyte count (10^9/L) (n=118)	0.3 (-0.69:2.39)	0.33 (-0.64:1.75)	0.728m
Monocyte count (10^9/L) (n=119)	0.11 (-0.42:0.64)	0.1 (-0.22:10.67)	0.905m
Eosinophil count (10^9/L) (n=119)	0.01 (-0.16:0.4)	0.03 (-0.07:0.28)	0.614m
Platelet count (10^9/L) (n=118)	40 (-133:464)	25 (-43:180)	0.808m
Mean platelet volume (fL) (n=117)	-0.2 (-2.60:1.4)	-0.1 (-1.30:1.4)	0.222m
PCT (%) (n=99)	-1.7 (-14:9.3)	-2.80 (-8.90:7)	0.784m
C-reaktive protein (mg/dl) (n=116)	-4.75 (-175.70:102.2)	-5.7 (-107:16.7)	0.436m
D-dimer (ng/mL) (n=93)	-97 (-1916:10503)	-84 (-2621:3892)	0.798m
Ferritin (uq/L) (n=99)	1 (-228:1934)	-2 (-202:117)	0.408m
Troponin I (ng/ml) (n=31)	0 (-0.07:0.05)	0 (-0.04:0.01)	0.884m
Procalsitonin (ng/ml) (n=114)	-0.01 (-2.12:8.04)	-0.02 (-0.57:12.88)	0.803m
INR (n=114)	0 (-0.55:0.65)	0 (-0.12:0.35)	0.594m
Eosinophil/Monocyte ratio (n=119)	0.04 (-0.24:1.71)	0.04 (-0.09:0.56)	0.394m

Non-normally distributed data are expressed as median (minimum-maximum). normally distributed data as mean ± standard deviation and n (%). m Mann-Whitney U test, † Independent Paired Sample t Test., PCT: Plateletcrit

Table 4. Variables affecting length of hospitalisation

Variables	Univariate linear regression			Multiple linear regression		
	B	Std. Error	p	B	Std. Error	p
Age	-0.003	0.077	0.967			
BMI	0.309	0.197	0.120	0.141	0.213	0.512
Severity of Lung involvement on thorax CT	2.174	0.549	<0.001	1.071	0.501	0.034
Fever	2.110	0.571	<0.001	0.162	0.495	0.744
Saturation	-0.472	0.135	0.002	-0.460	0.125	<0.001
25 Hydroxyvitamin D	-0.048	0.048	0.314			
Lopinavir/ritonavir use	3.168	0.879	<0.001	0.860	1.078	0.429
Hydroxychloroquine sulphate	-0.558	1.758	0.751			
Oseltamivir use	1.453	2.316	0.532			
Enoxaparin sodium	2.485	0.990	0.013	2.209	1.393	0.118
C-reactive protein	0.027	0.012	0.024	0.012	0.010	0.239
D-dimer	0	0	0.492			
Troponin I	-11.529	10.988	0.296			
Mpv	-0.316	0.364	0.387			
Platelet count	-0.004	0.006	0.568			
Lymphocyte count	-2.238	0.906	0.015	-0.960	0.800	0.235
INR	1.385	3.386	0.683			
PCT	0.017	0.042	0.690			
Eosinophil/Monocyte ratio	-3.692	3.553	0.301			

Adjusted R Square= 0.339, Constant= 39.427. Laboratory values at the time of hospitalisation were taken as laboratory values. CT: Computerised tomography, BMI: Body mass index. Mpv: Mean platelet volume, PCT: Plateletcrit. B: Regression coefficient, Std: Standard

As a result of the analysis performed to determine the variables affecting the severity of lung involvement on thorax CT, only lymphocyte count was determined as the independent variable affecting the severity of lung involvement on thorax CT (Table 5). As the lymphocyte

count decreased, the severity of lung involvement on thorax CT increased.

Table 5. Variables affecting the severity of lung involvement on thorax CT.

		Prediction	Wald	95% CI	p
Threshold values	Lung involvement severity=1	-5.325	0.462	-20.675 - 10.025	0.497
	Lung involvement severity=2	-3.424	0.192	-18.736 - 11.889	0.661
Variables	Age	-0.014	0.105	-0.095 - .068	0.745
	Trimester of pregnancy	0.161	0.237	-0.488 - 0 .811	0.626
	25 Hydroxyvitami D	-0.020	0.482	-0.075 - 0.036	0.487
	C-reactive protein	0.004	0.390	-.009 - 0.016	0.532
	D-dimer	0.000	1.044	.000 - 0.001	0.307
	Saturation	-0.027	0.114	-0.187 -	0.132
	Eosinophil/ Monocyte ratio	-6.142	3.441	-12.631 - 0.348	0.064
	Lymphocyte count	-1.399	4.898	-2.638 -	-0.160

Model fit test (pearson) p= 0.559, Parallel curves assumption test p=0.939. Laboratory values were taken as laboratory values at the time of hospitalisation., CI: Confidence interval

DISCUSSION

Although most of the studies in the literature examining the relationship between vitamin D and COVID-19 argue that vitamin D has a positive effect on infection, disease severity and mortality, there are also studies claiming the opposite. In the meta-analysis conducted by Chen et al,[13] studies involving a total of 536,135 patients until 5 June 2021 were analysed. It was stated that the average age of the patients in the studies was between 49 and 69 years, most studies were conducted in America, 5 studies in Europe, 1 study in Asia and 1 study in Australia. Vitamin D deficiency was accepted as <20ng/ml and insufficiency as 20-30ng/ml, and it was determined that low vitamin D level did not increase the risk of COVID-19 infection and mortality. It was found that each 10ng/ml increase in serum vitamin D level had no effect on infection and mortality, and vitamin D supplementation did not reduce the need for intensive care and mortality. In the study conducted by Hastie et al.[14] the data of 343.484 patients uploaded to the United Kingdom Biobank database were analysed and the relationship between vitamin D level and COVID-19 disease was investigated. It was found that the severity and mortality of COVID-19 disease were associated with advanced age, male gender, black race, obesity and diabetes mellitus, but not with vitamin D level.

Studies have shown that patients with severe COVID-19 disease have lower blood lymphocyte counts compared to other patients.[15] It is thought that the progressive decrease in lymphocyte count may be an early clinical indicator of severe COVID-19 disease.

In the meta-analysis conducted by Meng et al.[16] by analysing 24 studies including 3547 patients, comorbidities, major symptoms, laboratory findings that may be associated with the severity of the disease in patients diagnosed with COVID-19 were tried to be determined. In the study, the rate of severe disease was found to be 30%. 54% of the cases consisted of male gender. As a result of meta-analysis of 24 studies, the most common clinical symptoms were found to be fever 80% and cough 59%. The most common comorbidity was hypertension 19%, diabetes 9%, cardiovascular disease 8%. Patients with chronic respiratory diseases, chronic kidney disease and cardiovascular diseases were found to have a higher risk of progression to severe disease. The common laboratory findings of the patients included in the study were leucopenia, lymphopenia and elevated CRP. Two groups were defined as severe and non-severe disease. The most significant difference between the groups was measured as CRP and CRP values in the severe disease group were found to be 1.66 higher on average than in the non-severe group. Neutrophil/ Lymphocyte ratio and Erythrocyte Sedimentation Rate were also found to be higher in the severe disease group. In a review of 30 studies including 5570 patients, Wang et al.[17] found that the Neutrophil/Lymphocyte ratio was higher in patients with severe disease and its sensitivity and specificity were 82% and 77%, respectively. In our study, similar to the results of this review, we found that the number of lymphocytes decreased as the severity of COVID-19 involvement increased in pregnant women undergoing thoracic CT and the result was statistically significant (p=0.027).

