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Evaluation of endometrial receptivity in recurrent pregnancy loss and recurrent implantation failure

Tekrarlayan gebelik kaybı ve tekrarlayan implantasyon başarısızlığında endometrial reseptivitenin değerlendirilmesi

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Abstract

Objective: The cause of implantation defects in patients with recurrent implantation failure (RIF) and recurrent pregnancy loss (RPL) has not been clearly established. We aimed to evaluate the immunohistochemical changes in HOXA-11, β1 integrin, focal adhesion kinase (FAK), cluster of differentiation 44 (CD44), and extracellular matrix protein 1 (ECM1) molecules during the receptive endometrial period in patients with RIF and RPL.

Materials and Methods: This study was retrospectively conducted at a university hospital. After the exclusion of cases with pathology that may cause a change in the level of receptors in the endometrium, biopsies performed during the receptive period were selected, and the patients were categorized into RPL (n=15), RIF (n=16), control (n=16) groups. All preparations were immunohistochemically stained for HOXA-11, β1 integrin, FAK, CD44, and ECM1.

Results: HOXA-11 and β1 Integrin expression changes were similar between the RIF and control groups. However, FAK expression was significantly increased in the RIF group ($p<0.01$). Additionally, ECM1 and CD44 expressions were significantly decreased in the RIF group compared with the control group ($p<0.01$). There was no significant difference in the endometrial staining of HOXA-11, FAK, and ECM1 in patients with a history of RPL. However, β1 Integrin and CD44 levels were significantly decreased in the RPL group compared with the control group ($p<0.05$).

Conclusion: Implantation is a complex process, and altered adhesion mechanisms involved in endometrial receptivity may be related to defective implantation in patients with RIF and RPL. Among the adhesion molecules, the expression of CD44, β1 integrin, FAK, and ECM1 molecules varies in inappropriate implantation compared with the normal population.

Keywords: Adhesion molecules, implantation, endometrial receptivity, recurrent implantation failure, recurrent pregnancy loss

Öz

Amaç: Tekrarlayan implantasyon başarısızlığı (RIF) ve tekrarlayan gebelik kaybı (RPL) olan hastalarda implantasyon başarısızlığının nedeni net olarak belirlenememiştir. Bu çalışmada, RIF ve RPL hastalarında, endometriumun reseptif döneminde, HOXA-11, β1 integrin, fokal adezyon kinaz (FAK), farklılaşma kümesi 44 (CD44) ve ekstraselüler matris proteini 1 (ECM1) moleküllerinin immünohistokimyasal değişikliklerini değerlendirmeyi amaçladık.

Gereç ve Yöntemler: Bu çalışma bir üniversite hastanesinde retrospektif olarak yapıldı. Endometriumda, reseptör seviyesinde değişikliğe neden olabilecek patolojisi olan olgular dışlandıktan sonra, endometriumun reseptif döneminde yapılan biyopsiler seçildi. Hastalar RPL (n=15), RIF (n=16), ve kontrol (n=16) grupları olarak 3 gruba ayrıldı. Tüm preparatlar HOXA-11, β1 integrin, FAK, CD44 ve ECM1 için immünohistokimyasal olarak boyandı. Boyanma özellikleri değerlendirildi.

Bulgular: HOXA-11 ve β1 integrin ekspresyon değişiklikleri, RIF ve kontrol grupları arasında benzerdi. Ancak RIF grubunda FAK ekspresyonu anlamlı düzeyde artmıştı ($p<0,01$). Ayrıca RIF grubunda ECM1 ve CD44 ekspresyonlarının kontrol grubuna göre anlamlı düzeyde azaldığı görüldü ($p<0,01$).

PRECIS: We evaluated endometrial receptivity during the implantation window of the endometrium in patients with RIF and RPL using immunohistochemistry.

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RPL öyküsü olan hastalarda HOXA-11, FAK ve ECM1'in endometriyal boyanmasında anlamlı fark yoktu. Ancak RPL grubunda β1 integrin ve CD44 düzeylerinin kontrol grubuna göre anlamlı düzeyde düşük olduğu belirlendi (p<0,05).

