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Serum Progesterone and Serial β-hCG Levels in Predicting the Outcome of Early Pregnancies with Doubtful Viability: Prospective Research

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Abstract

Objective: To evaluate the doubling rate of maternal serum serial beta human chorionic gonadotropin (β-hCG) and a single initial serum progesterone level to predict fetal viability before ultrasonography in women diagnosed with intrauterine pregnancy (IUP) of undetectable viability.

Methods: Three hundred thirty six pregnant women who applied to the outpatient Clinic at Okmeydanı Hospital between March and December 2018 were evaluated on a "prospective observational" basis. The study was completed with 100 pregnant women diagnosed with IUP involving suspected fetal viability by transvaginal ultrasonography only, who met the inclusion criteria. Serum β-hCG and progesterone levels were measured at the first admission. After 48 h, control serum β-hCG was taken and the increase rates were calculated. Early pregnancy loss was diagnosed by (transvaginal) TV-USG. Patients were divided into two groups as fetal heartbeat (FHB) positive and FHB negative. Pregnancy results were compared with β-hCG increase rates and progesterone levels.

Results: No statistically significant result was obtained between FHB +/- groups in terms of maternal age, previous pregnancy anamnesis, nationality, presenting symptoms, or ultrasound findings. The study, which was conducted with a confidence interval of 95%, found the viability rate to be 70% with a β-hCG increase rate of 31% and 100% in the case of an increase of 181%. For progesterone, when the value was 5.9 ng/mL, the viability rate was 49% and 100% at 37.5 ng/mL and above. The efficacy values of β-hCG increase and first progesterone level in predicting viability were found to be ROC AUC: [0.748 (0.621-0.874)] and ROC AUC: [0.796 (0.685-0.907)], respectively.

Conclusion: Either Serial β-hCG ratio or serum progesterone level can be used alone to predict the pregnancy outcome in early pregnancy. With the dissemination of similar studies, estimation modalities can be improved, and TV-USG examinations can help shorten the waiting time for results to reduce the anxiety of families, hospital admissions and health expenses.

Keywords: Early pregnancy loss, viability, serial β, -hCG, progesterone

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INTRODUCTION

Early pregnancy loss is a frequently encountered problem during the reproductive period, which is the longest period of female life, and it is reported as the most common complication of pregnancy. It occurs in approximately 10-15% of all clinically recognized pregnancies and affects one in every three women (1). One-third of women and approximately 80% of all pregnancy loss cases occur in the first quarter (2).

Bleeding and pain are the most common reasons why women receive medical advice during early pregnancy. This is an important cause of anxiety in women. Detection of intrauterine pregnancy (IUP) by transvaginal ultrasonography (TV-USG) following a positive beta human chorionic gonadotropin (β-hCG) excludes ectopic pregnancy except heterotopic pregnancy. However, especially during the follow-up of pregnancy of unknown locations (PUL), pregnancy viability cannot be determined at the first visit when IUP is detected (3). When an IUP is detected, the second most important step is to determine its viability. These 1- or 2-week follow-up visits may cause long-term anxiety for women, and these visits increase the cost and workload in the related healthcare facilities (4).

β-hCG is called human chorionic gonadotropin and is a pioneer in the early detection of pregnancy (1). There are two types of this hormone, alpha and beta. β-hCG hormone in a non-pregnant woman is in the range of 0-10 mlU/mL. β-hCG hormone begins to be secreted by the placenta with the realization of fertilization. Approximately 11 days after fertilization, high values of β-hCG hormone can be detected in the blood sample. In the case of pregnancy, this value should increase and continue every 2 days, exponentially compared with the previous day. If no stable increase is observed, negative pregnancy-related conditions may be in question. Serum progesterone is a test used to measure the amount of progesterone in the blood (1). Progesterone is a hormone produced mainly in the ovaries. Progesterone plays a key role in pregnancy. It is produced after ovulation in the second half of the menstrual cycle. It helps prepare a woman 's uterus for a fertilized egg to be implanted. It also prepares the uterus for pregnancy by inhibiting contraction of the uterine muscle and the breasts for milk production. It has different values throughout the menstrual cycle, at menopause, and in each trimester of pregnancy. Its unit is ng/mL or nmol/L. (Example: Pregnancy 1st trimester: 11.2 to 90.0 ng/mL or 35.62 to 286.20 nmol/L). Serial measurements of serum β-hCG, the increase percentages, and serum progesterone measurement used for the same purpose as serum β-hCG in early pregnancies are highly important in the differentiation of normal and abnormal pregnancies as well as in the prediction of fetal viability. However, both involve significant differences in the literature (5,6). No cut-off value or predictive power of any of these markers could be determined for the definitive diagnosis of IUP viability.