In the study conducted by Sinaci et al.[18] in our country, vitamin D levels of patients hospitalised and planned for treatment due to COVID-19 were found to be statistically significantly lower. In the same study, a statistically significant relationship was examined between the severity of COVID-19 disease and vitamin D level, and accordingly, vitamin D level was found to be significantly higher in patients in the moderate and severe COVID-19 group compared to patients in the mild COVID-19 group. In contrast to the data in this study, no statistically significant finding was found when data that may indicate the course of the disease such as the need for intensive care, COVID-19 involvement in thoracic CT scans, laboratory values, and hospitalisation times of the patients were compared between the two groups with vitamin D levels below and above 20 ng/ml in our study. Although the need for intensive care was 16.9% in the group with vitamin D below 20 ng/ml and 8.3% in the group with vitamin D above 20 ng/ml, this data was not statistically significant.

In the meta-analysis conducted by Oscanoa et al.[19] the relationship of vitamin D with the severity of COVID-19 disease and mortality was investigated. The mean age of the patients was 60.8 years and 53.8% were male. In 17 studies, it was found that 25 hydroxyvitamin D levels below 20 ng/ml were associated with an increased risk of severe COVID-19 disease, and in 13 studies it was associated with increased mortality. 7 studies included CRP values and all of them had values >10mg/L. 7 studies showed that male gender had a higher risk of disease severity and mortality compared to females. Similarly, in 3 studies included in the meta-analysis conducted by Pereira et al.[21] it was found that 25 Hydroxyvitamin D level below 20 mg/ml increased the risk of hospitalization and mortality increased in 5 studies. In the meta-analysis conducted by Kazemi et al.[20] it was found that there was no relationship between vitamin D level and the need for intensive care. In a meta-analysis of more than 10 thousand cases aiming to determine the causes of severe disease in COVID-19 infection, including 61 studies by Fang et al.[22] it was found that advanced age, male gender and the presence of comorbidities (hypertension, diabetes, cardiovascular disease, cerebrovascular disease, chronic obstructive pulmonary disease, hepatitis B disease) were each

directly related to the severity and prognosis of COVID-19 disease. It was found that chronic kidney disease was the comorbidity that increased mortality the most, and chronic obstructive pulmonary disease was the comorbidity that led to the need for intensive care and mechanical ventilation the most.

In this study, no significant difference was found between the groups with vitamin D levels above 20 ng/ml and below 20 ng/ml in terms of the need for intensive care. The effect of vitamin D level on mortality could not be compared with the literature since no pregnant woman died due to the disease during our study period. We think that the absence of mortality and the low need for intensive care in our study are related to the fact that our patients had no comorbidities, their mean age was 29.3 years and all of them were women.

Limitations

The limitations of our study are the small sample size, the fact that vitamin D levels are not routinely checked in healthy pregnant women, the comparison of vitamin D levels of pregnant women diagnosed with COVID-19 with healthy pregnant women, and the lack of vitamin D levels in outpatient pregnant women with positive COVID-19 RT-PCR test and no indication for hospitalization. In addition, the patients included in the study were from two different hospitals and since the kits of all parameters were not always available in the laboratory for each patient, some parameters of some patients could not be studied during hospitalization or discharge, and only comparisons were made between those with both values.

CONCLUSION

Vitamin D has become very popular during the pandemic process. However, our study showed that although our patient numbers were not high and we could not reach pregnant women with COVID-19 who were followed up as outpatients, vitamin D level did not have a significant relationship with any of the parameters such as clinical, laboratory findings, severity of the disease and hospitalization periods related to COVID-19. In addition, vitamin D level varies according to geographical location, race and seasons. Therefore, if vitamin D is to be used as an isolated marker in studies, we think that multicenter, high-participant and especially randomized controlled studies will contribute more to the literature.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Gazi Yaşargil Training and Research Hospital Non-Interventional Clinical Researches Ethics Committee (Date: 27/07/2021 Decision No: E-58146266) and Dicle University Faculty of Medicine Non-interventional Clinical Researches Ethics Committee (Date: 27/05/2021 Decision No: 339).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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The importance of CA-125 and clinical markers in ovarian cancer

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ABSTRACT

Aims: In this study, considering all the known facts about ovarian cancer; The aim of this study is to retrospectively examine the factors related to the etiopathogenesis, diagnosis and prognosis of ovarian cancer, to determine the population at risk, and to try to catch cancer before it progresses or at an early stage by controlling it more frequently and early.

Methods: A total of 99 patients who were operated for adnexal mass in Dicle University Faculty of Medicine, Department of Obstetrics and Gynecology between 1 January 2011 and 31 December 2020 and whose final pathology resulted as malignant were included in our study. Patients with borderline results were not included in our study. Of these 99 patients age, gravity-parity, menopausal status, presence of additional disease, symptoms, CA-125 level, tumor burden, tumor diameter and structure, presence of ascites, presence of implant, lymph node involvement, frozen pathology result, tumor type, stage, complications were investigated.

Results: In this study, the mean age at diagnosis was 51.04 years. It was observed that 55.6% of the patients were postmenopausal. The most common tumor type was identified as epithelial tumors. It has been determined that the patients are mostly in the advanced stage. When the relationship between the stage and the presence of lymph node and ascites fluid was examined, it was observed that lymph node involvement and presence of ascitic fluid increased in advanced stages. It has been observed that the universe progresses as the CA-125 level rises. It has been demonstrated that CA-125 is higher in patients with residual tumors. In addition, CA-125 levels were higher in patients with lymph node involvement than in those without involvement, in patients with bilateral tumours than in those with unilateral tumours, in patients with ascites than in those without ascites, and in epithelial type tumours than in other tumour types.

Conclusion: Although scientific research has been carried out on many markers for ovarian cancer, especially Ca-125, it is difficult to detect it at an early stage since routine ovarian cancer screening is not possible under today's conditions. Even though it is not specific, if some symptoms such as abdominal pain are present in older women, considering ovarian cancer among the preliminary diagnoses may help detect more patients at an early stage.

Keywords: Ca-125, ovarian cancer, postmenopausal, lymph node, acid fluid

INTRODUCTION

Ovarian cancer is the third most common gynecologic cancer in women in addition, less common in breast cancer, but three times more lethal.[1] The lifetime risk of developing ovarian cancer in a woman in the general population is approximately 1.3%. The overall incidence of ovarian cancer in the US was 11.5 per 100,000 women between 2010 and 2014. Population differences in ovarian cancer risk have been attributed mainly to ethnicity and partly to the prevalence of risk factors. The five-year survival rate is approximately 40%.[2,3] Ovarian cancers are usually asymptomatic in early stages. Therefore, when they are diagnosed, they are usually at an advanced stage. Some important risk factors of ovarian cancer are early menarche, late menopause, nulliparity and infertility. Apart from abdominal pain, some nonspecific

symptoms such as bloating, fast eating or difficulty in satiety, and changes in urinary frequency may also be seen in ovarian cancers. In the presence of a palpable mass on palpation of the pelvis, pathologies of the ovaries, uterus, tubae, intestines and urinary system should come to mind. Therefore, systemic examination is important. The incidence of ovarian cancer is parallel to age. Early diagnosis of patients with adnexal masses is very important to reduce mortality, improve the patient's quality of life and reduce treatment costs. 90% of ovarian cancers originate from epithelial tissues. The epithelium covering the ovarian surface originates embryologically from the cholomic epithelium. Other ovarian tumors include germ cell tumors, sex cord stromal tumors and metastatic ovarian tumors.[1]

Some tumor markers such as cancer antigen 125 (CA125), alpha-fetoprotein (AFP), beta-human chorionic gonadotropin (β-HCG), carcinoembryonic antigen (CEA) are tumor markers used in ovarian tumors.[4] Another method that will help in the diagnosis is imaging. Ultrasonography (USG) can reveal the localization, size, solid or cystic structure, border irregularity and relationship with other pelvic organs of an adnexal mass.[5]

The stage of the disease at the time of diagnosis and the size of residual tumor tissue are the most important prognostic factors in ovarian cancer. The primary treatment modality for ovarian cancer is surgery. Primary staging surgery is performed in early stage ovarian cancers and cytoreductive (debulking) surgery is performed in advanced ovarian cancers.[6]

In this study, we retrospectively examined the factors related to the etiopathogenesis, diagnosis and prognosis of ovarian cancer; We aimed to retrospectively examine the factors related to the etiopathogenesis, diagnosis and prognosis of ovarian cancer and to determine the population at risk and to try to catch it before it progresses to cancer or at an early stage so that it can be controlled more frequently and early.

