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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