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The effect of gonadotropin gap for non-growing follicles in poor ovarian response: Might this be a new strategy?

Zayıf over yanıtında büyümeyen foliküller için gonadotropinlere ara vermenin etkisi: Yeni bir strateji olabilir mi?

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Abstract

Objective: Cessation of gonadotropin stimulation might affect follicular growth in patients in POSEIDON groups 3 and 4, which are unresponsive to high-dose stimulation.

Materials and Methods: In this retrospective study, data were extracted from the medical records of patients treated at the Acıbadem Maslak Hospital Assisted Reproductive Technologies Unit between November 2010 and December 2020. Eighty-five patients who fulfilled the inclusion criteria were included in the study. Gonadotropin stimulation was discontinued if the follicle diameter increased by 2 mm within 7 days after the initiation of stimulation in patients in groups 3 and 4. The outcomes of the treatment strategy and pregnancy were recorded.

Results: Follicular growth was observed in 40% (34/85) of patients, of whom 52.9% (18/34) had 2pn embryos. Ten of the 85 patients (11.8%) underwent embryo transfer, resulting in biochemical pregnancy for two patients and healthy live birth for one patient.

Conclusion: When high-dose stimulation is ineffective, discontinuing gonadotropin administration during ovarian stimulation may provide patients with the opportunity to conceive using their own biological oocytes. To the best of our knowledge, this is the first study to report a live birth rate using this strategy.

Keywords: Poor ovarian response, diminished ovarian reserve, failure to ovarian stimulation, gonadotropin gap, in vitro fertilization

Öz

Amaç: Yüksek doz stimülasyona yanıt vermeyen POSEIDON grup 3 ve 4 hastalarda gonadotropin stimülasyonunun kesilmesinin folikül büyümesi üzerine etkisini araştırmayı amaçladık.

Gereç ve Yöntemler: Bu retrospektif çalışmada, Kasım 2010-Aralık 2020 tarihleri arasında Acıbadem Maslak Hastanesi Yardımcı Üreme Teknikleri Ünitesinde tedavi gören hastaların tıbbi kayıtlarından veriler elde edilmiştir. Dahil edilme kriterlerini karşılayan 85 hasta çalışmaya alınmıştır. POSEIDON grup 3 ve 4 hastalarda stimülasyon başlangıcından itibaren 7 gün içinde folikül çapı 2 mm'den az arttığında gonadotropin stimülasyonu kesilmiştir. Tedavi stratejisi ve gebelik sonuçları kaydedilmiştir.

Bulgular: Hastaların %40'ında (34/85) folikül büyümesi gözlemlenmiş ve bu hastaların %52,9'unda (18/34) 2pn embriyolar elde edilmiştir. Seksen beş hastadan on tanesine (%11,8) embriyo transferi yapılmış ve iki hastada biyokimyasal gebelik, bir hastada sağlıklı canlı doğum elde edilmiştir.

PRECIS: Discontinuing gonadotropin stimulation in poor ovarian responders may enable follicular growth and conception, with the potential for live birth using biological oocytes.

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Sonuç: Yüksek doz stimülasyonun etkisiz olduğu durumlarda, over stimülasyonu sırasında gonadotropin uygulamasının kesilmesi, hastalara kendi biyolojik oositlerini kullanarak hamile kalma şansı sağlayabilir. Bildiğimiz kadarıyla, çalışmamız bu stratejiyle canlı doğum oranını bildiren ilk çalışmadır.

Anahtar Kelimeler: Zayıf over yanıtı, azalmış over rezervi, over stimülasyonunda başarısızlık, gonadotropinin kesilmesi, in vitro fertilizasyon

Introduction

Poor ovarian response (POR) is a common problem encountered during in vitro fertilization (IVF) cycles and is associated with low success rates and high treatment costs[1]. Although the definition of POR varies in the literature, the POSEIDON classification system is widely accepted for categorizing patients according to their ovarian reserve status[2]. This system takes into account factors such as age, ovarian reserve markers [anti-Müllerian hormone (AMH), antral follicle coun (AFC)], and the number of oocytes retrieved in previous cycles of conventional ovarian stimulation to divide patients with poor prognosis into four groups. Group 1 consisted of patients under the age of 35 years who demonstrated sufficient ovarian reserve parameters (AFC ≥5, AMH ≥1.2 ng/mL), and those with unexpected poor or suboptimal ovarian response. Group 2 included patients aged >35 years with similar ovarian reserve parameters. Patients younger than 35 years old with poor ovarian reserve parameters (AFC <5, AMH <1.2 ng/mL) are categorized in group 3, whereas group 4 consisted of patients older than 35 years old with poor ovarian reserve parameters[3]. Documentation of at least two POR episodes is necessary to define a patient as a poor responder[4].