METHODS

The study was carried out with the permission of the Dicle University Faculty of Medicine Ethics Committee (Date: 21.01.2022, Decision No: 37). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. A total of 99 patients with adnexal masses and have complaints such as abdominal pain, bloating who were operated in Dicle University Faculty of Medicine, Department of Obstetrics and Gynecology between 1 January 2011 and 31 December 2020 and whose final pathology was malignant were included in our study. Patients with Borderline pathology results were not included in the study. In addition, patients with hypertension, diabetes, drug and alcohol abuse and smoking were excluded from the study. Patient data were obtained by retrospectively scanning hospital digital records and archive files.

The age, gravida-parity, menopausal status, presence of comorbidities, symptoms, and CA-125 levels of the operated patients were obtained from archival files and hospital digital record system. Tumor burden was calculated from the surgery notes based on the intraoperative tumor size >1cm. USG imaging was performed abdominally and transvaginal. According to this imaging, tumor diameter and structure, presence of ascites were recorded. The presence or absence of implants during the operation was obtained from the surgery notes. Lymph node involvement, frozen pathology result and tumor type were obtained from the final pathology reports. Stages of the patients were calculated and recorded according to the 2013 FIGO (International federation of gynecology and obstetrics) criteria. Finally, the presence or absence of intraoperative complications was obtained from the surgery notes and files of the patients.

Statistical Analysis

The data obtained from the study were analyzed using the SPSS package program (Statistical Package for Social Sciences; IBM SPSS Statistics for Macintosh, Armonk, NY) version 25. Descriptive analyses were expressed as number (n) and percentage (%) for categorical data and mean±standard deviation (mean±standard deviation) for continuous data. The compatibility of continuous variables with normal distribution was evaluated by Kolmogorov-Smirnov test. Pearson chi-square test was used to compare categorical variables between groups. Mann-whitney U-test was used to compare variables that did not conform to normal distribution in two groups and Kruskal-Wallis test was used to compare variables in more than two groups. Statistical significance level was accepted as $p<0.05$ in the analyzes.

RESULTS

A total of 99 female patients, the youngest of whom was 17 and the oldest of whom was 81 years old, were included in this study and their mean age was 51.04±14.89 years. The mean gravida was 5.55±4.37 and the mean parity was 5.07±3.86. It was observed that 21.2% of our patients were nulliparous.

Patients were divided into two age groups as under 45 years and 45 years or older. While 66.7% (n:66) of the patients were 45 years and older, 33.3% (n: 33) were younger than 45 years. When the menopausal status of the patients was analyzed, 55.6% (n:55) were postmenopausal.

When the symptoms of the patients admitted with adnexal mass and included in the study were examined, it was found that the most common symptom was abdominal pain (n:67), which was observed in 67.7% of the patients, followed by menstrual irregularity (n:15) and bloating.[13]

CA-125 levels of the patients included in the study were examined as a tumor marker. The patients were divided into three groups on the basis of 35 units, which is accepted as a positive value for CA-125 in our laboratory, and 300 units, which has been shown to be significant in studies: 21 patients (21.20%) had CA-125 values <35,51 patients had CA-125 values between 35-300 and 27 patients had CA-125 values >300 (Table 1). Regarding the nature of the mass, the most common type (59.6%) was solid-cystic tumor, followed by cystic tumor in 21.2% and solid tumor in 18.2%. Lymph nodes were positive in 20.2% of patients. In addition, ascites was detected in 45.5% of all patients included in the study. Details are shown in Table 1.

Frozen pathology was requested in 80 of the patients during the operation. Accordingly, 88.7% (n:71) of the frozen pathology results were reported as malignant. In 7 patients (8.7%), the frozen result was borderline, while 2(2.5%) patients were reported as benign. In 19 patients, frozen pathology was not requested.

Table 1. Evaluation of patients according to CA-125 values, mass structure, lymph node positivity, presence of ascitic fluid, presence of implant

		Count (n)	Percent (%)
CA-125 Groupings	Below 35 units	21	21.20%
	Between 35-300 units	51	51.50%
	Above 300 units	27	27.30%
	Total	99	100.00%
Mass structure	Solid	18	18.20%
	Cystic	21	21.20%
	Solid + cystic	59	59.60%
	No lesion	1	1.00%
	Total	99	100.00%
Lymph node involvement	Positive	20	20.20%
	Negative	79	79.80%
	Total	99	100.00%
Presence of acidic fluid	Present	45	45.50%
	Absent	54	54.50%
	Total	99	100.00%

The results of pathologic evaluation of all postoperative material were also analyzed. Accordingly, the most common tumor type in patients with adnexal masses was epithelial tumors with 74.75% (n:74). Sex cord stromal tumors were found in 12.1% (n:12) and germ cell tumor types in 13.15% (n:13) of the patients. While 54.5% (n:54) of the tumors were unilateral, 45.5% (n:45) were bilateral.

According to tumor staging, it was determined that patients were most frequently diagnosed in Stage 3C (34.3%), and the second most frequently in Stage 1A (29.3%). The results of the evaluation of the patients according to their stages are shown in Figure 1.

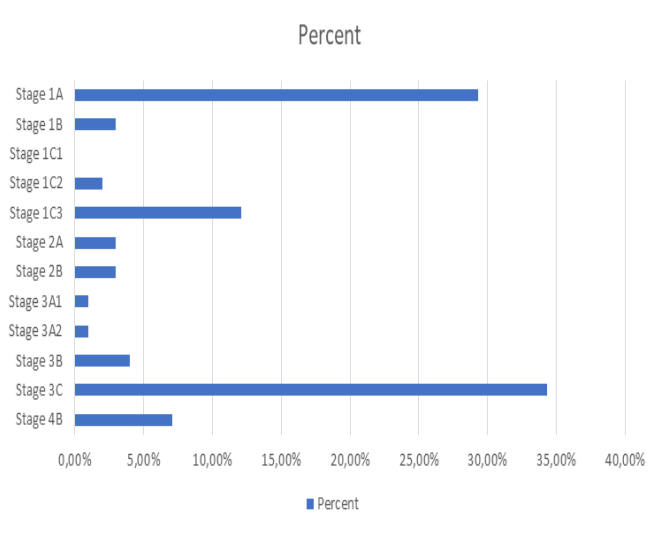

Figure 1. Evaluation of patients with adnexal masses according to their stages

The relationship between tumor stage and CA-125 levels in patients with adnexal masses was also examined. Accordingly, when the patients who were divided into 3 groups according to CA-125 levels were evaluated according to their stages, it was determined that the stage progressed as the CA-125 level

