

Analysis of the epidemiologic, clinical, laboratory, ultrasonographic, and anatomopathological profile of women with hydatidiform mole at two referral centers in Northeastern Brazil

Analýza epidemiologického, klinického, laboratorního, ultrasonografického a anatomicko-patologického profilu žen s hydatidiformní molou ve dvou referenčních centrech v severovýchodní Brazílii

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Summary: Objective: To determine the profile of women undergoing uterine evacuation for suspected hydatidiform mole (HM) according to their clinical, laboratory, ultrasound, and anatomopathological characteristics at two referral centers in Northeastern Brazil. **Methods:** Retrospective cohort study was performed in two referral centers between October 2016 and December 2022 with women undergoing uterine evacuation for suspected HM. Socio-demographic characteristics, clinics, biochemistry, ultrasound, anatomopathology, and outcome were evaluated. **Results:** A total of 507 women were admitted with clinical suspicion of gestational trophoblastic disease, of which 334 were confirmed, with 107 being in Center-1 and 227 being in Center-2. Mean distance between the referral center and the patient's home was 88 km. Mean age of the women was 27 ± 9 years, with a predominance of 19 to 39 years (72%), and approximately 60% of the cases were diagnosed ≤ 12 weeks of gestation. Vaginal bleeding was observed in 79% of women. Transvaginal ultrasound showed a typical appearance in 90% of the examinations. The macroscopic aspect was described as a vesicle in 70% of cases. Uterine evacuation was mainly performed by uterine curettage (43%). The majority of women had no complications (69%). The outcome considered to be remission was achieved in 37.1% of cases, but 38.9% abandoned follow-up, and 9% did not start follow-up after hospital discharge. **Conclusion:** The distance traveled by women to the referral centers was significant, but the majority of women had no complications. Remission was observed in 37.1% of women, but there was a high abandonment rate of 38.9%.

Key words: hydatidiform mole – clinics – ultrasound – anatomopathology – outcomes

Souhrn: Cíl: Zjistit profil žen podstupujících evakuaci dělohy pro podezření na hydatidiformní molu (HM) podle jejich klinických, laboratorních, ultrazvukových a anatomicko-patologických charakteristik ve dvou referenčních centrech v severovýchodní Brazílii. **Metody:** Retrospektivní kohortová studie byla provedena ve dvou referenčních centrech v období od října 2016 do prosince 2022 u žen podstupujících evakuaci dělohy pro podezření na HM. Hodnotily se sociodemografické charakteristiky, klinické parametry, biochemie, ultrazvuk, anatomická patologie a výsledky. **Výsledky:** Celkem bylo přijato 507 žen s klinickým podezřením na gestační trofoblastickou nemoc, u 334 z nich byla HM potvrzena, u 107 pacientek v centru 1 a 227 v centru 2. Průměrná vzdálenost mezi referenčním centrem a domovem pacientky byla 88 km. Průměrný věk žen byl 27 ± 9 let, s převahou 19–39 let (72 %), a přibližně 60 % případů bylo diagnostikováno v ≤ 12 týdnu těhotenství. Vaginální krvácení bylo pozorováno u 79 % žen. Transvaginální ultrazvuk vykazoval typický vzhled u 90 % vyšetření. Makroskopický aspekt byl popsán jako vezikula v 70 % případů. Evakuace dělohy byla prováděna především děložní kyretáží (43 %). Většina žen neměla žádné komplikace (69 %). Výsledek považovaný za remisi byl dosažen v 37,1 % případů, ale 38,9 % žen přestalo docházet na kontroly a 9 % nebylo po propuštění z nemocnice sledováno. **Závěr:** Vzdálenost, kterou ženy urazily do referenčních center, byla významná, ale většina žen neměla žádné komplikace. Remise byla pozorována u 37,1 % žen, ale byl zde vysoký podíl žen (38,9 %), které přestaly na kontroly docházet.

Klíčová slova: hydatidiformní mola – klinické parametry – ultrazvuk – anatomická patologie – výsledky

Introduction

Gestational trophoblastic disease (GTD) is characterized by abnormal proliferation of various types of trophoblasts, including benign forms such as molar pregnancy, complete hydatidiform mole (CHM), and partial hydatidiform mole (PHM), as well as malignant forms, collectively referred to as gestational trophoblastic neoplasia (GTN) [1]. The incidence of GTD, especially HM, is low in the population and varies according to geographic distribution. HM is estimated to occur in 1 in 1,000 pregnancies in North America and Europe; however, the incidence of the disease is thought to be at least two to three times higher in Brazil [2]. In the Cariri region, State of Ceará, Northeastern Brazil, the estimated incidence of GTD is 1.015% of pregnancies [3].

The extremes of reproductive age are well recognized as a risk factor for the development of CHM, with adolescents having a 7-fold risk and women > 40 years having a 2-fold risk, while the distribution of PHM cases is uniform [4]. However, changes in the epidemiology of GTD have been observed in several countries [1]. Some studies also report a reduction in the age range and mean gestational age at uterine evacuation in women with CHM, as well as smaller uterine volumes, the latter attributed to an earlier diagnosis [5]. CHM and PHM develop malignancy in 18–28% and 2–4% of cases, respectively, in the United States [6]. In 2010, a study concluded that heterozygous complete moles have a higher risk of progression to GTD than homozygous complete moles. Cytogenetic analysis was performed using a short tandem repeat (STR) polymorphism from molar tissue and parental serum samples. It is important to note that this study involved a small, screened population and further research is needed on this topic [7].

