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Clinical, Diagnostic and Treatment Characteristics of Trophoblastic Disease in Post-Menopausal Woman: A Case Report and Review of Literature

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1. Abstract

1.1. Background: Gestational Trophoblastic Disease (GTD) in a heterogeneous group of disorders originating from placenta and between them hydatiform mole, both complete and partial, is the most common condition. Pregnancy in menopause period is an uncommon event but when it occurs the risk of a molar pregnancy is 5-10 times higher.

1.2. Detailed Case Description: This report describes a case of a 54-year-old peri-menopausal patient who accessed our Hospital in August 2023 for persistent metrorrhagia in the last 2 months. Based on ultrasound finding of endometrial cavity entirely occupied by inhomogeneous, vacuolized endometrium with a maximum thickness 83 mm, a diagnostic hysteroscopy with endometrial biopsy is performed: complete mole was the histological examination result. Increased betaHCG value of 338874 mUI/ml was evidenced. An encephalo-thorax-abdomen CT scan confirmed the presence of 12x15 cm diameter uterine neoformation. Encephalic and chest CT scans are negative for secondary tumors. After bilateral LPS hystero-annessiectomy, complete hydatiform mole was diagnosed. A postoperative betaHCG weekly follow-up was indicated and the last value of betaHCG was 8.8 mUI/ml.

1.3. Discussion: This paper summarizes clinical, diagnostic features and treatment options for gestational trophoblastic disease in postmenopausal women highlighting the importance of performing adequate surgery to reduce the risk of recurrence.

1.4. Conclusions: Hysterectomy is superior to uterine evacuation to prevent recurrences, but the association of the two procedures could further reduce the risk of tumor diffusion and consequently the risk of recurrence.

2. Introduction

Gestational Trophoblastic Disease (GTD) is a heterogeneous group of disorders originating from the placenta. This group includes the hydatiform moles comprising complete hydatiform moles (CHM) and partial hydatiform moles (PHM). Both CHM and PHM are generally considered to be benign disorders, but they can develop into Gestational Trophoblastic Neoplasia (GTN). This second group of diseases refers to lesions with frequent local invasion or metastasis and is composed by postmolar gestational trophoblastic neoplasia, invasive mole, chorioncarcinoma, placental site trophoblastic tumor, epithelioid trophoblastic tumor) [1]. The anatomopathological origin of both GTDs and GTNs can be related to normal pregnancy, abortion or miscarriage. Due to the pathophysiological relationship of these disorders with pregnancy, GTDs and GTNs most commonly occurs in reproductive age. The incidence of CHM and PHM is between 1 and 2 per 1000 pregnancies in Europe and North America [2] with a ratio of 3:1 respectively.

Pregnancy in menopause period is an uncommon event but when it occurs the risk of a molar pregnancy is 5-10 times higher related to abnormal chromosomes [3]. Therefore, a correct diagnosis and management of older age GTDs represents a challenge for specialists and requires a specific differential diagnosis [4]. This report describes a case of CHM in a 54 years patient with a systematic review of literature cases.

3. Detailed Case Description

A 54-year-old peri-menopausal patient with a history of 2 spontaneous full-term deliveries (the last in 2000) accessed our Hospital in August 2023 for persistent metrorrhagia for 2 months. She reported irregular menses for the past few months, the last in April 2023. She took Norethisterone acetate until 07/23/2023 with little benefit. Gynecological examination of the vulva and vagina was normal; abundant clots were visualized at speculum placement. Abdominal palpation revealed an enlarged uterus (extended to the transversal umbilical line). Transvaginal ultrasound showed an inverted uterus with an irregular profile due to the presence of the International Federation of Gynecology and Obstetrics (FIGO) classification G5 posterior isthmic myoma measuring 77 x 43 mm. The endometrial cavity was entirely occupied by inhomogeneous, vacuolized endometrium, with 83 mm maximum thickness, apparently non-vascularized (Figure 1). A first beta human chorionic gonadotropin (βHCG) assay was performed on 8/16/2023 and resulted elevated to 338874.0 mUI/ml. A diagnostic hysteroscopy with endometrial biopsy and finding on histological examination of a complete mole was performed. It was decided to perform an encephalo-thorax-abdomen Computed Tomography (CT) scan (Figure 2) with contrast medium, which confirmed the presence of the known uterine neoformation with a diameter of 12x15 cm imprinting the bladder, which appeared free of endoluminal filling defects. Encephalic and chest CT scans were negative for secondarisms. The patient was treated with bilateral laparoscopic hystero-annessiectomy surgery after hysterosuction on 8/28/2023. Histologic examination on material taken with hysterosuction during surgery (Figure 3) revealed brownish-grey material with multiple vesicular formations of 375g total weight and size ranging from 7 to 0.5 cm major axis.

