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Is chemotherapy necessary for patients with molar pregnancy and human chorionic gonadotropin serum levels raised but falling at 6 months after uterine evacuation?

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HIGHLIGHTS

- Only 0.8% of women have raised but falling hCG 6 months post molar evacuation.
- More than 80% of such cases will enter remission without further therapy.
- GTN treated after observation has comparable outcomes to immediate chemotherapy.

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ABSTRACT

Objective. To compare the outcomes of Brazilian patients with molar pregnancy who continue human chorionic gonadotropin (hCG) surveillance with those treated with chemotherapy when hCG was still positive, but falling at 6 months after uterine evacuation.

Methods. Retrospective chart review of 12,526 patients with hydatidiform mole treated at one of nine Brazilian reference centers from January 1990 to May 2016.

Results. At 6 months from uterine evacuation, 96 (0.8%) patients had hCG levels raised but falling. In 15/96 (15.6%) patients, chemotherapy was initiated immediately per FIGO 2000 criteria, while 81/96 (84.4%) patients were managed expectantly. Among the latter, 65/81 (80.2%) achieved spontaneous remission and 16 (19.8%) developed postmolar gestational trophoblastic neoplasia (GTN). Patients who received chemotherapy following expectant management required more time for remission (11 versus 8 months; $p = 0.001$), had a greater interval between uterine evacuation and initiating chemotherapy (8 versus 6 months; $p < 0.001$), and presented with a median WHO/FIGO risk score higher than women treated according to FIGO 2000 criteria (4 versus 2, $p = 0.04$), but there were no significant differences in the need for multiagent treatment regimens (1/15 versus 3/16 patients, $p = 0.60$). None of the women relapsed, and no deaths occurred in either group.

Conclusion. In order to avoid unnecessary exposure of women to chemotherapy, we no longer follow the FIGO 2000 recommendation to treat all patients with molar pregnancy and hCG raised but falling at 6 months after evacuation. Instead, we pursue close hormonal and radiological surveillance as the best strategy for these patients.

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1. Introduction

Gestational trophoblastic disease (GTD) is an abnormality of pregnancy that includes benign clinical forms (complete hydatidiform moles – CHM and partial hydatidiform moles – PHM) with variable potential to develop gestational trophoblastic neoplasia (GTN), in its various spectra (invasive mole, choriocarcinoma, placental site trophoblastic tumor, and epithelioid trophoblastic tumor) [1–3]. Although GTD develops in 1:1000 pregnancies in North America and 1:2000 pregnancies in Europe, it is estimated to occur five to ten times more frequently in Brazil [4,5]. Serial monitoring of human chorionic gonadotropin (hCG) levels after molar uterine evacuation is essential to detect malignant progression and initiate chemotherapy [6]. In Brazil, despite many difficulties, this postmolar follow-up is done in 38 GTD Reference Centers, spread throughout this country of continental dimensions [7,8].

The Brazilian Reference Centers of GTD have adopted the criteria established by the International Federation of Gynecology and Obstetrics (FIGO) for the diagnosis of postmolar GTN: rising (>10%) hCG levels for three consecutive weeks or plateaued for four weeks, if there is a histologic diagnosis of choriocarcinoma, or when the hCG level remains elevated for 6 months or more from the molar uterine evacuation [9]. The most common reason for the diagnosis of postmolar GTN and the start of chemotherapy is a plateau or rise in hCG values [10]. However, some investigators have indicated that it is safe to maintain hormonal surveillance among patients with molar pregnancy whose hCG levels are raised but falling beyond the 6 months after uterine evacuation and that spontaneous remission will occur in most cases without chemotherapy [10–15].

While some organizations, such as the European Organisation for Treatment of Trophoblastic Diseases, argue that the presence of hCG raised but falling in the 6th month after molar evacuation is not an indication to begin chemotherapy, there appears to be a controversy [2,16]. FIGO initially advised initiating chemotherapy when hCG was elevated but falling at 6 months after molar evacuation in 2000, retracted this opinion in 2012, but then resumed the recommendation in the FIGO Cancer Report in 2015 [9,17,18].

