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ORIGINAL ARTICLE

Evaluation of gestational trophoblastic diseases; 10 years' experience in tertiary obstetric care center

[1]İbrahim KALE
[2]Cumhur Selçuk TOPAL

[1]Department of Obstetrics and Gynecology, University of Health Sciences, Turkey. Ümraniye Training and Research Hospital, İstanbul, Turkey

[2]Department of Pathology, University of Health Sciences, Turkey. Ümraniye Training and Research Hospital, İstanbul, Turkey

ORCID ID
İK : 0000-0001-7802-7199
CST : 0000-0001-6782-2373

ABSTRACT

Objective: The aim of this study is to review the demographic characteristics and clinical outcomes of patients diagnosed with gestational trophoblastic disease (GTD).

Material and Methods: Data of patients with histopathologically confirmed diagnosis of GTD between 2010 and 2020 were retrospectively reviewed from hospital records.

Results: There were 94 partial hydatidiform mole (PHM), 61 complete hydatidiform mole (CHM), 23 exaggerated placental site (EPS), and 22 placental site nodule (PSN) cases with the prevalence of 0.18%, 0.12%, 0.045%, and 0.039%, respectively. As gestational trophoblastic neoplasia, 1 invasive mole, 1 choriocarcinoma, and 1 placental site trophoblastic tumor were detected. While the PHM group and the CHM group were similar in terms of obstetric history, the mean age and body mass index were lower in the CHM group (p=0.04, p=0.00, respectively). Mean platelet volume and plateletcrit levels were lower and neutrophil lymphocyte ratio was higher in CHM compared to PHM (p=0.00 p=0.02, p=0.00, respectively). At diagnosis, the serum β-hCG level was higher and the gestational week was earlier, and the rate of detecting molar pregnancy by ultrasound was higher in the CHM group than in the PHM group (p=0.00, p=0.02, p=0.00, respectively). The need for a second evacuation and methotrexate chemotherapy were higher in the CHM group than in the PHM (p=0.02, p=0.00, respectively). While molar pregnancy and EPS coexistence were diagnosed in four patients, no such coexistence was found in PSN.

Conclusion: Compared to PHM, CHM, which is more common in young people, requires more second evacuation or methotrexate treatment, and ultrasonography seems to be more effective in diagnosis. Unlike PSN, EPS can be seen with molar pregnancies and is rarely a cause of postpartum hemorrhage.

Keywords: Epidemiology of GYN cancers, gestational trophoblastic disease, placental pathology.

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Correspondence: İbrahim KALE, MD. Türkiye Sağlık Bilimleri Üniversitesi, Ümraniye Eğitim ve Araştırma Hastanesi, Kadın Hastalıkları ve Doğum Kliniği, İstanbul, Turkey.
Tel: +90 216 632 18 18 **e-mail:** dribakale@hotmail.com
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INTRODUCTION

Gestational trophoblastic disease (GTD) is a broad spectrum that includes benign and malignant diseases caused by trophoblast cells of the placenta. While partial hydatidiform mole (PHM) and complete hydatidiform mole (CHM) forms the benign group, invasive mole, gestational choriocarcinoma, placental site trophoblastic tumors (PSTT), and epithelioid trophoblastic tumors are malignant histopathological types.[1] Furthermore, exaggerated placental site (EPS) and placental site nodule (PSN) are rare non-tumor lesions arising from intermediate trophoblasts within the GTD spectrum.[2]

Although there is a wide variation in the prevalence of hydatidiform moles in studies reported from different countries, the overall prevalence of CHM is about 1–3/1000 pregnancies, while in PHM it is three/1000 pregnancies. Other histopathological types of GTD are less common.[3] Adolescent age or advanced maternal age, genetic basis, ethnicity, recurrent spontaneous abortion, and previous mole hydatidiform history are known risk factors for GTD.[4] Treatment options for GTD differ according to the type of disease and include aspiration abortion, chemotherapy, hysterectomy, or a combination of these. It is essential to monitor the decrease in serum β-hCG level in the follow-up of the patient after therapeutic procedures.

Since the prevalence, treatment modalities and outcome of GTD may differ from country to country; we conducted this study to describe the 10-year experience of a tertiary obstetric care center in GTD.

