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Does hormonal contraception during molar pregnancy follow-up influence the risk and clinical aggressiveness of gestational trophoblastic neoplasia after controlling for risk factors?

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HIGHLIGHTS

- Hormone contraception does not increase the risk of gestational trophoblastic neoplasia.
- Hormone contraception does not alter severity of gestational trophoblastic neoplasia.
- Hormone contraception does not delay hCG regression.

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ABSTRACT

Objective. To evaluate the influence of hormonal contraception (HC) on the development and clinical aggressiveness of gestational trophoblastic neoplasia (GTN) and the time for normalization of human chorionic gonadotropin (hCG) levels.

Methods. A retrospective cohort study was conducted with women diagnosed with molar pregnancy, followed at the Rio de Janeiro Trophoblastic Disease Center, between January 2005 and January 2015. The occurrence of postmolar GTN and the time for hCG normalization between users of HC or barrier methods (BM) during the postmolar follow-up or GTN treatment were evaluated.

Results. Among 2828 patients included in this study, 2680 (95%) used HC and 148 (5%) used BM. The use of HC did not significantly influence the occurrence of GTN (ORa: 0.66, 95% CI: 0.24–1.12, p = 0.060), despite different formulations: progesterone-only (ORa: 0.54, 95% CI: 0.29–1.01, p = 0.060) or combined oral contraception (COC) (ORa: 0.50, 95% CI: 0.27–1.01, p = 0.60) or with different dosages of ethinyl estradiol: 15 mcg (ORa, 1.33, 95% CI 0.79–2.24, p = 0.288), 20 mcg (ORa: 1.02, 95% CI: 0.64–1.65, p = 0.901), 30 mcg (ORa: 1.17, 95% CI: 0.78–1.75, p = 0.437) or 35 mcg (ORa: 0.77, 95% CI: 0.42–1.39, p = 0.386). Time to hCG normalization ≥10 weeks (ORa: 0.58, 95% CI: 0.43–1.08, p = 0.071) or time to remission with chemotherapy ≥ 14 weeks (ORa: 0.60, 95% CI: 0.43–1.09, p = 0.067) did not significantly differ among HC users when compared to patients using BM, when controlling for other risk factors using multivariate logistic regression.

Conclusions. The use of HC during postmolar follow-up or GTN treatment does not seem to increase the risk of GTN or its severity and does not postpone the normalization of hCG levels.

1. Introduction

Molar pregnancy is a reproductive anomaly that affects 1 in 200–400 pregnant women in Brazil [1], an incidence 5 to 10 times higher than in

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the United States and Europe [2,3]. This disease may present as either of two different clinical and cytogenetic forms, characterized by complete hydatidiform mole (CHM) and partial hydatidiform mole (PHM), which represent the benign spectrum of gestational trophoblastic disease (GTD) [4].

The clinical importance of molar pregnancy is the risk of progression to gestational trophoblastic neoplasia (GTN), the malignant form of GTD, that occurs in about 15–20% of women following CHM and 1–5% of women after PHM [2–4]. The main strategy to diagnose GTN is to evaluate the levels of human chorionic gonadotropin (hCG) in the postmolar follow-up. The increase of hCG levels over two consecutive weeks, or a plateau (changes <10%) for three consecutive weeks confirms the progression of molar pregnancy into GTN [5]. Fortunately, the early treatment of GTN achieves cure in >98% of cases, even with the presence of multiple metastases [1,6].

To maintain the reliability of hCG as a biological marker for GTN, including making the initial diagnosis of GTN, monitoring the response to chemotherapy, and surveilling for recurrent GTN after chemotherapy (which happens in 3% of patients with low risk GTN and in 7–10% of patients with high risk GTN), patients are advised to avoid pregnancy during the postmolar follow-up. In general, this means until 6 months after hCG level normalization without a diagnosis of GTN and until 12 months after the last cycle of chemotherapy if a patient requires GTN treatment [7–9].

Despite the World Health Organization (WHO) guidelines which maintain that the use of hormonal contraception (HC) does not increase the risk of postmolar GTN or retard hCG normalization [10], some medical associations such as the Royal College of Obstetricians and Gynaecologists [11] and the Royal Australian and New Zealand College of Obstetricians and Gynaecologists [12] have concerns about initiating HC after molar evacuation, when hCG levels are still high. This concern is based on studies from the 1970s, which suggested that the use of HC increased the risk for postmolar GTN and postponed hCG normalization [13–15]. However, the contemporary relevance of those studies has been questioned, as patients at that time used contraception with higher hormonal levels than today [16].