The histologic examination on bilateral hystero-annexectomy showed an enlarged uterus (17x11x9.5 cm) site of CHM. No invasive components were present, while intramural leiomyomas and chronic cystic endocervicitis were observed. The right and left ovaries reported hemorrhagic corpora lutei, and the tubes were regular. A postoperative βHCG assay recheck was performed on 8/29/2023 (95218 mUI/ml) and on 8/30/23 (39249 mUI/ml). seriated follow-up was performed with weekly seriate control of βHCG that showed steadily decreasing values. βHCG resulted 2330 mUI/ml on 06/09/2023 and 632 mUI/ml on 09/13/2023. 8.8 mUI/ml last assay was performed on 10/11/2023 (Figure 4).

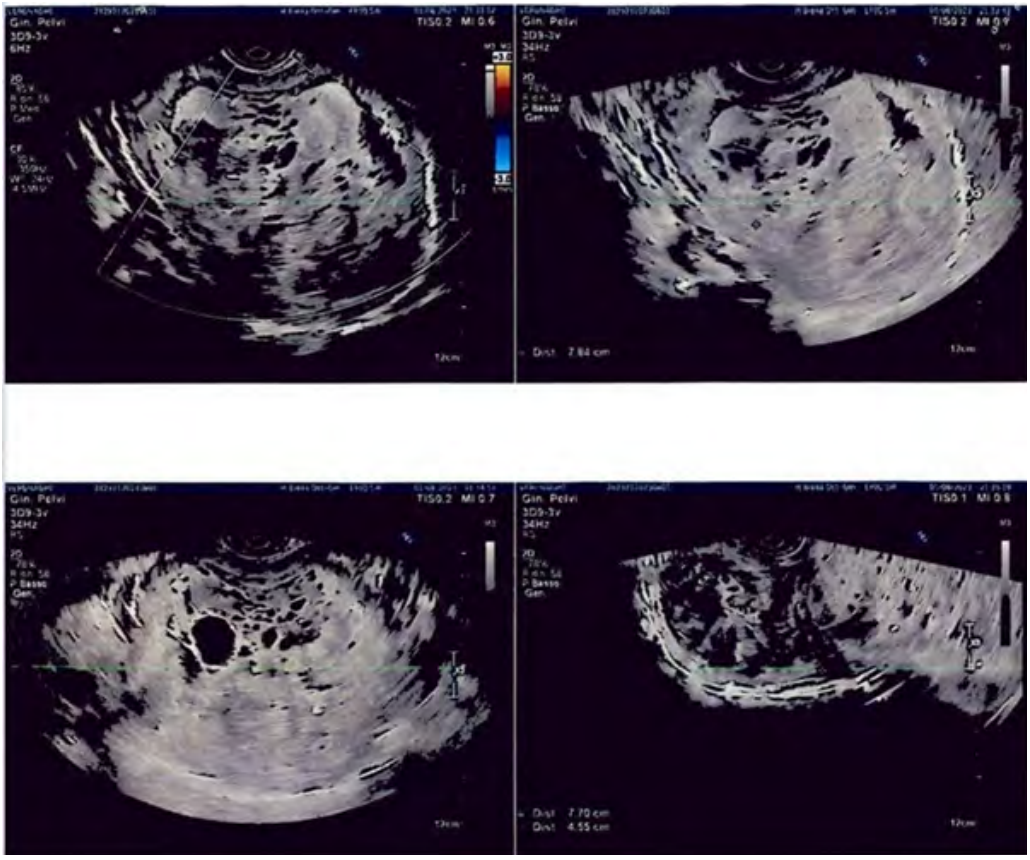

Figure 1: Transvaginal ultrasound showing thickened endometrial material with snowstorm pattern.