MATERIAL AND METHODS

This is a retrospective study in which records of the patients, who were diagnosed of GTD at Umraniye Training and Research Hospital, Department of Obstetrics and Gynecology, Istanbul, Turkey, between January 2010 and May 2020 were collated. Patients' age, body mass index (BMI), obstetric history, blood type, clinical presentation, ultrasonographic findings, serum β-hCG level at diagnosis, and treatment modalities were recorded. The data were analyzed using the Statistical Package for Social Sciences version 25.0 software program (SPSS Inc., Chicago IL, USA). When checked with the Kolmogorov Smirnov test, the distribution of the data appeared normal. While evaluating the study data, besides descriptive statistical methods (mean, standard deviation, frequency), t-test and Chi-square analysis were used to determine statistical significance. $p<0.05$ was considered statistically significant.

RESULTS

During this study period, 94 PHM, 61 CHM, 1 invasive mole, 1 choriocarcinoma, 1 PSTT, 23 EPS and 22 PSN were diagnosed. In this 10-year period with a total of 50400 deliveries, the prevalence of hydatidiform mole in our clinic was 0.3% (partial 0.18% and complete 0.12%), EPS prevalence was 0.045% and PSN was 0.039%. The distribution and ratios of GTD and GTN by years are shown in Table 1.

Patients diagnosed with PHM and CHM were compared in terms of demographic data and hemogram parameters. While the two groups were similar in terms of obstetric history (gravida, parity, miscarriage, D and C and ectopic pregnancy), the mean age and BMI were significantly lower in the CHM group (p=0.04, p=0.00, respectively). Of the 155 patients, 94 of whom were diagnosed with PHM and 61 with CHM, none had a history of molar pregnancy. In addition, none of the patients had any uterine surgery other than

Table 1: The prevalence rates of GTD and GTN in Ümraniye Training and Research Hospital, Gynecology and Obstetrics Clinic, according to the years 2010–2020

Year	Number of deliveries	Number and incidance rate of mole hydatidiform n (%)	Number and incidance rate of EPS n (%)	Number and incidance rate of PSN n (%)	Number and incidance rate of total GTD n (%)	Number and incidance rate of GTN n (%)
2010	2850	13 (0.45)	1 (0.03)	0 (0.00)	14 (0.49)	1 (0.03)
2011	2744	9 (0.32)	2 (0.07)	1 (0.03)	12 (0.43)	0 (0.00)
2012	3480	3 (0.08)	2(0.05)	1 (0.02)	5 (0.14)	0 (0.00)
2013	3680	7 (0.19)	0 (0.00)	0 (0.00)	7 (0.19)	0 (0.00)
2014	4795	7 (0.14)	1 (0.02)	4 (0.08)	12 (0.25)	0 (0.00)
2015	4462	18 (0.40)	0 (0.00)	1 (0.02)	19 (0.42)	0 (0.00)
2016	6403	14 (0.21)	2 (0.03)	3 (0.04)	19 (0.29)	2 (0.03)
2017	7087	12 (0.16)	2 (0.02)	1 (0.01)	15 (0.21)	0 (0.00)
2018	6022	22 (0.36)	6 (0.09)	1 (0.01)	29 (0.36)	0 (0.00)
2019	5270	20 (0.37)	4 (0.07)	8 (0.15)	32 (0.60)	0 (0.00)
2020	3607	30 (0.83)	3 (0.08)	2 (0.05)	35 (0.97)	0 (0.00)
Total	50400	155 (0.30)	23 (0.04)	22 (0.04)	200 (0.39)	3 (0.005)

GTD: Gestational trophoblastic disease; GTN: Gestational trophoblastic neoplasia; EPS: Exaggerated placental site; PSN: Placental site nodule.

Table 2: Comparison of demographic data and hemogram parameters of patients diagnosed with partial and complete hydatidiform mole

