DOI: 10.4274/anatoljmed.2024.75046
Anatol J Gen Med Res 2024;34(2):219-26

CLINICAL RESEARCH / KLİNİK ARAŞTIRMA

ANATOLIAN JOURNAL of GENERAL MEDICAL RESEARCH

Exploring the Effect of Aspirin on Preeclampsia Clinic: Does It Make Any Difference Even If It Does Not Prevent the Disease?

Aspirinin Preeklampsi Kliniğine Etkisinin Araştırılması: Hastalığı Önlemese Bile Kliniği Hafifletiyor Mu?

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Cite as: Sağkol Karaduman H, Uygur L, Demirci O. Exploring the Effect of Aspirin on Preeclampsia Clinic: Does It Make Any Difference Even If It Does Not Prevent the Disease?. Anatol J Gen Med Res. 2024;34(2):219-26

Abstract

Objective: To find out whether there is a benefit in aspirin prophylaxis for alleviating the adverse outcomes of preeclampsia even if it would not prevent the disease. Preeclampsia is one of the major complications of pregnancy, which has life-long consequences for the mother and the baby. For the past few decades, aspirin prophylaxis has taken attention as a prevention method. However, it does not ensure the prevention of the disease. This study investigated whether aspirin still has a beneficial effect in easing the clinic even if it does not prevent the disease.

Methods: This retrospective study includes 541 preeclamptic patients in a tertiary center. The patients were allocated into two groups: Those who took aspirin prophylaxis during pregnancy (study group) and those who didn't (control group). Maternal clinical parameters, complications of preeclampsia, and fetal/neonatal outcomes were compared between the groups.

Results: No significant difference was found in clinical parameters suggesting preeclampsia with severe features. HELLP syndrome was significantly higher in the study group. Maternal complications like eclampsia, renal failure, pulmonary edema, disseminated intravascular coagulation, abruptio placenta, and transfusion of blood products didn't differ between the groups. Neonatal outcomes were significantly worse in the study group.

Conclusion: In this study, aspirin was not found to improve maternal and neonatal outcomes in an already established preeclampsia clinic. However, the imbalance in maternal baseline risk profile remarkably affected the results. Future studies with larger sample sizes and groups with comparable risk profiles should be conducted.

Keywords: Preeclampsia, aspirin, maternal complications, perinatal outcomes

Öz

Amaç: Hastalığı önlemese bile preeklampsinin maternal ve fetal olumsuz sonuçlarını hafifletmede aspirin profilaksisinin bir faydası olup olmadığının araştırılmasıdır. Preeklampsi, anne ve bebek için yaşam boyu sonuçları olan, gebeliğin en önemli komplikasyonlarından biridir. Aspirin, erken preeklampsiyi önlemede etkisi kanıtlanmış bir yöntem olarak klinik uygulamaya girmiştir. Ancak hastalığın önlenmesini garanti etmez. Bu çalışmada aspirinin hastalığı önleyemediği olgularda bile hastalığın maternal ve fetal kliniği iyileştirmede faydalı etkisinin olup olmadığı araştırılmıştır.

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Received/Geliş tarihi: 25.06.2024
Accepted/Kabul tarihi: 22.07.2024

Öz

Yöntem: Bu, üçüncü basamak bir merkezdeki 541 preeklamptik hastayı içeren retrospektif bir çalışmadır. Hastalar gebelikte aspirin profilaksisi alanlar (çalışma grubu) ve almayanlar (kontrol grubu) olmak üzere iki gruba ayrıldı. Gruplar arasında annenin klinik parametreleri ve preeklampsinin komplikasyonları ile fetal/neonatal sonuçlar karşılaştırıldı.

Bulgular: Ciddi özellikler gösteren preeklampsiyi düşündüren klinik parametrelerde anlamlı farklılık saptanmadı. HELLP sendromu çalışma grubunda anlamlı olarak daha yüksekti. Eklampsi, böbrek yetmezliği, akciğer ödemi, yaygın damar içi pıhtılaşma, plasenta dekolmanı, kan ürünleri transfüzyonu gibi maternal komplikasyonlar gruplar arasında farklılık göstermedi. Çalışma grubunda neonatal sonuçlar anlamlı derecede daha kötüydü.