The aim of this study was to compare maternal serum series β-hCG and a single serum progesterone level with TV-USG for predicting fetal viability in women with IUP and to create a prediction modality using only serum markers.

METHODS

Our study was conducted in the Obstetrics and Gynecology Clinic of University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital on a single-center "prospective observational" basis between March 2018 and December 2018. The study was started after obtaining the approval of the Ethics Committee for Clinical Research of University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital under protocol number 841 on 13/03/2018. The participants were informed verbally, and in writing, and written consent was obtained.

Inclusion criteria were as follows: consent for participation in the study, being older than 18 years of age, diagnosis of IUP by TV-USG, and early pregnancy with no fetal heartbeat detected/suspected (Crown-rump Length: CRL <7 mm, mean of three orthogonal measurements Gestational Sac Diameter: mGSD <25 mm). Exclusion criteria; Being under the age of 18, having multiple pregnancies, and chronic drug use were determined. The sample size was reached by performing G*power analysis considering at least 3 similar articles in the literature. Our study included 336 pregnant women who applied to our outpatient clinic and accepted to participate in the study. One hundred-fifty-six pregnant women did not meet at least one of the inclusion criteria, 28 pregnant women did not want to continue in the study, despite initially agreeing to participate in it, and 20 pregnant women who met at least one of the exclusion criteria were excluded from the study. During the follow-ups, 32 pregnant women could not be reached, and they were also excluded from the study. Therefore, the study was completed with 100 pregnant women (Figure 1). All women were evaluated by experienced obstetricians using ultrasound devices equipped with 6-12 MHz transvaginal transducer and B-mode imaging. Pregnancy of Uncertain Viability criteria in patients with IUP confirmed by TV-USG were taken as no heartbeat below CRL <7 mm, and no embryo below mGSD <25 mm. Anamnesis information such as maternal age, previous pregnancy anamnesis, nationality, admission symptoms, and ultrasound findings of the patients were noted at the first

admission. Viability determination was performed by TV-USG on days 7, 11, and 14 pregnant women with fetal heartbeat detected or diagnosed with fetal viability (Viable: FHB (fetal heartbeat): +) were not invited to further controls. Pregnant women with undetectable fetal heartbeat were held until day 14 at the latest, and if no fetal heartbeat could be detected they were diagnosed with "early pregnancy loss" (Non-viable: FHB: -).

Serum β-hCG and progesterone levels were measured at the first admission. After 48 h, control serum β-hCG was taken and the increase rates were calculated. Serum β-hCG and progesterone levels were measured with Roche β-hCG and Progesterone II Electrochemiluminescence Immunassay (ECLIA) in Roche Cobas e411 and e602 analyzers, respectively.

As a result, patients were divided into two groups as fetal heartbeat positive group (FHB: +) and early pregnancy loss group (FHB: -). These results were interpreted with the percentage of serum β-hCG increases and progesterone value at initial admission in light of the literature

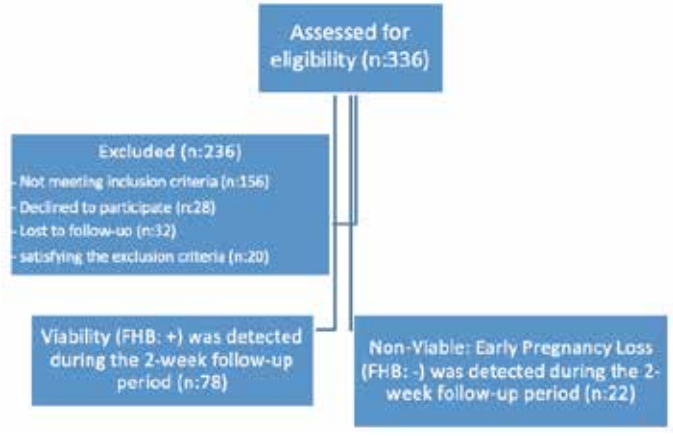

Figure 1. Flow diagram of the study

Statistical Evaluation

These two parameters were evaluated by means of the Mann-Whitney U test and Wilcoxon test. However, z-scores and percentiles adjusted according to the gestational week were used to calculate both β-hCG and serum progesterone levels. Thus, it was considered that the first progesterone level was not constant and β-hCG levels would decrease over time. A receiver operating characteristic (ROC) curve was used for the estimations, effect level, and cut-off values of numerical parameters. SPSS 22.0 (Chicago, IL, USA) was used for statistical analysis. A P-value: <0.050 is considered significant for a confidence interval of 95%.