Sonuç: İmplantasyon karmaşık bir süreçtir ve endometrial reseptivitede rol oynayan adezyon mekanizmalarındaki değişimler, RIF ve RPL'li hastalarda defektif implantasyonla ilişkili olabilir. Adezyon molekülleri arasında CD44, β1 integrin, FAK ve ECM1 moleküllerinin ekspresyonu, defektif implantasyon durumunda, normal popülasyona göre değişkenlik gösterir.

Anahtar Kelimeler: Adezyon molekülleri, implantasyon, endometrial reseptivite, tekrarlayan implantasyon başarısızlığı, tekrarlayan gebelik kaybı

Introduction

The human endometrium undergoes dynamic changes during the secretory and proliferative phases of the menstrual cycle, ultimately becoming receptive to embryo implantation within a brief timeframe referred to as the "implantation window"[1]. Successful implantation requires precise timing of a live blastocyst's arrival at this receptive endometrium[2]. Despite this well-established knowledge, in vitro fertilization (IVF) procedures still face significant challenges, with implantation failure accounting for approximately 50-75% of pregnancy losses[3]. While half of early pregnancy losses can be attributed to abnormal embryo karyotypes, the remaining 50% are linked to inadequate interactions between the embryo and the endometrium[4].

Despite treating organic endometrial conditions, such as chronic endometritis and endometrial polyps, some patients still experience recurrent implantation failure (RIF) and recurrent pregnancy loss (RPL). Recently, studies on endometrial receptivity have gained momentum in understanding the immunological mechanisms underlying implantation and the concept of the implantation window[5]. Numerous immunohistochemical (IHC) markers that may influence endometrial receptivity have been identified, and their expression levels could vary in different uterine pathologies[6]. However, a comprehensive understanding of all these markers is still needed, and the elucidation of specific markers remains indefinite.

The implantation process involves intricate interactions among growth factors, cell adhesion molecules, extracellular matrix proteins, and cytokines. Many of these factors have been previously identified in the receptive endometrium during the implantation window. Limited data for HOXA-11, focal adhesion kinase (FAK), cluster of differentiation 44 (CD44), β1 integrin, and extracellular matrix protein 1 (ECM1) among these markers are available. While some real-time polymerase chain reaction (PCR) studies have presented changes in the expression of HOXA-11, a transcription factor in the homeobox gene family, during the implantation window, IHC studies on this marker are limited[7]. β1 integrin and FAK are molecules involved in cell adhesion processes and have previously been implicated in the ectopic implantation of the endometrium in endometriotic implants[8,9]. Although their expression during the implantation process has been demonstrated[10], their alterations in the context of RIF and RPL have yet to be characterized. Similarly, studies examining the expression of cell adhesion molecules CD44 and ECM1, which are believed to affect the implantation process in infertile patients, are limited in the context of RIF[11].

Materials and Methods

This retrospective case-control study was conducted at the Department of Obstetrics and Gynecology, Gazi University Faculty of Medicine. The study received ethical approval from the Gazi University Ethics Committee of Clinical Studies (approval no: 2019-129, date: 20.05.2019). All experiments were conducted in compliance with applicable guidelines and regulations. Patient data were reviewed from the hospital's medical records. The ethics committee determined that obtaining informed consent from the patients was unnecessary because of the retrospective nature of the study.

Data Collection and Patient Selection

Patients who applied to the obstetrics and gynaecology clinic at our institution between January 2019 and January 2020 and underwent endometrial biopsy for any reason at ages ranging from 21 to 40 years were examined for this study (n=349). Of these, three groups were formed based on their obstetrical history: the RPL group (group 1), the RIF group (group 2), and the control group (group 3). RIF was defined as the absence of pregnancy despite transferring at least four high-quality embryos in at least three fresh or frozen-thawed embryo transfer cycles[12]. RPL was defined as experiencing three or more miscarriages of unknown cause before 20 weeks of gestation[13]. All patients with RIF or RPL who met the abovementioned criteria were included in the study. The control group comprised patients with at least one child who underwent endometrial biopsy for reasons other than infertility, and no endometrial pathology was reported in any of the control group patients.

Patients with endometrial pathology, including endometrial polyps, chronic endometritis, or submucous leiomyoma, were excluded. In addition, patients whose endometrial biopsies were performed outside the receptive period of the endometrium (between the 21st and 24th days of the menstrual cycle was accepted as the receptive period) were excluded. We also excluded patients with systemic diseases affecting endometrial receptivity, such as diabetes mellitus, gynecological malignancies, or any malignancies associated with estrogen or progesterone receptors. Patients with endometrial biopsy results compatible with ectopic pregnancy and infertile patients with conditions such as endometriosis or hydrosalpinx were also excluded. A flowchart of the study and patient selection is shown in Figure 1.