Table 2. Association between grouped CA-125 level and tumor stage

	CA-125 < 35		CA-125 between 35-300		CA-125 > 300		Total	
Stage	Count (n)	Percent (%)	Count (n)	Percent (%)	Count (n)	Percent (%)	Count (n)	Percent (%)
Stage 1A	17	58.60%	9	31.00%	3	10.30%	29	100.00%
Stage 1B	0	0.00%	3	100.00%	0	0.00%	3	100.00%
Stage 1C2	2	100.00%	0	0.00%	0	0.00%	2	100.00%
Stage 1C3	2	16.70%	9	75.00%	1	8.30%	12	100.00%
Stage 2A	0	0.00%	3	100.00%	0	0.00%	3	100.00%
Stage 2B	0	0.00%	3	100.00%	0	0.00%	3	100.00%
Stage 3A1	0	0.00%	1	100.00%	0	0.00%	1	100.00%
Stage 3A2	0	0.00%	0	0.00%	1	100.00%	1	100.00%
Stage 3B	0	0.00%	4	100.00%	0	0.00%	4	100.00%
Stage 3C	0	0.00%	18	52.90%	16	47.10%	34	100.00%
Stage 4B	0	0.00%	1	14.30%	6	85.70%	7	100.00%
Total	21	21.20%	51	51.50%	27	27.30%	99	100.00%

The presence of lymph nodes and ascites were also evaluated according to the stages. Accordingly, patients with lymph node positivity were found to be at significantly more advanced stages. Similarly, patients with ascites were at more advanced stages, while patients without ascites were at earlier stages. The findings are shown in Table 3. The mean CA-125 levels in patients with residual tumors were also evaluated. Accordingly, the mean CA-125 value of patients with residual tumor after surgery (1079.1±1484.5) was significantly higher than that of patients without residual tumor (314.5±877.4) (p:0.001). In addition, the mean CA-125 value was higher in patients with bilateral tumors (p: 0.001).CA-125 values were also evaluated according to the presence of lymph nodes and ascites. The mean CA-125 values were significantly higher in patients with positive lymph nodes and ascites compared to patients with negative lymph nodes and ascites (p values:p: 0.001 and p:0.001, respectively) (Table 4).

Table 3. Evaluation of lymph node positivity and presence of ascites according to stages

	Lymph Node Positive		Lymph Node Negative		Total		
Stage	Count (n)	Percent (%)	Count (n)	Percent (%)	Count (n)	Percent (%)	P value
Stage 1A	0	0.00%	29	100.00%	29	100.00%	
Stage 1B	0	0.00%	3	100.00%	3	100.00%	
Stage 1C2	0	0.00%	2	100.00%	2	100.00%	
Stage 1C3	0	0.00%	12	100.00%	12	100.00%	
Stage 2A	0	0.00%	3	100.00%	3	100.00%	
Stage 2B	0	0.00%	3	100.00%	3	100.00%	0.001***
Stage 3A1	0	0.00%	1	100.00%	1	100.00%	
Stage 3A2	0	0.00%	1	100.00%	1	100.00%	
Stage 3B	2	50.00%	2	50.00%	4	100.00%	
Stage 3C	11	32.40%	23	67.60%	34	100.00%	
Stage 4B	7	100.00%	0	0.00%	7	100.00%	
Total	20	20.20%	79	79.80%	99	100.00%	
	Acidic fluid present		**Acidic fluid absent**		**Total**		
Stage	Count (n)	Percent (%)	Count (n)	Percent (%)	Count (n)	Percent (%)	P Value
Stage 1A	8	27.60%	21	72.40%	29	100.00%	
Stage 1B	1	33.30%	2	66.70%	3	100.00%	
Stage 1C2	1	50.00%	1	50.00%	2	100.00%	
Stage 1C3	3	25.00%	9	75.00%	12	100.00%	
Stage 2A	0	0.00%	3	100.00%	3	100.00%	
Stage 2B	0	0.00%	3	100.00%	3	100.00%	0.001***
Stage 3A1	1	100.00%	0	0.00%	1	100.00%	
Stage 3A2	1	100.00%	0	0.00%	1	100.00%	
Stage 3B	3	75.00%	1	25.00%	4	100.00%	
Stage 3C	22	64.70%	12	35.30%	34	100.00%	
Stage 4B	5	71.40%	2	28.60%	7	100.00%	
Total	45	45.50%	54	54.50%	99	100.00%	

***Pearson chi-square test was used and a significant difference was found

increased (p: 0.001). Stage evaluation according to grouped CA-125 level is shown in Table 2.

Table 4. CA-125 Evaluation according to lymph node involvement and presence of ascites in the patient

	CA-125		
	Mean	Standard deviation	p value
Lymph node positive	810.35	861.17	
Lymph node negative	469.67	1,192.20	0.001**
Total (lymph node)	538.49	1,137.52	
Acidic fluid present	947.42	1,421.14	
Acidic fluid absent	197.72	675.01	0.001**
Total (Acidic fluid)	538.49	1,137.52	

** Mann-Whitney U test was used and a significant difference was found.

DISCUSSION

Our study revealed that ovarian cancer is mostly detected in older, postmenopausal women and frequently in advanced stages. CA-125, the most commonly used tumor marker, was found to be associated with stage, residual tumor, lymph node involvement, presence of ascites, bilaterality of the tumor and tumor type. In addition, lymph node involvement and asciticemia, which may be related to stages, were also examined and it was found that lymph node involvement and asciticemia were parallel with the increase in stage.

It has been observed that the frequency of ovarian cancer, which is also detected at an early age, increases with advancing age,[7] in addition, in some studies, when patients were divided into two groups: under 45 years of age and 45 years and over, it was observed that 58.8-83% of the patients were over 45 years of age and when menopause was accepted as the cut-off point, the rate of postmenopausal women with ovarian cancer was reported to be 45-71% in the literature.[8,9] In our study, 55.6% of the patients were in the postmenopausal period and 66.7% of the patients were 45 years of age or older, 33.3% were younger than 45 years of age. In addition, the mean age at the time of diagnosis of ovarian cancer was found to be compatible with the data in the literature.

The most common symptoms reported in patients with ovarian cancer are pelvic pain/ abdominal pain; symptoms such as bloating, urinary incontinence, and weight loss may also be observed.[10] Vine et al.[11] showed abdominal pain (64%), bloating or feeling of fullness (62%) and abdominal distension or hardness (59%) as the most common symptoms. In this study, abdominal pain was the most common symptom in 67.7% of the patients.

Regarding the histological type of ovarian tumors, Reid et al.[12] showed that the rate of epithelial ovarian tumors was 90%, sex-cord stromal tumors 5%- 6% and germ cell tumors 2%-3%. In another study, these rates were 77.4%, 11.3% and

7.5%, respectively.[8] In this study, the most common tumor type was epithelial tumors with 74.75%. Sex cord stromal tumors were found in 12.1% of the patients and germ cell tumor type in 13.15%.

In 2020, in a review of 871 cases, the concordance rate between frozen section and final diagnoses was 93.8%.[13] In a study for frozen section, diagnostic accuracy, sensitivity and specificity were 95.8%, 98.7% and 94.7% for benign ovarian tumors, 91.1%, 82.0% and 93.0% for borderline ovarian tumors, and 93.1%, 88.2% and 99.7% for malignant ovarian tumors, respectively. According to tumor types, the positive predictive value of frozen section analysis was highest in germ cell tumors (99.3%). This was followed by sex cord stromal tumors (96.7%). The most discordant group was found to be epithelial ovarian tumors.[14] In another meta-analysis, 40% of patients with at least borderline diagnosis on frozen section had invasive carcinoma on paraffin section.[15] In this study, 88.7% of the patients were reported as malignant on frozen section. In 7 patients (8.7%), the frozen result was borderline and in 2 patients the material was reported as benign. Frozen pathology was not performed in 19 patients.