In Brazil, the likelihood of developing GTN after molar pregnancy has been estimated to be 15–25% [8]. From an

individual perspective, although almost all women with HM have a normal reproductive future [9], the risk of a repeat molar pregnancy increases up to 5-fold after the first molar pregnancy [6]. As a result of the increased use of ultrasound in the first trimester of pregnancy, the clinical presentation of HM has changed dramatically. In some cases where the clinical course is not very expressive, it will be necessary to wait for more data, such as an elevated blood human chorionic gonadotropin (hCG) level or an ultrasound examination with a more typical pattern, to confirm the clinical suspicion [10].

In Brazil, ultrasound is performed by a physician who may specialize in radiology or gynecology and obstetrics. Ultrasound scans are provided by the public health system, but there are some disparities between different regions of the country, as some cities offer immediate access, such as the first trimester scan, while others offer only one scan during pregnancy. Obstetric care in Brazil is characterized by two models: private (self-funded or through health insurance companies) and public (regulated by SUS, acronym in Portuguese, Brazil's Unified Health System, at no cost to the user). In the public system, women diagnosed at an early stage of pregnancy may initially receive care from a multidisciplinary team, including a nurse and a physician, at primary health care facilities. If there is a comorbidity or risk factor, the patient is referred to a secondary level for high-risk prenatal care or to a tertiary level for more complex maternity facilities.

For proper management of HM, it is recommended that the woman be referred to a referral center where she will receive appropriate treatment and guidance to minimize negative outcomes and psychological impact of the disease. The prognosis of patients with GTN improves 9-fold when treatment is performed in trophoblastic reference centers [11]. The only modifiable variable

associated with a reduction in the lethality of GTN is its management at reference centers [12]. The care of women with GTD is directed to independent reference centers, supported as needed by the Brazilian Association of Gestational Trophoblastic Disease (ABDTG, acronym in Portuguese). Currently, there are 47 referral centers throughout the country, almost all of which are public services, mainly located in teaching and university hospitals.

The management of GTD after diagnostic suspicion involves performing uterine evacuation in women with reproductive desire, preferably through uterine vacuum aspiration. Hysterectomy may be an alternative in those of advanced age with offspring [13]. The best described technique for evacuating the uterus is a vacuum or electric aspiration guided by ultrasound. However, because it requires the constant purchase of disposable materials, many hospitals do not have a sufficient supply to sustain its use. The material resulting from molar evacuation is typically sent in for histopathologic analysis when the procedure is performed at reference centers.

After discharge from the hospital, hCG blood level monitoring is essential in order to promote early detection of malignant progression or post-molar GTD. For outpatient follow-up of women with GTD, referrals to reference centers may require transportation from the patients' hometowns or they have to be arranged by the women themselves. Public health systems of the cities are responsible for facilitating patient transportation to the reference center, with local health departments responsible for coordinating and providing this support. However, in Brazil, due to the great distances and several socio-economic disparities, it is known that it is more difficult to return weekly for this post-molar follow-up [14].

The objective of this study was to determine the profile of women undergoing uterine evacuation for suspected

HM, according to their clinical, laboratory, ultrasound, and anatomopathological characteristics, in two referral services in the state of Ceará, Northeastern Brazil.

Methods

Patients

A retrospective cohort study of women with suspected HM was conducted between October 2016 and December 2022 in two tertiary referral centers in the state of Ceará, Northeastern Brazil. This study was approved by the Ethics Committee of the Federal University of Ceará. Informed consent was not applicable. The two reference public health centers were the Assis Chateaubriand Maternity School in Fortaleza city (Center-2), a reference center for high-risk pregnancies with a specialized GTD outpatient clinic with 94 obstetric beds including an obstetric clinic and maternal intensive care unit beds. The Northern Region Hospital (Center-1) in Sobral city is a general hospital with an obstetric service for suspected cases of GTD with 43 obstetric beds for high-risk pregnancies.

Inclusion criteria were women with a diagnosis of HM, suspected by ultrasound examination in cases of early pregnancy or first trimester vaginal bleeding, who had undergone uterine evacuation. The exclusion criteria were women whose pathology revealed miscarriage or an unknown result, except for those whose clinical, laboratory, and/or ultrasound history maintained a strong suspicion of HM.

Variables

Socio-demographic characteristics

- Municipalities/Services: Fortaleza/Center-2 and Sobral/Center-1.
- Distance in kilometers between the patient's home and referral center, measured using Google Maps.
- Age in years, divided into the following age groups: ≤ 15 years, 16 to 18 years, 19 to 39 years, and ≥ 40 years.
- Gestational age: gestational age based on the last menstrual period.

- Total number of pregnancies, including the current one.
- Parity (number of deliveries).

Clinics

- Vaginal bleeding;
- Anemia: hemoglobin blood level < 11 mg/dL in a blood count taken before uterine evacuation, and severe anemia hemoglobin ≤ 7.0 mg/dL.
- Preeclampsia: arterial blood pressure $\geq 140 \times 90$ mmHg on two occasions 4 hours apart and proteinuria (≥ 300 mg/dL in 24 hours of collection or protein/creatinine ratio ≥ 0.3 mg/dL or 1+ on two occasions 4–6 hours apart or $\geq 2+$ in any single urine sample – qualitative) [15].
- Hyperemesis gravidarum: nausea and vomiting requiring medication.
- Thyrotoxic crisis: TSH blood levels < 0.5 mUI/mL associated with the need for beta-blockers for clinical improvement [16].
- Pulmonary symptoms.

Biochemistry, Ultrasound, and Anatomopathology

- Typical image of HM: hyperechoic endometrial echo filled with hypoanechoic, irregular images [1].
- Non-developing pregnancy:
 - incomplete miscarriage: partial expulsion of the products of pregnancy with an endometrial echo ≥ 16 mm;
 - anembryonic pregnancy: retention of pregnancy material, closed uterine cervix, mean gestational sac diameter > 20 mm without an embryo, or mean gestational sac diameter < 20 mm with an embryo without growth in 7 days;
 - retained miscarriage: crown-rump length (CRL) > 6 mm without cardiac activity or CRL < 6 mm without growth in 7 days;
 - tecalutein cyst: multiple simple anechogenic cysts (4 to 8 cm), usually bilateral.
- hCG blood levels: pre-evacuation levels.