Sonuç: Bu çalışmada, preeklampsi gelişmiş olan hastalarda hastalığın aspirin profilaksisi altında gelişmiş olmasının maternal, fetal, neonatal sonuçları iyileştirdiği bulunamamıştır. Ancak maternal bazal risk profilindeki, ko-morbiditelerdeki dengesizlik sonuçları önemli ölçüde etkilemiştir. Gelecekte eşit risk profiline sahip gruplarla geniş örneklem sayılı çalışmalar yapılmalıdır.

Anahtar Kelimeler: Preeklampsi, aspirin, maternal komplikasyon, perinatal sonuçlar

Introduction

Preeclampsia (PE) is a multisystemic disorder that affects 2-8% of pregnancies, accounting for 10 million pregnant women worldwide per year[1]. It causes significant maternal and perinatal morbidity and mortality. It has lifelong consequences such as chronic hypertension, renal failure, cardiovascular and cerebrovascular diseases for the mother. Additionally, for the baby, the risk of chronic diseases related to prematurity or fetal growth restriction, such as cerebral palsy, neurodevelopmental impairment, respiratory diseases, hypertension, insulin resistance, obesity, cardiovascular diseases, and renal dysfunction, is increased[2]. For many years, numerous studies have been conducted to identify those women who are at risk of PE, and to invent preventative treatments for those women[3]. Despite the algorithms that can detect 96% of the cases who require delivery <34 gestational weeks for preeclampsia, and the well-proved preventative effect of aspirin, which can reduce preterm PE by 62%, the prevalence of the disease has not been changed dramatically for the last few decades[3,4]. This fact raises two main questions: What factors reduce the preventional effect of aspirin? Is there any beneficial effect of aspirin on maternal and perinatal outcomes, even if it cannot prevent the development of preeclampsia?

This study aims to compare the maternal and perinatal outcomes between those patients who develop PE while under treatment with aspirin and those who develop PE while not being treated with aspirin. The second aim is to identify the characteristics of the patients that reduce the effect of aspirin on preventing preeclampsia.

Materials and Methods

This retrospective observational cohort study was approved by the Local Ethics Committee of University of Health Sciences Turkey, Zeynep Kamil Women and Children Diseases Training and Research Hospital (approval date: 10.05.2023, no: 79). It was conducted following the ethical standards described in an appropriate version of the 1975 Declaration of Helsinki, as revised in 2000. Informed consent stating that the data can be used for scientific purposes has been routinely provided from all the patients who applied to the clinic. It was conducted in the Maternal Fetal Medicine clinic of a single tertiary center. Patients diagnosed with PE in the antepartum, intrapartum, or postpartum period between January 2020 and December 2023 were retrospectively recruited via electronic patient records. Exclusion criteria were as follows: Multiple pregnancies, adolescent pregnant, intrauterine fetal infections, chromosomal or structural fetal anomalies, patients with known heart disease or hemorrhagic diatheses, Coronavirus disease-2019 infection during pregnancy, obstetric complications resulting in preterm delivery irrelevant to PE (preterm premature rupture of membranes, placental insertion or invasion anomalies, cholestasis, uncontrolled diabetes, spontaneous preterm delivery, etc.). Obstetric history, conception method, personal and familial medical history, use of tobacco, alcohol, and other substances, laboratory results, peripartum clinical findings, and peripartum maternal, fetal, and neonatal complications were obtained from the hospital's electronic records and manual patient charts. Regarding the laboratory results, the 24-hour-urine protein level in the last week of the antepartum period, antepartum hemoglobin on the day of delivery, and postpartum count of blood cells, liver, and renal function tests in the first 6 hours of the postpartum period were recorded for the analyses.

Patients were divided into two groups: Those not prescribed aspirin during pregnancy (control group) and those under aspirin prophylaxis (study group). Maternal demographic data associated with risk of PE, clinical data during

the hospital follow-up, peripartum laboratory results, peripartum maternal complications related to PE, and fetal and neonatal outcomes were compared between the two groups.

Statistical Analysis

Categorical variables are expressed as frequency (n) and percentage (%), and continuous variables are expressed as mean, standard deviation, median, minimum and maximum value. Normality behaviors were assessed with the Kolmogorov-Smirnov test. In comparisons between the two groups, the Mann-Whitney U test was used when the normality level was not met, and the Independent Samples t-test (Independent Samples t-test) was used when it was met. Associations between categorical variables were assessed by chi-square/Fisher's Exact analysis. IBM SPSS.25 program was used in all analyses, and $p<0.05$ was accepted as the significance level.