Endometrial biopsy was performed in the midluteal phase (cycle days 21-24) using a pipeline catheter (Plasti-Med, İstanbul, Turkey) or a 3-mm Novak curette.

Interpretation of Morphology

An experienced pathologist examined the hematoxylin and eosin-stained slides and re-examined them for endometrial dating before immunohistochemistry. Endometrial dating was performed according to Noyes criteria[14].

Immunohistochemistry

Paraffin-embedded blocks were sectioned at a four μm thickness, deparaffinize in xylene, and inserted into the Ventana-XT (Roche, US) automated staining device.

The antibodies used were polyclonal rabbit anti-human against HOXA-11 (1:500 dilutions, Thermo Fischer Scientific, US), monoclonal rabbit anti-human against β1 integrin (clone: EPR16895, 1:1000 dilutions, Abcam, US), monoclonal rabbit anti-human against FAK (clone: EP69Y, 1:250 dilutions, Abcam, US), monoclonal rabbit anti-human against CD44 (clone: EPR1013Y, 1:100 dilutions, Abcam, US), and monoclonal rabbit anti-human against Extracellular Matrix Protein-1 (clone: EPR6701, 1:250 dilutions, Abcam, US). Positive controls included endometrial biopsies, colon, spleen, hepatocellular carcinoma, tonsil, and kidney.

Evaluation of Staining

IHC staining was independently evaluated by two authors without knowledge of the clinicopathological information. The immunoreactive scores of the markers were independently noted in the endometrial stroma and epithelium. The first statistical analysis was performed between the positive and negative cases. Cases that showed staining but were statistically insignificant were re-evaluated and compared again for immunoreactivity according to their extent and intensity. The staining intensity method was as follows: If the staining area was less than 10% or the staining intensity was low, it was called mild staining; if the staining area was 11-100% or the staining intensity was high, it was considered intense staining.

Outcome Measures

The primary outcome measure was whether there was a significant difference in immunoreactive scores of the endometrial receptivity-related markers, showing positive and negative staining in patients with RIF and RPL compared with the control group. The secondary outcome measure involved assessing the differences in staining intensities.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS, version 21.0, Statistics,