- Hemoglobin and hematocrit blood levels: pre-evacuation levels recorded in medical records.
- Chest X-ray: record of findings such as ground-glass infiltrates, pleural effusion, pulmonary nodules.
- Macroscopic aspect: vesicles, ovular/placental remnants.
- Anatomopathology: PHM, CHM, unclassified HM, miscarriage/decidual remnants, and GTN.

Outcomes

- Spontaneous remission: three normal weekly hCG blood levels ≤ 5 mUI/mL – followed by 6 normal monthly tests for HCM and 1 test in 1 month for HPM.
- GTN, post-treatment discharge: progression to GTN (hormonal or anatomopathological diagnosis), surgical and/or chemotherapy treatment, and follow-up to outpatient discharge.
- Abandonment of follow-up: started outpatient follow-up but did not complete it, with hCG blood levels > 5 mUI/mL at the last evaluation.
- Incomplete follow-up: started outpatient follow-up but did not complete follow-up, with hCG blood levels at the last evaluation < 5 mUI/mL.
- No follow-up: no outpatient returns after discharge.
- Prenatal care: new pregnancy during outpatient follow-up.

Statistical analysis

Variables were presented as mean and standard deviation, median, percentiles, Min. and Max., frequency, and prevalence. The Mann-Whitney U-test was used to analyze the characteristics of the women and to check that the data did not follow a Gaussian distribution. Pearson's chi-squared test and Fisher's exact test were used to investigate associations between categorical variables. A 5% significance level was used. Statistical analyses were performed using the R statistical program version 3.2.2 and Excel 2016 (Microsoft Corp., Redmond, WA, USA).

Results

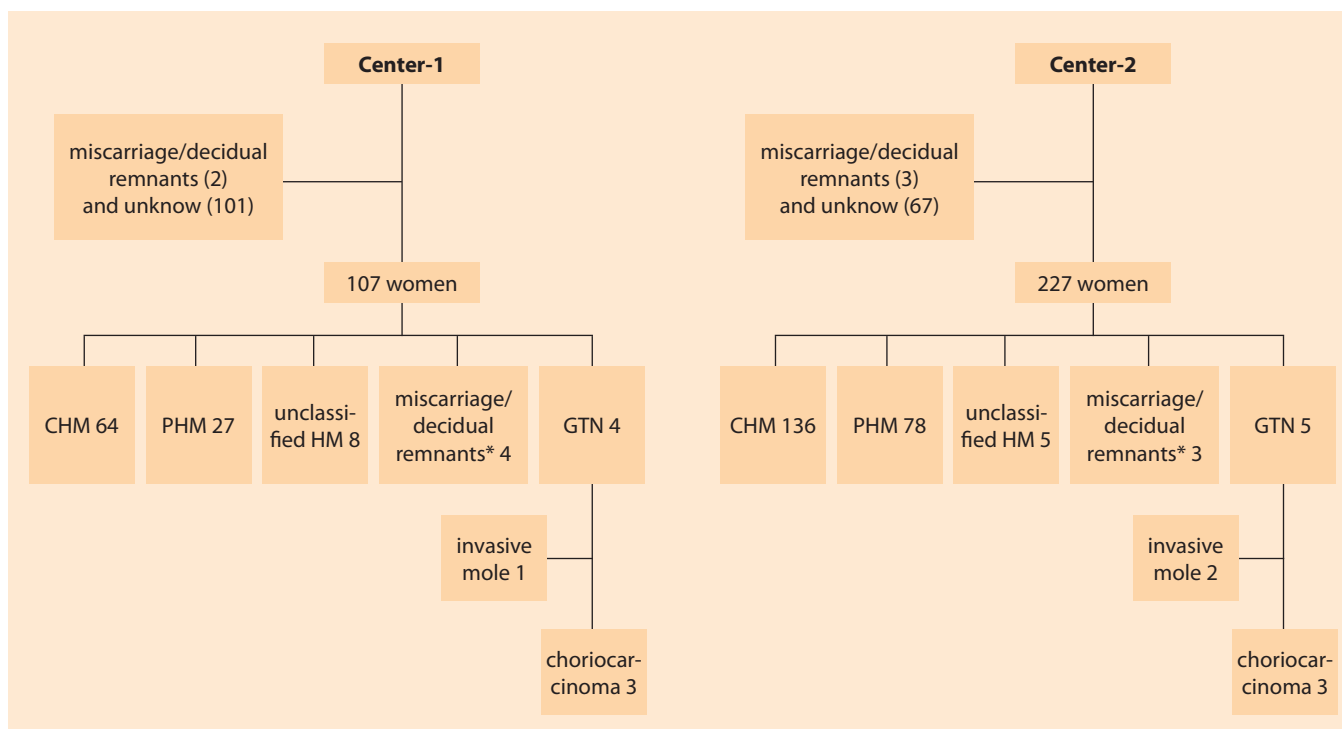
During the study period, 507 women with clinical suspicion of HM were admitted to both referral centers. We initially excluded 5 cases whose pathology was unknown (2 Center-1 and 3 Center-2) and 168 that turned out to be miscarriages (101 Center-1 and 67 Center-2). Of the 334 patients selected, 107 were from Center-1 and 227 were from Center-2. Among the 107 women from Center-1: 64 HCM, 27 HPM, 8 unclassified HM, 4 miscarriage/decidual remnants, 4 GTN (1 invasive mole and 3 choriocarcinomas). In the 227 women in Center-2: 136 HCM, 78 HPM, 5 unclassified HM, 3 miscarriages/decidual remnants, and 5 GTN (2 invasive moles and 3 choriocarcinomas). It should be noted that the 7 women with pathology of miscarriage/decidual remnants (4 Center-1 and 3 Center-2) who

remained in the analysis were kept because they had a strong suspicion of HM (clinical, laboratory, and ultrasound findings). The ratio between the types of HM followed up in each service was as follows for Center-2: 227 HM (136/59.9% HCM; 78/34.4% HPM; 5/2.2% unclassified HM; 5/2.2% GTN; 3/1.3% miscarriages/decidual remnants); Center-1: 107 HM (64/59.8% HCM; 27/25.2% HPM; 8/7.5% unclassified HM; 4/3.7% GTN; 4/3.7% miscarriages/decidual remnants) (Scheme 1).

