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Human Chorionic Gonadotropin Regression Curves after Partial or Complete Molar Pregnancy in Flanders: Are They Different from Regression Curves from the Eighties?

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Gestational trophoblastic disease · Gestational trophoblastic neoplasia · Human chorionic gonadotropin

Abstract
Background/Aims: We updated human chorionic gonadotropin (hCG) regression curves created in the eighties after evacuation of complete and partial molar (CM and PM, respectively) pregnancies using modern hCG assays. We created similar curves for patients in need of chemotherapy (gestational trophoblastic neoplasia [GTN]). ***Methods:*** A total of 126 patients who were diagnosed with gestational trophoblastic disease from 1990 to 2014 were included. We compared curves from 2 groups, CM and PM, with historical ones. The third group was a comparison of GTN patients receiving first-line chemotherapy and patients in need of a switch of chemotherapy. ***Results:*** The regression curves were comparable to historical ones. According to the latter, mean time to normalization was 14–15 weeks after evacuation. We observed a normalization within 12 (CM) and 12.7 (PM) weeks. In addition, a remarkable but not statistically significant vertical shift (20 IU/L higher) was observed prior to day 60 compared with historical curves. The comparison in GTN patients showed a statistical significant difference, even at day 7. ***Conclusion:*** The presented hCG regression curves in the Flemish region were comparable with the ones of the eighties but with a vertical shift, hypothetically due to more sensitive assays. In addition, regression curves in GTN patients receiving chemotherapy can be used to evaluate response.

Background/Aims

Gestational trophoblastic disease (GTD) encompasses a broad spectrum of rare tumors that arise from the cells in the placental villous trophoblast. These can be divided into 3 main groups, based on histological characteristics [1, 6]. The 2003 WHO classification divides the benign non-neoplastic trophoblastic lesions (placental site nodule and exaggerated placental reaction) within the first group. The second group includes complete and partial molar (CM and PM, respectively) pregnancies, which are usually benign. In Western countries, the incidence of a complete hydatidiform mole is around 1 per 1,000 pregnancies and 3 per 1,000 for a partial hydatidiform mole. Malignant forms that are capable of local invasion or forming distant metastases can also occur. This is called

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gestational trophoblastic neoplasia (GTN). The risk of malignant transformation depends on the pre-malignant subtype, with 15% of the complete and 0.5–1% of the partial hydatidiform moles being persistent. There is a very high probability that hydatidiform moles are pre-programmed to behave malignantly [1, 2, 6]. Remarkably, GTN is a unique neoplastic disease due to the fact that these tumors are genetically related to fetal tissue and, therefore, represent a semi-allograft in the patients [7].

The third group comprises the primary malignant types such as choriocarcinoma, and rare variants such as placental site trophoblastic tumor. The incidence in Western countries is 1 in 50,000 deliveries or 0.2% of cases of GTD, respectively.

In this article, we focus on CM and PM pregnancies. These share a common feature, that is, the production of human chorionic gonadotropin (hCG). This is an excellent and sensitive serum tumor marker for the diagnosis, treatment, and follow-up of patients with GTD. As recommended by the International Federation of Gynecology and Obstetrics (FIGO), the onset of malignant change, termed persistent GTD or GTN, is signified by a plateaued or rising hCG concentration. Accurate measurement of hCG is key for effective management of GTD [1–3]. The hCG molecules in GTD are more heterogeneous and degraded than those in normal pregnancies; therefore, an assay that will detect all main forms of hCG and its multiple fragments should be used to follow-up patients with GTD. To exclude rare false positive results due to interference with heterophile antibodies, a urinary hCG test needs to be performed especially in cases of low not normalizing values, because these antibodies are not excreted in urine [2].

GTN is treated with chemotherapy with an overall survival rate of nearly 100%, while preserving the patient's reproductive function [1, 3].

Our group is the Flemish part of the Belgian trophoblastic disease referral center. Together with the University of Liège, we created a register to voluntarily include patients with trophoblastic disease [23]. The pathological specimens are then revised by our center. An individual follow-up taking into account the pathology, medical history, and levels of hCG, measured in local laboratories, is presented by an hCG regression curve in comparison with the regression curves of our study.