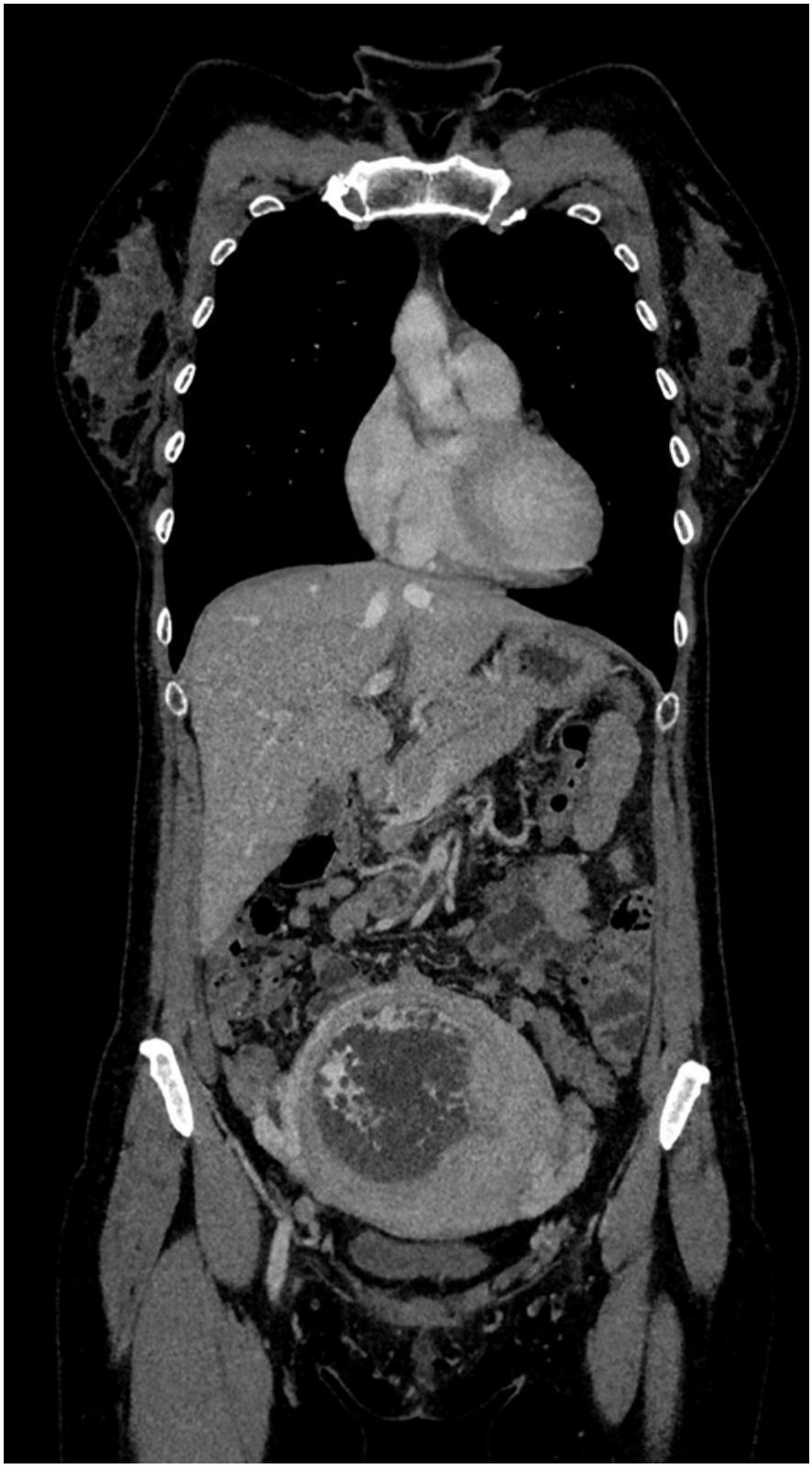

Figure 2: Venous phase sagittal Computed Tomography scan showing an enlarged uterus due to a hypodense mass characterized by inhomogeneous contrast enhancement.