During the evaluation period, the services had the following number of deliveries: Center-2 33,222 deliveries (19,922 cesarean sections and 13,300 vaginal deliveries), and Center-1 10,752 deliveries (7,866 cesarean sections and 2,886 vaginal deliveries). The ratio of the number of deliveries to the incidence of HM between

the services was as follows: 62 per 1,000 deliveries at Center-2 and 99 per 1,000 deliveries at Center-1. Regarding the referral center where the women were seen, more than half were seen in Center-2 (227/68%) and another half in Center-1 (107/32%). The mean total distance traveled between the referral center and the patient's home was 88 ± 106 km. This distance was approximately 2 km greater in Center-1 than in Center-2, and there was statistical significance ($P = 0.029$) (Tab. 1).

As for the year in which the women were seen in the two services, there was a predominance of the years 2022 (82/25%), 2020 (74/22%), and 2019 (71/21%). Mean age of the women seen at the two centers was 27 ± 9 years, with a predominance of 19 to 39 years (242/72%). Gestational age could not be determined in 26% of the women.



Scheme 1. Flowchart of the women included, distributed among the reference centers according to anatomopathological diagnosis.

* Women with a strong suspicion of hydatidiform mole (clinical, laboratory, and/or ultrasound findings) who remained among the evaluated cases.

Schéma 1. Vývojový diagram zahrnutých žen, rozdělených mezi referenční centra podle anatomickepatologické diagnózy.

* Ženy se silným podezřením na hydatidiformní molu (klinický, laboratorní a/nebo ultrazvukový nález), které zůstaly mezi hodnocenými případy.

Tab. 1. Socio-demographic characteristics of women with hydatidiform mole in both referral centers.

Tab. 1. Sociodemografické charakteristiky žen s hydatidiformním molem v obou referenčních centrech.

Socio-demographic characteristics	N	Total	Referral centers		P [§]
			Center-1 N = 107	Center-2 N = 227	
Distance between patient's home and reference center (kilometers)	334	88 ± 106 69 (0–129)*	89 ± 71 90 (40–111)*	87 ± 119 23 (0–146)*	0.029
Year	334				
2016		15 (4.5%)	13 (12.1%)	2 (0.9%)	
2017		25 (7.5%)	18 (16.8%)	7 (3.1%)	
2018		35 (10.5%)	14 (13.1%)	21 (9.3%)	
2019		71 (21.3%)	20 (18.7%)	51 (22.5%)	
2020		74 (22.2%)	18 (16.8%)	56 (24.7%)	
2021		32 (9.6%)	4 (3.7%)	28 (12.3%)	
2022		82 (24.6%)	20 (18.7%)	62 (27.3%)	
Age (years)	334	27 ± 9 25 (20–32)*	27 ± 8 26 (21–32)*	26 ± 9 25 (20–32)*	0.503
Age group (years)	334				0.883
≤ 15		21 (6.3%)	6 (5.6%)	15.0 (6.6%)	
16–18		37 (11.1%)	10 (9.3%)	27.0 (11.9%)	
19–39		242 (72.5%)	80 (74.8%)	162.0 (71.4%)	
≥ 40		34 (10.2%)	11 (10.3%)	23.0 (10.1%)	
Gestational age (weeks)	247	12.6 ± 4.2 12 (10–15)*	12.7 ± 3.7 12 (10–15)*	12.6 ± 4.5 12 (10–15)*	0.294
Categorized gestational age (weeks)	247				0.137
> 12		99 (40.1%)	37 (46.8%)	62 (36.9%)	
≤ 12		148 (59.9%)	42 (53.2%)	106 (63.1%)	
Total number of pregnancies, including current	334				0.031
≥ 1		201 (60.2%)	68 (63.6%)	133 (58.6%)	
1		128 (38.3%)	35 (32.7%)	93 (41.0%)	
without register		5 (1.5%)	4 (3.7%)	1 (0.4%)	
Parity	334				0.032
≥ 1		185 (55.4%)	63 (58.9%)	122 (53.7%)	
0		144 (43.1%)	40 (37.4%)	104 (45.8%)	
without register		5 (1.5%)	4 (3.7%)	1 (0.4%)	
Previous GTD	334	8 (2.4%)	2 (1.9%)	6 (2.6%)	> 0.999

*Mean ± Standard Deviation/Median (Min.–Max. value)
[§]Mann-Whitney, Chi-squared, and Fisher Exact tests
 GTD – gestational trophoblastic disease/gestační trofoblastické onemocnění, N – number/počet

Considering the available gestational age, the mean was 12.6 ± 4.2 weeks and 60% of the cases occurred in the period ≤ 12 weeks of gestation (148/334) (Tab. 1).

Regarding parity, the majority of women were multiparous with at least one previous delivery (185/55%), with a higher percentage of multiparous

in Center-1 (63/58.9%) compared to Center-2 (122/53.7%) ($P = 0.032$). Regarding the number of pregnancies, ≥ 1 pregnancies predominated (201/60%) with a higher percentage of the number of pregnancies in Center-1 (68/63.6%) compared to Center-2 (133/58.6%) ($P = 0.031$). Regarding the history of GTD, only 8/2.4%

reported this disease in the obstetric history (Tab. 1).

