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Gestational trophoblastic neoplasia after spontaneous human chorionic gonadotropin normalization following molar pregnancy evacuation

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HIGHLIGHTS

- The risk of postmolar GTN after hCG normalization following evacuation is 0.4%.
- Recrudescent GTN is more likely if hCG normalization requires more than eight weeks.
- Most cases of recrudescent GTN occur more than six months after hCG normalization.

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ABSTRACT

Objective. To evaluate the risk of gestational trophoblastic neoplasia (GTN) after spontaneous human chorionic gonadotropin normalization in postmolar follow-up.

Methods. Retrospective chart review of 2284 consecutive cases of hydatidiform mole with spontaneous normalization of hCG following uterine evacuation treated at one of five Brazilian reference centers from January 2002 to June 2013.

Results. After hCG normalization, GTN occurred in 10/2284 patients (0.4%; 95% CI 0.2%–0.8%). GTN developed in 9/1424 patients (0.6%; 95% CI 0.3%–1.2%) after a complete hydatidiform mole, in 1/849 patients (0.1%; 95% CI < 0.01%–0.7%) after a partial hydatidiform mole, and in 0/13 patients (0%; 95% CI 0%–27%) after a twin molar pregnancy. The median time to GTN diagnosis after hCG normalization was 18 months, and no diagnoses were made before six months of postmolar surveillance. Patients who required more than 56 days to achieve a normal hCG value had a ten-fold increased risk of developing GTN after hCG normalization (9/1074; 0.8%; 95% CI 0.4%–1.6%) compared to those who reached a normal hCG level in fewer than 56 days (1/1210;0.08%; 95% CI < 0.01%–0.5%; $p = 0.008$). All patients presented with symptoms at the time of GTN diagnosis.

Conclusion. GTN after spontaneous hCG normalization following molar pregnancy is exceedingly rare, and the few patients who do develop GTN after achieving a normal hCG value are likely to be diagnosed after completing the commonly recommended six months of postmolar surveillance. Current recommendations for surveillance after hCG normalization should be revisited.

1. Introduction

Gestational trophoblastic disease (GTD) encompasses several distinct clinical entities, from benign complete and partial hydatidiform moles to malignant invasive moles, choriocarcinoma, placental site trophoblastic tumor, and epithelioid trophoblastic tumor; malignant forms of GTD are grouped together under the term gestational trophoblastic neoplasia (GTN) [1]. Serial monitoring of human chorionic gonadotropin (hCG) levels after molar evacuation is essential to detect progression to GTN and to initiate chemotherapy [2]. In Brazil, GTD is estimated to occur in 1:200–400 pregnancies, an incidence five to ten times more frequent than in North America or Europe [3,4].

The greatest challenge to postmolar follow-up is adherence to hCG monitoring. GTD remission is defined as three consecutive normal

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weekly hCG measurements (less than the reference range on a given center's assay, usually less than 5 mIU/mL) followed by 6 months of normal monthly hCG measurements. However, this is challenging in developing countries or where travel distances are great [5,6]. Many patients stop returning for hCG levels once they achieve a normal hCG level. Consequently, large numbers of patients are lost to follow-up, and only half attend all the medical visits planned for postmolar surveillance [7,8].

To improve compliance, some authors have suggested a reduction in the length of postmolar monitoring [9]. For example, previous work has shown that a patient who reaches a normal hCG value within 56 days after uterine evacuation is extremely unlikely to develop GTN [10,11]. Shortening the hCG surveillance period would free patients from extended postmolar surveillance after hCG normalization, when the risk of malignancy seems to be negligible [12–18]. However, reports of recrudescent disease, meaning GTN after hCG normalization, have occurred, raising questions about the safety of an early discontinuation of serial hCG levels [19,20]. Here we estimate the incidence of GTN after hCG normalization, assess the timeframe in which recrudescent disease is most likely to appear, and describe the clinical characteristics of these patients.

2. Material and methods

2.1. Study design

This is a retrospective cohort study of consecutive patients with molar gestations treated at one of five Brazilian Gestational Trophoblastic Disease Reference Centers: in Rio de Janeiro (Maternity School of Rio de Janeiro Federal University, Antonio Pedro University Hospital of Fluminense Federal University, Maternity Ward of Santa Casa da Misericórdia do Rio de Janeiro — data entered by MM and audited by AB), in Goiânia (Clinical Hospital of Goiás Federal University — data entered by JR and audited by MGCV) and in Botucatu (Clinical Hospital of São Paulo State University — data entered by IM and audited by AB) from January 2002 to June 2013. Reporting was structured according to Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement guidelines [21].