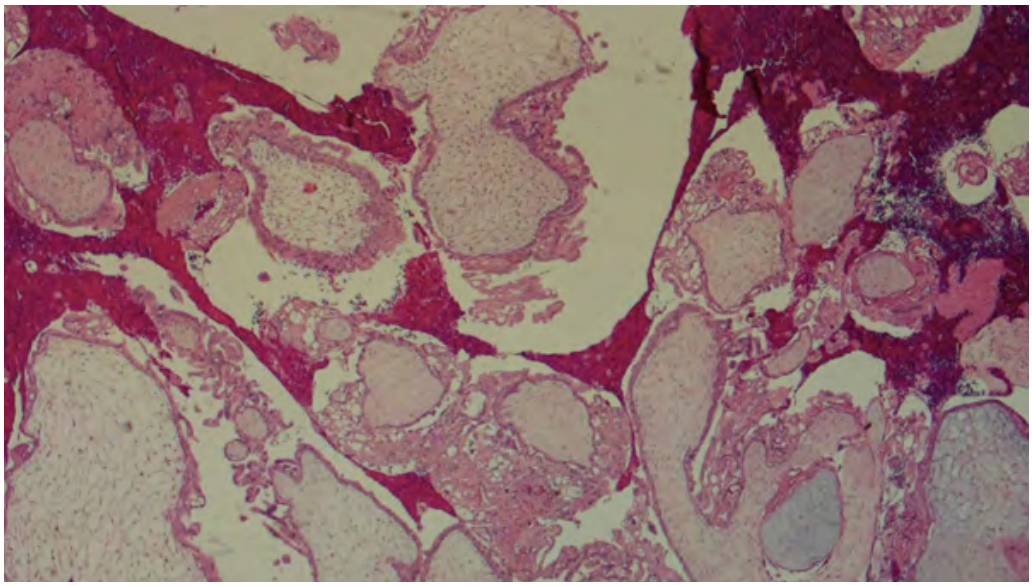

Figure 3: Marked hydropic villi with associated circumferential trophoblastic hyperplasia and cytologic atypia in complete hydatiform mole specimen (hematoxylin-eosin, original magnification 20x).

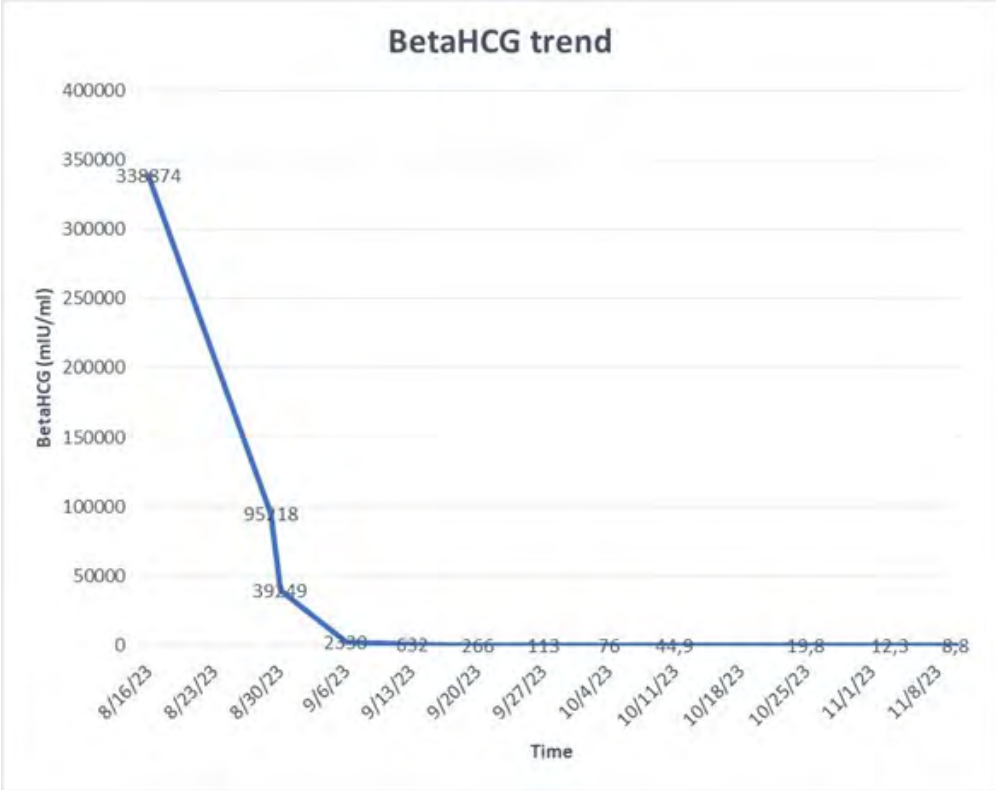

Figure 4: BetaHCG decrease trend.