CA-125 is a marker that is examined in ovarian tumors in many aspects such as tumor type, stage, presence of ascites mai, presence of residual tumor after surgery. When the literature is reviewed in terms of the relationship between tumor stage and CA-125 levels, there are studies suggesting that there is a relationship between CA-125 and stage, but there are also studies reporting that there is no relationship.[16,17] In this study, when the patients who were divided into 3 groups according to CA-125 levels were evaluated according to their stages, it was observed that the stage progressed as the CA-125 level increased and there was a relationship between stage and CA-125.

There are also studies showing that CA-125 level is associated with suboptimal resection and is higher in patients with suboptimal resection.[17,18] Modarres-Gilani et al.[19] showed that when the cut-off value for CA-125 was taken as 450 U/ml, optimal resection was performed in 86% of patients below this value and in 52% of patients above this value. In this study, residual tumor and CA-125 levels were evaluated. Accordingly, the mean CA-125 value of the patients who had residual tumor at the time of surgery was significantly higher than the patients who did not have residual tumor. In addition, postoperative residual tumor volume has been emphasized in many studies and it has been argued that residual tumor volume is prognostic and affects survival.[20,6] In some studies, the rate of cases with a residual tumor size of less than 1 cm has been observed between 33% and 87%.[19,21-22] In this study, the rate of patients with residual tumor diameter <1 cm was 70.7%.There are many studies examining the relationship between tumor stage and lymph node metastases and it has been reported that lymph node metastases is more common in advanced stages and lymph node metastases in early stage ovarian cancers is between 6 - 30%.[23-25] In this study, lymph node positivity was evaluated according to the stages and although patients with positive lymph nodes were found to be at significantly more advanced stages, the fact that no positive lymph node was observed in any of the patients with early stage ovarian cancer suggests that studies involving a larger patient group are needed. The majority of women with ovarian cancer present to hospital at an advanced stage (stage III or stage IV), which may include ascites.[26] Fewer studies have compared LGSOC (low grade serous ovarian cancer) and HGSOC (high grade serous ovarian cancer) and found a higher prevalence of ascites in HGSOC. And the presence of ascites showed a significant difference between these two groups. The presence of ascites is also highly correlated with the extent of the disease. The presence of ascites was observed in >90% of women with stage III and IV ovarian cancer. It was also found that patients with high levels of ascites (>1000 ml) had higher CA-125 levels than those with low levels of ascites (<200 ml), which was associated with better surgical outcomes and late recurrence.[27] Although the amount of ascites was not evaluated in this study, when we evaluated CA-125 values according to the presence of ascites, the mean CA-125 values were found to be significantly higher in patients with ascites compared to those without ascites as in the study by Ivanov et al.[18] Again, when we evaluated the presence of ascites detected in 45.5% patients in this study according to the stages; it was observed that patients with ascites were in more advanced stages while patients without ascites were in earlier stages. The rate of ascites in patients in advanced stages was 68%, which supports the literature. In addition, when we evaluated CA-125 values according to lymph node positivity in this study, the mean CA-125 values were significantly higher in patients with positive lymph nodes compared to those with negative lymph nodes. The reason for this positivity may be that CA-125 values is higher in advanced stages and both lymph node positivity and ascites are more common in advanced stage tumors.

Limitations

The limitations of our study were the small number of patients and the inability to perform frozen sections in some patients.

CONCLUSION

Since routine ovarian cancer screening is not possible in today's conditions, the increasing frequency of ovarian cancer with age and its rates in the postmenopausal period are important in terms of early diagnosis and better understanding of age-related risk factors, identification of common symptoms, patient information, and may contribute to the development of strategies for symptom management in clinical practice.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Dicle University Faculty of Medicine, Ethics Committee (Date: 21.01.2022, Decision No: 37).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Review

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The intersection of technology and infertility: pioneering approaches in genetic editing and artificial intelligence

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ABSTRACT

Infertility, a global health concern, impacts millions of individuals and couples, entailing profound emotional and socio-economic consequences. Recent advances in genetic editing and artificial intelligence (AI) herald a new frontier in infertility treatment, offering precision, personalization, and enhanced efficacy. This compilation explores the integration of clustered regularly interspaced short palindromic repeats associated proteins (CRISPR-Cas) 9 gene editing and AI-driven diagnostics and treatment strategies in the context of reproductive medicine. Through a comprehensive review of current research, clinical applications, and ethical considerations, this paper highlights the transformative potential of these technologies while addressing the associated challenges. The synergy of genetic editing and AI not only promises to improve outcomes for individuals battling infertility but also raises important questions about accessibility, privacy, and ethical implications. By examining these developments, we aim to provide insights into the future of infertility treatments and the evolving landscape of reproductive medicine.

Keywords: Infertility, genetic editing, CRISPR-Cas9, artificial intelligence, reproductive medicine

INTRODUCTION

Infertility, characterized by the inability to achieve a pregnancy after 12 months or more of regular unprotected sexual intercourse, is a global health concern that affects approximately 15-20% of couples worldwide. This condition not only poses significant challenges to individuals' physical and emotional well-being but also imparts substantial socio-economic burdens on families and healthcare systems. The journey of infertile couples through the maze of available treatments is fraught with high costs, emotional distress, and varying degrees of success, reflecting the complexity of human reproduction and the multitude of factors that can influence fertility.[1]

Historically, the approach to managing infertility has evolved significantly, from the use of simple remedies and interventions in ancient times to the development of assisted reproductive technologies (ART) in the modern era. The latter half of the 20th century marked a pivotal moment in reproductive medicine with the advent of in vitro fertilization (IVF), a technique that has since revolutionized the treatment of infertility. Despite these advancements, a substantial proportion of couples remain unsuccessful in their quest for parenthood, underscoring the need for continuous innovation and improvement in fertility treatments.[2]

Into this landscape of ongoing challenge and change, genetic editing and artificial intelligence (AI) emerge as revolutionary technologies with the potential to fundamentally transform the field of infertility treatment. Genetic editing, particularly through the clustered regularly interspaced short palindromic repeats associated proteins (CRISPR-Cas) 9 system, offers unprecedented precision in modifying the DNA sequences of living organisms, allowing for the correction of genetic defects that contribute to infertility. This technology not only holds promise for eradicating inherited genetic disorders but also opens new avenues for understanding and treating infertility at its genetic roots.[3]

Parallel to the developments in genetic editing, AI and machine learning algorithms are making significant strides in the diagnosis and treatment of infertility. By analyzing vast datasets and identifying patterns beyond human recognition, AI can enhance the accuracy of infertility diagnoses, optimize treatment protocols, and improve the selection process for viable embryos in IVF procedures. The integration of AI into reproductive medicine promises to personalize and refine infertility treatments, making them more effective and accessible to a wider population.[4]

The introduction of CRISPR-Cas9 genetic editing and AI into the domain of infertility treatment represents a convergence of biotechnology and information technology that has the potential to address the limitations of current treatment modalities. This article aims to explore the transformative

potential of these technologies, examining their applications, challenges, and ethical considerations in the context of reproductive medicine. Through a detailed review of the latest research and clinical practices, we will delve into how genetic editing and AI are reshaping the landscape of infertility treatment, offering new hope and possibilities for individuals and couples facing the challenges of infertility.