Results

A total of 670 patients with PE were identified, and 541 of them were included. Table 1 demonstrates the demographic and clinical features of the entire cohort. It was remarkable that 38.3% of the cohort had a family history for hypertension, and 14% had chronic hypertension.

Table 2 shows clinical data and complications related to PE in the current pregnancy for the entire cohort.

A total of 157 patients were included in the study group, and 384 cases were included in the control group. Table 3 summarizes the comparison of demographic data and medical history of the two groups. Maternal age, body mass index, artificial reproductive techniques pregnancy, diabetes, chronic hypertension, history of preeclampsia, and history of preterm PE were significantly higher in the study group. Comparison of the laboratory results revealed that there was no significant difference between the groups in terms of antepartum and postpartum hemoglobin levels, decline in the hemoglobin level after the delivery, postpartum thrombocyte, alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, uric acid, creatinine level. Twenty-four-hour-urine protein level was higher in patients who were not under aspirin prophylaxis, yet it did not reach statistical significance ($p=0.060$).

Table 4 demonstrates the comparison of clinical data of the current pregnancy and complications associated with preeclampsia. The need for antihypertensive therapy was higher, and the GW at which antihypertensive medications were first administered was earlier in the study group. Antepartum hospitalization was longer in the study group, whereas the postpartum hospitalization period was similar between the groups. None of the clinical criteria suggesting PE with severe features was different between the patients who were under aspirin prophylaxis and those who were not. Except for HELLP and the need for cesarean section (C/S), none of the complications related to PE were different between the groups. HELLP and C/S were significantly lower in the control group. Interestingly, uterine atony bleeding was lower in the aspirin group.

Regarding neonatal outcomes, GW at birth, birth weight, and APGAR score at 1st minute were significantly higher, and the neonatal intensive care unit (NICU) hospitalization period was shorter in the control group. NICU admission and LBW rates were slightly lower in the control group, although not statistically significant. Neonatal mortality was significantly higher in the study group. Composite adverse neonatal outcomes were similar between the groups (Table 5).

Table 1. Demographic data, obstetric and non-obstetric medical history of the entire cohort

	n	Mean ± SD	Median (min-max)
Age	541	31.27±6.11	31.00 (19.00-44.00)
Gravidity	541	2.57±1.70	2.00 (1.00-13.00)
Parity	541	1.04±1.28	1.00 (0.00-9.00)
BMI	541	32.61±5.52	31.60 (19.90-50.70)
	n	**%**	
Tobacco/substance consumption	39	7.2	
Family history of HT	207	38.3	
ART pregnancy	26	4.8	
GDM/DM	99	18.3	
Pregestational DM	22	0.04	
Autoimmune disease/APAS	9	1.7	
Chronic hypertension	75	14	
Chronic renal disease	1	0.2	
History of PE	122	22.6	
History of preterm PE	36	6.7	

BMI: Body mass index, ART: Artificial reproductive techniques, HT: Hypertension, GDM: Gestational diabetes mellitus, DM: Diabetes mellitus, APAS: Antiphospholipid antibody syndrome, PE: Preeclampsia, SD: Standard deviation

Table 2. Clinical data and complications related to preeclampsia in the current pregnancy			
	n	**Mean ± SD**	**Median (min-max)**
MAP (mmHg)*	541	108.83±12.43	106.67 (73.33-147.33)
SBP (mmHg)*	541	144.92±17.75	140.00 (100.00-200.00)
DBP (mmHg)*	541	90.78±11.21	90.00 (60.00-130.00)
Duration of antenatal hospitalization (days)	541	3.42±5.91	1.00 (0.00-41.00)
Duration of postnatal hospitalization (days)	541	3.75±2.01	3.00 (2.00-35.00)
GW at diagnosis	541	34.16±4.22	35.00 (19.00-41.00)
	n		**%**
Antihypertensive medication	252		46.6
Antihypertensive medication before 20 GWs	67		26.6
PE with severe features	402		74.3
SBP ≥160 mmHg	148		27.4
SDP ≥110 mmHg	40		7.4
FGR	171		31.6
Amniotic fluid volume abnormalities	77		14.4
Neurologic symptoms	242		44.8
GIS symptoms	79		14.6
HELLP	39		7.2
Eclampsia	10		1.8
Abruptio placenta	43		7.9
Fetal distress	146		27.0
Fetal demise	14		2.6
Need for transfusion of blood products	31		5.7
Uterine atony	23		4.3
DIC	3		0.6