We must be cautious before dismissing this FIGO recommendation since postponing the chemotherapy in these patients with molar pregnancy and hCG levels present over 6 months after uterine evacuation could worsen the prognosis of the GTN, due to the potential development of tumor mutations and consequent chemoresistance (an important cause of mortality among Brazilian women with GTN) [4]. Furthermore, delay could increase the FIGO risk score for these patients as the "interval between antecedent pregnancy and start of chemotherapy" is included in the current FIGO/WHO Prognostic Scoring System, which would mean higher risk scores and potentially more treatment with multiagent regimens for patients due to delayed initiation of treatment [19–22].

The present study was undertaken to compare the outcomes of Brazilian patients with molar pregnancy that continued hCG surveillance with those treated with chemotherapy when hCG was still positive, but falling at 6 months after uterine evacuation. We also wanted to identify risk factors that were associated with the development of GTN in patients who continued hCG monitoring. The study was initiated to advance our understanding if it was prudent to continue hCG monitoring versus initiating chemotherapy in patients with elevated but falling hCG levels 6 months after molar evacuation.

2. Material and methods

2.1. Study design

This is a retrospective cohort study of patients with molar pregnancy followed at one of nine Brazilian GTD 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 AB and audited by MB), in Goiânia (Clinical Hospital of Goiás Federal University – data entered by MV and audited by MB), in Porto Alegre (Mario Totta Maternity Ward at Irmandade da Santa Casa de Misericórdia Hospital – data entered by EU and audited by MB), in Caxias do Sul (General Hospital of Caxias do Sul – data entered by JMM and audited by MB), in São Paulo (São Paulo Hospital of São Paulo Federal University and São Paulo Clinics Hospital of University of São Paulo – data entered by SYS and LL and audited by MB) and in Botucatu (Clinical Hospital of São Paulo State University – data entered by IM and audited by MB) from January 1990 to May 2016.

2.2. Study participants

Molar pregnancy was suspected when women presented with symptoms of pregnancy or vaginal bleeding combined with an elevated hCG level. The diagnosis of molar pregnancy in all cases was strengthened by sonographic evaluation of the uterus. All patients had uterine evacuation performed using suction curettage with histopathological confirmation of CHM or PHM.

This study includes all patients treated at one of the above centers during the study period, who adhered to the postmolar follow-up and presented with hCG levels raised but falling at 6 months after uterine evacuation, and whose medical records were complete and available for review. The following patients were excluded: those with non-molar pregnancy; who had hysterectomy to treat molar pregnancy (12 patients); those who became pregnant during the postmolar follow-up (148 patients) or were lost to postmolar follow-up (178 patients); with histological diagnosis of choriocarcinoma (98 patients), placental site trophoblastic tumor (26 patients) or epithelioid trophoblastic tumor (9 patients); and women later found to have false-positive or ("phantom") hCG (36 patients).

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 gonadotropin remission. Remission was defined as three consecutive weekly results of hCG values below 5 IU/L. After that, medical visits and measurement of hCG levels continued monthly for six months in the case of spontaneous remission. After chemotherapy, all the patients underwent follow-up for at least a year with monthly hCG surveillance after the first normal hCG value was obtained. When patients did not attend the scheduled visits, a social worker and hospital psychologist actively tried to contact them by phone and telegram to identify what was hindering compliance and to motivate them to return to follow-up.

The patients with molar pregnancy with hCG levels raised but falling at 6 months after uterine evacuation and not immediately treated with chemotherapy were strictly followed with weekly hCG measurement and monthly chest radiograph and Doppler ultrasound scan of the pelvis in order to detect invasive mole or early metastasis. Until the year 2000, all patients were systematically treated with chemotherapy in these cases. After that, the adoption of expectant management or immediate treatment of these patients was made after medical discussion, informed consent and individualization of the case. No formal randomization was used.

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