

Maternal and Fetal Outcomes in Pregnant Women with Takayasu's Arteritis: Single Center Experience over Ten Years

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ABSTRACT

Background This study aims to assess pregnant women's maternal and fetal outcomes with Takayasu's arteritis (TA).

Material and Methods The study comprised ten pregnant women at the time of diagnosis or afterwards among the 50 patients diagnosed with TA between 2003 and 2021. Twenty-one pregnancy outcomes of 10 patients were obtained from hospital records and telephonic interviews. Two pregnancies were excluded due to timing before diagnosis.

Results Based on the angiographic classification, six patients had type 1, two had type 2b, and two had type 1+4 TA. 63.15% of pregnancies were planned, and the rheumatologist approved 42.10%. Live birth occurred in 16 (84.2%) of 19 pregnancies, three pregnancies (15.7%) resulted in abortion and two (10.5%) of 19 pregnancies ended in neonatal death. In five (26.3%) of the 19 pregnancies, the disease was activated during pregnancy. Two neonatal deaths were from the two patients diagnosed with preeclampsia during pregnancy. Pre-existing hypertension and active disease are shared features of these two patients. After one year of follow-up, six pregnancies (31.5%) had active disease, and four (66.6%) had active disease both before and during pregnancy. While fetal data analysis revealed no congenital anomalies, four pregnancies resulted in low birth weight and intrauterine growth retardation (21.05%).

Conclusions The risk of developing preeclampsia and neonatal death should be considered, especially in TA patients with pre-existing hypertension who become pregnant during active disease.

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INTRODUCTION

Takayasu's arteritis (TA) is a rare systemic granulomatous vasculitis affecting large vessels.^{1,2} It is most frequently seen in young females and has a male-to-female ratio of ¼. Age at onset is less than 30 in approximately 90% of patients.¹ As the disease mainly affects young women of childbearing age, pregnancy is more common than in other vasculitides.^{2,3} Although it is a common disease in young women, it is relatively uncommon to be diagnosed during pregnancy.⁴ Diagnosis is often delayed due to the insidious onset of the disease and nonspecific initial symptoms.³ However, obstetricians may be unfamiliar with diagnostic criteria, clinical activity evaluation, and management.⁵

While most pregnancies in women with TA are successful, they are predisposed to complications, particularly during the peripartum period.² New-onset arterial hypertension (HT), worsening of pre-existing chronic HT, preeclampsia, increased risk of arterial occlusion, development of an aortic aneurysm, heart failure, and cerebrovascular accident are critical complications for the mother.⁶ Severe HT and preeclampsia affect 8% of the general population and 40% of TA patients.² Increased blood volume, cardiac load, and a continual inflammatory process in the vasculature may aggravate vascular lesions in a pregnant woman with TA.⁷ Intrauterine growth retardation (IUGR), low birth weight (LBW), and even stenosis, which restricts regional blood flow and leads to fetal death, are all increased fetal risks compared to normal pregnancies.^{6,8,9} In a systematic literature review of more than 200 pregnancies in women with TA, 20% of pregnancies were complicated by IUGR or LBW.¹⁰ Maternal and fetal complications are more likely to occur in those with severe maternal disease.² As a result, achieving optimal outcomes for mother and baby requires a focus on good management of this process.¹¹

There is limited data to guide the management of vasculitis during pregnancy. It's important to discuss maternal and obstetric complications in TA patients due to disease activity and primary organ damage.^{11,12} Ideally, patients should have minimal disease activity for at least six months before conception, which should be maintained by drugs that can be used during pregnancy.^{11,13} No systematic reports or guidelines exist on monitoring pregnant TA patients and their treatment before, during, and after pregnancy.¹⁴ Unanswered questions include the risk factors for adverse obstetric outcomes and the effect of immunosuppressive drugs,

aspirin, and antihypertensive medications on pregnancy outcomes.¹⁵

As a result, we summarised the data from 19 pregnancies of 10 patients complicated by TA to determine convenient and effective peri-pregnancy treatment measures and monitoring methods.

MATERIAL AND METHODS

Among the 50 patients we followed up with TA diagnosis between 2003 and 2021, 10 patients who were pregnant at the time of diagnosis or after that were included in the study. All patients were diagnosed using the American College of Rheumatology 1990 classification criteria.¹⁶ This study was conducted with the approval of the Uludağ University Faculty of Medicine Clinical Research Ethics Committee, 2011-KAEK-26/332.