*: Data on the day of first hospitalization, MAP: Mean arterial pressure, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, GW: Gestational weeks, PE: Preeclampsia, FGR: Fetal growth restriction, GIS: Gastrointestinal system, DIC: Disseminated intravascular coagulation, SD: Standard deviation

Discussion

A significant number of studies have been conducted to illuminate the pathophysiology of preeclampsia. A great body of evidence has been accumulated about the prediction of high-risk patients and preventative methods to reduce the incidence of the disease[5-7]. PE can be defined as a syndrome in which multiple overlapping pathways lead to systemic inflammation and endothelial cell activation, resulting in endothelial damage, platelet aggregation, and thrombosis in maternal circulation and placenta[6]. Aspirin has been proposed to block the cascade by selectively inhibiting cyclooxygenase-1, resulting in a reduction of thromboxane A2, which is responsible for activating and aggregating platelets, endothelial damage, and thrombosis[3]. ASPRE trial proved that administration of daily 150 mg aspirin initiated before 16th GW reduced preterm PE by 62% in high-risk patients[8].

It is obvious that aspirin prophylaxis does not prevent all PE cases, and lots of pregnancies are still complicated with PE despite aspirin. In fact, according to a hypothesis that was supported by a secondary analysis of ASPRE, aspirin does not prevent it, but it delays the onset of PE[9].

Looking from a different point of view, in this study, we questioned whether being under aspirin prophylaxis during pregnancy mitigates the severity of the disease, maternal complications, and fetal/neonatal adverse outcomes in the case of preeclampsia, or not. Given the common pathophysiology of PE and placenta-associated adverse outcomes, it was anticipated that even if aspirin could not prevent preeclampsia, the clinic and perinatal complications

Table 3. The comparison of maternal characteristics, medical and obstetric history of the groups

	Control group (n=384) ASA (-)		Study group (n=157) ASA (+)		
	Mean ± SD	Median (min-max)	Mean ± SD	Median (min-max)	p
Age[a]	30.83±6.33	30.00 (19.00-44.00)	32.35±5.41	33.00 (19.00-44.00)	0.006
Gravidity[a]	2.44±1.73	2.00 (1.00-13.00)	2.87±1.61	3.00 (1.00-9.00)	<0.001
Parity[a]	1.02±1.34	1.00 (0.00-9.00)	1.11±1.11	1.00 (0.00-4.00)	0.077
BMI[a]	32.18±5.40	31.20 (19.90-50.70)	33.64±5.70	32.95 (22.50-49.40)	0.003
	n	%	n	%	
Tobacco/substance use[b]	30	7.9	9	5.8	0.398
ART[b]	9	2.3	17	10.8	<0.001
Familial history of HT/ PE[b]	141	36.7	66	42.0	0.248
GDM/DM[b]	60	15.6	39	24.8	0.012
Autoimmune disease[c]	6	1.6	3	1.9	0.723
Chronic HT[b]	25	6.6	50	31.8	<0.001
APAS[c]	1	0.3	3	1.9	0.076
Chronic renal disease[c]	0	0.0	1	0.6	0.291
History of PE[b]	54	14.1	68	43.3	<0.001
History of preterm PE[b]	10	2.6	26	16.6	<0.001

BMI: Body mass index, ART: Artificial reproductive techniques, GDM: Gestational diabetes mellitus, DM: Diabetes mellitus, HT: Hypertension, APAS: Antiphospholipid antibody syndrome, PE: Preeclampsia, SD: Standard deviation, [a]: Mann-Whitney test, [b]: Chi-square test, [c]: Fisher's Exact test

of PE should have been mitigated in those preeclamptic patients under aspirin prophylaxis compared to those who are not.

No significant difference was detected in maternal complications and severity of PE except for HELLP syndrome. Unexpectedly, the incidence of HELLP syndrome was higher in the aspirin group despite the expectations in favor of the aspirin group given the mechanism of action, which increases the ratio of endothelial prostacyclin to platelet thromboxane providing better vascular endothelial functions and anti-thrombosis[10]. It can be speculated that the endothelial damage had already begun before the onset of PE in this group because 41.9% required antihypertensive medications before the 20th week of pregnancy or before the pregnancy at all. Moreover, since the long-term negative cardiovascular effect of a previous PE is well-proved in the literature, the higher rate of PE history in the study group supports the above-mentioned "already damaged vascular endothelium" statement[11]. The higher rate of C/S in the study group was a consequence of higher gravidity and higher rate of previous C/S history; therefore, it should not be regarded as a complication of preeclampsia.