Variables	Partial hydatidiform mole (n=94)	Complete hydatidiform mole (n=61)	p
Age (years)	32.54±7.46	29.93±8.72	**0.04***
BMI (kg/m^2)	29.24±3.53	27.81±2.87	**0.00***
Gravida	2.99±1.78	2.85±1.83	0.64*
Parity	1.72±1.45	1.57±1.63	0.55*
Miscarriage	0.39±0.79	0.31±0.72	0.51*
D and C	0.01±0.10	0.08±0.33	0.05*
Ectopic	0.02±0.15	0.03±0.18	0.66*
Cesarean history			
Yes	31 (33%)	14 (23%)	0.179**
No	63 (67%)	47 (77%)	
Hemogram parameters			
Leukocyte count	8765.53±2258.62	8360.49±2512.69	0.29*
Neutrophil count	5932.45±1887.64	5702±2053.67	0.47*
Monocyte count	468.83±173.38	610.16 ±908.36	0.14*
Lymphocyte count	2173.30±819.47	2092.46±656.97	0.51*
Hemoglobin (g/dl)	11.95±1.37	11.71±1.16	0.25*
Hematocrit (%)	35.91±3.63	35.01±3.33	0.12*
Platelet count	266393.62±65964.35	259032.79±60220.14	0.48*
MPV (fL)	9.34±1.68	8.65±1.41	**0.00***
PCT (%)	0.25±0.07	0.22±0.05	**0.02***
PDW (%)	16.94±1.83	17.10±1.30	0.56*
NLR	2.65±1.04	3.18±1.43	**0.00***
MLR	0.26±0.34	0.29±0.36	0.56*
PLR	129.75±46.34	138.92±48.86	0.24*

*: Student t-test; **: Chi-square test; BMI: Body mass index; MPV: Mean platelet volume; PCT: Plateletcrit; PDW: Platelet distribution width; NLR: Neutrophil lymphocyte ratio; MLR: Monocyte lymphocyte ratio; PLR: Platelet lymphocyte ratio. P<0.05 was considered statistically significant and written in bold.

caesarean section. The PHM and CHM groups were similar in terms of caesarean delivery history (p=0.179). Both groups were similar in terms of leukocytes, neutrophils, monocytes, lymphocytes and platelet counts, hemoglobin and hematocrit levels. Mean platelet volume (MPV) and plateletcrit (PCT) levels were significantly higher in the PHM group (p=0.00, p=0.02, respectively).While the MO/LY and PLT/LY ratios were similar in both groups, the NEU/LY ratio was significantly higher in the CHM group (p=0.56, p=0.24, p=0.00, respectively) (Table 2). Of the 155 hydatidiform mole patients, 82 (52.9%) had blood group A, 41 (26.4%) had O, 23 (14.8%) had B, and nine (5.8%) had AB.

In the CHM group, 67.2% of the patients presented with vaginal bleeding, while 23% were asymptomatic. In the PHM group, 56.4% of the patients were asymptomatic, while 38.3% had vaginal bleeding. At diagnosis, the serum β-hCG level was statistically significantly higher and the gestational week was earlier in the CHM group than in the PHM group (p=0.00, p=0.02, respectively). Cluster of grapes or snowstorm image was detected in 67.2% of the patients in the CHM group on ultrasound examination, while this rate was 6.4% in the PHM group. In the ultrasound examination, 43.6% of the patients in the PHM group had missed abortion and 38.3% had anembryonic pregnancy, while these rates were 11.5% and 9.8%, respectively, in CHM. The rate of detecting molar pregnancy by ultrasound was significantly higher in the CHM group than in the PHM group (p=0.00). When both groups were compared in terms of treatment modality, the number of patients who had a 2nd time curettage or suction evacuation and the number of patients who received methotrexate chemotherapy was significantly higher in the CHM group than in the PHM group (p=0.02, p=0.00, respectively). Hysterectomy procedure was performed in five patients in the CHM group while there was no hysterectomy in the PHM group (Table 3).

Patients diagnosed with EPS and PSN were also compared among them. The two groups were similar in terms of mean age, BMI and obstetric history. There was a history of caesarean in five

Table 3: Comparison of clinical presentation, ultrasonographic findings and treatment modality of patients diagnosed with partial and complete hydatidiform mole