The data of 21 pregnancies of ten patients were evaluated retrospectively, and patients whose pregnancies were during or after TA diagnosis were included in the study. Patients were contacted by phone and asked about their pregnancy. Due to timing before diagnosis, two pregnancies were excluded. Nineteen pregnancies were evaluated.

The angiographic classification of TA was defined based on the classification proposed by Hata *et al* in 1996.¹⁷ Patients with TA were also classified according to Ishikawa's severity criteria,¹⁸ which include the following three groups: Group 1 (patients without complications), Group 2 (patients with one of the following complications: retinopathy, secondary HT, aortic regurgitation, or aortic or arterial aneurysm); Group 2 was further subdivided into severity classes 2a (not severe) and 2b (severe); and Group 3 (patients with two or more of the complications mentioned above).

Patient characteristics, disease severity (TA activity), maternal adverse events (new-onset arterial HT, worsening of pre-existing chronic HT, preeclampsia, eclampsia, hemolysis, elevated liver enzymes, low platelet [HELLP] syndrome), time (preterm delivery), and mode of delivery (caesarean section [C/sec], normal spontaneous vaginal delivery [NSVD]) and newborn outcomes (LBW, IUGR, neonatal intensive care unit [NICU], congenital anomaly, fetal death) were evaluated. LBW was defined as a birth weight of less than 2,500 g, while preterm delivery was defined as delivery before the 37th

week of pregnancy.¹⁹ IUGR was defined as the fetus's weight being less than the 10th centile for gestational age.²⁰ In this study, we defined pregnancy morbidities as spontaneous abortion, therapeutic abortion, and fetal and maternal complications such as preterm birth, LBW, IUGR, congenital anomaly, NICU admission, preeclampsia or eclampsia, gestational HT, or gestational diabetes mellitus (DM).²¹

The World Health Organization (WHO) defines fetal death as the intrauterine death of a fetus, as a baby with no signs of life at or after 28 weeks of gestation for international comparison.²² Neonatal death is defined as an infant death before 28 days of age.²³ Early neonatal deaths occur before the first seven days from birth, and late neonatal deaths occur between seven and 27 days of age. Postneonatal death is an infant death between 28 and 365 days of age.²³

While determining the activation of our patients, we used the Indian Takayasu Clinical Activity Score 2010 (ITAS).²⁴ ITAS2010 with acute phase reactants (APR) (ITAS-A) was calculated by combining ITAS2010 with APR (either erythrocyte sedimentation rate [ESR] or C-reactive protein [CRP]) as suggested by Misra *et al.*²⁴

Statistical analysis

Statistical analysis was performed with the Statistical Package for the Social Sciences 26.0 (SPSS, Chicago, IL) program. Continuous variables were expressed as medians with interquartile ranges, whereas categorical variables were expressed as percentages. The distribution of variables was checked with the Kolmogorov-Smirnov test.

Table 1. General characteristics of the patients (n: 10).[†]

Age (years)	33.5 ± 6.04 – 34 (24:41)
Age of disease onset (years)	23.3 ± 5.43 – 23 (16:34)
Disease duration (years)	10.2 ± 5.9 – 9 (3:19)
BMI (kg/m ²)	25.8 ± 5.1 – 25.8 (17.8:35.2)
Diagnosed during pregnancy	
Yes	2 (20%)
No	8 (80%)
Angiographic classification at diagnosis	
I	6 (60%)
I+4	2 (20%)
2b	2 (20%)
Ishikawa classification at diagnosis	
I	7 (70%)
2a	1 (10%)
2b	2 (20%)
3	0
Activation of disease before pregnancy [‡]	
Remission	14 (73.6%)
Active	2 (10.5%)
Unknown	3 (15.7%)
Activation of disease during pregnancy [‡]	
Remission	12 (63.1%)
Active	5 (26.3%)
Unknown	2 (10.5%)
Activation of disease at 3 months post-pregnancy [‡]	
Remission	7 (36.8%)
Active	3 (15.7%)
Unknown	9 (47.3%)
Activation of disease one year after pregnancy [‡]	
Remission	10 (52.6%)
Active	6 (31.5%)
Unknown	3 (15.7%)

BMI: body mass index.