With regard to vaginal bleeding at admission, 79% (264/334) of the women seen reported this complaint. The percentage of women with vaginal bleeding was higher in Center-2 (195/86.3%) compared to Center-1 (64/64.5%) ($P < 0.001$). Among symptomatic women,

Tab. 2. Clinical, ultrasonography and surgical characteristics of women with hydatidiform mole in both referral centers.

Tab. 2. Klinické, ultrasonografické a chirurgické charakteristiky žen s hydatidiformní molou v obou referenčních centrech.

	N	Total	Center-1	Center-2	P [§]
Vaginal bleeding	333	264 (79.3%)	69 (64.5%)	195 (86.3%)	< 0.001
Associated symptoms					
preeclampsia	334	14 (4.2%)	1 (0.9%)	13 (5.7%)	0.043
thyrotoxic crisis	334	2 (0.6%)	0 (0.0%)	2 (0.9%)	> 0.999
hyperemesis gravidarum	334	25 (7.5%)	5 (4.7%)	20 (8.8%)	0.180
Quantitative blood hCG levels pre-evacuation (mUI/mL)	320	196,046 ± 163,007 / 225,000 (86,783–225,000)*	235,827 ± 254,297 / 163,995 (41,505–301,078)*	179,250 ± 98,736 / 225,000 (107,930–225,000)*	0.925
Categorized pre-evacuation quantitative blood hCG levels (mUI/mL)	320				0.002
< 100,000		84 (26.3%)	34 (35.8%)	50 (22.2%)	
100,000–225,000		59 (18.4%)	23 (24.2%)	36 (16.0%)	
> 225,000		177 (55.3%)	38 (40.0%)	139 (61.8%)	
Typical transvaginal ultrasound	333	301 (90.4%)	93 (86.9%)	208 (92.0%)	0.139
Thecalutein cysts	333	26 (7.8%)	8 (7.5%)	18 (8.0%)	0.877
Thorax X-ray	334				0.002
with findings		11 (3.3%)	0 (0.0%)	11 (4.8%)	
without findings		10 (3.0%)	0 (0.0%)	10 (4.4%)	
not performed		313 (93.7%)	107 (100.0%)	206 (90.7%)	
Type of uterine evacuation	326				< 0.001
manual vacuum aspiration		110 (33.7%)	16 (15.8%)	94 (41.8%)	
combination of techniques		65 (19.9%)	19 (18.8%)	46 (20.4%)	
electric vacuum aspiration		6 (1.8%)	6 (5.9%)	0 (0.0%)	
conventional uterine curettage		144 (44.2%)	60 (59.4%)	84 (37.3%)	
cesarean section		1 (0.3%)	0 (0.0%)	1 (0.4%)	

*Mean ± Standard Deviation/Median (Min.–Max. value)
[§] Mann-Whitney, Chi-squared, and Fisher Exact tests
hCG – human chorionic gonadotropin/lidský choriogonadotropin, N – number/počet, X-ray – rentgen

hyperemesis gravidarum (25/7.5%), preeclampsia (14/4.2%), and thyrotoxic crisis (2/0.6%) were more frequently detected. Preeclampsia was more frequent in Center-2 (13/5.7%) compared to Center-1 (1/0.9%) ($P = 0.043$) (Tab. 2).

The mean pre-evacuation hCG blood levels were $196,046 \pm 163,007$ mUI/mL, and this value was unknown in 14/4.19% of the women. Blood hCG levels upon admission were as follows: < 100,000 (26.3%), 100,000 to 225,000 (18.4%), and > 225,000 mUI/mL (55.3%). There was a statistical difference when categorized quantitative hCG blood levels were evaluated ($P < 0.001$). When transvaginal ultrasound was

performed, all were performed upon arrival and 301/90% had a typical HM appearance. A total of 26/7.8% had theca lutein cysts. Regarding chest X-rays, 313/93.7% of the women did not perform this examination and of those who underwent this examination, 11 (3.3%) had X-ray findings that varied between nodules, opacities, effusions, and signs of congestion. There was statistical significance in the inter-center comparison analysis ($P = 0.002$). Regarding the type of uterine evacuation, conventional uterine curettage predominated (144/43%), followed by manual vacuum aspiration (110/33%). However, when the services were analyzed separately,

manual vacuum aspiration was used more often in Center-2 (94/41.8%) than in Center-1 (16/15.8%) ($P < 0.001$). Of the women studied, one was admitted at 22 weeks of gestation with PHM and acute pulmonary edema. After an unsuccessful attempt at labor induction and curettage, she underwent cesarean section due to her acute condition (Tab. 2).

Regarding the macroscopic aspect, majority of specialists described the presence of vesicles in the operative report (233/70%), with this description dominating in Center-2 (179/78.9%), whereas in Center-1 there was a greater balance between the presence of

Tab. 3. Anatomopathology and intraoperative complications of women with hydatidiform mole in both referral centers.

Tab. 3. Anatomopatologie a peroperační komplikace žen s hydatidiformní molou v obou referenčních centrech.