Variables	Partial hydatidiform mole (n=94) n (%)	Complete hydatidiform mole (n=61) n (%)	p
Age of gestation (week)	9.9±3.01	8.62±1.71	**0.00***
β-hCG level (mIU/ml)	93375.32±140817.45	214634.37±385638.40	**0.02***
Clinical features at presentation			
Asymptomatic	53 (56.4)	14 (23.0)	–
Vaginal bleeding	36 (38.3)	41 (67.2)	–
Hyperemesis	0 (0)	1 (1.6)	–
Abdominal pain	5 (5.3)	5 (8.2)	–
Ultrasonographic findings at presentation			
Cluster of grapes or snowstorm image	6 (6.4)	41 (67.2)	–
Anembryonic pregnancy	36 (38.3)	6 (9.8)	–
Missed abortion	41 (43.6)	7 (11.5)	–
Normal endometrium image	9 (9.6)	7 (11.5)	–
Non-viable pregnancy over 20 weeks	1 (1.1)	0 (0)	–
Cesarean scar pregnancy	1 (1.1)	0 (0)	–
Theca lutein cyst	3 (3.2)	3 (4.9)	–
Ultrasound examination			
Detected	6 (6.4)	37 (60.7)	**0.00****
Not detected	88 (93.6)	24 (39.3)	
Need for 2nd curettage or suction evacuation			
Yes	5 (5.3)	10 (16.4)	**0.02****
No	89 (94.7)	51 (83.6)	
Need for methotrexate chemotherapy			
Yes	1 (1.1)	10 (16.4)	**0.00****
No	93 (98.9)	51 (83.6)	
Need for hysterectomy			
Yes	0 (0)	5 (8.2)	–
No	94 (100)	56 (91.8)	

*: Student t-test; **: Chi-square test. P<0.05 was considered statistically significant and written in bold.

patients in the EPS group and 8 patients in the PSN group. While the coexistence of EPS and PHM was observed in two patients and the coexistence of EPS and CHM in two patients, the coexistence of hydatidiform mole was not observed in the PSN group. In the ultrasonographic evaluation, four patients in the EPS group had a pregnancy >20 weeks, 11 had missed abortion, five had normal endometrium image and three had cluster of grapes or snowstorm image. In the PSN group, ultrasonographic examination of 20 patients revealed normal endometrium image and two patients had missed abortion (Table 4). Two patients in the EPS group were diagnosed in the hysterectomy specimen due to postpartum atony, and one patient in the PSN group was diagnosed in the hysterectomy specimen performed for endometrial hyperplasia.

DISCUSSION

Although the prevalence of hydatidiform mole reported in the literature varies according to geographical regions, Asian countries are the regions with the highest prevalence. It has been reported from 1 to 3/1000 pregnancies in Japan, China and Korea, to over 10/1000 pregnancies in Indonesia and India.[5] The reported prevalence of choriocarcinoma is approximately 1 in 40,000 pregnancies in North America and Europe, and 3–9 in 40,000 pregnancies in Asian countries and Japan.[3] In this study, we found the prevalence of hydatidiform mole as three in 1000 births, and the prevalence of choriocarcinoma, invasive mole and PSTT as 1 in 50400 births.

In a study from England, it was stated that the prevalence of molar pregnancy increased from 1:611 in 1997 to 1:528 in 2008, and

Table 4: Comparison of demographic data and ultrasonographic findings of patients diagnosed with exaggerated placental site and placental site nodule

Variables	Exaggerated placental site (n=23)	Placental site nodule (n=22)	p
Age (years)	31.78±6.45	30.32±7.75	0.49*
BMI (kg/m^2)	30.68±2.37	30.46±2.33	0.75*
Gravida	3.30±1.92	3.14±1.42	0.74*
Parity	1.78±1.48	1.50±0.86	0.43*
Miscarriage	0.52±1.08	0.45±0.67	0.80*
D and C	0.09±0.29	0.14±0.47	0.67*
Ectopic	0.04±0.21	0.09±0.29	0.53*
Cesarean history			0.27**
Yes	5 (21.7%)	8 (36.4%)	
No	18 (78.3%)	14 (63.6%)	
Coexistence with PHM	2	0	–
Coexistence with CHM	2	0	–
Ultrasonographic findings at presentation			
Cluster of grapes or snowstorm image	3 (13%)	0 (0%)	–
Missed abortion	11 (47.8%)	2 (9.1%)	–
Normal endometrium image	5 (21.7%)	20 (90.9%)	–
Pregnancy over 20 weeks	4 (17.3%)	0 (0%)	–

*: Student t-test; **: Chi-square; BMI: Body mass index; PHM: Partial hydatidiform mole; CHM: Complete hydatidiform mole.

this increase in the prevalence was higher in patients over 45 years of age rather than adolescents.[6] Furthermore, Lybol et al.[7] reported that the prevalence of GTD increased significantly in the Netherlands from 1995 to 2008. Although they attributed this increase in part to increasing maternal age, increasing Asian live birth rates, improved diagnostic techniques and an increase in case documentation, they thought that other unknown factors were effective in the increase. Similar to these studies, we also found a significant increase in the prevalence of GTD in our clinic between 2010 and 2020. Although there was no significant increase in the number of births, we attributed this increase in the prevalence of GTD to our hospital being a tertiary reference hospital in recent years.