The values were expressed as n (%), mean ± standard deviation – median (interquartile range) and (minimum:maximum).

[†]Evaluation was made based on the course of 21 pregnancies, two of which occur before diagnosis (n: 19 pregnancies). [‡]Evaluation was made on pregnancies.

RESULTS

Based on the angiographic classification, six patients had type 1, two had type 2b, and two had type 1 + 4 TA (Table 1). The mean gestational age was 29.5 ± 4.2 years (Table 2). 63.15% of pregnancies were planned, and the rheumatologist approved 42.10%.

Live birth occurred in 16 of 19 pregnancies (84.2%),

and three (15.7%) resulted in abortion. There were three patients (30%) with chronic HT. Preeclampsia was seen in two of 19 pregnancies (10.5%) and two of 10 patients (20%). These two patients were diagnosed with TA during an investigation into preeclampsia during their pregnancy. Pregnancy outcomes of 19 pregnancies in 10 patients with TA were shown in Table 3. The mean gestational age at delivery of the

Table 2. Pregnancy and fetal data of patients (n: 10).

Total pregnancies [†]	19
Live births	16 (84.2%, 94.1% [‡])
Age of delivery (years)	$29.5 \pm 4.2 - 30$ (23:38)
Maternal age > 35 years at delivery	One patient and two pregnancies
Duration between diagnosis and pregnancy (months)	$63.8 \pm 48.7 - 48$ (1:180)
Spontaneous abortion (= missed abortus)	1 (5.2%)
Therapeutic abortion	2 (10.5%)
Mode of delivery	
Normal spontaneous vaginal delivery	4 (21.05%)
Caesarean section	12 (63.1%)
Unknown	3 (15.7%)
Pregnancy plan	
Planned pregnancy	12 (63.15%)
Unplanned pregnancy	7 (36.8%)
Approval of the rheumatologist	
Has approval	8 (42.10%)
No approval	10 (52.6%)
Unknown	1 (5.2%)
Perinatal follow-ups	
Yes	14 (73.6%)
No	0
Unknown	5 (26.3%)
Fetal outcomes	
Birth weight (g)	$2,742 \pm 954 - 2,895$ (530:4,100)
Gestation week	$32.6 \pm 11.5 - 38$ (7:41)
Preterm birth < 37 weeks gestation [‡]	4 (25%)
Low birth weight	4 (21.05%)
Intrauterine growth retardation	4 (21.05%)
Neonatal death [§]	1 (5.2%)
Post neonatal death [¶]	1 (5.2%)
Intrauterine fetal death	0
Neonatal intensive care unit	2 (10.5%)
Congenital malformation	0
Maternal complications	
Chronic hypertension	3 (15.7%)
Preeclampsia	2 (10.5%)
Gestational diabetes mellitus	1 (5.2%)
Pregestational diabetes mellitus	0
Thyroid diseases [∞]	3 (15.7%)

The values were expressed as n (%), mean \pm standard deviation – median (interquartile range) and (minimum: maximum).

[†]Evaluation was made based on the course of 21 pregnancies, two of which occurred before diagnosis (n: 19 pregnancy). [‡] Abortions were not included. [§] Neonatal death occurred in the sixth day of the birth = Early neonatal death. [¶] Postneonatal death occurred in the 240. day of the birth. [∞] If we exclude two therapeutic abortions. [∞] hypothyroidism, subacute thyroiditis, and toxic adenoma.

Table 3. Detailed pregnancy outcomes of 19 pregnancies in 10 patients with Takayasu's arteritis.