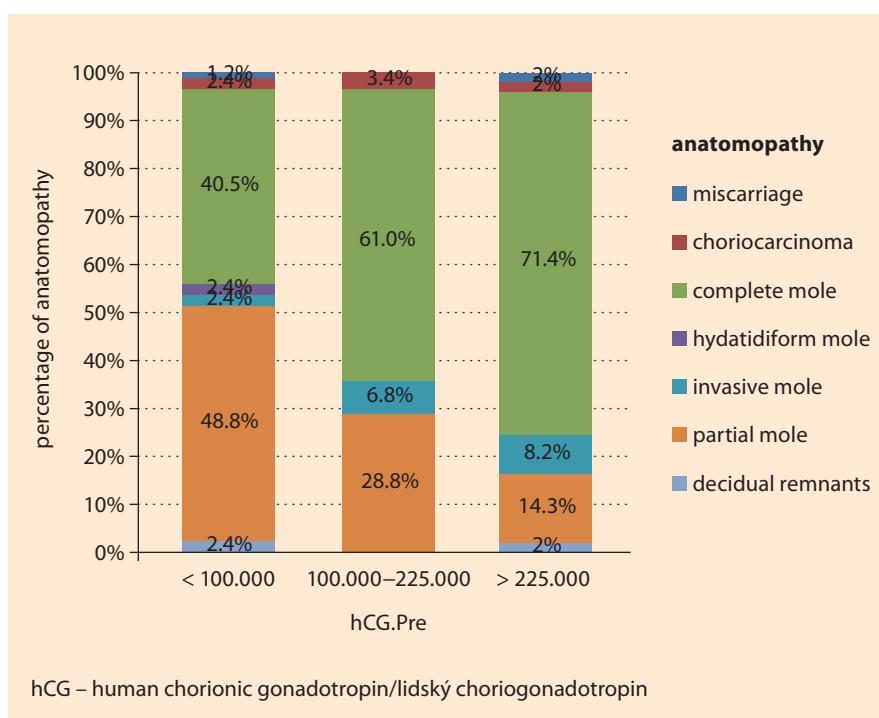
	N	Total	Center-1	Center-2	P [§]
Macroscopic appearance	334				< 0.001
ovular/placental remnants		91 (27.2%)	47 (43.9%)	44 (19.4%)	
vesicles		233 (69.8%)	54 (50.5%)	179 (78.9%)	
without register		10 (3.0%)	6 (5.6%)	4 (1.8%)	
Complications					
uterine perforation	334	1 (0.3%)	1 (0.9%)	0 (0.0%)	0.320
vaginal hemorrhage	334	3 (0.9%)	0 (0.0%)	3 (1.3%)	0.554
severe anemia	334	5 (1.5%)	2 (1.9%)	3 (1.3%)	0.657
without complication	334	229 (68.6%)	69 (64.5%)	160 (70.5%)	0.271
Anatomopathology	334				0.018
miscarriage		4 (1.2%)	1 (0.9%)	3 (1.3%)	
choriocarcinoma		6 (1.8%)	3 (2.8%)	3 (1.3%)	
complete hydatidiform mole		200 (59.9%)	64 (59.8%)	136 (59.9%)	
hydatidiform mole		13 (3.9%)	8 (7.5%)	5 (2.2%)	
invasive mole		3 (0.9%)	1 (0.9%)	2 (0.9%)	
partial hydatidiform mole		105 (31.4%)	27 (25.2%)	78 (34.4%)	
decidual remnants		3 (0.9%)	3 (2.8%)	0 (0.0%)	

[§] Chi-squared, and Fisher Exact tests

N – number/počet

vesicles (54/50.5%) and ovular/placental remnants (47/43.9%) ($P < 0.001$). Regarding complications from admission to follow-up, a total of 229/69% had no complications. Among those with complications, the following were identified: vaginal bleeding (3/0.9%); perforation (1/0.3%); and anemia (20/5.9%), of which 5 were severe anemia. In terms of anatomopathology, a total of 200 (60%) had CHM, 105 (31%) had PHM, and 13 (3.9%) had an unclassified HM. The percentage of HCM was similar between the services, with 64.0/59.8% in Center-1 and 136.0/59.9% in Center-2 ($P = 0.018$) (Tab. 3).

Categorization of quantitative blood hCG levels into parameters: $> 100,000$; $100,000\text{--}225,000$; and $> 225,000$ mUI/mL. It was observed that the highest pre-evacuating quantitative blood hCG levels ($> 225,000$ mUI/mL) were found in women with HCM – 71.4% (Graph 1, Tab. 4). Tab. 5 shows the correlation between quantitative blood hCG

**Graph 1. Association between pre-emptying quantitative hCG and anatomopathological analysis.**

Graf 1. Asociace mezi preemtivní kvantitativní hCG a analýzou anatomické patologie.

Tab. 4. Association between quantitative blood hCG levels pre-evacuation and anatomopathology.

Tab. 4. Asociace mezi kvantitativními hladinami hCG v krvi před evakuací a anatomopatologií.

Anatomopathology variable	hCG levels pre-evacuation (mUI/mL)				p [§]
	total	< 100,000	100,000–225,000	≥ 225,000	
Center-1	95 (100%)	34 (35.8%)	23 (24.2%)	38 (40%)	0.008
miscarriage	1 (1.1%)	0 (0%)	0 (0%)	1 (2.6%)	
choriocarcinoma	3 (3.2%)	1 (2.9%)	2 (8.7%)	0 (0%)	
complete mole	54 (56.8%)	15 (44.1%)	13 (56.5%)	26 (68.4%)	
hydatidiform mole	8 (8.4%)	0 (0%)	4 (17.4%)	4 (10.5%)	
invasive mole	1 (1.1%)	1 (2.9%)	0 (0%)	0 (0%)	
partial mole	25 (26.3%)	15 (44.1%)	4 (17.4%)	6 (15.8%)	
decidual remnants	3 (3.2%)	2 (5.9%)	0 (0%)	1 (2.6%)	
Center-2	225 (100%)	50 (22.2%)	36 (16%)	139 (61.8%)	0.032
miscarriage	3 (1.3%)	1 (2%)	0 (0%)	2 (1.4%)	
choriocarcinoma	3 (1.3%)	1 (2%)	0 (0%)	2 (1.4%)	
complete mole	136 (60.4%)	19 (38%)	23 (63.9%)	67.6%	
hydatidiform mole	5 (2.2%)	2 (4%)	0 (0%)	3 (2.2%)	
invasive mole	1 (0.4%)	1 (2%)	0 (0%)	0 (0%)	
partial mole	77 (34.2%)	26 (52%)	13 (36.1%)	38 (27.3%)	
decidual remnants	77 (34.2%)	26 (52%)	13 (36.1%)	38 (27.3%)	

[§] Fisher Exact tests

hCG – human chorionic gonadotropin/lidský choriogonadotropin

Tab. 5. Correlation between quantitative blood hCG levels categorized by gestational age and anatomopathology.

