

Disease profile and incidence of hydatidiform mole in Vitoria (Brazil) between 2003-2016

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Summary

Introduction: Gestational trophoblastic disease (GTD) includes a group of both clinical and anatomopathological conditions derived from placental trophoblasts, which can evolve to metastatic, invasive or premalignant forms, such as complete or partial hydatidiform mole. This work describes the profile of GTD and its incidence in a philanthropic hospital in Vitória (Brazil). **Materials and Methods:** The authors performed a descriptive, retrospective study with 117 female patients having histological confirmation of GTD diagnosis between the years of 2003 and 2016. Patients were selected based on analysis of all medical records on the Department of Gynecology and Obstetrics of the Santa Casa de Misericórdia de Vitória hospital. **Results:** About 75% of all cases (88 patients) were diagnosed as complete mole, whereas about 25% (29) were diagnosed as partial mole. The authors also found eight cases of gestational trophoblastic neoplasia (GTN), of which seven cases with invasive mole and one case with choriocarcinoma. The authors observed a slightly higher incidence during (southern) springtime, but no clear association between mole type and age, gravidity or parity could be established. **Discussion:** It still not clear how socio-geographic factors may increase the incidence of hydatidiform mole around the world. While in some regions of the globe, particularly, in developed countries, we find equality of incidence of complete and partial mole, in many other countries we observe a major incidence of complete mole. Thus, precise medical records are key to establish a regional profile, especially in a wide country as Brazil; nonetheless, it is of the utmost importance to follow specific protocols to correctly identify and treat both cases.

Key words: Complete mole; Partial mole; Gestational trophoblastic disease; hCG levels.

Introduction

Gestational trophoblastic disease (GTD) refers to a wide variety of tumors of placental origin including complete hydatidiform mole (CHM) and partial hydatidiform mole (PHM) [1]. Gestational trophoblastic neoplasia (GTN) is a term applied to malignant conditions such as invasive mole, choriocarcinoma, placental site trophoblastic tumor, and epithelioid trophoblastic tumor [2-4]. Complete mole is particularly important because it is associated with a significant risk of persistent GTD [5, 6]. However, nowadays death secondary to GTN is uncommon due to advances in treatment and survival rate is above 90% in most countries. Occasional fatalities in GTN treatment may occur firstly if an incorrect initial therapy is administrated, by presence of comorbidities during the treatment or by psychosocial issues that may interrupt the therapy [7].

The characterization of incidence and etiology of molar pathology around the world is a difficult task, among the factors because the difference in clinical definitions, the absence of a worldwide (or at least, a countrywide) database and the inability in precisely characterize a risk group for the disease [8, 9]. For instance, in North America, West Europe, New Zealand, and Australia, it ranges between 0.6 to 1.1 per 1,000 gestations [10], whereas in Brazil this ratio is

about five per 1,000 gestations [11, 12].

The universal practice of using ultrasonography (US) in gestational follow-up has been a great tool for the early detection of the GTD, usually in the first trimester of pregnancy. Clinical presentation related to GTD is variable and it may include vaginal bleeding, preeclampsia, anemia, enlarged uterus, persistence of theca lutein cysts in the ovaries, hyperthyroidism, and hyperemesis [13-17]. Such symptoms are typically observed in complete mole rather than partial mole, although the US practice and the monitoring of hCG levels have significantly reduced the numbers of symptomatic presentations [14, 18]. PHM cases may present with vaginal bleeding but are typically indistinguishable from incomplete or missed abortion. In such cases, the diagnosis can be helped by US though confirmation of partial mole comes from histologic review of curettage specimens [15,17].

Garret *et al.* noted that risk of recurrent hydatidiform mole can increase at least ten times for subsequent pregnancy outcomes [19, 20]. They noted that there is a genetic link to recurrent complete molar pregnancy, e.g. NLRP7. Also, after two molar pregnancies, 23% of subsequent outcomes will result in a new molar gestation [21]. Furthermore, the risk of molar pregnancy is considerably higher

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when pregnant women are in upper or lower age limits, particularly for CHM cases [22-24].

If a suspicious case of CHM or PHM is found (by physical examination, hCG levels, US or medical history), detailed preoperative clinical examinations are required [15, 25]. The following procedure is the evacuation of uterine cavity, usually by suction evacuation, followed by curettage and histological confirmation of the diagnosis [26]. In follow-up after evacuation, instead of clinical or images factors, regression curve of hCG level must be the main prognostic factor in order to evaluate trophoblastic tumor risk [27]. Thus, periodical (weekly) measurements of hCG level should be carried on until it vanishes and then, monthly measurements up to one year later, associated with physical examination. Nonetheless, at least in South America, high loss to follow-up is observed even before negative hCG level and attendance rate oscillates between 18 and 63% [28, 29].