Patients with diminished ovarian reserve or expected POR are classified into POSEIDON groups 3 and 4, which comprise 10% and 55% of all IVF patients, respectively[1]. Due to the smaller number of oocytes and fewer embryos produced, patients classified as POSEIDON have a lower chance of achieving a cumulative live birth per cycle compared with non-POSEIDON patients[5]. Although several protocols have been developed to improve ovarian stimulation and outcomes in these patients, their effectiveness remains a topic of debate.

In this study, we aimed to evaluate the efficacy and outcomes of cessation of gonadotropin during ovarian stimulation in patients in POSEIDON groups 3 and 4, which are unresponsive to high-dose stimulation.

Material and Methods

Study Population

The medical records of patients treated at Acıbadem Maslak Hospital Assisted Reproductive Technologies Unit between November 2010 and December 2020 were scanned, and 85 eligible patients were included in the study. Patients in approximately 27-47 years of age who met the POSEIDON criteria groups 3 or 4 were included in the study. Patients with an increase in follicle diameter of 2 mm within 7 days after the initiation of gonadotropin treatment were recruited in the study. Patients with severe male characteristics were excluded. The study was approved by the Acıbadem Mehmet Ali Aydınlar University Medical Research Ethics Committee (decision no: ATADEK-2021-04/31, date: 24.02.2021).

Ovarian Stimulation Protocol

Patients diagnosed with POR according to the POSEIDON criteria underwent transvaginal ultrasound (TVUSG) on the 2nd or 3rd days of the menstrual cycle. A flowchart of the ovarian stimulation protocol is presented in Figure 1. Briefly, ovarian stimulation was started with 300 IU follicle-stimulating hormone (FSH) (Gonal F, Serono) and 300 IU hMG (Merional, IBSA, Switzerland) when at least 1 antral follicle was detected. On the 5th days of stimulation, TVUSG was repeated, and if an increase of at least 2 mm in dominant follicle size diameter was observed, gonadotropin treatment was continued at the same dose. If the increase in follicle diameter was 2 mm, ovarian stimulation was continued for 2 more days, and follicular growth was restored. If the increase was still less than 2 mm in