GENETIC EDITING AND INFERTILITY TREATMENT

Infertility, a condition affecting millions of couples worldwide, has a multifaceted etiology, with genetic causes accounting for a significant proportion of cases. Genetic abnormalities, including chromosomal anomalies and gene mutations, can lead to various forms of infertility, such as impaired sperm production or function in men and ovulatory disorders in women.[5] The complexity and diversity of genetic factors involved underscore the need for innovative approaches to diagnosis and treatment.

The advent of CRISPR-Cas_9 technology has marked a revolutionary leap in the field of genetic editing, offering a powerful tool for modifying DNA with unprecedented precision, efficiency, and flexibility. Developed from a naturally occurring genome editing system in bacteria, the CRISPR-Cas_9 technology allows for the targeted alteration of genetic material, opening new avenues for the treatment of genetic disorders, including those leading to infertility.[6]

Historically, the development of CRISPR-Cas_9 technology can be traced back to the discovery of CRISPR and CRISPR-Cas_9 in bacteria, serving as an adaptive immune system against viruses. The transformation of this biological phenomenon into a versatile genetic editing tool was achieved through the characterization of its mechanism, which involves the Cas_9 nuclease guided by a specifically designed RNA sequence to a target DNA site, where it induces a double-strand break. This break can then be repaired through non-homologous end joining or homology-directed repair, allowing for the addition, deletion, or alteration of specific DNA sequences.[3]

In the context of infertility treatment, CRISPR-Cas_9 technology has been applied to correct genetic abnormalities that lead to the condition. For example, mutations in the Y chromosome affecting sperm production and autosomal recessive disorders like cystic fibrosis-related infertility have been targeted using CRISPR-Cas_9 demonstrating the potential to restore fertility through genetic correction.[7] Recent studies have showcased the successful application of CRISPR-Cas_9 in animal models, correcting gene mutations responsible for infertility and paving the way for clinical applications in humans.[8] However, the application of CRISPR-Cas_9 in infertility treatment raises significant ethical considerations. The prospect of germline editing, which would result in genetic changes being passed on to future generations, has ignited a debate on the moral implications of such interventions. Concerns over the potential for creating "designer babies" with selected traits further complicate the ethical landscape, highlighting the need for stringent regulatory frameworks and ethical guidelines to govern the use of genetic editing technologies in reproductive medicine.[9]

Despite its transformative potential, CRISPR-Cas_9 technology faces several challenges and limitations. Off-target effects, where unintended genetic modifications occur, pose a risk for unforeseen consequences and necessitate the development of strategies to enhance the specificity and accuracy of the technology. Additionally, genetic mosaicism, resulting from the editing of some but not all cells, can compromise the efficacy of treatment and necessitates further research to optimize the application of CRISPR-Cas_9 in infertility treatment.[10]

In conclusion, while CRISPR-Cas9 technology represents a groundbreaking advancement in the treatment of infertility with a genetic basis, it is accompanied by ethical dilemmas, technical challenges, and limitations that must be carefully addressed. The ongoing development of this technology and its applications in reproductive medicine warrants a multidisciplinary approach, combining scientific innovation with ethical stewardship to ensure the responsible use of genetic editing for the benefit of individuals and couples affected by infertility.

ARTIFICIAL INTELLIGENCE IN DIAGNOSING AND TREATING INFERTILITY

The advent of AI and machine learning in medical diagnostics has inaugurated a new era in healthcare, offering unprecedented precision, efficiency, and personalization in treatment. AI's application spans various domains, including oncology, neurology, and cardiology, with its role in reproductive medicine and infertility treatment emerging as a particularly promising area of development.[11]

AI and machine learning algorithms excel in identifying patterns within large datasets, surpassing traditional statistical methods in predicting outcomes and diagnosing conditions. In the realm of infertility treatment, these technologies are employed to analyze complex biological and clinical data, offering innovative approaches to diagnosis, treatment optimization, and the personalization of care plans.[12]

One of the most significant applications of AI in infertility treatment is in predictive analytics, which assesses the likelihood of treatment success. By analyzing factors such as patient age, genetic information, lifestyle variables, and previous treatment outcomes, AI algorithms can predict the efficacy of treatments like IVF, helping clinicians and patients make informed decisions about their care.[13]

Furthermore, AI plays a crucial role in embryo selection during the IVF process. Advanced imaging techniques, combined with machine learning algorithms, evaluate embryo viability more accurately than the human eye, predicting implantation success rates and improving overall IVF outcomes. This technology not only increases the likelihoo d of pregnancy but also reduces the risk of multiple gestations by identifying the single best embryo for transfer.[14]

Personalized treatment plans, tailored to the individual's unique profile, represent another breakthrough facilitated by AI in infertility treatment. By analyzing detailed patient data, AI algorithms can optimize treatment protocols, adjust

medication dosages, and recommend lifestyle changes, thereby enhancing the chances of successful pregnancy.[15]

Recent advancements in AI have led to success stories that underscore its potential in transforming infertility treatment. Studies have documented cases where AI-assisted embryo selection resulted in higher pregnancy rates compared to traditional selection methods, marking a significant milestone in the application of AI in reproductive medicine.[4] However, the integration of AI into infertility treatment raises several ethical considerations. Data privacy concerns emerge as patient data are used to train AI models, necessitating robust safeguards to protect sensitive information. Algorithmic bias is another critical issue, where AI models may inadvertently reflect or amplify biases present in the training data, potentially leading to unequal treatment outcomes across different patient groups.[16]

Challenges and future prospects for AI in infertility treatment include its integration into clinical practice and ensuring accessibility. The successful adoption of AI technologies requires not only technological infrastructure but also training for healthcare professionals to interpret and apply AI-driven insights effectively. Moreover, ensuring equitable access to AI-enhanced treatments across different socio-economic and geographical areas remains a paramount concern, calling for strategies to democratize access to these advanced technologies.[17]

In conclusion, AI and machine learning represent transformative forces in the diagnosis and treatment of infertility, offering new hope to countless individuals and couples. As these technologies continue to evolve, they promise to further refine the precision, efficacy, and personalization of infertility treatments. Nonetheless, realizing the full potential of AI in this field will require addressing the ethical, technical, and accessibility challenges, ensuring that the benefits of AI-enhanced treatments are available to all who need them.

THE SYNERGY OF GENETIC EDITING AND AI IN REPRODUCTIVE MEDICINE

The convergence of genetic editing and AI in reproductive medicine is setting the stage for a paradigm shift in the diagnosis, treatment, and management of infertility. The integration of these two cutting-edge technologies offers a holistic approach that not only addresses the genetic underpinnings of infertility but also optimizes treatment protocols through predictive analytics and personalized medicine. This synergy promises to enhance the efficacy of treatments, reduce associated risks, and pave the way for new therapeutic possibilities.

Genetic editing, particularly through CRISPR-Cas9 technology, provides a powerful tool for correcting genetic anomalies that contribute to infertility. By precisely targeting and modifying DNA sequences, CRISPR-Cas9 can potentially rectify mutations in genes implicated in infertility, such as those affecting sperm production, egg quality, and embryo development.[18] This precise correction at the genetic level represents a significant advancement over traditional treatment methods, offering the potential for a permanent cure for certain types of genetic-based infertility.