4. Discussion

We performed a systematic literature review following Cochrane's review methods guide and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Data was searched through the following databases: PubMed, Scopus, Ovid MEDLINE, the Cochrane Database of Systematic Reviews, and Embase. Communications of international gynecology and oncology congresses and studies reported in ClinicalTrials.gov were also screened to identify relevant literature. The main search terms were trophoblastic disease AND menopause. The search was supplemented with a comprehensive evaluation of relevant and related articles' references. It was not restricted according to date but was limited to English and French language. The search was performed to include articles by November 2023. The following data were extracted: author, year of publication, median age of patients, βHCG initial values, ultrasound technique and characteristics, computed tomography (CT) features, histology and treatment. The search of the databases and registries found 189 items. Subsequently, only CHM reports were considered in the analysis. After assessing article eligibility based on the selection criteria, 20 articles [5-24] were finally retained (Figure 5).

The descriptive data of reports were extracted and reported in Tables 1.

Older age, ethnicity, genetic defects, and spontaneous miscarriage represent the most common risk factors for HM [25]. Bandy et al. [26] demonstrated an increased relative risk of a molar pregnancy of up to 519 for women over 50 years. In this group, the risk of malignant gestational trophoblastic disease was also higher (37.5%), but it was not statistically significant. Our data are consistent with literature and the median age is 54.7 years. In a case control study on 139 CM and 49 PM spontaneous miscarriage was associated with an augmentation of risk (odds ratio 3.1 for CM) as well as infertility (odds ratio 2.4) [27]. In our study, abortion was reported in 17 out of 20 cases and surprisingly only 1 patient was nulliparous [19]. The remaining 16 patients were multiparous (range 2-14 pregnancies) and the number of miscarriages appears relatively low (range 1-4). A personal or family history of GTD is a documented risk factor for CHM. The most common karyotype is 46 XX with a reduplication of the haploid paternal genome and exclusion of the maternal DNA, while only 5–10% of CHM have a Y chromosome consistent with dispermic fertilization [28, 29]. A genetic component of repetitive moles can be explained by NLRP7 and KHDC3L maternal germline mutations, that are observed in 48–80% and 10–14% of patients with repetitive moles, respectively [30]. These genes are implicated in maternal imprinting influencing both oocyte development and environment characteristics. For this reason in recurrent hydatidiform moles, DNA testing should be performed and when NLRP7 or KHDC3L mutation are detected, oocyte donation should be proposed [31]. Unfortunately, the genetic analysis of karyotype is not reported in the reports available in the literature, so it was not possible to analyze this data, which could be the subject of further studies. CHM classic clinical signs are vaginal bleeding, uterine enlargement greater than expected for gestational age, theca-lutein cysts due to ovarian hyperstimulation by high serum hCG values, hyperemesis, preeclampsia, hyperthyroidism, and respiratory insufficiency [1]. These symptoms can also occur in normal pregnancies and are explained by BHCG action on the uterus and central nervous system. In our analysis, the most common admittance symptom is vaginal bleeding (75%), followed by abdominal pain or distention or bloating (55%) and nausea (40%). No asymptomatic patients were reported. Sun et al. [32] report that even the classical presentation of hydatidiform mole with symptoms of abnormal bleeding significantly decreased during the duration of their study from 84% in the early cohort of patients to 46% in the later cohort. This can probably be explained by earlier diagnosis and evacuation. The descriptive data of diagnostic features and treatment of population were reported in Table 2. Transvaginal ultrasound is the first diagnostic imaging when GTD is suspected [33]. The advances in ultrasound imaging and the wide availability of high-resolution TVUS have shifted the diagnosis of HMs from the second to the first trimester of pregnancy [34]. This had a significant impact on the reduction of complications as it is proved that medical complications occur in approximately 25% of patients with uterine enlargement greater than 14–16 weeks gestational size but less frequently among patients with smaller uteri [35]. Ultrasound diagnosis of CHM is very sensitive with the reported detection rates between 80% and 95% [36, 37]. Ultrasound feature suggestive of a CHM is thick and cystic tissue often entirely occupying the uterine cavity with the typical snowstorm appearance and without a visible gestational sac. In the articles examined in our study, ultrasound description appears heterogeneous, moreover the size of the uterus and the endometrial thickness are not always reported: only 8/20 reports describe endometrial thickness and the average thickness is 68 mm. Since this diagnosis is uncommon in menopausal patients, operator experience is decisive in determining the accuracy of this diagnosis, especially if early pregnancy complications are not evident and clearly recognized and βHCG samples are not available [38]. Due to hyperplastic trophoblastic cells in CHM, patients have marked BHCG elevations, even if a diagnostic cut-off is not documented. In our analysis, the average value of BHCG was 362.658 UI/mL. Because of BHCG high rates, the risk of false negatives can be increased because of the saturation of antibodies called the "hook effect". The presence of elevated βHCG, older age and suggestive ultrasound is consistent with CHM diagnosis [1]. It is not easy to differentiate CHM from PHM, even if the latter presents lower βHCG values, less suggestive ultrasound and less relevant clinical features. The diagnosis must be confirmed by anatomopathological analysis after curettage and analysis of the p57 protein. This cyclin-dependent kinase inhibitor is a paternally