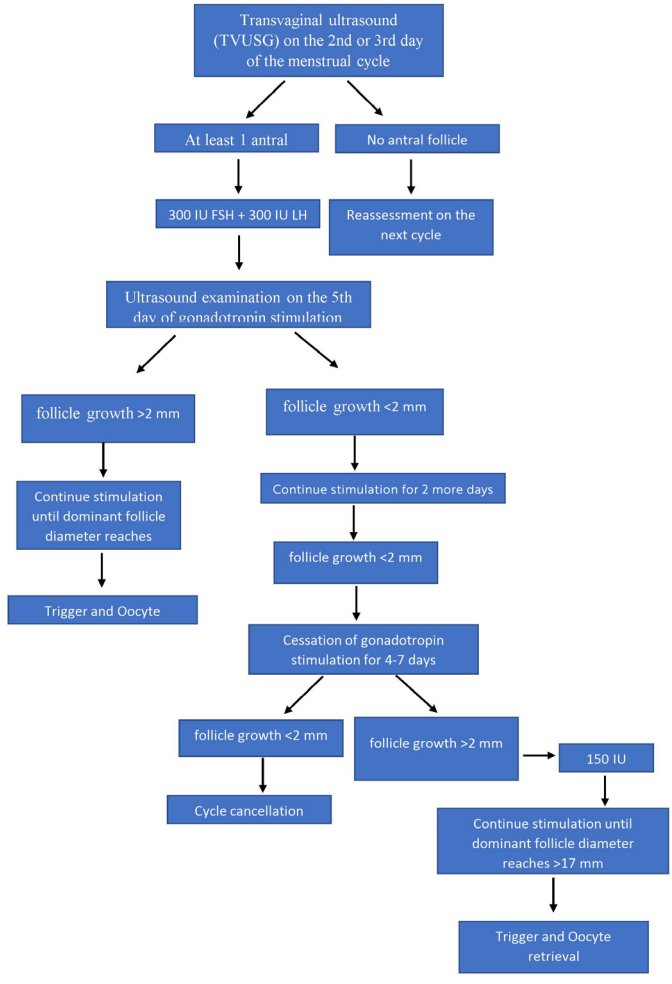

Figure 1. Flowchart of the ovarian stimulation protocol

the third control, the gonadotropin stimulation was suspended for 4-7 days. After 4-7 days without gonadotropin stimulation, follicles were checked with TVUSG again, and in case of no change in dominant follicle size compared to the last ultrasound examination, the cycle was canceled. If the follicle size increased by more than 2 mm, then 150 IU HMG (FSH+LH) was initiated. When the leading follicle diameter exceeded 17 mm, 250 mg of rhCG (Ovitrelle, Serono) was administered to trigger final oocyte maturation. Oocyte retrieval was performed at 34 hours after the trigger.

IVF Outcomes

Oocyte denudation was performed four hours after retrieval, and intracytoplasmic sperm injection (ICSI) was applied to all mature oocytes. Embryos were cultured until day 3 or day 5. The decision on the embryo transfer day was based on the preferences of both the patient and the treating physician.

The protocol for frozen embryo transfer (FET) included the initiation of oral contraceptives on days 2-5 of the menstrual cycle after ovarian stimulation, followed by subcutaneous injection of 3.75 mg of leuprolide acetate depot (Lucrin; Abbott) in the midluteal phase. Endometrial priming was initiated with oral estradiol (Estrofem; Novo Nordisk) at a daily dose of 4 mg for 5 days, which was gradually increased to 8 mg per day. After 14 days of estradiol administration, if the endometrial thickness reached 8 mm or more and the progesterone level remained below 1.0 ng/mL, vaginal progesterone (Crinone gel 8% BID; Merck) was introduced twice daily, accompanied by 17-hydroxyprogesterone caproate (Proluton Depot; Bayer) administered twice weekly, and FET was scheduled. In cases in which the endometrial thickness was 8 mm, a 7.8 mg estradiol patch (Climara; Bayer) was added, and the patient was reassessed after 4 days. If the lining was still measured below 8 mm, the cycle was canceled. For fresh ET, luteal phase support consisted of daily vaginal progesterone (Crinone gel 8% BID; Merck) initiated the day following oocyte retrieval.

Pregnancy outcomes were assessed 12 days after ET using serum β-hCG measurement. Clinical pregnancy was defined by the presence of a gestational sac with detectable fetal heart activity, and live birth was defined as delivery after 28 gestational weeks.

Statistical Analysis

Data analysis was performed using SPSS software version 22 (SPSS-IBM 2.3, Inc., Chicago, IL, USA). The Shapiro-Wilk test was employed to assess the normality assumption of continuous variables, which was further evaluated visually through histograms and Q-Q plots. Comparisons between two groups were conducted using the Mann-Whitney U test. Continuous variables were expressed as medians with interquartile ranges (IQR), whereas categorical variables were described using frequencies and percentages (%). A p-value 0.05 was considered statistically significant.

Results

A total of 85 patients diagnosed with POR were enrolled in the study. The sociodemographic characteristics of the patients are summarized in Table 1. The median age of the patients was 41 (IQR: 37-44) years. The median duration of infertility among the couples was calculated as 48 (IQR:24-96) months. Ovarian reserve parameters including AFC, FSH, and AMH were also analyzed in the study (Median levels were 2.0 (IQR: 1-3), 23 (IQR: 11.6-37.7), 0.07 (IQR: 0.14-0.2), repectively.

The flowchart of the IVF outcomes is presented in Figure 2. After cessation of gonadotropin treatment, an increase in follicle diameter was detected in 34 of 85 (40%) patients. Among the patients who underwent egg retrieval, 29.4% (10/34) had no oocytes; 11.8% (4/34) experienced premature ovulation, and 17.6% (6/34) were unable to obtain an oocyte during the egg retrieval procedure. A total of 35 oocytes (minimum-maximum: 1-4) were obtained from the remaining 24 patients. Thirty of these 35 oocytes were mature (M2). One of the M2 oocytes was frozen. The remaining 29 M2 oocytes underwent ICSI,

Table 1. Patient characteristics and cycle parameters are presented as medians and IQR