The current study was undertaken to evaluate the clinical presentation and incidence of complete and partial mole over more than a decade of records in the Gynecologic and Obstetric department of a philanthropic hospital in Vitória, Brazil. The authors consider this report important because it may provide a comparative statistic relative to the main centers in Brazil with large population, such as Rio de Janeiro or São Paulo. Furthermore, since Vitória is proportionally a narrow city compared to those two (for instance, 8% in number of inhabitants relative to São Paulo and 15% relative to Rio de Janeiro), the authors must check if the profile of GTD in their region is close to them or, as long Brazil is a wide country, if the local socioeconomic factors play a role to the incidence of GTD countrywide.

Materials and Methods

The emergency service of gynecology of the Santa Casa de Misericórdia de Vitória has become a reference center in Espírito Santo state, being responsible for the greatest number of records in this field in the last years. Between 2003-2016, all medical records and laboratorial exams available of patients diagnosed with GTD by histopathological confirmation performed by a specialist in pathological gynecology were analyzed and reviewed. In this descriptive, retrospective study, information such as maternal age, gestational age (estimated from the last menstrual cycle), gravidity, parity and hCG levels were reviewed and correlated. All statistical analysis used to compare continuous variable were performed considering the Mann-Whitney non-parametric test, with significance level set at $p < 0.05$. All the analyses were approved by the partners of Ethics in Human Being Researches Committee of the Escola Superior de Ciências da Santa Casa de Misericórdia de Vitória.

Results

Between 2003-2016, 117 were identified women with a molar pregnancy. From these, 88 (75.2%) patients were histologically confirmed as having a complete mole and 29

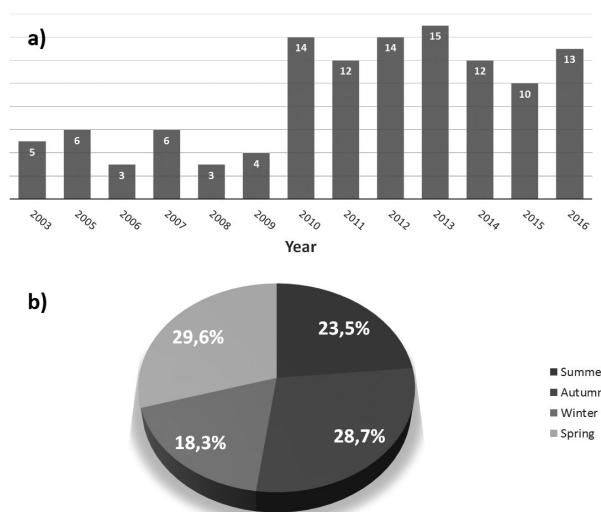


Figure 1. — a) Absolute number of GTD (complete and partial mole) records and b) average annual seasonality during 2003-2016 in the present center.

Table 1. — Comparison of clinical features among patients with complete and partial mole (2003-2016)

	CHM	PHM	<i>p</i>
Total of cases (%)	88 (75,2)	29 (24,8)	-
Median age (IQR)	23 (14-49)	23 (15-46)	0.39
Mean age (Σ)	24.6 (8.7)	24.9 (8.5)	0.25
Median gravidity (IQR)	1 (1-6)	2 (1-6)	0.12
Median parity (IQR)	0 (0-4)	0 (0-5)	0.38
Declared color (%)	18 white (21) 69 pardo (78) 1 black (1)	1 white (3.5) 28 pardo (96.5)	-
Median hCG at evacuation (IU/L)	142.176	69.743	< 0.001
Postmolar nTG (%)	6 (6,8)	2 (6,8)	-

* IQR: Interquartile Range, σ : standard deviation, IU: International Units.

(24.8%) were histologically diagnosed as having a partial mole. Furthermore, from the total number of cases, the authors found eight GTN, of which seven (5.9%) were invasive moles and one (0.8%) was choriocarcinoma. Furthermore, the authors observed an abrupt increase in the number of GTD records in 2010, as shown in Figure 1a. This important step is due the recognition of the present center as a local reference in treating of gestational trophoblastic disease. Comparatively, the annual average occurrence passed from 4.5 cases between 2003-2009 to 12.8 after 2010.

Figure 1b shows the annual average seasonality from 2003-2016, considering the evacuation date. The authors observed a slight prevalence of records in the (south) spring in opposition to the winter, with respective rates of 29.6%

and 18.3%. Very few data concerning seasonality of GTD is found in literature, but these results are in agreement with other studies, particularly, performed in Nigeria [35] and Singapore [36].

Table 1 summarizes all the data extract from the medical records comparing the two populations, i.e., the CHM and PHM. No statistically significant differences were observed in main features such as mean age, median age, parity or gravidity, including respective Interquartile range (IQR) factors, which is reflected in the high value for statistical relevance factor p . Thus, establishing a precise correlation among these factors and the kind of mole it still not possible.