The purpose of this study is to update the hCG regression curves which were created in the 70s and 80s and are still often being used in clinical practice today for the follow-up of patients with GTD. Taking into account the changes in hCG detection testing, we believe an update is warranted. In addition, the use of a regression curve for GTN patients during chemotherapy might be a simple and elegant way to evaluate the response [22].

Methods

Patients

The study group consisted of all patients diagnosed with GTD and treated in our institution from 1990 until 2014, as well as patients who were referred to our center for a second opinion. The study design was a retrospective observational study including 126 patients. This study was approved by the Ethical Committee of the University Hospitals Leuven (ML8771).

For groups I and II, we included patients with CM and PM pregnancies. We excluded all persistent molar pregnancies who received chemotherapy, as well as those with choriocarcinomas and placental site trophoblastic tumors. In cases where a differential diagnosis was made between a molar pregnancy and a hydropic abortion, patients were excluded when the pathological revision of the slides concluded with a hydropic abortion. All slides were reviewed by the same pathologist. None of the included patients became pregnant during the time of follow-up.

Patients were then divided into 2 different groups for analysis. The first group consisted of 34 uncomplicated complete hydatidiform moles and the second group consisted of 92 patients with a PM.

For group III, we included 34 patients with GTN. Twenty-eight patients were treated with first-line chemotherapy, which consisted of methotrexate. The other 6 patients were in need of a switch of chemotherapy.

Statistics

We created hCG regression curves using the GLIMMIX procedure in SAS (version 9.3).

The hCG levels were modeled using generalized linear mixed models. A log link function was considered to guarantee strictly positive predicted values for hCG level, and a gamma distribution for the response was assumed. The random-effects structure contains a random intercept and random slope over time. The fixed-effects structure models time and, depending on the specific setting, baseline hCG level or type of chemotherapy. Additionally, interactions between baseline hCG level and time and between type of chemotherapy and time were tested. Given the clearly nonlinear trend of hCG levels over time, we modeled time using cubic splines with 4 or 5 knots. Model comparisons were based on the Akaike information criterion.

In groups I and II, we plotted the regression curves starting on the day of the curettage and created a logarithmic regression of the hCG values (IU/L) in function of days after the curettage.

In group III, a similar procedure was performed, starting on the day of the first cycle of chemotherapy.

Additionally, we evaluated general parameters such as mean age, mean gravidity, type of used hCG test, and number of blood samples taken during follow-up.

An overall survey of the used hCG test in Flemish laboratories revealed a general heterogeneity in the types of tests that were used. Ten different hCG assays were used. All those assays detected hCG and the free β subunit of hCG and are, therefore, called "total" hCG assays. This is particularly important because pathological hCG

secretion is associated with the formation of intact hCG in combination with disproportionate quantities of free alpha subunits or, more commonly, free β subunits. However, standardization of hCG assays is still far from complete; all assays react differently with the numerous hCG isoforms and show only modest agreement. Therefore, it is important to use the same assay in following the course of therapy of tumors [21].

The "hCG + β test" [18], which we use in UZ Leuven, was the most often applied test in the largest laboratories. The regression curve of Schlaerth et al. [13] was created by determinations of serum β subunit hCG as measured by radioimmunoassay (not otherwise specified) in one laboratory.

Results

The characteristics of the patients of study groups I and II and their statistical analyses are shown in Figure 1. The CM pregnancies accounted for 25% and the second group consisting of PM pregnancies for 75% of the patients. Median age was 31.8 years in CM and 29.4 years in PM ($p = 0.201$). We calculated a median gravidity of 2.9 and 2.3 pregnancies in the group of CM and PM, respectively (not significant).

The hCG regression curves are shown in Figures 2–4. We created a logarithmic regression of the hCG values (IU/L) in function of days after the curettage. We projected the regression curve of Schlaerth et al. [13] and observed a similar course. Between day 35 and 63, we noted a small but statistically significant shift in group II (mean 20 IU/L higher for our new curves compared with the historical curves, $p = 0.03$). For group I, we could not calculate a statistically significant difference.

A total normalization, meaning a hCG value of less than 2 IU/L, was seen in 84 and 89 days after the curettage for groups I and II, respectively. This was not statistically significant ($p = 0.742$). The normalization of the serum hCG observed in our series within a mean of 12 and 12.7 weeks for CM and PM, respectively, is shorter than that observed by Schlaerth et al. [13] (mean 14–15 weeks after evacuation).