RESULTS

Our study was started with 100 pregnant women. The patients were divided into two groups as the Viable Group; fetal heartbeat positive group (FHB:+) (n=78) and Non-viable group; (early pregnancy loss), fetal heartbeat negative group (FHB:-) (n=22) (Figure 1).

Table 1 shows the β-hCG values (control at first admission and at hour 48) and percentage of increase, serum progesterone value at first admission, TV-USG findings, and measurements of the patients participating in the study.

The mean increase in β-hCG was 54.3±36.2%, and the mean progesterone value at the first admission was 15.5±8.3. Fetal heartbeat was positive (viability +) in 78% of women (n=78) and negative (early pregnancy loss) in 22% (n=22).

Table 2 shows between the fetal heartbeat -positive and -negative groups, the serum β-hCG value at first admission showed no statistically significant difference (P>0.05). The control β-hCG values obtained after 48 h in both groups showed a significant increase (P<0.05) compared with the first admission. In the group with fetal heartbeat positive, the increase rate between

Table 1. Ultrasound and laboratory findings of patients participating in the study

All Cases	Min-max	Median	Mean ± SD/n-%
First examination β-hCG	302-200,727	18,430	25,880-30,951
Control β-hCG	848-235,654	28,817	35,962-38,268
Percentage increase in β-hCG %	0.8-181.3	52.5	54,3±36,2
Progesteron	3.3-50.0	13.7	15.5 8.3
Viability	Early pregnancy loss (FHB:)	22	22.0%
	Detected viability (FHB:+)	78	78.0%
Ultrasonography	mGSD (no CRL)	81	81.0%
	CRL detected	19	19.0%

FHB: Fetal heartbeat, USG: Ultrasoundgraphy, CRL: Crown rump length, mGSD: Mean orthogonal gestational sac diameter, Control: Second visit/β-hCG unit: mIU/mL, Serum progesterone unit: ng/mL

the two β-hCG values taken at 48 h intervals was found to be significantly higher than that in the group without fetal heartbeat (P<0.05). When the initial serum progesterone levels of the groups with and without fetal heartbeat were compared, a statistically significant difference was found between the groups (P=0.000). It was significantly higher in the FHB -positive group than in the negative group (P<0.05) (Table 3).

Figure 2 shows the predictive power graph of serum β-hCG increase rates taken at 48 h intervals in the likelihood of fetal heartbeat. According to the chart, the probability of fetal heartbeat was 70%, while the rate of increase in β-hCG value was 31%, and the probability of fetal heartbeat was 80%, 90%, 95%, and 100%, while the rate of increase in β-hCG value was 49%, 73%, 97%, and 181%, respectively. Significant efficacy (p=0.000) [0.748 (0.621-0.874] of β-hCG increase was observed in predicting the groups with and without fetal heartbeat (Figure 3: ROC curve). Significant efficacy (p=0.000) [0.796 (0.685-0.907)] of the progesterone value was observed in predicting the group with and without fetal heartbeat (Figure 4: ROC curve).

When the serum progesterone value was 5.9 ng/mL, the fetal heartbeat was 49%, and when the serum progesterone value was 10.5 ng/mL or above, the fetal heartbeat was 69%, 12 ng/mL and above 75%, 13.4 ng/mL and above 80%, 18.0 ng/mL and above 90%, 21.7 ng/mL and above 95%, 29.3 ng/mL and above 99%, and 37.5 ng/mL and above 100%.

There was no statistically significant difference in ultrasound findings between the two groups.