Concurrently, AI and machine learning algorithms are revolutionizing the field by analyzing complex datasets to predict the success of infertility treatments, including IVF. AI can identify patterns and factors that influence treatment outcomes, enabling the development of personalized treatment plans that maximize the chances of success.[15] Moreover, AI-driven embryo selection techniques enhance the IVF process by accurately predicting embryo viability, thereby improving implantation rates and reducing the likelihood of multiple pregnancies. The synergy between genetic editing and AI extends to the realm of gene therapy for inherited disorders that impact fertility. AI algorithms can assist in the identification of genetic mutations that cause infertility, while CRISPR-Cas_9 can be employed to correct these mutations in affected individuals or embryos. This collaborative approach not only aims to restore fertility but also prevents the transmission of genetic disorders to future generations, offering a profound impact on reproductive health.[19]

Recent studies underscore the potential of combining genetic editing with AI in reproductive medicine. For instance, research has demonstrated the use of AI to optimize the selection of CRISPR-Cas_9 targets for genetic correction, enhancing the efficiency and accuracy of gene editing in preclinical models.[20] Moreover, the development of AI platforms that predict the outcomes of gene editing interventions in reproductive cells or embryos heralds a new era of precision medicine in fertility treatments. However, the integration of genetic editing and AI in reproductive medicine raises ethical and social concerns. Issues such as the potential for germline editing, the creation of "designer babies," and the equitable access to these advanced technologies necessitate careful consideration and regulation. Ensuring that these technologies are used responsibly and ethically, with a focus on improving human health and well-being, remains a paramount concern for the scientific and medical communities.[21] In conclusion, the synergy of genetic editing and AI represents a frontier in reproductive medicine with the potential to significantly improve the diagnosis and treatment of infertility. By combining the precise targeting capabilities of CRISPR-Cas_9 with the predictive power of AI, this integrated approach offers new hope for individuals and couples facing fertility challenges. As research and development in this area continue to advance, it is imperative that ethical, legal, and social implications are addressed to ensure that the benefits of these technologies are realized in a manner that is equitable and just.

DISCUSSION

The synergy between genetic editing and AI in reproductive medicine represents a frontier of innovation with the potential to address some of the most persistent challenges in infertility treatment. The convergence of these technologies not only enhances the precision and effectiveness of treatments but also raises significant ethical, societal, and practical considerations that warrant a comprehensive discourse.

Genetic editing, particularly through CRISPR-Cas$_9$ offers the promise of correcting genetic abnormalities that lead to infertility, thus providing targeted treatments that could increase the chances of successful pregnancy outcomes. Meanwhile, AI and machine learning algorithms have shown remarkable success in improving diagnostic accuracy, optimizing treatment protocols, and selecting viable embryos for IVF procedures. The integration of these technologies could lead to a more personalized approach to infertility treatment, where interventions are tailored to the specific genetic and physiological profiles of individuals or couples.[22,23] However, the application of genetic editing and AI in reproductive medicine is not without its challenges. Ethical concerns, particularly regarding germline editing and the potential for creating "designer babies," have sparked debate among scientists, ethicists, and the public alike. The possibility of introducing irreversible changes into the human germline necessitates cautious deliberation and robust ethical guidelines to prevent misuse and ensure that the technology is used for therapeutic purposes only.[24,25]

Moreover, the use of AI in infertility treatment raises questions about data privacy, algorithmic bias, and the equitable access to these advanced technologies. Ensuring that AI systems are transparent, fair, and accessible to diverse populations is essential for their ethical and effective integration into clinical practice.[26]

CONCLUSION

The integration of genetic editing and AI into reproductive medicine heralds a new era of possibilities for treating infertility. These technologies have the potential to transform the landscape of infertility treatment, offering more precise, effective, and personalized therapeutic options. However, realizing this potential requires navigating a complex array of ethical, technical, and societal challenges.As we move forward, it is imperative that the development and application of genetic editing and AI in reproductive medicine are guided by rigorous scientific standards, ethical principles, and a commitment to equity. Collaborative efforts among scientists, clinicians, ethicists, policymakers, and patients will be crucial in addressing the challenges and harnessing the opportunities presented by these technologies.The future of infertility treatment lies in the balance of innovation and responsibility. By carefully managing the risks and ethical implications, we can unlock the full potential of genetic editing and AI to provide hope and solutions to those facing the challenges of infertility.

ETHICAL DECLARATIONS

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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I was born in Tarsus and graduated from a high school in Tarsus in 2000, and then from İstanbul Faculty of Medicine in 2006. I completed my training as a Gynecology and Obstetrics specialist and became a specialist in 2011. After working at Babaeski State Hospital, I returned to İstanbul and started working at Private Medistate Kavacık Hospital. I am an academician at Nişantaşı University. I became an Associate Professor in 2021 and I have a son.

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Case Report

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Treatment experience with laser of perianal giant condylomas in a pregnant patient

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ABSTRACT

Condyloma acuminatum is a multitude of large, giant polypoid lesions with an exophytic appearance that occur in and around the vagina, cervix, anal, and perineal regions as a result of human papilloma virus (HPV) infection. The most commonly preferred treatments for these lesions currently include surgical excision, laser, electrocautery, and/or trichloroacetic acid application. A 33-year-old woman with her second pregnancy, parity 1, complained of a painful, bleeding, itchy mass around the anus at the gynecologic control approximately 1 week before delivery. She stated that these masses, which were very small a few months ago, had grown rapidly in the last few weeks. No condyloma was detected in the cervix and vagina. During the general surgical examination, giant condylomas with fragile bleeding were detected in the perianal region on the right and left sides of the anal entrance. Condylomas measuring 6*4.5*4 cm on the largest area and 2.5*2.1 cm on the smallest area on the right side of the anal opening and 12*4*4* on the left side were excised with laser and sent to pathology for examination. The excised areas were cauterized again with the help of a laser. The operation was terminated after hemostasis control. The pathology result was reported as squamous papilloma. Laser treatment of giant condylomas can be an effective and preferable method for pregnant women.

Keywords: Condyloma acuminatum, pregnant patient, surgical excision

INTRODUCTION

Multiple large polypoid lesions with exophytic appearance that occur in the vaginal cervix anal and perineal region as a result of human papilloma virus (HPV) infection are called Buschke-Löwenstein tumor (BLT) or giant condyloma acuminatum (GCA).[1] The prevalence of HPV infection during pregnancy is around 46%. Although the reason for the rapid growth and increase in lesions caused by HPV during pregnancy is not known for certain, it is assumed to be caused by physiologic changes in the external genital organs, partial suppression of the immune system, and increased estrogen hormone. Because the onset is likely to occur at the age of 25 to 34 years, which is the age of childbearing, this condition can occur during pregnancy.[2] The main symptoms of condyloma acuminata are pain, itching, increased vaginal secretions, and bleeding, but many cases are asymptomatic, and the condition may be first discovered during pregnancy.[3] Other views suggest that vaginal discharges and genital discharges that increase during pregnancy increase the possibility of HPV to transform into condyloma.[4,5]

Local treatments (imiquimod cream), laser therapy, cryotherapy, photodynamic therapy, trichloroacetic acid therapy, local hypothermia, surgical excision, and electrosurgery are used in the treatment of condyloma. In addition, drugs such as interferon, 5-fluorouracil cream, and cidofovir have also been used in the past in pregnant women but are no longer recommended. Furthermore, sinecatechins, podophyllin resin, and podophyllotoxin should not be used in pregnant women.[6,7]

It is very unlikely that these tumor-like lesions may show malignant degeneration. The recurrence rate after these treatments is high (up to 50%). Multiple sessions are usually required for successful treatment. Additionally, applying such treatments during pregnancy may cause some complications, such as severe bleeding, local bacterial infections, pain, preterm labor, and miscarriage.[7-9]

With this case report, we wanted to emphasize that laser treatment of giant condylomas may be an effective and preferable method in pregnant women.

CASE

A 33-year-old woman with her second pregnancy, parity 1, complained of a painful, bleeding, itchy mass around the anus at the gynecologic control approximately one week before delivery. She stated that these masses, which were very small a few months ago, had grown rapidly in the last few weeks. No condyloma was detected in the cervix and vagina.