imprinted but maternally expressed gene so, lacking maternal genome, this protein is not expressed in CHM while it is present in PHM [39]. There is no actual indication to perform thorax Computed Tomography (CT) for stading purposes. In 2015 Proce et al. [40] published a study on 191 patients (169 low risk and 22 high risk using FIGO 2000 classification score 41) who underwent staging thorax CT-scan. Using information from CT imaging, only a further 20 patients would have been reclassified as high risk. The authors concluded that no potential advantage in terms of patient outcome and significantly increased radiation dose was offered by thorax CT; for that reason, routine CT imaging of the thorax in the initial assessment of new patients with gestational trophoblastic neoplasia was not justified. In our literature review, initial imaging was performed in 16/20 cases (80%). Only in 2 cases [11, 20] (10%) pulmonary metastasis were documented. The initial fertility preservation treatment of HM is suction dilation and curettage (D&C), preferably performed with the largest cannula and ultrasound guidance [42, 43]. Total hysterectomy with salpingo-oophorectomy represents closure treatment for women who have accomplished their reproductive desire and eliminates the risk of occult metastases. In a recent metanalysis [44], hysterectomy was demonstrated to improve post-molar gestational trophoblastic neoplasia prevention over uterine evacuation with an odds ratio of 0.19 ($p = 0.0004$). Our analysis confirmed hysterectomy as the election treatment (90%) in two cases [8,18] during surgery were performed omentectomy, appendectomy, and pelvic lymphadenectomy. During the planning of our patient's treatment, we decided to perform a former evacuation and subsequent hysterectomy. No cases of association of these two procedures have been reported in literature. However, considering the risk of tumor spread during invasive surgery, performing uterine evacuation before hysterectomy could reduce this risk and consequently the risk of recurrence. Prophylactic chemotherapy after hysterectomy is not recommended because of increased toxicity and drug resistance, despite of post-molar GTN risk reduction [45]. In our study on 4 patients received chemotherapy after surgery but in 2 cases this decision was related to the unexpected finding of pulmonary metastasis at CT scan [11, 20]. In the other 2 cases [13, 24] chemotherapy was administrated after dilation and curettage probably in order to avoid cloture surgery. Post-evacuation surveillance with BHCG, possibly with an assay that can identify all forms of BHCG, is mandatory to identify the development of post-molar GTN [2] early. A recent meta-analysis by Albright et al. [45] confirmed that the overall incidence of post-molar GTN after evacuation of CHM is 15.7% (95% CI 15.0–16.5%). If BHCG values normalize in less than 56 days after evacuation, the risk of developing GTN drops to 0.03%, 0.3% if it normalizes 56 days after. For this reason, it is recommended that follow-ups continue after 3 months of BHCG normalization. It has been described that the risk of post-molar GTN in women older than 50 who perform evacuation can achieve 60%, a hysterectomy should be proposed to these patients [46]. Prophylactic chemotherapy after hysterectomy is not recommended because of increased toxicity and drug resistance, despite post-molar GTN risk reduction [47].