2.2. Study participants

Patients were identified from the registries of the participating reference centers. Patients were diagnosed with gestational trophoblastic disease when presenting with pregnancy symptoms or vaginal bleeding combined with sonographic evidence of molar pregnancy and an elevated hCG level. All patients had uterine evacuation performed using suction curettage with histopathological confirmation of partial or complete hydatidiform mole. All histological material of patients who developed GTN after hCG normalization was re-examined using immunohistochemical methods and evaluation of $p57^{KIP2}$ expression to confirm the diagnosis of the type of hydatidiform mole.

This study includes all patients treated at one of the above centers during the study period who adhered to at least 24 months of follow-up and whose medical records were complete and available for review. Patients who did not continue hCG surveillance before achieving a normal hCG value or who did not have extended follow-up after achieving a normal hCG value were excluded.

2.3. Postmolar follow-up

Postmolar follow-up, in addition to contraception as suggested and provided to patients, consisted of clinical examinations and laboratory tests, including the measurement of hCG levels until disease remission. At the Brazilian reference centers, normalization of the hCG was defined as three weekly normal hCG values below the reference range of 5 mIU/mL. Complete remission was defined as three weeks of weekly normal hCG values followed by six months of monthly normal hCG values below the reference range of 5 mIU/mL. Patients then continued to be followed clinically. When patients did not attend the scheduled visits, a social worker and hospital psychology worker actively tried to contact them by phone and telegram to identify what was hindering compliance and to motivate them to return to follow-up.

Measurement in all five Reference Centers employed the Siemens Diagnostic Products Corporation (DPC) Immulite® assay. The reference value for normal results was an hCG value below 5 mIU/mL.

2.4. Diagnosis, staging, and risk factors for gestational trophoblastic neoplasia

Progression to GTN was diagnosed using the criterion established by Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) (2002): rising (more than 10%) hCG levels for three consecutive weeks or plateaued for four weeks [22]. Patients with a histological diagnosis of choriocarcinoma or metastases detected during postmolar follow-up, particularly in the lungs and pelvis, were also classified as GTN cases. Lung metastases were detected using a chest X-ray, although computed tomography (CT) scan was also sometimes used as an aid in follow-up and treatment.

GTN was staged according to the FIGO (2002) criteria: I — disease confined to the uterus; II — disease extends to the outside of the uterus, but is limited to the genital structures; III — disease extends to the lungs, with or without genital tract involvement; and IV — all other metastatic sites. Prognostic scoring for resistance to chemotherapy followed the FIGO/WHO Prognostic Scoring System [22].

2.5. Outcomes

The primary outcome was the occurrence of GTN after hCG normalization in postmolar follow-up. Secondary outcomes included response to chemotherapy and overall survival for cases of GTN.

2.6. Variables

Collected patient variables included the patient age in years, the type of antecedent molar pregnancy (complete, partial, or twin molar pregnancy), and the time to hCG normalization in days. Among cases of GTN, selected variables included the time interval to GTN diagnosis after hCG normalization in months, patient symptoms at the time of malignancy diagnosis, hCG levels in mIU/mL before treatment, staging according to FIGO (2002) criteria, the prognostic risk score defined according to the WHO/FIGO Prognostic Scoring System, choice of chemotherapy regimen, and the number of chemotherapy cycles.

2.7. Statistical analysis

The incidence of GTN among analyzed groups was compared using Fisher's exact test. A p-value < 0.05 was considered statistically significant. 95% confidence intervals (CI) of proportions were calculated using the modified Wald method. The SPSS 21.0 software (SPSS, Inc., Chicago, IL) was used for statistical analyses.

2.8. IRB approval

This study was approved by the Institutional Review Board of the Maternity School Hospital of Rio de Janeiro Federal University, associated with the Brazilian Committee on Ethics in Research — Brazilian Institute of Health, under protocol number 572887.

3. Results

From January 2000 to June 2013, 3684 patients were treated at the participating Reference Centers for molar pregnancy (Fig. 1). Among these, 673 patients were excluded from the study: 652 patients where

follow-up was discontinued after (601 patients) or before (51 patients) hCG normalization and 21 patients who became pregnant during follow-up. Among the remaining 3011 patients, 2016 had a complete hydatidiform mole among whom 592 patients (29%) developed GTN, 982 patients had a partial hydatidiform mole among whom 133 patients (13.5%) developed GTN, and 13 patients had a twin molar pregnancy, among whom 2 patients (15%) developed GTN. Overall, 727 patients developed GTN before the first normal hCG value, leaving a final study population of 2284 patients.