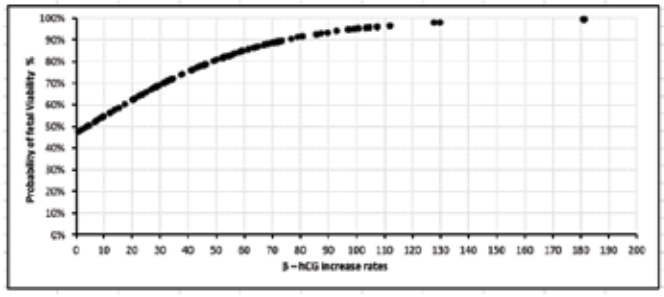

Figure 2. Chart of the likelihood of fetal heartbeat with serum β-hCG increase rates

β-hCG: Beta human chorionic gonadotropin

Table 2. Comparison of serial β-hCG, percentage of increase, and serum progesterone values between FHB +/- (viable/non-viable: Early pregnancy loss) groups

	Early pregnancy loss (FHB-)	Detected viability (FHB+)	P value
	Mean SD	**Mean SD**	
β-hCG			
First examination	16,874-16,029	28,420-33,644	0.090[m]
Control β-hCG	20,031-16,602	40,455-41,409	0.012[m]
Percentage increase(%)	32.5 32.7	60.4 34.9	0.001[m]
In-group change (P)	0.001[w]	0.001[w]	
Progesterone	9.9 6.5	17.1 8.1	0.001[m]

m: Mann-Whitney U test, [w]: Wilcoxon test
FHB: Fetal heartbeat/control: The second Visit/β-hCG unit: mIU/mL/Serum progesterone unit: ng/mL

Table 3. Comparison of TV-USG findings and measurements in FHB+/- groups

		Early pregnancy loss FHB:-		Detected viability (FHB:+)		P
		Mean ± SD/n-%	**Median**	**Mean ± SD/n-%**	**Median**	
USG	Only mGSD	19	86.4%	62	79.5%	0.468[X2]
	CRL detected	3	13.6%	16	20.5%	
USG measurement (mm)						
mGSD		10.8±4.7	10.0	11.8±4.9	12.0	0.419[m]
CRL		3.7±2.1	3.2	3.4±1.2	3.3	0.955[m]

[m]: Mann-Whitney U/[X2]: chi-squared test
FHB: Fetal heartbeat, CRL: Crown rump length, mGSD: Mean orthogonal gestational sac diameter, SD: Standard deviation, USG: Ultrasonography

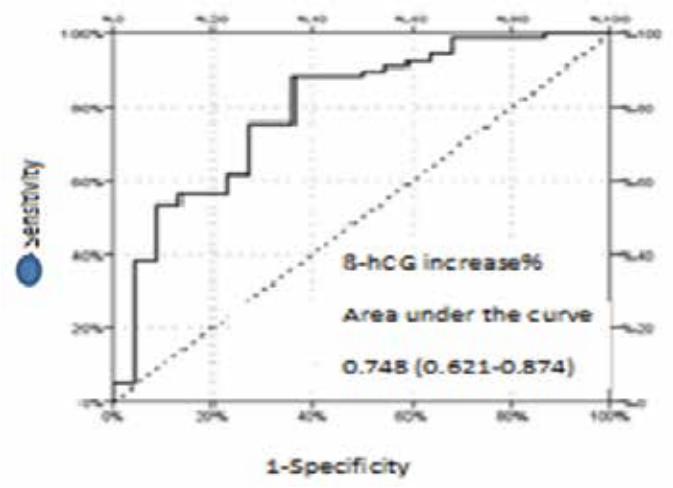

Figure 3. ROC analysis of β-hCG increase percentage in FHB +/- group prediction

β-hCG: Beta human chorionic gonadotropin, ROC: Receiver operating characteristic, FHB: Fetal heartbeat