	Median (IQR)
Age (year)	41 (37-44)
Partner's age (year)	40 (36-46)
BMI (kg/m^2)	25.7 (23-28.4)
Infertility duration (months)	48 (24-96)
Number of previous IVF attempts	2 (24-96)
Number of AFC	2.0 (1-3)
FSH (mIU/mL)	23 (11.6-37.7)
AMH (ng/mL)	0.07 (0.14-0.2)

AMH: Anti-Müllerian hormone, FSH: Follicle stimulating hormone, BMI: Body mass index, IVF: In vitro fertilization, AFC: Antral follicle count, IQR: Interquartile range

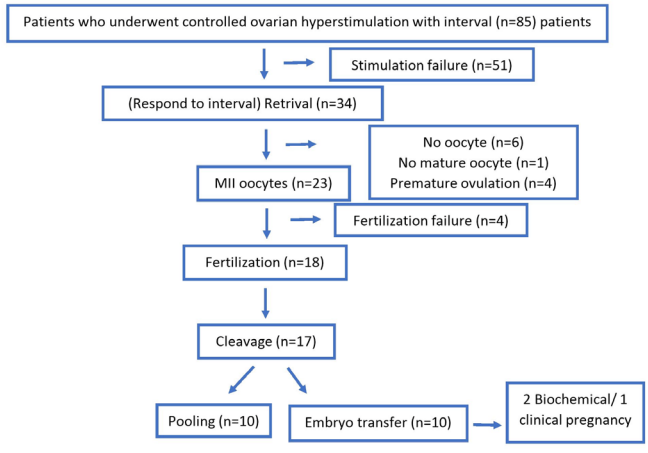

Figure 2. The flowchart of IVF outcomes

IVF: In vitro fertilization

leading to 23 2pn embryos in 18 patients (52.9%). Among these patients, 1 patient had 2 blastocyst stage embryos, 3 patients had 2 cleavage stage embryos and, 13 patients had 1 cleavage stage embryos. One patient did not have embryos that reached the cleavage stage. All the embryos of 7 patients were frozen based on the patient preference or embryo banking. Ten patients among 85 patients underwent embryo transfer (11.8%). Out of 10 patients who underwent embryo transfer, two was fresh and 8 was frozen embryo transfers. Two frozen embryo transfers were performed with cleavage embryos that resulted in a positive pregnancy test but did not result in clinical pregnancy. A blastocyst transfer was performed in another patient, resulting in a healthy live birth.

Parameters for patients with a rebound (group 1) and no rebound (group 2) to gonadotropin cessation were compared. Two groups were similar regarding age, AFC, and AMH levels. None of the patients in group 1 had significantly higher FSH levels compared to group 2 [13.1 (IQR: 9.1-27.0)] vs. 26.5 (IQR: 18.6-45); p=0.032). Also, the days of stimulation and total gonadotropin doses were similar between the two groups (Table 2).

Discussion

POR typically refers to patients with low ovarian reserve who cannot respond sufficiently to stimulation[6]. These patients account for approximately 9-24% of clinical practice[7]. ASRM/SART data show that 14.1% of IVF cycles are canceled and that 50% of canceled cycles consist of patients with a poor response[8]. As the number of obtained oocytes decreases, the declining pregnancy rates cause anxiety in both clinicians and couples. Optimal treatment for improving ovarian response in patients with POR is currently a controversial issue. The current data are insufficient to demonstrate the superiority of any treatment protocol or drug in terms of pregnancy rates among patients with a poor response[9,10]. In the present study, we showed that discontinuing the use of gonadotropins for 5-7 days in patients who did not respond to high-dose stimulation resulted in continued follicle development during the drug-free period in 40% of the patients. In total, 30 MII oocytes were obtained from 24 of 34 patients whose follicles continued to develop. Therefore, cessation of gonadotropins in this difficult-to-manage patient group may be important for the patient to have a chance of pregnancy with her own oocytes before being directed toward experimental treatments or donation.