Tab. 5. Korelace mezi kvantitativními hladinami hCG v krvi kategorizovanými podle gestačního věku a anatomopatologie.

group	variable	N	total*	Anatomopathology		p [§]
				complete mole, N = 93*	partial mole, N = 53*	
Categorized gestational age period (weeks)						
> 12	quantitative blood hCG levels (mUI/mL)	151	189,064 ± 162,184 225,000 (81,370–225,000)	206,547 ± 138,845 225,000 (135,892–225,000)	158,810 ± 193,914 107,930 (19,767–225,000)	< 0.001
≤ 12	quantitative blood hCG levels (mUI/mL)	90	210,249 ± 185,639 225,000 (70,033–225,000)	219,984 ± 66,038 225,000 (190,903–257,556)	none	0.010

*Mean ± Standard deviation, Median (25–75%)

§Kruskal-Wallis test

hCG – human chorionic gonadotropin/lidský choriogonadotropin, N – number/počet

*Mean ± Standard deviation, Median (25–75%)

[§] Kruskal-Wallis test

hCG – human chorionic gonadotropin/lidský choriogonadotropin, N – number/počet

levels categorized by gestational age and anatomopathology.

Regarding the outcome, spontaneous remission, defined as normal blood hCG levels during the 6 months following the first normal blood hCG levels after uterine evacuating, was achieved in 124/37.1%. The percentage of follow-up to spontaneous remission was higher in Center-2 (93/41%) than in Center-1 (31/29%). It was found that 73/21.9% did not complete follow-up (18/16.8% in Center-1 and

55/24.2% in Center-2). The loss to follow-up was higher in Center-1 (26/24.3%) than in Center-2 (31/13.7%). Another 30/9.0% never started follow-up (15/14.0% in Center-1 and 15/6.6% in Center-2). Two women became pregnant again during follow-up (one patient in each Center). There was a statistically significant difference between the two Centers in terms of outcome (Tab. 6).

Of the 334 women included in the study, a total of 73 were diagnosed

as GTN. Of these, 9 were characterized as GTN based on the pathology report (6 choriocarcinomas and 3 invasive moles). Another 64/21% were diagnosed as GTN, identified after laboratory follow-up as they evolved with a plateau for at least 3 weeks, elevation of hCG blood levels for at least 2 weeks, or persistence of hCG blood levels for ≥ 6 months after uterine evacuation according to the FIGO classification. In this population, 35 (54.6%) were CHM, 19 (29.6%) were

Tab. 6. Outcomes of women with hydatidiform mole in both referral centers.

Tab. 6. Výsledky žen s hydatidiformní molou v obou referenčních centrech.

Outcome	N	Total	Center-1	Center-2	P [§]
	334				0.010
remission*		124 (37.1%)	31 (29.0%)	93 (41.0%)	
gestational trophoblastic neoplasia and discharge after treatment		48 (14.4%)	16 (15.0%)	32 (14.1%)	
incomplete follow-up		73 (21.9%)	18 (16.8%)	55 (24.2%)	
abandonment of follow-up*		57 (17.1%)	26 (24.3%)	31 (13.7%)	
without follow-up		30 (9.0%)	15 (14.0%)	15 (6.6%)	
prenatal care		2.0 (0.6%)	1.0 (0.9%)	1.0 (0.4%)	

[§]Chi-squared test; *Spontaneous remission = normal blood hCG levels for 6 consecutive tests after the first normal blood hCG levels following uterine evacuation; abandonment of follow-up = leaving follow-up before reaching spontaneous remission
hCG – human chorionic gonadotropin/lidský choriogonadotropin, N – number/počet

PHM, 3 (4.68%) were unclassified HM, and 7 (10.9%) women were followed up even with pathology of miscarriage/decidua remnants due to the high clinical suspicion having been treated for GTN. Of the 73 women followed up for GTN (9 by anatomopathological diagnosis and 64 by biochemical diagnosis during post-molar follow-up), 66% of women (48/73) were followed up to outpatient discharge, while another 34% of women (25/73) abandoned the follow-up before outpatient discharge, and of those who abandoned, 9 were still positive for hCG blood levels. The mean follow-up time between uterine evacuation and outpatient discharge was 335 ± 224 days (216–369), with the mean time being longer in Center-2 (353 ± 236 days) compared to Center-1 (240 ± 108 days) ($P = 0.008$).

Discussion

This study identified 334 cases of GTD, 107 from Center-1 and 227 from Center-2. It is important to note that the cases evaluated may not reflect the total number of women affected by GTD in the state of Ceará, Northeastern Brazil. The reason for this could be the fragility of the assertive diagnosis, leading to procedures aimed at non-evolving pregnancies of another classification (miscarriage or anembryonic pregnancy)

in women in whom GTD was not suspected in the first trimester. In addition, women admitted with a less typical history or with irregular vaginal bleeding, who had already undergone uterine evacuation at other services and who did not have a new surgical procedure in these centers and therefore did not have histopathologic material for analysis, may also be underreported.

Considering the two Centers, 200 women had CHM (60%), 105 had PHM (31%), 13 had unclassified HM (3.9%), and 9 had histopathologic GTN (2.7%). In a previous study in 10 reference centers in Brazil with 5,250 women, 63.2% had CHM and 29.5% had PHM [17]. Nadhan et al. [18] reported that the most common form of GTD, HM, has an incidence of 1 case per 1,000 pregnancies in North America and Europe. In Brazil, HM is estimated to occur in 1 in 200 to 1 in 400 pregnancies, approximately 5 to 10 times more commonly than in North America and Europe [19].