The mean number of available blood samples was 7.4 and 5.1 for CM and PM, respectively.

Furthermore, we tested the accuracy of our regression curves. Therefore, we compared the β-hCG regression plots of patients diagnosed with GTN, before start of chemotherapy, with the CM and PM groups. According to the FIGO criteria, the presence of GTN should be diagnosed in the following scenarios. The first one encompasses a plateau of the hCG concentration (a decline of less than 10% for at least 4 values over 3 weeks). Secondly, a rise of the serum hCG concentration or an increase of more than 10% of 3 values over 2 consecutive weeks (days 1, 7, and 14) is also defined as a GTN [1, 3]. In the group of the complete hydatidiform moles, we created a testing curve representing 8 patients with a 95% CI. However, in the group of the PM pregnancies, only 2 patients could be included.

Figure 4 represents the regression curves of the CM and PM pregnancies together. It shows a minimal but not statistically significant difference in course ($p = 0.2$).

Group III is represented in Figure 5. We created an hCG regression curve of patients during chemotherapy. A testing curve representing 6 patients before the necessary switch of chemotherapy was made with a 95% CI. We observed a statistically significant difference on day 7 ($p = 0.03$) and even clearer on day 70 ($p = 0.0007$).

Discussion

The primary objective of this study was to update the hCG regression curves, using the current hCG assays used in the Flemish region. In regard to the number of patients with CM and PM, we found a ratio of 1 CM-related to 3 PM-related GTD. This result matches the incidence of a CM (1 per 1,000 pregnancies) and a PM (3 per 1,000 pregnancies) in Western Europe.

Given the fact that current hCG assays are extremely sensitive, this assay is an ideal tumor marker and follow-up should mainly rely on serial measurements. Nowadays, the regression curves created by Schlaerth et al. [13] are still often used. In the series of Schlaerth et al. [13], no difference was made between CM and PM. However, it has been reported that spontaneous regression in serum hCG is more rapid in patients with PMs than in those with invasive and CMs [14]. In our study, we constructed curves for each type separately. There was no significant difference between CM and PM in our series. The curve of Schlaerth et al. [13], which represents a similar Western population, fell into our 95% CI for both groups, but was on the lower confidence limits of our CM and PM curves in the period of 30–60 days after evacuation. This vertical shift was noticed in our curves of both CMs and PMs (but only statistically significant for group II between day 35 and 63), which confirmed the presumption of a higher sensitivity in the current hCG tests. Again, we have to emphasize that the regression curves of Schlaerth et al. [13] were composed of CM and PM pregnancies while we looked at them separately. In conclusion, we can presume a higher sensitivity in the current hCG test but it is not proven.