Patient characteristics were similar among the five reference centers (Table 1). Among the study population, 1210/2284 patients (53%; 95% CI 51%–55%) had hCG levels normalize before 56 days, whereas 1074/2284 patients (47%; 95% CI 45%–49%) required more than 56 days.

Of the 2884 patients who had spontaneous hCG normalization, 10 patients (0.4%; 95% CI: 0.2%–0.6%) developed GTN after hCG normalization. Table 2 summarizes these cases. The GTN stage was I for 6/10 patients (60%), III for 3/10 patients (30%) and IV for 1/10 patients (10%); 8/10 patients (80%) had low-risk GTN (median risk score: 4, range 4–6) and 2/10 patients (20%) had high-risk GTN (risk scores 7 and 14). One patient died of her disease. For the patients who underwent subsequent surgical procedures for GTN, the pathology in three cases revealed choriocarcinoma and in one case placental site trophoblastic tumor.

Overall, the rate of recrudescent disease varied by the type of molar pregnancy. GTN progression after hCG normalization occurred in 9/1424 patients (0.6%; 95% CI: 0.3–1.2%) after complete hydatidiform mole, 1/849 patients (0.1%; 95% CI: 0–0.7%) after partial hydatidiform mole, and 0/13 patients (0%; 95% CI: 0–27%) after twin molar pregnancy. The risk ratio for developing GTN after hCG normalization for complete hydatidiform moles compared to partial hydatidiform mole was 5.3, although given the small number of cases of GTN this did not reach statistical significance ($p = 0.10$).

Time to normalization for hCG appeared to influence the risk of GTN after hCG normalization. GTN after hCG normalization occurred in 1/1210 patients (0.08%; 95% CI: 0–0.5%) with a hydatidiform mole whose hCG levels returned to normal before 56 days, compared to 9/1074 patients (0.8%; 95% CI: 0.4–1.6%) where hCG normalization took longer than 56 days for a risk ratio of 10.1 ($p = 0.008$).

4. Discussion

In 2007, Sebire et al. recommended shortening the duration of hCG surveillance following complete or partial molar pregnancy from two years to six months, based on data from the UK that the risk of recrudescent disease after a normal hCG value was less than 0.1% [10]. In that study, they also noted that 98% of patients who developed GTN did so within 6 months and that the only patients who developed GTN after hCG normalization recurred more than a year after uterine evacuation. In the present work, we have reproduced these results in a large cohort of Brazilian women. As in the British study, we show that the risk of GTN after hCG normalization is extremely low, and the most commonly recommended hormonal surveillance schedule, monitoring for six months after hCG normalization, is completed before the few cases of recrudescent disease develop. Our study adds to the growing body of world literature that the risk of GTN after hCG normalization is minimal and that further truncation of the hCG surveillance period after hCG normalization may be possible [6,9–12].

Interestingly, we noted only one case of GTN after normalization of the hCG following a partial hydatidiform mole. This was also the only case of GTN after hCG normalization that occurred in fewer than 56 days from uterine evacuation. Of the studies that have focused on GTN after hCG normalization, ours is only the second reported case of partial hydatidiform mole as antecedent to GTN; moreover, the previous report did not include the use of immunohistochemistry ($p57^{KIP2}$) or genetic studies to confirm the diagnosis [20]. Consequently, we conclude that the 0.1% risk of GTN after hCG normalization in patients with partial hydatidiform mole is too low to justify an extension of hormonal follow-up after the first normal hCG level. For these patients, it seems reasonable to dispense with hCG surveillance altogether once a normal hCG level is achieved.

For patients with complete hydatidiform moles, the risk of recrudescent GTN after hCG normalization is higher, about 1% in our series. Our study confirms previous reports that hydatidiform moles after which the hCG levels return to normal in up to eight weeks (56 days) behave differently from those in which normalization takes longer [10,11,23]. However, even among patients who develop postmolar GTN after achieving a normal hCG, most cases will be diagnosed beyond the six months of hCG surveillance. While a longer time to hCG normalization is a negative prognostic sign, it appears that extended hCG monitoring, even in these cases, does not lead to earlier diagnosis of GTN. Therefore, one could likely abridge the hCG surveillance period after hCG normalization even for complete moles. Although prospective data will be needed to assess the optimum duration of surveillance, three months is likely sufficient. This provides enough time to demonstrate a stable normal hCG level and to provide patients with the counseling and reinforcement necessary to ensure they return to the reference center if any symptoms suggestive of GTN do develop after discharge.