In the present study, three patients got pregnant, two of which resulted in biochemical pregnancy and one resulted in healthy live birth. To the best of our knowledge, this study is the first to report a live birth after cessation of gonadotropin. Consistent with our results, previous studies have shown that pregnancy rates are quite low in poor responders[11]. Yin et al.[12] reported a per-patient cumulative live birth rate (CLBR) of 6.1% and a per-cycle CLBR of 2.7% in 244 patients aged 40-50 years classified as poor ovarian responders according to the Bologna criteria, and emphasized that these rates were significantly lower than those of normo-responder patients. When cumulative live birth rates were stratified by age, CLBR per cycle and per patient were found to be 4.3% and 8.8%, respectively, in the 40-43 age group. No significant differences were observed among the other age groups, and these rates were reported as 1.8% and 4.0% for patients aged 44-45, and 0.8% and 2.3% for patients aged over 45 years, respectively[12]. Polyzos et al.[13] evaluated the efficacy of ovarian stimulation in 485 patients fulfilling Bologna criteria and reported a pregnancy rate of 9.9% after fresh embryo transfer. Another study including 26,697 cycles of 19,781 patients stratified by the POSEIDON criteria in a Chinese population concluded that the cumulative live birth rates in POSEIDON groups 3 and 4 were 14.7% and 6.58%, respectively[14]. A recent study by Fanton et al.[15] suggested that the cumulative live birth rate is positively associated with the number of retrieved oocytes, and this relationship remained significant even after stratifying the patients by age, AMH, BMI, and infertility diagnosis.

One of the largest series in the literature that examined the relationship between the number of collected oocytes and live birth rates was reported by Sunkara et al.[16] this study included 400,135 cycles with fresh embryo transfer, and 49% of the patients were women aged 35 years or older. The authors reported that although live birth rates decrease with advanced maternal age, there is a strong correlation between the number of retrieved oocytes and live birth rates. Polyzos et al.[13] reported

Table 2. Hormone profiles, AFC, and IVF stimulation parameters were compared between the groups

Variables	Group 1 no response (n=51)	Group 2 response (n=34)	p
Age (year)	40 (34-44)	41 (39-44)	0.117
FSH (mIU/mL), median (IQR)	26.5 (18.6-45.0)	13.1 (9.1-27.0)	0.032
AMH (ng/mL)	0.03 (0.01-0.11)	0.08 (0.03-0.20)	0.112
Number of AFC	2 (1-3)	2 (1-3)	0.492
Day of stimulation	8 (7-9)	8 (7-11)	0.152
Total gonadotropin dose (IU)	4200 (3600-4800)	4800 (3300-5700)	0.430

All parameters are presented as median (IQR)
FSH: Follicle stimulating hormone, IQR: Interquartile range, AMH: Anti-Mullerian hormone, AFC: Antral follicle count, IVF, In vitro fertilization

that the number of retrieved oocytes was the only variable significantly associated with live births in poor responders. The authors also mentioned that there was no notable difference in live birth rates between patients aged 40 years and those aged >40 years of age. On the other hand, considering the increased risk of aneuploidy with advancing age, it is clear that the number of oocytes needed to increase the rates of live birth will vary. It has been reported that younger patients with expected POR require an average of 4-7 oocytes to obtain one euploid blastocyst, while older patients require an average of 12 oocytes[17]. Our approach may be a viable option for poor responders who struggle to achieve an adequate number of oocytes because each additional oocyte has been reported to increase the live birth rate by 5%[16,18].

The physiological basis of ovarian response in a group of patients after cessation of gonadotropin stimulation is controversial. During the menstrual cycle, the released FSH isoforms change. This change also occurs in different stages of the reproductive period as women age. This structural heterogeneity, which is called glycoform, arises from the hormone's varying degrees of glycosylation and glycan compositions[19,20]. The acidic isoforms of FSH are abundant in the early and mid-follicular phases, whereas they are less prevalent during the pre-ovulatory and ovulatory periods. In addition, the abundant form during the menopausal period is the acidic form. It has been shown that different types of FSH isoforms have diverse functions in granulosa cells, subsequently affecting oocyte maturation[21]. To the best of our knowledge, the only published report on a series of patients who exhibited follicular growth following cessation of gonadotropin was by Gleicher et al.[22]. They investigated 49 patients who did not respond to the maximum dose of exogenous gonadotropin. Gonadotropin stimulation was ceased for 4-6 days and follicular response was reported in 24 of the patients (49%). The authors suggested that follicular development may occur in patients who respond to stimulation during the stimulation-free period because of the increase in endogenous FSH, which is more compatible than exogenous FSH. After discontinuation of exogenous FSH in some patients, there may be an increase in the release of FSH isoforms that are more compatible for FSH receptors in granulosa cells in the late follicular-preovulatory phase due to negative feedback between gonadotropin withdrawal and hypothalamus.