This study showed a long distance between the patient's home and the referral center, with a mean of 88 km, and the presence of women from other Brazilian states. Silva et al. [20] and Clark et al. [21] highlighted the 80 km cut-off point as a negative factor in the clinical condition, making it difficult to access specialized centers and worsening

the clinical condition of GTD. On the other hand, another study considered that 50 km would already be a distance with a potentially unfavorable outcome, including death from GTD [14]. A retrospective historical cohort study of GTN women followed at 8 Brazilian referral centers showed that when the distance between the patient's home and the referral center was ≥ 56 km, there was also an increase in the occurrence of metastatic disease, the need for multi-agent chemotherapy, loss to follow-up during chemotherapy, the occurrence of chemoresistance, relapse, and death from GTN [22].

Regarding age, we found that the mean age of the women was 27 years. It should be noted that we did not observe a significant difference in the age of the women between the two centers. Yuk et al. [23] and Taye et al. [24] observed that women > 40 years had a higher risk of developing GTD, while Mulisya et al. [25] observed this profile in women younger than 25 years. Regarding gestational age at diagnosis of GTD, the women had a mean of 12.6 weeks, with minimal difference between the two centers. The mean gestational age at diagnosis is currently around 10 to 12 weeks, which is in line with our results [26]. It should be noted that both centers are located in the Northeast of

Brazil, a region with great socio-economic and public health disparities. In addition, previous history of GTD was low (8/2.4%) in both centers, confirming the literature indicating that the risk of GTD following a molar pregnancy is low (0.6 to 2.0%) [27].

When the clinical complaints of the two centers were evaluated, it was found that a total of 79.3% of the women had vaginal bleeding. This finding is consistent with a study that found 90.1% of women with HM had abnormal vaginal bleeding [28]. Early diagnosis of HM confirms a lower frequency of associated symptoms such as hyperemesis gravidarum (7.5%), preeclampsia (4.2%), and thyrotoxic crisis (0.6%), which was confirmed in this study and is consistent with the findings in the literature [29,30]. A systematic review of data available between 2002 and 2010 found that the incidence of preeclampsia ranged from 1.2 to 4.2% and that of eclampsia ranged from 0.1 to 2.7%, with higher rates in regions with lower socioeconomic status [31]. The most severe form of vomiting in pregnant women, known as hyperemesis gravidarum, accounts for 1.1% of all cases of nausea and vomiting in pregnancy [32]. Transient gestational thyrotoxicosis (TGT) or transient gestational hyperthyroidism is the main differential diagnosis of Graves' disease and the most common clinical presentation, occurring in up to 5% of pregnancies and limited to the first half of pregnancy. There is an increased risk of TGT in conditions with elevated hCG levels, such as twin pregnancies, hydatidiform mole, and choriocarcinoma [33].

It has been shown that early miscarriages often mimic GTD on transvaginal ultrasound because hydropic and cystic images are seen that simulate HM [34]. This may also explain the high percentage of ultrasound examinations (90%) with a mole-like appearance found in this study. A meta-analysis aimed at evaluating the diagnostic value and accuracy of ultrasound in the diagnosis of

HM in all trimesters of pregnancy highlighted that although the sensitivity was relatively low at 52.2%, the specificity was high at 92.6% [36].

Regarding the type of uterine evacuation, in Center-2, manual vacuum aspiration predominated in 41.8% of cases, with another 20.4% using a combination of techniques. In a study by Matos et al. [35], 51.9% underwent uterine curettage and 30.4% underwent manual vacuum aspiration. In a retrospective study comparing manual vacuum aspiration with electrical aspiration in women with GTD in Rio de Janeiro, Brazil, similar results were observed between the two groups, with manual vacuum aspiration being associated with a lower rate of synechiae [36]. Padrón et al. [36] described that in women who underwent vacuum aspiration, whether electrical or manual, it was associated with uterine curettage to ensure complete uterine evacuation, which may explain the combination of techniques used in 65/19.9% of women in our study.

Regarding the macroscopic aspect of GTD, we observed that in Center-2 there was a predominance of vesicles (179.0/78.9 vs. 44.0/19.4%), while in Center-1 there was a greater balance between ovular/placental remnants and vesicles (47.0/43.9 vs. 54.0/50.5%), with a statistical difference. This finding highlights the subjectivity of macroscopic evaluation of uterine evacuation material reinforcing the importance of histopathologic analysis to confirm the disease [37].

Regarding the outcome, it was observed that remission predominated in both centers; however, there were still high rates of abandonment of follow-up and of women not being followed up. These data are of particular concern because they reveal a number of women who were lost to follow-up with a positive hCG serum, and who were unknown to the centers. Timely diagnosis of recurrent GTN is challenging because in most cases women are asymptomatic

and the new increase in hCG serum is insidious. Otherwise, in the absence of follow-up, women return with signs and symptoms of metastases [38]. On the other hand, we observed that a total of 51.4% of women, including both benign and malignant forms of GTD, completed adequate follow-up and were safely discharged. In the analysis of the 325 women followed up for HM, 64 were diagnosed with GTN after biochemical follow-up (21.8%). A previous study also showed that although the majority of CHM are benign, the risk of developing GTN can be as high as 18–19% [39].

In summary, the prevalence of GTD was 65.8% with a total of 32.1% from Center-1 and 67.9% from Center-2. The distance traveled by women to the referral centers was significant, but the majority of women had no complications. Remission was observed in 37.1% of women with HM. In addition, there was a high abandonment rate of 38.9%, which can be explained by the numerous social and demographic barriers.

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