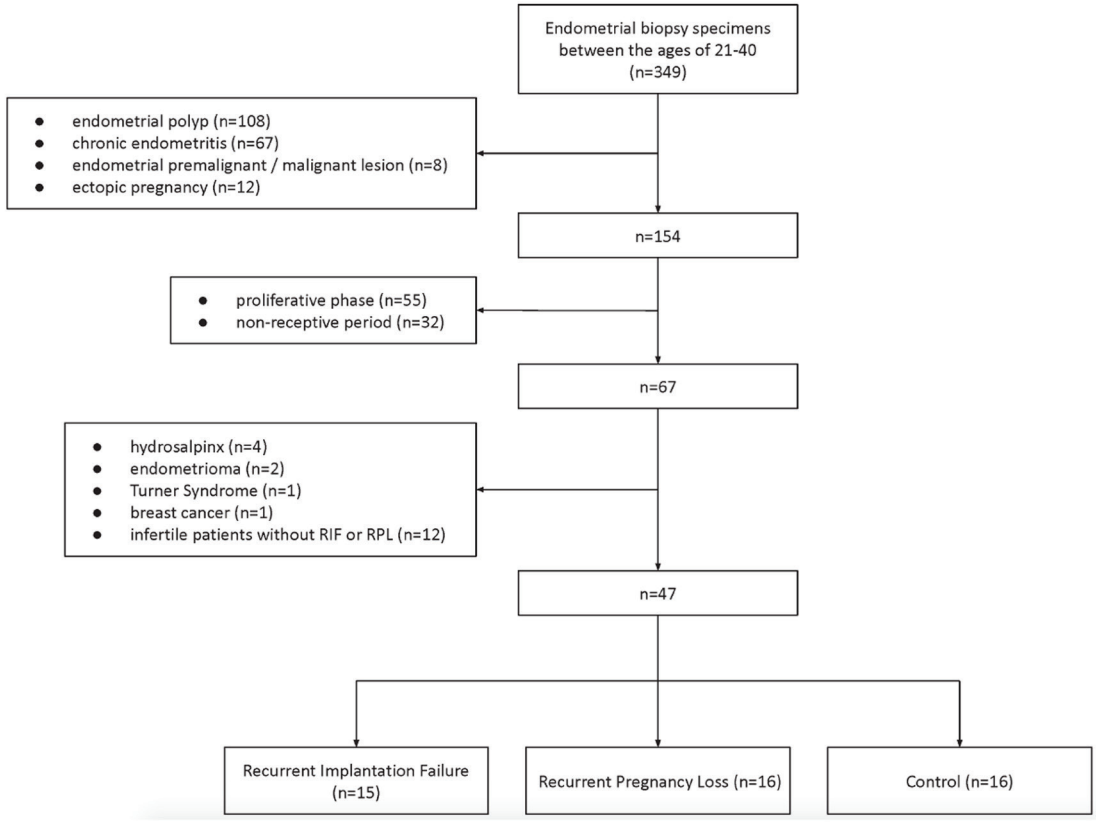

Figure 1. Patient selection

RIF: Recurrent implantation failure, RPL: Recurrent pregnancy loss

2013, Chicago, IBM, USA). The compliance of the variables with normal distribution was examined using graphical (histograms, probability plots) and analytical (Shapiro-Wilk test) methods. One-Way ANOVA was performed to analyze demographic characteristics using the Bonferroni post-hoc test. For categorical data, either the chi-square test or Fisher's exact test was used. Data are presented as mean ± standard deviation or percentages. Statistical significance was defined as $p<0.05$.

Results

The demographic characteristics and obstetric history of the women enrolled in the study are summarized in Table 1.

Endometrial stromal and glandular staining changes of the IHC markers in the RPL and RIF groups compared with the control group are shown in Table 2. Glandular ECM1 staining was decreased and FAK staining was increased in patients with RIF compared with control patients. The results of our study on integrin immunostaining in the RIF group showed a non-significant mild increase compared with controls (100% in the RIF group and 94% in the control group). In patients with RPL, there was a significant decrease in the endometrial glandular staining of CD44 compared with controls (Figure 2). HOXA-11 did not show glandular staining in any patient group. No significant difference was found regarding the other molecules analyzed.

For endometrial stromal staining, there was a decrease in CD44 staining in both the RIF and RPL groups. In addition, a decrease in endometrial stromal β1 integrin staining was observed in RPL patients (Figure 2). HOXA-11 had nearly complete stromal staining in all groups. No statistically significant difference was found in the endometrial stromal staining for the other molecules in both patient groups (Table 2).

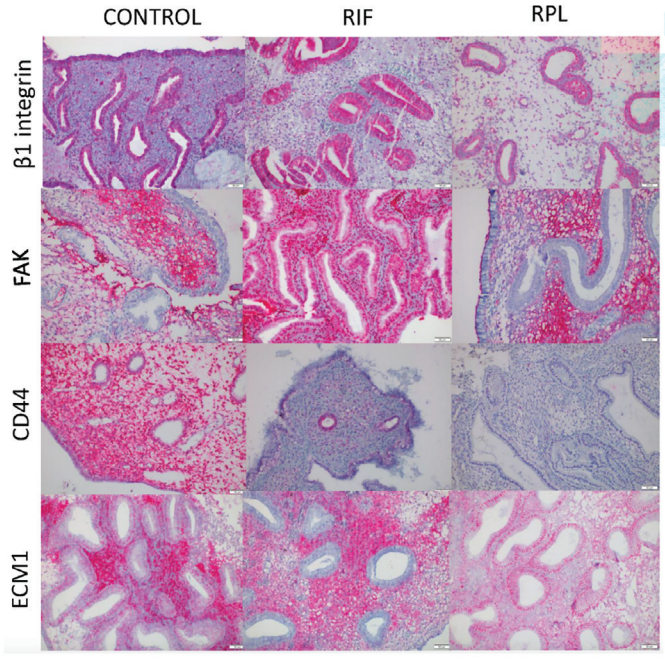

Figure 2. Endometrial staining in all groups

When the pictures were examined in order, β1 Integrin had intense glandular staining in all groups. Although stromal staining was strong in the control and RIF groups, stromal staining was not observed in the RPL group. What is remarkable for FAK is the absence of glandular staining in the RIF group. CD44 did not show stromal staining in the RIF group; in the RPL group, neither stromal nor glandular staining was observed. The absence of glandular ECM1 staining was noted in the RIF group.