Our study does have some important limitations. Data were collected from hospital databases and not population databases. As referral centers, these data may overestimate the true prevalence of GTN in the general population. While the 29% rate of GTN following complete mole reported here is consistent with other large centers, the 13.5% rate of GTN following partial mole is high compared to most series. The proportion of partial moles may fall at the higher end of the

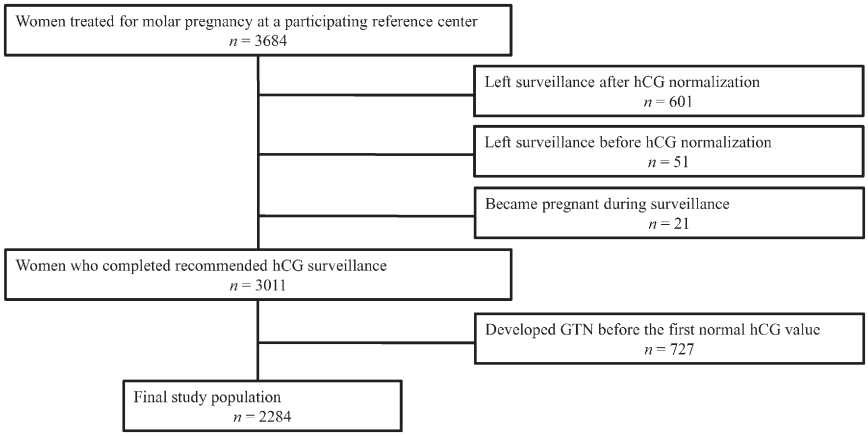

Fig. 1. Flow diagram of study population.

Table 1
Patient characteristics by participating reference center.

	Reference center					
	Maternity-SCMRJ	ME-UFRJ	HUAP-UFF	HC-UFG	HC-UNESP	Total
Cases of molar pregnancy (n)	1011	120	327	536	290	2284
Age, years (median ± sd[a])	23 ± 5	24 ± 4	24 ± 4	23 ± 6	25 ± 5	23 ± 4
Gestational age at molar pregnancy diagnosis, weeks (median ± sd)	11 ± 1	9 ± 1	10 ± 1	11 ± 3	9 ± 1	10 ± 2
hCG prior to uterine evacuation, mIU/mL (median)	190,000	120,000	110,000	180,000	150,000	175,000
Time to remission, weeks (median ± sd)	12 ± 7	10 ± 5	11 ± 6	14 ± 9	12 ± 6	12 ± 6
Cases of GTN after hCG normalization (n)	7	0	1	1	1	10
Rate of GTN after hCG normalization (cases per 100)	0.7	0	0.3	0.2	0.3	0.4

ME-UFRJ = Maternity School of Rio de Janeiro Federal University.
HUAP-UFF = Antonio Pedro University Hospital of Fluminense Federal University,
Maternity-SCMRJ = Maternity Ward of Santa Casa da Misericórdia do Rio de Janeiro.
HC-UFG = Clinical Hospital of Goiás Federal University.
HC-UNESP = Clinical Hospital of São Paulo State University.
[a] sd = standard deviation.

spectrum as not all cases were subject to central pathologic review and most referring centers do not routinely use genetic or immunohistochemical analyses to distinguish partial from complete moles. Thus, there may have been a number of complete moles in this population that were misdiagnosed as partial moles; this is the reason we subjected all cases of apparent recrudescent disease to confirmatory pathologic review and immunohistochemical testing. This is a retrospective study, consequently we needed to exclude patients who may have entered remission but did not complete the prescribed six months of hCG surveillance; some of these women may have developed GTN after normalization of the hCG and were never diagnosed. While the number of patients not completing the recommended 6 months of hCG surveillance was 18.3%, in fact this is substantially better than the 31–51% of patients not completing hCG surveillance reported in several American series [6,7,13]. There may also have been women who developed GTN more than 24 months after hCG normalization but were not followed longer clinically. All cases of GTN after hCG normalization in this study were assumed to be recrudescent disease, although in these cases a second trophoblastic tumor cannot be completely excluded. However, no patients showed signs or symptoms of a new interim molar pregnancy, making recurrence more likely. The retrospective nature also limits our analysis to the variables that are contained in the patient registries. Finally, a commercial kit designed to diagnose pregnancy was used to measure hCG levels, and not to discriminate all its fractions, and no systematic genetic studies were conducted to rule out the possibility that the tumor originated in another pregnancy [18,24].