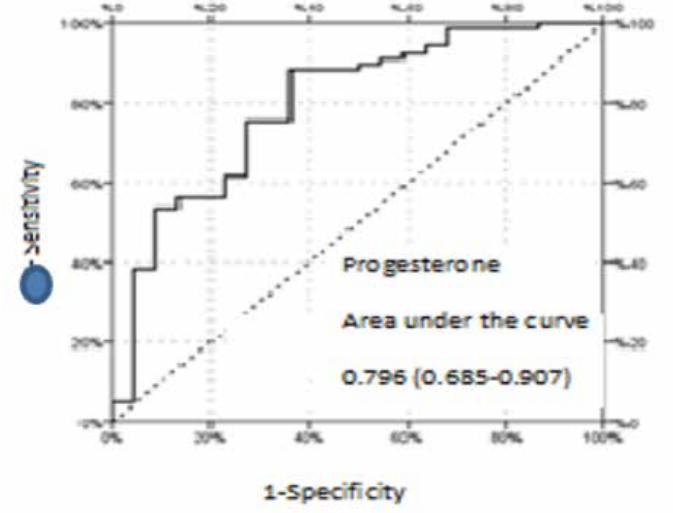

Figure 4. Serum progesterone level ROC analysis in FHB +/- group prediction

ROC: Receiver operating characteristic, FHB: Fetal heartbeat

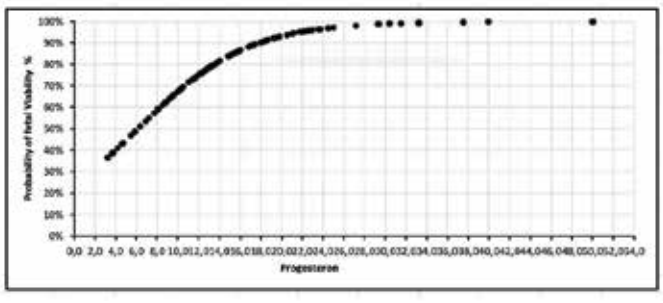

Figure 5. Serum progesterone unit: ng/mL

Chart of initial serum progesterone levels and the probability of fetal heartbeat

DISCUSSION

TV-USG has always been a classical method for predicting pregnancy outcomes in cases where viability is suspected in patients with early pregnancy, but many publications have recently studied β-hCG and progesterone values, which are serum biochemistry markers. In our study using these parameters, we found that serial β-hCG follow-ups and serum progesterone tests were effective in predicting the viability of pregnancy and compared our results with those of the current literature.

In the literature, the probability of an intrauterine cystic structure belonging to the gestational sac is 99.5% and the probability of a false sac is 0.5% (7,8). In ectopic pregnancies, the rate of false sacs was reported to be 10% (8-10). In our study, 2 of 100 patients were diagnosed with ectopic pregnancy. Considering that 81% of 100 patients had a gestational sac, the rate of false sacs in patients with an observed gestational sac was 2.46%. This is highly above the 0.5% rate stated in the literature. Considering that only 10% of ectopic pregnancies have a false sac, it is interesting that such a high rate was found only in a study on intrauterine pregnancies. This led us to conclude that clinicians should be more careful in ultrasonography examination and understand the distinction between double decidual ring appearance and actual gestational sac.

In the initial and 48-hour follow-up serum β-hCG controls, a statistically significant difference was found between the fetal heartbeat-positive group and the fetal heartbeat-negative group. Puget et al. (1) found that serum β-hCG predicts viability with 100% sensitivity and 31% specificity when the doubling rate is 75% Barnhart et al. (5) found the rate of determination of viability to be 124% increase in 2 days. Bignardi et al. (11) found that the rate of determining viability with β-hCG doubled was 78% sensitive and 67% specific. As the main purpose of our study, the fact that β-hCG doubling rate predicts viability is also consistent with many recent studies, although the rates are different. What makes our study different is that the prediction of viability is mentioned by giving only certain ratios in the literature (1,12), while in our study, a percentage is assigned to each patient in terms of viability at each increase rate of β-hCG (Figure 2). With this information, we believe that a clear rate will be provided to the patients during early pregnancy and that both the anxiety of the patients due to uncertainty and their own anxiety will be reduced by physicians providing clear information and ratio to the patients. In addition to creating an early pregnancy prediction modality, our study examined the increase rates of β-hCG in the ROC curve, determined high sensitivity cutoff values, and confirmed that the β-hCG increase rate in recent

literature could be used to predict early pregnancy outcomes. In our study, live pregnancy was achieved even with a low rate of β-hCG increase of 31%. Therefore, physicians should not diagnose pregnancy loss early, and early interventions should be avoided. The cut-off value determined in the 95% confidence interval was achieved with a minimum 97% increase in β-hCG at the hour 48. A 100% heartbeat positivity was achieved with an increase of 181%.