RPL: Recurrent pregnancy loss, RIF: Recurrent implantation failure, FAK: Focal adhesion kinase, ECM1: Extracellular matrix protein 1 CD44: Cluster of differentiation 44

Table 1. Demographic features and the obstetric history of the patients

Variable	RPL (n=16)	RIF (n=15)	Control (n=16)	p-value
Age (year)	34.2±3.6	35.1±2.4	36.7±3.1	0.07
BMI (kg/m^2)	24.3±3.7	23.9±2.7	26.3±3.2	0.21
Previous live birth	0.13±0.34	0.13±0.35	2.13±0.71	*
Previous abortion	3.00±0.81	0.07±0.25	0.13±0.34	**

Data are noted as mean value ± standard deviation. RPL: Recurrent pregnancy loss, RIF: Recurrent implantation failure, BMI: Body mass index
*: Control between RPL: p<0.01 Control between RIF: p<0.01 RIF between RPL: p=1.00
**: Control between RPL: p<0.01 Control between RIF: p=1.00 RPL between RIF: p<0.01

Table 2. Staining changes of the endometrial β1 integrin, FAK, HOXA-11, CD44, and ECM1 in the RPL and RIF groups compared to the control group

Molecule	RPL	RIF
Stromal β1 integrin	Decreased (p=0.03)	No difference (p=0.43)
Epithelial β1 integrin	No difference (p=0.50)	No difference (p=0.52)
Stromal FAK	No difference (p=0.11)	No difference (p=0.52)
Epithelial FAK	No difference (p=0.11)	Increased (p<0.01)
Stromal HOXA-11	(p=0.50)	(p*)
Stromal CD44	Decreased (p<0.01)	Decreased (p=0.02)
Epithelial CD44	Decreased (p=0.04)	No difference (p=0.55)
Stromal ECM1	No difference (p=0.30)	No difference (p=0.12)
Epithelial ECM1	No difference (p=0.14)	Decreased (p<0.01)

RPL: Recurrent pregnancy loss, RIF: Recurrent implantation failure, FAK: Focal adhesion kinase, ECM1: Extracellular matrix protein 1, CD44: Cluster of differentiation 44
*: Analysis was not possible as both groups showed 100% staining.

A staining intensity method mentioned in the evaluation of the staining section was also used to compare groups in which there was no difference in the staining properties of the molecules studied. No difference was detected. Stainings in the endometrium are shown in Figure 2.

Discussion

In this study, endometrial receptivity-related IHC markers, including HOXA-11, β1 integrin, FAK, CD44, and ECM, were evaluated in patients with RIF and RPL and their expression changes in endometrial biopsy staining were compared with those in control patients. We found a significant decrease in endometrial glandular ECM1 and stromal CD44 staining in patients with RIF. However, glandular FAK staining increased in these patients. In addition, there was a significant decrease in the endometrial stromal β1 integrin staining and endometrial glandular and stromal staining of CD44 in patients with RPL.

With the increasing use of IVF technologies, endometrial receptivity studies have gained more importance because of RIF in some patients. Studies that provide insight into the molecular mechanisms of endometrial receptivity in patients with RIF and RPL will allow an understanding of the etiology and increase treatment options in both patient groups. It has been emphasized that endometrial receptivity is a complex process involving hormonal, biochemical, and molecular mechanisms, and molecular studies play a role in understanding receptivity and achieving successful implantation[15].

Integrins mediate cell-cell and cell-extracellular matrix adhesion, allowing uterine epithelial cells to bind more tightly. After the binding of integrins to cytoskeletal proteins, FAK, a tyrosine kinase at focal adhesion sites, is activated. Our study on integrin immunostaining in the RIF group showed a nonsignificant mild increase compared with controls. In addition, the epithelial FAK level was higher in the RIF group. These findings suggest that there may be an increase in the barrier function of the endometrium in cases of RIF, which supports the results of a previous study on rats. This study showed that increased focal adhesions could act as a barrier to implantation by making uterine endometrial cells more compact to the blastocyst[10].