Extended follow-ups to diagnose GTN after hCG normalization are more than just inconveniences for the patient. Extended surveillance is actually associated with lower adherence to hCG monitoring [6–9]. This is coupled with the stress generated by postmolar follow-up and the delay in becoming pregnant again, which itself increases the risk of having another episode of GTD [25–28]. The clinical approach to GTN diagnosed after hCG normalization does not differ from the clinical approach used for patients with postmolar GTN diagnosed before achieving a normal hCG level [29]. Our study suggests, however, that GTN diagnosed after reaching a normal hCG level may indicate a more aggressive course. In the population under study here, the prevalence of metastatic disease was 40%, greater than the 25% expected for Brazilian women with this cancer [5]. Moreover, a large number of patients (40%) had to undergo surgery to be cured. These cases also highlight the importance of a careful histological and immunohistochemical study to evaluate human placental lactogen to diagnose placental site trophoblastic tumors, which were found in 10% of our cohort and in 16% in the French cohort [18]. PSTT should be suspected especially in cases with relatively low hCG levels where patients are not responding to chemotherapy.

In conclusion, while there is currently no clinical trial to define the ideal duration of postmolar follow-up, the risk of GTN after hCG

Table 2
Characteristics of patients with gestational trophoblastic neoplasia (GTN) diagnosed after human chorionic gonadotropin (hCG) normalization.

	Patient									
	1	2	3	4	5	6	7	8	9	10
Age, years	20	21	25	30	33	37	39	40	42	45
Antecedent mole	Complete	Complete	Partial	Complete	Complete	Complete	Complete	Complete	Complete	Complete
Time to hCG remission, days	70	63	42	70	77	97	134	210	112	84
Time to GTN diagnosis, months	18	10	6	18	18	24	24	96	18	12
Symptoms at diagnosis of GTN	Amenorrhea	Vaginal Bleeding	Amenorrhea	Amenorrhea	Amenorrhea	Amenorrhea	Dyspnea	Hemptysis	Vaginal Bleeding	Nausea
Stage: prognostic risk score	III:6	I:4	I:4	I:5	I:4	I:5	III:7	IV:14	I:4	III:5
hCG level prior to chemotherapy, mIU/mL	431	82	987	2000	220	1200	5000	44,500	50	2500
Chemotherapy: cycles[a]	1L:2 2L:1 4L:2	1L:5	1L:4	1L:5	1L:4	1L:5 2L:3	3L:5	3L:8	1L:4	1L:5 3L:3 4L:5
Surgery	Lung lobectomy	–	–	–	–	Hysterectomy	Hysterectomy	–	–	Hysterectomy
Histology[b]	CCA	–	–	–	–	CCA	CCA	CCA[c]	–	PSTT
Complete Remission	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No, died	Yes	Yes

[a] (1L = methotrexate and folinic acid rescue; 2L = actinomycin-D; 3L = etoposide, methotrexate and folinic acid rescue, actinomycin-D, cyclophosphamide and vincristine — EMA/CO; 4L = etoposide, cisplatin, methotrexate and folinic acid rescue, actinomycin-D — EP/EMA).
[b] CCA = choriocarcinoma, PSTT = placental site trophoblastic tumor.
[c] Material obtained at necropsy.

normalization is very low, and the few cases that do occur likely will develop beyond the six months of hCG surveillance currently recommended. In our cohort, all patients with GTN after a normal hCG value were diagnosed because they returned to the Reference Center with some complaint associated with pregnancy, such as amenorrhea or nausea, or because of clinical signs and symptoms of the neoplasia or its metastases, such as vaginal bleeding, hemoptysis or dyspnea. These findings highlight the importance of adequate patient counseling at discharge, so that patients will be informed to return to the Reference Center if they have any of these symptoms, where not only pregnancy, but also GTN after hCG normalization can be evaluated. This seems to be the most efficient strategy for an early diagnosis of GTN for our patients, as the extended hCG follow-up does not appear likely to improve early diagnosis or outcomes among the Brazilian population.

Disclosure/conflict of interest

The authors declare no conflicts of interest.

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