Patients	GPA	Classification Angiographic-Ishikawa	Comorbidities	Live birth	Age at delivery	Gestational age at delivery (or abortion) (week)	Birth weight (g)	Pregnancy morbidities	Mode of delivery	Disease activity of TA during pregnancy [†]	Medication during pregnancy	Daily dose of steroid during pregnancy [‡]
1 [†] -A	G5P3A2	I	2a	HT	Yes	24	26	530	Preeclampsia, postneonatal ex	C/sec	No antihypertensive	No
1-B					No	27	9	N/A	Spontaneous abortion (=missed abortion)	N/A	IFX, AZA, ASA, LT4	No
1-C					Yes	30	38+5	2,890	No	C/sec	IFX, AZA, HCQ, ASA, LMWH, LT4, antihypertensive	No
1-D					Yes	31	38+3	2,900	No	C/sec	AZA, HCQ, ASA, LMWH	5 mg
2-A	G3P2A1	IIb	I	None	Yes	27	39	3,750	No	C/sec	No	5 mg
2-B					No	31	7	N/A	Therapeutic abortion	N/A	IFX	No
2-C					Yes	33	38	2750	No	C/sec	TCZ (6 week), AZA, ASA	5-10 mg
3-A	G1P1A0	I	I	None	Yes	27	39	2,870	No	C/sec	CZP, ASA	5-10 mg
4 [†] -A	G2P2A0	IIb	I	None	Yes	32	40+5	4,100	Gestational DM	C/sec	ADA, LT4	10 mg
5-A	G1P0A0	I	I	None	Yes	28	39	3,365	No	NSVD	IFX, MMF	5 mg
6-A	G2P2A0	I	I	PsA	Yes	29	39	2,680	No	C/sec	ADA	2.5-10 mg
6-B					Yes	31	40	2,980	No	C/sec	No	5-10 mg
7-A	G3P2A1	I+IV	2b	HT	Yes	34	32	960	Preeclampsia, neonatal ex	C/sec	No antihypertensive	No
7-B					No	37	8	N/A	Therapeutic abortion	N/A	IFX, antihypertensive, ASA, LMWH, antithyroid	No
7-C					Yes	38	37	2,985	No	C/sec	No	No
8-A	G1P1A0	I	I	None	Yes	24	39+5	3,580	No	NSVD	MTX, HCQ	2.5-5mg
9-A	G2P1A0	III	I	None	Yes	23	35	2,030	Placental insufficiency	NSVD	TCZ (4 week), LMWH	5-10 mg
9-B					Yes	24	38+5	3,450	No	NSVD	ASA	10 mg
10-A	G1P1A0	I+IV	2b	HT, thalassaemia	Yes	31	35+6	2,010	Oligohydramnios	C/sec	AZA, HCQ, antihypertensive	30 mg

G: gravidity, P: parity, A: abortus, HT: hypertension, PsA: psoriatic arthritis, DM: diabetes mellitus, C/sec: caesarean section, NSVD: normal spontaneous vaginal delivery, ASA: acetylsalicylic acid, LT4: levothyroxine, LMWH: low-molecular-weight heparin, AZA: azathioprine, HCQ: hydroxychloroquine, MMF: mycophenolate mofetil, MTX: methotrexate, IFX: infliximab, TCZ: tocilizumab, CZP: certolizumab pegol, ADA: adalimumab, N/A: not available.

†1 and 4: Both patients had one pregnancy before diagnosis. ‡: ITAS/ITAS.A was used to assess disease activity. †: Prednisolone equivalent dose.

neonates was 32.6 ± 11.5 weeks. In four pregnancies (26.6%), preterm birth occurred before 37 weeks of gestation. Two of 19 pregnancies resulted in neonatal death (10.4%), and the need for NICU was also seen in these two pregnancies. No congenital malformations were observed, but LBW and IUGR were observed in four pregnancies (21.05%).

According to ITAS2010 and ITAS.A, the disease was active during pregnancy in five of the 19 pregnancies (26.3%) and four of 10 patients (40%) (Table 4). Six pregnancies (31.5%) were found to have active disease after one-year follow-up, and four (66.6%) had active disease both before and during pregnancy. When the patients were classified according to Ishikawa's severity criteria, only three were classified as class 2; three developed preeclampsia and oligohydramnios. Preeclampsia patients were in classes 2a and 2b. Another patient with oligohydramnios was found to be in 2b.

All patients except two used tumour necrosis factor-alpha (TNF- α) inhibitors before or during pregnancy. When the number of pregnancies was analysed, it was discovered that biologics were

utilised before pregnancy in ten pregnancies (52.6%). However, the biological agent was only sustained in three out of ten pregnancies (30%). Regarding the interrupted biological agent, two of the remaining seven pregnancies used tocilizumab, and five used TNF- α inhibitors. Steroid use was found in 12 of 19 pregnancies (63.1%); the maximum dosage observed was 30 mg, which just one woman used. Only two patients did not receive any treatment, including conventional, biologic disease-modifying antirheumatic drugs (DMARDs) and steroids. These two patients were the two patients who were diagnosed with TA as a result of preeclampsia during pregnancy.