During the general surgical examination, giant condylomas with fragile bleeding were detected in the perianal region on the right and left sides of the anal entrance (Figure 1, 2). Excision and cauterization of condylomas were planned by general surgery in the same session with C/S. OP was initiated through a Pfannenstiel incision in the patient under general anesthesia under sterile conditions with attention to privacy. The skin and subcutaneous abdominal folds were duly opened. The abdomen was incised. A KERR incision was performed in the lower uterine segment. The Ballottement test was applied to the baby's head, and a baby girl was delivered at 08:46, measuring 51/36/3560 g with an Apgar score of 8/9. Afterwards, general surgery was included in the operation, and no condyloma was detected in the rectum with the anoscope.

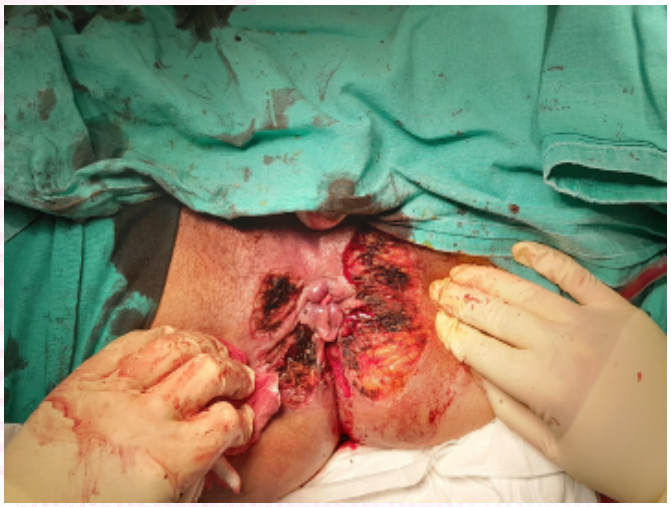

Figure 1. Preoperative giant condylomas with fragile bleeding were detected in the perianal region on the right and left sides of the anal entrance

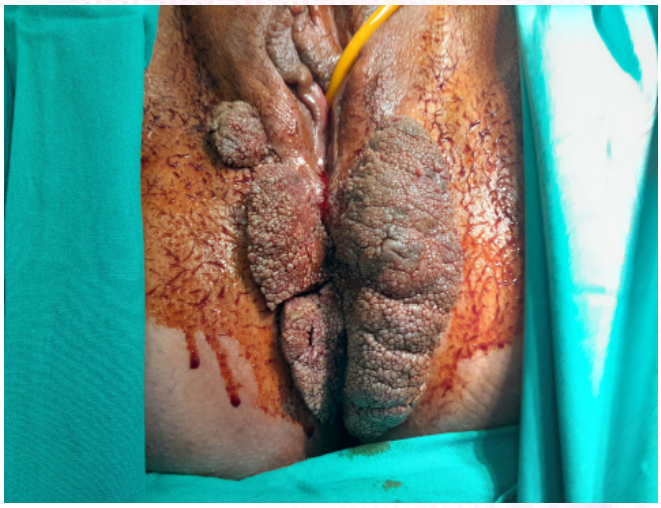

Figure 2. Postoperative giant condylomas with fragile bleeding were detected in the perianal region on the right and left sides of the anal entrance

Condylomas measuring 6*4.5*4 cm on the largest area and 2.5*2.1 cm on the smallest area on the right side of the anal opening and 12*4*4* on the left side were excised with laser and sent to pathology for examination. The excised areas were cauterized again with the help of a laser (Neo V Laser, 1470 mm diode laser device, registered with the republic of Turkiye ministry of health, global product number (Barcode): 7266703007132). The operation was terminated after hemostasis control. The pathology result was reported as squamous papilloma. No surgical or obstetric complications were observed in the postoperative period. Postoperative side effects were pain (pain intensity was evaluated with a visual analog scale), healing time (it took 30 days for the wound to close completely), and minimal scar formation (There was approximately 5 cm of scar tissue on both lateral sides of the anus due to secondary closure.). No new condyloma formation or recurrence was detected in the follow-up of the patient for about one year.

DISCUSSION

Active vulvovaginal HPV type 6 and 11 infections may have different clinical pictures. Transmitted HPV has the potential to be self-eradicated or to enter the latent phase, where it can persist for years as a subclinical infection. It may form benign lesions as well as transform into a precancerous lesion with accompanying oncogenic subtypes. Furthermore, it may also result in HPV-induced tumor-like masses.[8,9] Condyloma acuminatum (CA) refers to the tumor-like masses that range in size from a few millimeters to 1-2 cm and are caused by HPV infection. Up to 30% of CA in non-pregnant women may regress spontaneously under the influence of humoral and cellular immunity. The viral genome can be detected in normal epithelium months or even years after the healing of visible lesions (latent or subclinical infection).[7] It does not show spontaneous regression in pregnancy, and recurrence is common due to treatment failure.[8] Maternal complications such as vaginal bleeding, vaginal obstruction, and urethral obstruction can occur, increasing the ratio of the cesarean section.[9-11] However, Cohen et al.[11] did not report an increased rate of complications in fetuses born to mothers with CA.Depending on the size and number of lesions, condylomas can cause obstructions in the mother's birth canal, which can cause problems during delivery. No complications developed in the mother and baby after delivery and condyloma excision and cauterization in our case.

Furthermore, although at a low rate, the HPV is known to be transmitted to the baby through the birth canal. Although Caesarean section is associated with a low risk of virus transmission, cases have been reported. The choice of treatment during pregnancy is crucial. No conclusive evidence shows that any of the available treatments is superior to another, and no single treatment alone is ideal for all patients or all warts.[12] External genital HPV lesions can be treated with trichloroacetic acid, liquid nitrogen, laser ablation, or electrocautery at any time during pregnancy.[13] Imiquimod, podophyllin, and podofilox should not be used freely during pregnancy.[12] Although the toxicity of imiquimod in pregnant women has not been thoroughly studied, animal studies have revealed no teratogenic or toxic effects. The Centers for Disease Control and Prevention does not recommend topical imiquimod treatment during pregnancy. However, it is not prohibited to use it during pregnancy, and the package leaflet for imiquimod cream states that it should be used during pregnancy "only when clearly needed." In fact, In a study reported that in the 1950s that about 35% of Japanese facilities were using imiquimod cream for pregnant women with condyloma acuminata. As there is only limited information available on the use of imiquimod in pregnancy, it is not recommended as a first-line treatment for pregnant women.[14]

The most preferred treatment method is surgery, and its efficacy has been proven in the early stages of the disease.[8] Surgical excision can be performed using conventional surgical techniques or electrocautery. The large tissue defect in the vulvar or perianal region after removal of the giant tumor may increase the incidence of complications such as inadequate tissue healing, inflammation and infection, miscarriage, and preterm delivery. Thus, partial-thickness skin grafting may be recommended after excision.[15]

Surgical excision and electrosurgery surgical excision using scalpels or scissors enables the direct removal of lesions, and electrosurgery involves the use of electrical energy to destroy lesions.[15] Some experts argue that laser treatment is more effective in reducing bleeding, pain, and scarring.[17-21]

CONCLUSION

There are many methods in the treatment of condyloma. As we have experienced in this case, the use of laser in the treatment of giant condylomas has shown that it can be a preferable treatment method with few complications and good treatment success.

ETHICAL DECLARATIONS

Informed Consent
All patients signed a free and informed consent form.

Referee Evaluation Process
Externally peer-reviewed.

Conflict of Interest Statement
The authors have no conflicts of interest to declare.

Financial Disclosure
The authors declared that this study has received no financial support.

Author Contributions
All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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