RPL is hypothetically considered to occur because of decreased selectivity in the endometrium or superfertilization[16]. In our study, a statistically significant decrease in β1 integrin levels in the endometrial stroma of patients with RPL supports this hypothesis. Decreased expression of β1 integrin in stromal cells may prevent endometrial cells from tightly bonding, thus reducing endometrial selection for the embryo. In this case, it may have resulted in an increased rate of early pregnancy loss. On the other hand, there was no difference in FAK levels in questioning the role of the FAK system. This result may be due to the small sample size and the method used in this study (i.e., we used IHC instead of molecular methods).

Studies using molecular methods have identified a strong relationship between HOXA-11 and implantation failure[17]. HOXA-11 also modulates cell-to-cell and cell-to-extracellular matrix adhesion[18]. In our study, the change in HOXA-11 expression could not be demonstrated immunohistochemically in the endometrium. Similarly, in research conducted with unexplained infertile patients with endometrioma, although an increase in HOXA-11 expression in the ectopic endometrium was detected by PCR, IHC staining for HOXA-11 protein level was not different[19].

The general literature shows that CD44 might play a role in implantation, and its expression physiologically increases in the secretory phase, including the implantation window period in the endometrium[20,21]. A decrease in the expression of CD44 in the mid-secretory phase of patients with RIF has recently been reported[22]. In our study, we similarly found decreased expression of CD44 in the endometrial stroma of patients with RIF, which may confirm the effect of CD44 on implantation. It was shown that CD44 also plays a role in unexplained miscarriages[23], and we found significantly decreased expression of CD44 in the endometrium of our patients with RPL. This finding suggests a defect in vascular invasion and placental angiogenesis in RPL cases, which may be a possible pathophysiological mechanism for increased abortion.

We observed decreased ECM1 staining in the endometrial glandular tissue in patients with RIF. Our data is the first to show that ECM1 was studied in the receptive period of the endometrium in patients with RIF. ECM1 is an extracellular matrix glycoprotein[24], and it was found that maternal-fetal surface ECM1 expression changed in first-trimester curettage materials, and ECM1 expression increased at the implantation site[25]. A previous study reported a decrease in ECM1 expression by PCR in the uterine lavage fluid of unexplained infertile patients; however, IHC staining did not show this decrease[11]. Endometrial samples in this study were performed in the proliferative phase and did not coincide with the implantation window. However, in our study, endometrial biopsies of patients with RIF were performed during the receptive midsecretory phase of the endometrium. Our study is also the first ECM1 study in patients with RPL. Although not statistically significant, a decrease in the endometrial glandular ECM1 level was detected in patients with RPL, which could impact the early pregnancy loss process. However, more studies are required to elucidate this result.

Defective implantation in RIF and RPL may also be related to altered adhesion mechanisms involved in endometrial receptivity. It is noteworthy that changes in the expression of these endometrial receptivity-related molecules may progress with implantation defects during the implantation window period. More new studies on adhesion molecules in these patient groups, whose pathophysiology is not fully understood, will contribute to a better understanding of the underlying mechanism.

Study Limitations

Our study's limitations include the small number of samples and the need for more use of additional IHC methods. Genetic analysis studies, including pregnancy outcomes with more patients in these patient groups, will contribute to the literature.

Conclusion

In conclusion, our findings strongly support the association between adhesion formation and pregnancy failure. Changes in the expression of adhesion-related CD44, ECM1, and FAK molecules have rarely been studied, and their effects have yet to be elucidated in patients with RIF and RPL. We detected changes in CD44, ECM1, and FAK molecule expression in these patient groups. Further research into these changes will help better understand the etiology of RIF and RPL.

Ethics

Ethics Committee Approval: The study received ethical approval from the Gazi University Ethics Committee of Clinical Studies (approval no: 2019-129, date: 20.05.2019).
Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: S.C., A.E., M.E., Concept: S.C., A.E., M.E., Design: S.C., A.E., Ö.E., M.E., Data Collection or Processing: S.C., M.A.İ., A.E., M.İ.G., Ö.E., M.E., Analysis or Interpretation: S.C., M.A.İ., A.E., E.D., M.İ.G., Ö.E., M.E., Literature Search: S.C., Writing: S.C., M.A.İ., A.E., E.D., M.E.
Conflict of Interest: No conflict of interest was declared by the authors.
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