DISCUSSION

Handling pregnant patients with TA is frequently challenging due to the disease's cardiovascular and cerebrovascular complications and the lack of pregnancy-specific therapy guidelines.²⁵ Exacerbation of pre-existing HT and preeclampsia are the most common complications of TA in pregnancy.²⁶⁻²⁸

Table 4. Disease activity evaluation based on ITAS2010/ITAS.A scoring.

Patients	Disease activity pre-pregnancy		Disease activity during pregnancy		Disease activity in the three months after pregnancy		Disease activity one year after pregnancy	
	ITAS2010	ITAS.A	ITAS2010	ITAS.A	ITAS2010	ITAS.A	ITAS2010	ITAS.A
1-A	N/A	N/A	Active (4)	N/A	N/A	N/A	Active (8)	Active (11)
1-B	Inactive	Inactive	Active (2)	Active (5)	Active (3)	Active (5)	Inactive	Inactive
1-C	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive
1-D	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive	N/A	N/A
2-A	Inactive	Inactive	Inactive	Inactive	N/A	N/A	Active (4)	Active (7)
2-B	Inactive	Inactive	N/A	N/A	Inactive	Inactive	Active (2)	Active (5)
2-C	Active (2)	Active (5)	Inactive	Inactive	Active (2)	Active (5)	Active (4)	Active (7)
3-A	Inactive	Inactive	Inactive	Inactive	N/A	N/A	Inactive	Inactive
4-A	Inactive	Inactive	Inactive	Inactive	N/A	N/A	Inactive	Inactive
5-A	Inactive	Inactive	Inactive	Inactive	N/A	N/A	Inactive	Inactive
6-A	Inactive	Inactive	Inactive	Inactive	N/A	N/A	Inactive	Inactive
6-B	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive
7-A	N/A	N/A	Active (6)	N/A	Active (3)	N/A	Active (2)	Active (4)
7-B	Inactive	Inactive	N/A	N/A	N/A	N/A	Inactive	Inactive
7-C	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive	N/A	N/A
8-A	Inactive	Inactive	Inactive	Inactive	Inactive	N/A	N/A	N/A
9-A	Active (2)	Active (5)	Active (2)	Active (5)	N/A	N/A	Inactive	Inactive
9-B	Inactive	Inactive	Inactive	Inactive	N/A	N/A	N/A	N/A
10-A	N/A	N/A	Active (4)	Active (6)	Inactive	Inactive	Active (3)	Inactive

ITAS2010: Indian Takayasu Clinical Activity Score 2010, ITAS.A: ITAS2010 with acute phase reactants, N/A: not available.

1-A and 7-A: The reason for being active was that the diagnosis was made during pregnancy. 1-B: spontaneous abortion, 2-B and 7-B: therapeutic abortion, 9-B: since the pregnancy was over, there was no three months or 1-year follow-up.

Infradiaphragmatic artery involvement, especially renal artery stenosis, appears to be the leading risk factor in most studies.^{4,15,26-29} However, in a French cohort of 98 pregnant women, preeclampsia and IUGR-related renal artery involvement were not observed.³⁰ Similarly, two individuals with preeclampsia in our research had pre-existing HT and only one developed thickening of the renal artery wall.

While the rate of intrauterine fetal death is 1-2% in the general population, it is 4-5% in TA patients.^{10,15,30,31} There were no intrauterine deaths in our patients, and the live birth rates were similar to those in healthy women, totalling 84%-94% (if we exclude two therapeutic abortions).¹⁵ However, two (10.4%) neonatal deaths from the two patients diagnosed with preeclampsia during pregnancy occurred in our research. One neonatal death on the sixth day of the birth was named "early neonatal death" due to severe intrauterine growth restriction and placental ischaemia due to preeclampsia. Also, one neonatal death occurred in the 240. day of the birth named "postneonatal death" preeclampsia-induced severe intrauterine growth restriction and placental ischaemia. These two patients had a shared history of pre-existing HT and active disease.