Puget et al. (1) found 100% pregnancy failure when the progesterone level was 6.2 ng/mL or less. In a recent French guideline, an abnormal IUP or ectopic pregnancy was found to be associated with an initial serum progesterone value of 3.2 ng/mL (3). In our study, a significant statistical result was obtained when the initial progesterone values of fetal and non-fetal heartbeats groups were compared. This was found to be consistent with the general literature (1,3). What makes our study different is that while the prediction of viability is mentioned in the literature only by giving certain ratios (11,13), in our study, a percentage can be assigned to patients in terms of viability at each value of the initial serum progesterone (Figure 5). This information makes it possible to give a clear rate to the patients during early pregnancy and reduce the anxiety of families caused by waiting for weeks. Furthermore, our study examined the initial serum progesterone level on the ROC curve, determined high sensitivity cutoff values, and confirmed that serum progesterone in the literature could be used to predict early pregnancy outcomes. A successful pregnancy was achieved even at an initial progesterone level of 3.71 ng/mL. Therefore, physicians are recommended to avoid early interventions. In addition, the cut-off value determined in the 95% confidence interval was provided at 21.7 ng/mL and above. A 100% heartbeat positivity was achieved with values of 37.5 ng/mL. The reason why we found slightly higher cut-off values compared with the general literature is the small number of patients, which is also a limitation of our study.

The 22% early pregnancy loss (EPL) rate obtained because of our study is higher than the EPL rate of 10-15% in the literature but also lower than the EPL rate of 31% after implantation (1,6,8). Although our population was a heterogeneous group of healthy and symptomatic patients, the presence of symptomatic patients at a higher rate than that in the community was considered as the likely reason for the higher rate of our EPL rates than the literature statistics. The reason why our EPL rate was lower than the EPL rate observed after implantation was considered to be the fact that patients with EPL were not evaluated without creating an intrauterine finding due to the inclusion of IUPs only with TV-USG in our population. Although the incidence of embryos was higher in the FHB -positive group than in the negative group, the incidence of gestational sacs or embryos between the FHB +/- groups was not statistically significant. This result is inconsistent with the literature because the literature states that the presence of embryos is more valuable than other ultrasound findings (yolk sac, GS) and is among the good prognostic factors (2,3). Pexster et al. (14) found variations of up to 20% between operators in CRL and mGSD measurement accuracy. It is possible to see many variations and cut-off values in the literature for diagnosis and definitions (15). Although our population is not as heterogeneous as the community and we do not study inter-operator variations, we believe that ultrasound is a subjective diagnostic tool. This is perhaps another reason why our ultrasound findings were not statistically significant in predicting early pregnancy outcomes.

Study Limitations

We acknowledge that this study has some limitations. This study did not evaluate female anxiety or satisfaction. However, there are observational findings that it provides psychological benefits. A limitation of our study was the small number of patients. Another limitation was that due to patients' previous pregnancy experiences and sociodemographic factors, patients who we predicted would be negative for FHB but could not demonstrate this ultrasonographically acknowledge this.

CONCLUSION

Because of the study, we planned to reduce the anxiety experienced by families due to the increasing patient burden and the length of time to wait for pregnancy results due to the early detection of pregnancies technologically, early detection of vitality, and a reproducible method

In this study, prediction scores for early pregnancy outcomes incorporating clinical signs, biological markers, or ultrasound findings in early pregnancy outcomes were developed, but a few studies are not sufficient to set aside TV-USG. Furthermore, the superiority of serum β-hCG and serum progesterone levels to each other was not evaluated in our study. TV-USG is an expensive examination tool for western countries, even if not for our country. Reducing subjectivity due to operators, such as ultrasound, and obtaining early results with diagnostic tools that do not require human interpretation can help reduce legal problems, families' anxiety, hospital admissions, and health costs. However, it should be noted that multicentric prospective studies with larger patient groups are needed.

Ethics

Ethics Committee Approval: The study was started after obtaining the approval of the Ethics Committee for Clinical Research of University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital under protocol number 841 on 13/03/2018.

Informed Consent: The participants were informed verbally, and in writing, and written consent was obtained.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: M.Y., E.N.Ç., Y.Ö., V.M., Concept: M.Y., G.D., S.G., V.M., Design: M.Y., G.D., S.G., O.Ş., V.M., Data Collection or Processing: M.Y., E.N.Ç., Analysis or Interpretation: M.Y., G.D., O.Ş., Y.Ö., Literature Search: M.Y., G.D., O.Ş., Y.Ö., Writing: M.Y., E.N.Ç., S.G., O.Ş., V.M.

Conflict of Interest: No conflict of interest was declared by the authors.

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