The fact that the study group (aspirin group) had a higher maternal age, gravidity, and a higher burden of chronic diseases like obesity, chronic hypertension, and diabetes had an extreme impact on the results. This was expected as the study group mostly consisted of patients who had been prescribed aspirin as they were deemed high-risk for PE due to those underlying co-morbidities in association with vasculopathy.

In a secondary analysis of the ASPRE trial, Shen et al.[12] reported that there was no prophylactic effect of aspirin for preventing preterm PE in high-risk risk patients with chronic hypertension compared to those who did not have chronic hypertension. Thus, they detected that chronic hypertension was strongly associated with the development of preterm PE despite aspirin prophylaxis[12]. In our study group, 31.8% of the patients had known chronic hypertension, and 41.9% needed antihypertensive therapy before the 20th GW, suggesting that a considerable amount of patients in this group had chronic vasculopathy which might have negatively affected the perinatal outcomes via uteroplacental insufficiency, irrespective of PE status. GW at birth, birth weight, APGAR score at 1st minute, NICU admission, and neonatal mortality were significantly higher in the study group despite aspirin prophylaxis. A previous

Table 4. Comparison of clinical data of the current pregnancy and complications related to preeclampsia

Parameters	Control group (n=384) (ASA -)		Study group(n=157) (ASA+)		
	Mean ± SD	**Median (min-max)**	**Mean ± SD**	**Median (min-max)**	**p**
MAP*[a] (mmHg)	108.44±11.83	106.67 (73.33-133.33)	109.77±13.79	110.00 (80.00-147.33)	0.433
SBP*[a]	144.35±17.22	140.00 (100.00-200.00)	146.32±18.99	140.00 (110.00-200.00)	0.491
DBP*[a]	90.49±10.65	90.00 (60.00-120.00)	91.49±12.49	90.00 (60.00 - 130.00)	0.546
Anti-hypertensive medications[b]	147	38.3	105	66.9	<0.001
Anti-hypertensive medications <20 GW[b]	23	15.6	44	41.9	<0.001
Onset of anti-hypertensive medications (GW)[a]	28.50±10.40	32.00 (0.00-40.00)	19.94±11.85	24.00 (0.00-38.00)	<0.001
Antenatal hospitalization duration (days)[a]	2.63±4.71	1.00 (0.00-32.00)	5.36±7.82	2.00 (0.00-41.00)	<0.001
Postpartum hospitalization duration (days)[a]	3.64±1.21	3.00 (2.00-12.00)	4.01±3.21	3.00 (2.00-35.00)	0.671
GW at diagnosis	34.91±3.63	36.00 (24.00-41.00)	32.33±4.97	33.00 (19.00-41.00)	<0.001
	n	**%**	**n**	**%**	
PE with severe features[b]	284	74.0	118	75.2	0.772
SBP ≥160 mmHg	102	26.6	46	29.3	0.517
DBP ≥110 mmHg[b]	25	6.5	15	9.6	0.219
Neurologic symptoms	170	44.3	72	46.2	0.690
GIS symptoms[b]	53	13.8	26	16.7	0.393
Pulmonary edema	5	0.01	2	0.012	1.00
HELLP[b]	22	5.7	17	10.8	0.037
Eclampsia[c]	7	1.8	3	1.9	1.00
Abruptio placenta[b]	32	8.3	11	7.0	0.605
IUFD[c]	12	3.1	2	1.3	0.370
FGR[b]	114	29.7	57	36.3	0.133
Fetal distress[b]	99	25.8	47	29.9	0.323
C/S[b]	313	81.5	147	93.6	<.001
Transfusion of blood products[b]	24	6.3	7	4.5	0.416
Atony[b]	21	5.5	2	1.3	0.028
DIC[c]	3	0.8	0	0.0	0.560