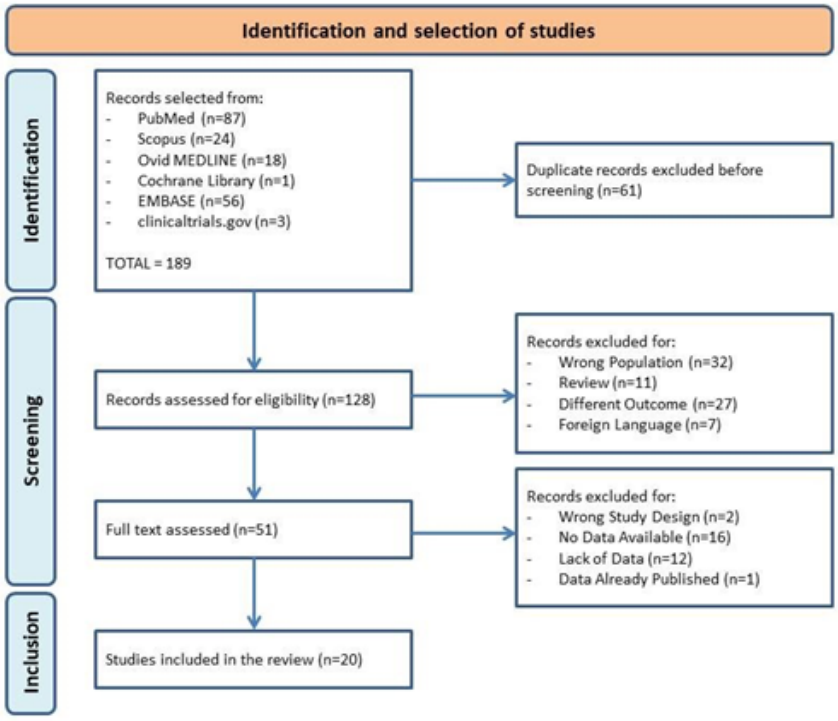

Figure 5: Identification and selection of studies Flowchart.

Table 1: Population anamnesis and symptoms.

Authors	Year	Age (years)	Presenting symptoms	Amenorrhea (months)	Obstetrical anamnesis	Hormonal replacement
Davidson S A et al.	1997	60	Vaginal bleeding, nausea, breast tenderness	4	G8 P8 A0	No
Roy KK et al.	2000	52	Vaginal bleeding, abdominal pain	24	G3 P3 A0	No
Garcia M et al.	2004	61	Vaginal bleeding	12	G4 P2 A2	Yes
Hirst J et al.	2004	55	Vaginal bleeding, aching joints, palpitations	-	-	Yes
Lok C A R et al.	2005	56	Vaginal bleeding, nausea, vomiting, agitation, palpitations, abdominal distension	3	G3 P3 A0	No
Abike F et al.	2008	56	Abdominal pain, nausea, vomiting	60	G5 P3 A2	No
Benabu-Saada L et al.	2008	54	Vaginal bleeding	12	G3 P2 A1	No
Camuzcuoglu H et al.	2009	57	Abdominal pain, nausea, vomiting	15	G14 P12 A2	No
Struthmann L et al.	2009	53	Vaginal bleeding, abdominal pain, nausea, vomiting, breast tenderness	3	G8 P6 A2	No
Oikonomidis P et al.	2011	54	Vaginal bleeding, abdominal pain	-	P2	No
Özdemir S et al.	2011	58	Vaginal bleeding, abdominal pain, nausea, vomiting	96	G5 P4 A1	No
Mehrotra S et al.	2012	60	Vaginal bleeding, abdominal pain	-	G5 P4 A0	No
Hatanaka K et al.	2012	53	Nausea	4	P2	No
Stolnicu S et al.	2014	51	Abdominal pain	36	G4 P3 A1	No
Begum J et al.	2016	52	Vaginal bleeding, loss of appetite	60	G0 P0 A0	No
Vogin G et al.	2016	52	Vaginal bleeding, epigastric pain, bloating, fatigue, weight gain	4	G3 P3 A0	No
El-Agwany AS et al.	2017	55	Vaginal bleeding	108	G7 P6 A1	No
Fatusic J et al.	2019	57	Vaginal bleeding	24	G7 P3 A4	No
Wang Q et al.	2021	52	Vaginal bleeding, abdominal bloating	24	G5 P3 A2	No
Ftiha F et al.	2022	48	Nausea	3	G2 P2 A0	No
Parpinel et al.	2023	54	Vaginal bleeding	4	G2 P2 A0	No