Beta-hCG levels were found to be higher in CHM group rather than in PHM group. These numbers are similar when compared to a 20-year study performed in USA [16], where Sun *et al.* found that the median values of hCG for complete and partial mole, respectively, 164.579 and 71.000 IU/liter. In this same work, a clinical history of thyroid problems was observed, such as clinical hyperthyroidism (about 2% in both groups) and biochemical hyperthyroidism (respectively, 16% for CHM and 5% for PHM). It is well known that high beta-hCG levels in the body may mimic TSH hormone [37], however, no indication of thyroid anomalies was found in the present patients.

The authors also evaluated the incidence of GTD concerning the self-declared color (or race) of the patients. Concerning PHM group, the great majority of women self-declared as mixed-race (“*pardo*”), whereas in CHM group they observed a distribution among mixed-race (78%), White (21%) and Black (1%). Based on the number of records in each group, it is not a surprise to find a broader distribution in CHM group, but self-declaration is a point that makes such direct correlation an important issue, as discussed in a previous study [32].

Vaginal bleeding was the main clinical presentation related to GTD that brought patients to the present service. Typically, such bleeding was of light to medium intensity, but this parameter itself does not allow to define a precise differential diagnosis. Usually, the present authors prefer the use of suction evacuation as a method of uterine cavity evacuation, because of the lower surgical time and risk, such as hemorrhage and uterine perforation, as exemplified in one study [38]. In such few cases, fractional dilatation and curettage was used, but recurettage is not a usual practice, since it is highly unadvised due to the high risk of uterine perforation and because it generally does not induce remission in treatment, as reviewed in one study [39]. After evacuation, all patients are followed-up for monitor the risk of GTN adopting the FIGO criteria [4, 40]. Then, the need for chemotherapy, excisional surgery or evidence of metastasis is considered. In the present study, the authors found equal rates (6.8%) for GTN in both, complete and partial mole groups. The choriocarcinoma originated from the CHM group. All GTN were diagnosed during the follow-

up after evacuation observing the hCG curve, as illustrated in another study [41]. No patient underwent hysterectomy during the time considered.

Discussion

The ratio between CHM and PHM observed in the present study corroborates a previous study performed in another center for GTD in Brazil in 2013 [30] and in other parts of the globe such as India [31] and Abu Dabi [32]. However, similar studies in developed countries point to equal rates of complete and partial mole [16, 33, 34]. Although partial mole may be confounded as a hydropic abortion, the current practice of histopathological differentiation by immunohistochemistry in the present center and the similarities of the results with other centers, particularly those from Brazil, suggests that these results are indeed representatives for the population. In a recent study, Braga *et al.* reported 12,526 patients with molar pregnancy in a reference center at Rio de Janeiro [42]. Although in this current manuscript the number of patients are considerably lower, one must be cautious when comparing absolute numbers. Brazil is a wide country (the total area is comparable to USA) and as observed in other less developed countries, socioeconomic issues are quite different depending on the regions, and the state. For instance, Rio de Janeiro has about 12 times the number of inhabitants relative to Vitoria and an economy five times larger. Thus, studies like the present are important to bring light to those differences concerning incidence of GTD and socioeconomic impact on it. For example, it is intriguing to find similar values for incidence of molar disease and median hCG levels like those from studies carried out in developed countries. It suggests that socioeconomic factor may play a crucial role that cannot be neglected.

For that reason, the present authors are currently establishing close collaboration with reference hospitals countrywide to adopt similar diagnostic and medical conduct protocols in order to render representative the incidence and etiology of GTD in Brazil. In that sense, a clear, detailed and unified medical record is key to achieve new insights on the profile of GTD in the present region and in Brazil. Data such as gestational age at evacuation, hyperemesis, anemia (specifically, $Hb < 11.0$) or uterine size must be part of the medical record, although these factors are not crucial for a conclusive diagnostic. Furthermore, the present authors highlight the importance of being a recognized local reference center for GTD and establish a close relationship with the main centers around the country.

Conclusion

The incidence as well as the clinical presentation of complete and partial mole in a reference hospital in Vitoria, Brazil, was described. In this descriptive, retrospective

study the authors found 117 cases of GTD between 2003-2016, which 75% were complete mole and 25% were partial mole with a predominance of occurrence in the (south) springtime. This result corroborates with studies performed in other reference centers in Brazil and suggests that socioeconomic factors may account for these rates. Nonetheless, more detailed studies are needed to establish the actual impact of this factor. In that sense, the consolidation of the present authors' service as a reference center and the close collaboration with other main centers in Brazil will conduct possible further studies.

The present authors found that the risk of developing a GTN is equivalent in both groups, but since partial mole can be ill diagnosed, it is crucial to adopt the conduct of performing histopathological exams in every specimen from abortion. Also, some practices have been shown as crucial, such as pelvic ultrasonography for early diagnosis and hCG curves in follow-up before uterine evacuation.

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