MAP: Mean arterial pressure, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, GW: Gestational weeks, PE: Preeclampsia, FGR: Fetal growth restriction, IUFD: Intrauterine fetal demise, GIS: Gastrointestinal system, DIC: Disseminated intravascular coagulation, C/S: Caesarean section, SD: Standard deviation, [a]: Mann-Whitney U test, [b]: Chi-square test; [c]: Fisher's Exact test, *: Mean blood pressure in the day of hospitalization

meta-analysis reported that aspirin prophylaxis initiated before 16 GW reduces the incidence of FGR, perinatal mortality, and PTB compared to no treatment or placebo[13]. ASPRE trial also suggested a reduction in perinatal death rates and LBW[8]. However, the studies either overestimated the intervention's effect size or underpowered for secondary outcomes. To our knowledge, no study in the literature reports the effect of aspirin on perinatal outcomes, excluding the impact of established preeclamptic status. In this study, the earlier GW at birth in the study group was the main reason for worse neonatal outcomes in the aspirin group compared to the control group. Regarding the "delay theory", which suggested that aspirin provided a 4.4 weeks delay in the gestational age at delivery for those who would have been delivered at 24 weeks if not treated with aspirin, we can speculate that aspirin might have provided positive

Table 5. Comparison of neonatal outcomes

	Control group (n=384) ASA (-)		Study group (n=157) ASA (+)		
	Mean ± SD	**Median (min-max)**	**Mean ± SD**	**Median (min-max)**	**p**
GW at birth[a]	35.41±3.35	36.00 (24.00-41.00)	33.87±3.81	35.00 (23.00 41.00)	<0.001
Birth weight[a]	2428.13±866.28	2515.00 (390.00-4430.00)	2175.03±953.42	2150.00 (360.00-4600.00)	0.005
APGAR 1. min[a]	6.99±1.15	7.00 (2.00-9.00)	6.65±1.34	7.00 (2.00-8.00)	0.008
APGAR 5. min[a]	8.38±0.83	9.00 (5.00-10.00)	8.25±0.91	8.00 (4.00-9.00)	0.128
NICU hospitalization (days)[a]	9.16±18.77	0.00 (0.00-150.00)	13.35±23.85	0.00 (0.00-174.00)	0.028
	n	%	n	%	
LBW[b]	141	37.9	72	46.8	0.060
NICU admission[b]	187	50.3	92	59.4	0.057
Composite adverse neonatal outcome[b]	125	34.2	63	42.3	0.086
Neonatal mortality[c]	3	1.1	6	5.9	0.013

[a]: Mann-Whitney U test, [b]: Chi-square test, [c]: Fisher's Exact test, GW: Gestational weeks, NICU: Neonatal intensive care unit, LBW: Low birth weight, ETE: Endotracheal intubation, SD: Standard deviation

effects on perinatal outcomes; however, the imbalance in the risk profiles of the groups led to completely opposite results in perinatal outcomes.

Study Limitations

This study has a major limitation. Due to the retrospective design of the study, the baseline risk status for preterm PE could not be calculated, and the remarkable imbalance between the groups regarding chronic medical conditions had an inevitable impact on the outcomes. Yet, the similarity in the maternal complications despite the significant maternal co-morbidities can be considered a positive protective effect of aspirin in the case of a preeclampsia.

Conclusion

The results of this study show that, in case of a pregnancy complicated with preeclampsia, being under aspirin treatment does not yield better maternal and perinatal outcomes and does not reduce the complications of preeclampsia. Nevertheless, considering there is no difference in maternal complications of PE (except for HELLP) despite a significantly higher burden of co-morbidities like chronic hypertension in the aspirin group, a beneficial effect of aspirin cannot fully be denied with this study. A larger study excluding the patients with chronic hypertension and providing a homogenous distribution of co-morbidities should be designed on this subject.

Ethics

Ethics Committee Approval: This retrospective observational cohort study was approved by the Local Ethics Committee of University of Health Sciences Turkey, Zeynep Kamil Women and Children Diseases Training and Research Hospital (approval date: 10.05.2023, no: 79). It was conducted following the ethical standards described in an appropriate version of the 1975 Declaration of Helsinki, as revised in 2000.

Informed Consent: Informed consent stating that the data can be used for scientific purposes has been routinely provided from all the patients who applied to the clinic.

Authorship Contributions

Surgical and Medical Practices: H.S.K., L.U., O.D., Concept: H.S.K., L.U., Design: H.S.K., L.U., Data Collection or Processing: H.S.K., Analysis or Interpretation: H.S.K., L.U., Literature Search: H.S.K., Writing: H.S.K., L.U.

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

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

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