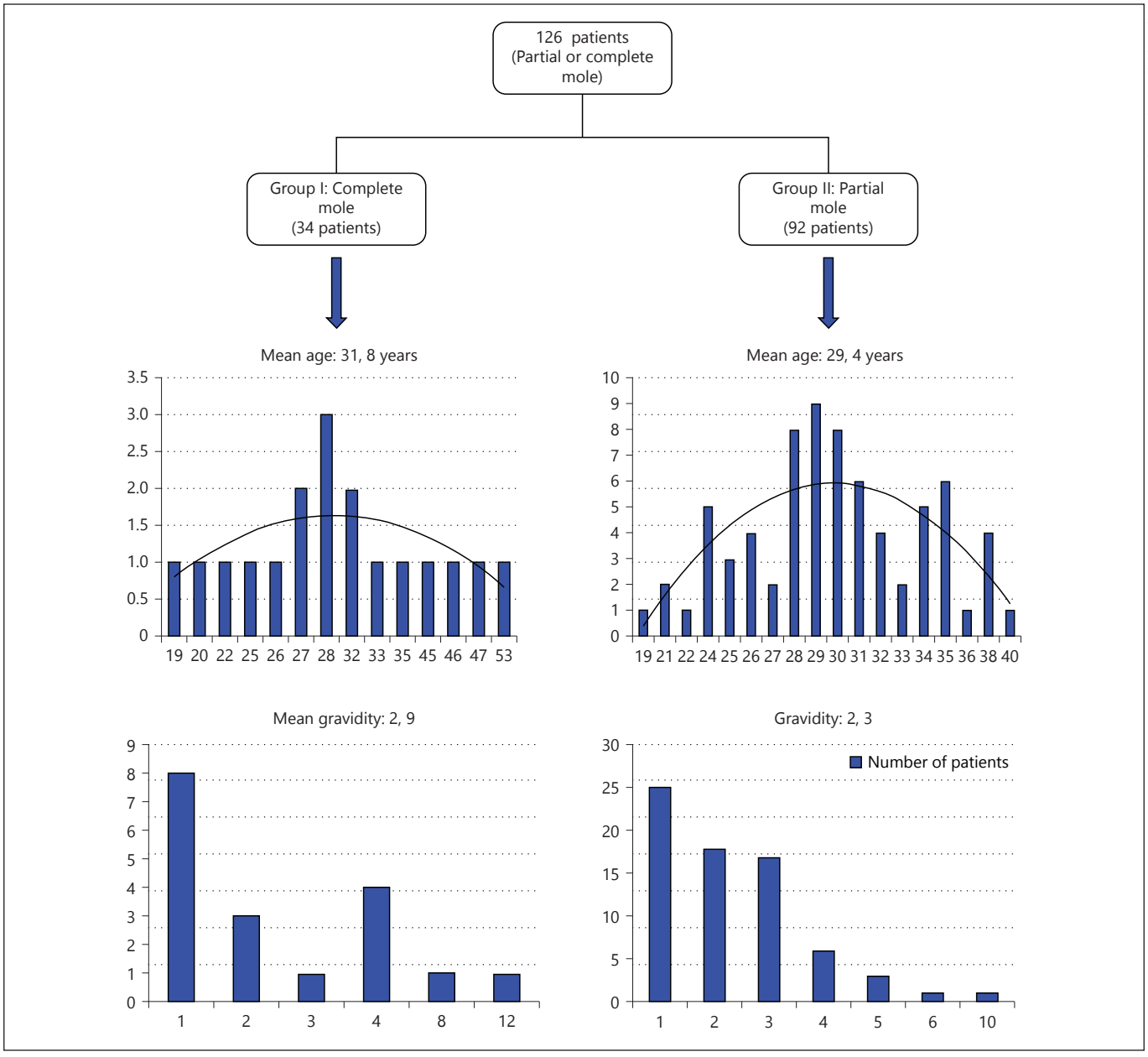

Fig. 1. Consort diagram of the 2 groups with age and gravidity distribution, respectively.

The curves show a reliable regression course for follow-up. However, a normalization of the serum hCG was observed within a mean of 12 and 12.7 weeks, respectively, in the current series, whereas according to Schlaerth et al. [13] all patients with a spontaneous progressive fall in hCG values achieved total remission within 14–15 weeks after evacuation. This might also be due to the currently used assays, utilized nowadays, compared with the assays used in the eighties. In our study, we did not take into account which hCG test was used [18], although there was an overall heterogeneity. This was both a limitation and an advantage because it is representative of the real-life practice. Furthermore, a comparison of 2 commercially available hCG immunoassays made by Matsui et al. [16], though none of those are used in our laboratories, showed a good correlation with a few discrepancies at the lower levels.