In studies investigating molar pregnancy risk factors, one of the most striking parameters was maternal age. In a study by Altman et al.,[8] women diagnosed with PHM were found to be significantly older than those diagnosed with CHM (mean age 29, mean age 26, respectively). Furthermore, in a different study, it was determined that adolescents were 7 times more likely to develop CHM and women with advanced maternal age were almost twice as likely, but in the PHM group, no relationship was found with maternal age.[9] Similar to these studies, in this study, we found the mean age of the CHM group as 29.9, and the mean age of the PHM group as 32.5 (p=0.04).

In a study published in 2015, it was stated that having a previous hydatidiform mole increased the risk of recurrent hydatidiform mole by 1% in the following pregnancy, and this risk was associated with CHM rather than PHM.[10] In a different study, Gadducci et al.[11] noted that the prevalence of subsequent molar pregnancy ranged from 0.7% to 2.6% after one CHM or PHM and was about 10% after the two previous CHMs. Unlike this information, in this study in which 155 hydatidiform mole cases were evaluated, no previous molar pregnancy history was found in any of the cases.

A popular subject that has been researched in recent years is the availability of hemogram sub-parameters in the diagnosis of some diseases or predicting the prognosis. In a study published in 2015, hemogram parameters were evaluated between GTD and normal healthy pregnant women. There was no difference between the two groups in terms of PLT count and MPV levels, while WBC count and PDW levels were found to be significantly lower in the GTD group than in healthy controls.[12] In another study, the leukocyte count and MPV levels were found to be significantly higher in the GTD group, while the lymphocyte and platelet counts were found to be lower than the healthy controls. In the same study, while both groups were similar in terms of neutrophil lymphocyte ratio (NLR), platelet lymphocyte ratio (PLR) was found to be significantly lower in the GTD group.[13] Zhang et al.[14] evaluated the hemogram parameters between patients with invasive mole and normal healthy women. The results showed that the level of RDW, lymphocyte count, NLR, and PLR were significantly higher and hemoglobin concentration, MCV, and PLT were significantly lower in the invasive mole group than the control group. In another study examining the effects of molar pregnancies on platelets, mean platelet count, MPV, PDW, and PCT levels were similar between GTD and control group.[15] In this study, we also evaluated the hemogram sub-parameters between CHM and PHM and found

that MPV and PCT levels were significantly lower and NLR was significantly higher in CHM compared to PHM (p=0.00, p=0.02, p=0.00, respectively).We think that in addition to genetic factors, blood cells may be directly or indirectly effective in the pathogenesis of GTD in a way that is not yet clear. We attribute the different results reported in studies investigating the relationship between GTD and hemogram sub-parameters in the literature, to the heterogeneity of the groups included in the study.

According to the information in the literature, although CHM and PHM have similar clinical features, patients with CHM most commonly present with vaginal bleeding at earlier weeks of gestation and with higher maternal serum β-hCG levels, while most PHM diagnoses are made as a result of pathological examination of missed or spontaneous abortion material.[16] Furthermore, in this study, according to the information in the literature, the gestational week at the time of diagnosis was significantly earlier and maternal serum β-hCG levels were higher in the CHM group compared to the PHM group (p=0.00, p=0.02, respectively). 67% of patients with CHM patients presented with the complaint of vaginal bleeding, and cluster of grapes or snowstorm image was detected in 67% of them on ultrasound examination. On the other hand, 56% of PHM patients were asymptomatic and only 6% of them had findings suggestive of molar pregnancy in the ultrasound examination. In this study, the effectiveness of ultrasound examination in detecting molar pregnancy was found to be significantly higher in the CHM group than in the PHM group (p=0.00). In the studies of both Memtsa et al.[17] and Kirk et al.,[18] similar to our study, the diagnostic feature of ultrasound examination in molar pregnancies was found to be higher in patients with CHM than in patients with PHM.