The physiological variability in the biological structure of FSH with age and ovarian reserve raises questions about the suitability of standard FSH preparations for controlled ovarian stimulation in all patients. Although the detection of FSH isoforms in peripheral blood is not yet commonly practiced in clinical settings, identifying the gonadotropin structure that is necessary for effective ovarian stimulation based on a woman's age and formulating appropriate preparations could potentially offer higher success rates and cost[23].

Berker et al.[24] investigated the impact of early administration of human menopausal gonadotropin (hMG) on IVF outcomes in POSEIDON group 3 and 4 poor responders and found that initiating hMG in the early follicular phase significantly improved live birth rates and reduced cycle cancelations due to fertilization failure. Although this approach did not increase the total number of oocytes retrieved, it appeared to enhance embryo quality, which is a key factor in maximizing pregnancy potential in poor responders. These results highlight the importance of optimizing gonadotropin timing to improve clinical outcomes in patients with limited ovarian response. As an alternative approach, the STOP-START protocol has been suggested for those unresponsive to high-dose controlled ovarian stimulation, providing an option before cycle cancelation[25]. This method involves temporarily pausing rFSH stimulation, followed by weekly ultrasound to detect new follicular growth, which is consistent with the "second wave" theory, which posits multiple follicle recruitment waves within a menstrual cycle. In a case series of 11 women, 63.6% underwent successful oocyte retrieval, and two patients (18.2%) achieved live births. The protocol's proposed mechanism suggests that suspending rFSH may help prevent receptor down-regulation and internalization, allowing FSH receptors to become available again, and supporting follicle development upon reinitiating stimulation. These results are consistent with our approach, in which temporarily pausing gonadotropins facilitated continued follicular development. Together, these strategies demonstrate the potential of intermittent stimulation methods to foster follicular growth in poor responders, offering a practical, time-efficient alternative for patients unresponsive to high-dose stimulation.

Recent advancements in the management of POR have also highlighted promising strategies, such as intraovarian injections of autologous platelet-rich plasma (PRP). In our recent large cohort study, we demonstrated that PRP treatment significantly improved ovarian reserve markers, including an increase in AFC and AMH levels, along with a reduction in FSH levels in patients with POR[26]. These findings support the notion that enhancing ovarian response in patients with POR may require innovative approaches, and PRP could serve as an adjunctive therapy before considering oocyte donation.

In the present study, no difference was detected in terms of demographic characteristics, the number of antral follicles, and AMH levels between the groups that showed a rebound effect on cessation of gonadotropins or not. However, FSH levels were significantly higher in the group that did not rebound from the gonadotropin gap. Gleicher et al.[22] also found no significant difference between the two groups regarding the highest FSH levels, last FSH levels, and initial estradiol levels. Only patients in the responding group were older, although not significantly older. The current data indicate that it is not yet possible to determine a parameter for predicting which patients will achieve follicular development by discontinuing stimulation. Therefore, it may be appropriate to provide a chance for a rebound response by discontinuing stimulation in all patients who do not respond to high-dose stimulation.

Study Limitations

The limitations of our study include its retrospective nature and relatively small sample size, which may limit the generalizability of the findings. However, this study provides valuable data regarding a management modality in patients with POR to high-dose gonadotropin stimulation.

Conclusion

Although pregnancy rates are not high, cessation of gonadotropin administration during ovarian stimulation could potentially offer patients the opportunity to conceive with their own biological oocytes in cases where high-dose stimulation is not effective. In countries where donation is not legal or in cases where it is not an acceptable option for couples, this strategy might be an alternative.

Ethics

Ethics Committee Approval: The study was approved by the Acıbadem Mehmet Ali Aydınlar University Medical Research Ethics Committee (decision no: ATADEK-2021-04/31, date: 24.02.2021).
Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Z.E.U.K., A.Y., Ö.K., Ş.Y.K., Ç.Y., Y.Ç., B.T., Concept: Z.E.U.K., A.Y., Ö.K., Y.Ç., B.T., Design: Z.E.U.K., Y.Ç., B.T., Data Collection or Processing: Z.E.U.K., A.Y., Ö.K., Ş.Y.K., Ç.Y., Y.Ç., B.T., Analysis or Interpretation: Z.E.U.K., Y.Ç., B.T, Literature Search: Z.E.U.K., Writing: Z.E.U.K., Y.Ç., B.T.
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