Patients with active or newly diagnosed vasculitis are more likely to experience disease flares, increasing their risk of premature delivery and miscarriage.²⁶ A recent study noted that preterm deliveries occur in 17% of patients, with ranges in the literature between 4 and 30% and fetal loss between 8 and 30%.^{14,25,30,32} Although the median gestational age at delivery was 38 weeks in our study, 25% of our cohort had preterm birth: two due to preeclampsia, one for suspected placental insufficiency, and one due to oligohydramnios. Moreover, as reported in the literature, all our patients had active disease during pregnancy.

Pre-pregnancy diagnosis and maintaining target blood pressure values with strict preconceptional disease control have improved successful pregnancy outcomes.^{3,4,32,33} The fact that two neonatal deaths occurred in our study in these two patients diagnosed during pregnancy, and the disease remained active one year after pregnancy demonstrated the critical nature of pre-pregnancy diagnosis and disease remission, consistent with the literature.

It is challenging to assess disease activation during pregnancy. Angiography is not recommended during pregnancy due to the risk of fetal damage from the

contrast material and radiation.⁹ ESR cannot be used for activity assessment as it may be elevated during pregnancy. CRP and colour Doppler ultrasound (US) are more appropriate for assessing pregnancy activity.^{9,34} Conversely, CRP is not a TA-specific marker and can be affected by infection, trauma, and other factors. As pregnancy progresses, abdominal vascular US usage decreases, and operator-dependent errors rise.⁹ We used ITAS-A to measure disease activation.

IUGR and LBW are the most frequently reported complications in newborns. Although previously reported rates ranged between 4% and 52%, this rate was found to be 20% in a literature review involving more than 400 pregnant women.²⁸ Bilateral renal artery involvement is the most significant risk factor.^{15,30,32} Renin synthesis increases when the renal artery is obstructed, which would explain HT and reduced uteroplacental circulation that causes growth restriction.³³ IUGR and LBW occurred in 21.05 % of pregnancies and 40% of patients in our study. One of these patients had involvement of both renal arteries, while the other one had involvement of only one renal artery.

Vaginal delivery and epidural anaesthesia are preferred in pregnant women with TA. C/sec is recommended in pregnant women with stage 2b and 3 TA to prevent cardiac decompensation due to increased blood pressure during uterine contractions and cardiac output during labour.⁸ Again, obstetric reasons such as IUGR, prolonged labour, and decreased fetal heartbeats are the primary reasons for C/sec, which occurs at a rate of approximately 50%.³⁵⁻³⁷ Concerns about the underlying disease accounted for 40% of the reasons for the C/sec one study.³⁸ In our study, it was observed that 63.1% of our patients had labour by C/sec. The high C/sec rate was considered a cause of concern among physicians related to TA.

Preconception counselling is vital for regulating cytotoxic drugs, folic acid replacement, and deciding the best time for pregnancy. The presence of chronic HT, vasculitis and active disease six months before conception are factors associated with poor pregnancy outcomes. Pregnancy should ideally be planned during the remission phase. Screening for blood pressure, renal function, cardiac status, and preeclampsia is crucial at regular prenatal visits. Fetal follow-up parameters should also be evaluated, including daily fetal kick count, gravidogram, serial fetal biometry, biophysical profile, and fetal Doppler US.³⁹

As with preconception counselling, patients should be encouraged to have routine postpartum follow-up (3 months), as 20-40% of patients experience flares during this period.²⁶ In our study, postpartum disease activation was 15.7%. This rate, however, may not be reliable, given that 47.3% of patients did not return for follow-up over this period. Our study allowed us to self-critique and showed that we should be more cautious when advising patients on postpartum third-month follow-up.

Several limitations existed in our study. This study didn't have enough pregnancies to accurately represent all TA patients' pregnancy morbidity. The retrospective design requires caution in interpreting our study's findings. However, this study will help collect more clinical data for prospective studies on this rare condition. Additionally, one-year follow-up data on disease activation help examine disease progression.

Conflict of Interest

The authors have no conflicts of interest to declare.

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Ethical Approval

The protocol of the study was approved by the Medical Ethics Committee of Uludag University Faculty of Medicine Clinical Research Ethics Committee, approved this study (REC number: 2011-KAEK-26/332, date: 18.07.2019).

Authors' Contribution

Study Conception: BY, ED, YP; Literature Review: BY, BNC, OS; Critical Review: BY, BNC, OS, ED, YP; Data Collection and/or Processing: BY, BNC; Analysis and/or Data Interpretation: BY, BNC; Manuscript preparing: BY.

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