Abbreviations: G: Gravida; P: Para; A: Abortions.

Table 2: Population diagnostic characteristics and treatment.

Authors	Initial BHCGv (mIU/mL)	US utherus size (mm/ weeks)	US mass thickness (mm)	US characteristics	Imaging	Surgery	Adjuvant treatment
Davidson S A et al.	266	16	-	Mixed solid and cystic mass	No MTS	TAH + BSO	-
Roy KK et al.	450000	16	-	Cystic spaces, mixed echogenicity	No MTS	TAH + BSO	-
Garcia M et al.	>200000	122 x 67 x 96	52	Complex echoes	No MTS	TAH + BSO	-
Hirst J et al.	96.463	-	50	Areas of fluid echogenicity, endometrium-myometrium junction interruption, increased vascularity	No MTS	TAH + BSO + Omental biopsy + Pelvica lymphadenectomy	-
Lok C A R et al.	> 100.000	24	119	Snowstorm pattern	No MTS	TAH	-
Abike F et al.	188	143 x 95	28	Cystic areas, mixed echogenicity	No MTS	TAH + BSO	-
Benabu-Saada L et al.	633	-	-	Glandular-cystic aspect, vesicular areas, high color score	Pulmonary MTS	Dilatation and curettage	CT
Camuzcuoglu H et al.	100	14	-	Vascular mass	No MTS	TAH + BSO	-
Struthmann L et al.	1.400.000	142 x 132 x 100	-	Snowstorm pattern	No MTS	Dilatation and curettage	CT
Oikonomidis P et al.	97	126 x 95	-	Snowstorm pattern	-	TAH + BSO	-
Özdemir S et al.	157	140 x 120 x 90	32	Vesicular areas	No MTS	TAH + BSO	-
Mehrotra S et al.	262.1	24	-	Snow storm pattern	-	TAH + BSO	-
Hatanaka K et al.	67.611	19	64	Complex echoes	No MTS	TAH+BSO	-
Stolnicu S et al.	-	-	-	70 mm right ovary mass	No MTS	TAH + BSO + Omenectomy + Appendectomy	-
Begum J et al.	400	22	-	Snowstorm pattern	-	TAH	-
Vogin G et al.	960	150 x 120	-	-	Pulmonary MTS	TAH + BSO	CT
El-Agwany AS et al.	290	-	-	Snowstorm pattern	No MTS	TAH + BSO	-
Fatusic J et al.	193.057	-	-	-	-	TAH + BSO	-
Wang Q et al.	1239	164 x 142 x 89	152	Hetherogenous mass	No MTS	TAH + BSO	-
Ftiha F et al.	242.296	-	32.2	Thickened heterogeneous endometrium	No MTS	Dilatation and curettage	CT
Parpinel et al.	338874	16	83	Vesicular areas, color score 1	No MTS	TAH + BSO	-

Abbreviations: BHCG: beta Huma Corionic Gonadotropine; US: ultrasound; MTS: metastasis; TAH: total abdominal and hysterectomy; BSO: bilateral salpingooforectomy; CT: Computed Tomography

5. Conclusions

The diagnosis and treatment of HM in menopausal patients is still complex. This is probably due to two items: on the one hand, the low incidence of the phenomenon in this age range, on the other hand, the operator's scarce ultrasound experience. Hysterectomy is superior to uterine evacuation to prevent recurrences, but the association of the two procedures could further reduce the risk of tumor diffusion. More extensive surgery including omentectomy, appendectomy or pelvic lymphadenectomy is not actually indicated although it has been reported in literature.

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