Although many studies about the impact of HC in patients with molar pregnancy and the risk of postmolar GTN attest to its safety [16–27], a recent metanalysis compiling all data on contraception in this population has shown that fewer than 800 patients with molar pregnancy using HC were effectively evaluated for the risks of this contraceptive method [16]. In the largest single study about this subject, although it included 2777 patients with CHM, only 154 were using HC, which sustains the concern about the use of HC immediately after molar evacuation [27]. It is also important to highlight that none of these previous studies evaluated the effect of different compositions or hormonal doses, or even the impact of confounding risk factors for GTN on their results, maintaining uncertainty about the safety of HC among women with molar pregnancy and postmolar GTN.

Therefore, the aim of this paper is to evaluate the potential influence of HC on the occurrence and clinical aggressiveness of GTN as well as the time for hCG normalization controlling for risk factors for GTN among Brazilian women with molar pregnancy. We also wanted to evaluate specifically the safety of HC, analyzing not only its formulations, but also the impact of different dosages when compared to the patients using barrier methods of contraception (BM).

2. Patients and methods

2.1. Study design

This is a retrospective cohort study of patients with molar pregnancy followed at the Rio de Janeiro Trophoblastic Disease Center (33a Maternity Ward of Santa Casa da Misericórdia in Rio de Janeiro, Antonio Pedro University Hospital of Fluminense Federal University and Maternity School of Rio de Janeiro Federal University) between January 2005 and January 2015.

The local Institutional Review Board approved this study under the protocol number 1.842.895.

2.2. Patients

The participants in this study were women diagnosed with molar pregnancy, confirmed by histopathology and/or immunohistochemistry [28], that exclusively used HC or BM throughout the post-molar pregnancy hCG surveillance or postmolar GTN follow-up. All patients included in this study were followed until remission and then underwent hCG surveillance for 6 months in cases of molar pregnancy with spontaneous remission or for 12 months after the end of chemotherapy for cases of postmolar GTN.

Patients were classified according to the contraceptive method into one of the following groups: BM (barrier method - male/female condom); progestin-only (PO), which included women using oral desogestrel 75 mcg used continuously or injection intramuscularly of medroxyprogesterone acetate 150 mg every three months; combined oral contraception (COC) such as ethinyl estradiol 15 mcg + gestodeno (Δ15-norgestrel) 75 mcg (EE 15), ethinyl estradiol 20 mcg + gestodeno 75 mcg (EE 20), ethinyl estradiol 30 mcg + gestodeno 75 mcg (EE 30) or ethinyl estradiol 35 mcg + cyproterone acetate 2 mg (EE 35), taken daily orally every 21 days, with a 7 day interval and subsequent resumption; or injection intramuscularly of combined contraception containing estradiol valerate 5 mg + norethisterone (norethindrone) enanthate 50 mg every month. All contraceptive methods were distributed free of charge to the patients during the entire postmolar or GTN follow-up and their prescriptions were validated according to the WHO medical eligibility criteria [10].

The following patients were excluded from this study: incomplete medical records (58 patients), lost to follow-up (38 patients), used another contraceptive method (78 patients), switched contraceptive method for some medical reason or personal desire (113 patients), started hormonal contraception >7 days after uterine evacuation (8 patients) or had histopathological diagnosis of placental site trophoblastic tumor (PSTT) or epithelioid trophoblastic tumor (ETT) (9 patients).

2.3. Postmolar follow-up

Once diagnosed with molar pregnancy, patients underwent uterine evacuation, ideally by suction curettage. A systematic postmolar follow-up was performed with weekly serum hCG measurement using the DPC Immulite® from Siemens throughout the study period. The remission of molar pregnancy or postmolar GTN was defined as three consecutive weekly hCG levels with values <5 IU/L [29]. Patients with molar pregnancy were followed with weekly hCG levels until normal for 3 consecutive weeks and then monthly until normal for 6 consecutive months. Patients with GTN were followed with weekly hCG levels until normal for 3 consecutive weeks and then monthly until normal for 12 consecutive months [1–3].

2.4. Diagnosis, staging, risk factors and treatment of GTN

We used the criteria established by the International Federation of Gynecology and Obstetrics (FIGO) 2000 for GTN diagnosis [5]. Before initiating chemotherapy, patients underwent metastatic screening for staging of GTN (stage I - disease confined to the uterus, II – involvement of the pelvic organs, III – presence of pulmonary metastasis, IV – occurrence of metastasis in other organs, notably liver and brain), as well as the FIGO/WHO prognostic risk score for chemoresistance [5]. Patients with stages I, II, and III low risk GTN (FIGO/WHO score ≤ 6) were treated with single agent chemotherapy using methotrexate (MTX/FA) 1 mg/kg intramuscularly on days 1, 3, 5, 7 with rescue of folinic acid 0.1 mg/kg orally on days 2, 4, 6, 8 or actinomycin-D (Act-D) 1.25 mg/m^2

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