In our clinic, molar pregnancy treatment is carried out by considering the patient's age, serum β-hCG follow-ups, and the desire for subsequent fertility. Patients whose serum β-hCG levels plateau or continue to increase during their molar pregnancy follow-ups are evaluated with ultrasound again, firstly curettage or suction evacuation is applied for the 2nd time, and then patients who still do not have satisfactory regression in β-hCG values receive methotrexate chemotrapy. In our study, the number of patients requiring curettage or suction evacuation for the 2nd time and receiving methotrexate was found to be significantly higher in the CHM group than in the PHM group (p=0.02, p=0.00, respectively). Only five patients in the CHM group underwent hysterectomy. The pathology results of two of five patients who underwent hysterectomy were persistent molar pregnancy, one invasive mole, one choriocarcinoma, and one PSTT. The patients were also evaluated in terms of GTD complications; increased intracranial pressure and papilledema developed in one patient diagnosed with PHM, and acute respiratory distress syndrome developed after hysterectomy in another patient diagnosed with CHM.

Information in the literature about EPS and PSN is limited to case series or case reports. PS is defined as excessive infiltration of the endometrium and myometrium at the implantation site by intermediate trophoblasts, while PSN is a lesion originating from intermediate trophoblasts representing incomplete involution of the placental implantation site. The differential diagnosis of these lesions was made using immunohistochemical stainings such as P63, HPL, Ki-67, and low molecular weight cytokeratin in addition to microscopic findings.[19]

It has been stated that EPS can be found in normal pregnancies as well as in approximately 1.6% of abortions.[19] In our study, approximately 48% of the patients diagnosed with EPS had missed abortion and 17% had a viable pregnancy over 20 weeks. Interestingly, there are case reports that EPS causes postpartum haemorrhage.[20,21] Similarly, we found that the pathology results of two patients who underwent hysterectomy due to postpartum haemorrhage were compatible with EPS. Another interesting information is the coexistence of EPS with molar pregnancies. Ozdemir et al.[22] reported the coexistence of CHM and EPS in the pathology report of a patient who had suction evacuation with suspicion of molar pregnancy. In this study, we found the coexistence of CHM in two patients diagnosed with EPS and the coexistence of PHM in two patients.

PSNs are incidental findings in uterine curettage or cervical biopsy or hysterectomy specimens and often cause menorrhagia or intermenstrual bleeding. It has been reported that surgical procedures such as cesarean section and curettage may increase the risk of developing PSN and 45–82% of cases had a history of cesarean section or curettage before their most recent pregnancy.[19,23] In our study, PSN was diagnosed in the curettage material performed in two patients after missed abortion, in the hysterectomy specimen performed due to endometrial hyperplasia in one patient, and in the curettage material performed in 19 patients due to abnormal uterine bleeding. It was stated that there was no recurrence or malignant potential development in the case series reported in the literature regarding the follow-up of PSNs.[23] Consistent with this information, there was no recurrence or malignant development in the follow-up of any PSN case detected in our study.

The limitations of this retrospective study are the fact that different physicians performed the ultrasound examinations of the patients over the years, time for serum β-hCG to be negative is not known in all patients because of the missing cases during the follow-ups and unknown obstetric histories after GTD treatment.

CONCLUSION

As a result, the overall prevalence of hydatidiform mole is low but has increased significantly in recent years in our clinic. We found that CHM is seen in younger patients than PHM and that the hemogram parameters MPV and PCT levels were significantly lower and NLR was significantly higher in CHM compared to PHM. Maternal serum β-hCG levels were higher in CHM at diagnosis, the gestational week was earlier, and the effectiveness of ultrasonography in detecting molar pregnancy was higher in the CHM compared to PHM. In addition, the number of patients who required evacuation for the 2nd time and who received methotrexate was higher in those diagnosed with CHM. While molar pregnancy and EPS coexistence were diagnosed in four patients, no such coexistence was found in PSN. Unlike EPS, which caused postpartum haemorrhage in two patients, patients with PSN generally presented with abnormal uterine bleeding complaints.

Statement

Ethics Committee Approval: The Ümraniye Training and Research Hospital Clinical Research Ethics Committee granted approval for this study (date: 08.04.2021, number: 103).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – İK; Design – İK; Supervision – CST; Resource – İK; Materials – CST; Data Collection and/or Processing – CST; Analysis and/or Interpretation – CST; Literature Search – İK; Writing – İK; Critical Reviews – CST.

Conflict of Interest: The authors have no conflict of interest to declare.

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