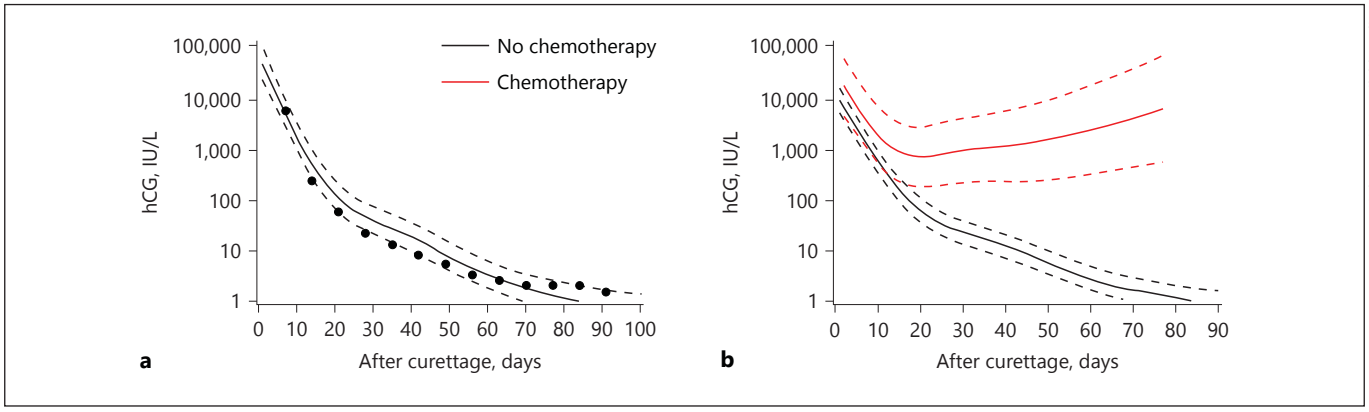

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Fig. 2. Group CM not needing chemotherapy. **a** hCG regression curve with 95% CI (–) and the projection of the regression curve of Schlaerth et al. [13] (● = mean values). **b** CM black line: not needing chemotherapy – red line represents 8 patients with CM in need of chemotherapy, before start of chemotherapy.

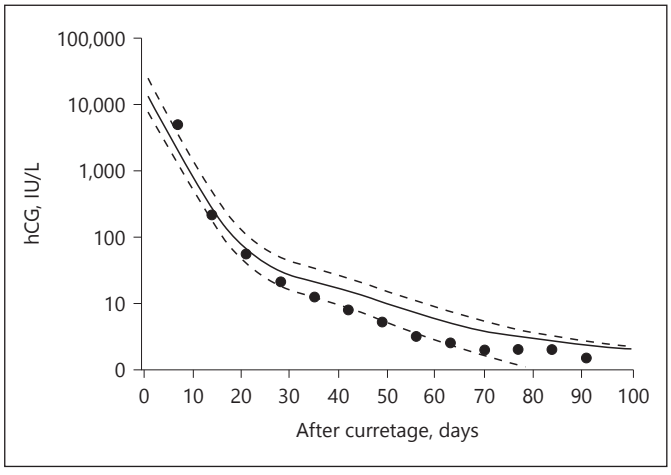

Fig. 3. Group PM. hCG regression curve (black full line) with 95% CI (–) and the projection of the regression curve of Schlaerth et al. [13] (● = mean values).

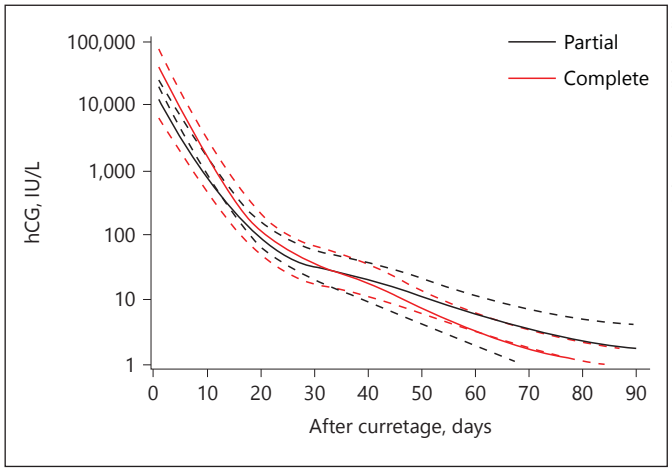

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Fig. 4. hCG regression curves of group I (red) and II (black) combined.

A recent publication of van Cromvoirt et al. [19] showed the creation of a 24-h urine hCG regression curve used as a tool in the follow-up of CM after evacuation. This is more patient friendly and, therefore, fewer patients will be lost to follow-up. Another promising method in the early detection of GTN is the slope of the linear regression of post-evacuation serum β-hCG where 3 blood samples were taken [20].

The second objective was to evaluate if a regression curve during first-line chemotherapy can be used as a tool to predict a need for a switch of chemotherapy. According to van Trommel et al. [22] the regression of hCG levels can identify the patients who are extremely likely to need alternative chemotherapy. The test in our study confirmed a statistically different course of the regression curves of patients responding well to methotrexate and patients in need of a switch of chemotherapy.

In conclusion, the presented hCG regression curves of CM and PM are comparable with the curve of the eighties published by Schlaerth et al. [13]. The current curves are about 20 IU/L higher than the historical curves in the period up to day 60 after evacuation. However, this was only statistically significant for PM between day 35 and 63. Both curves cross then as they normalize at a median of about 12.5 weeks compared with 14–15 weeks in the historical curves.

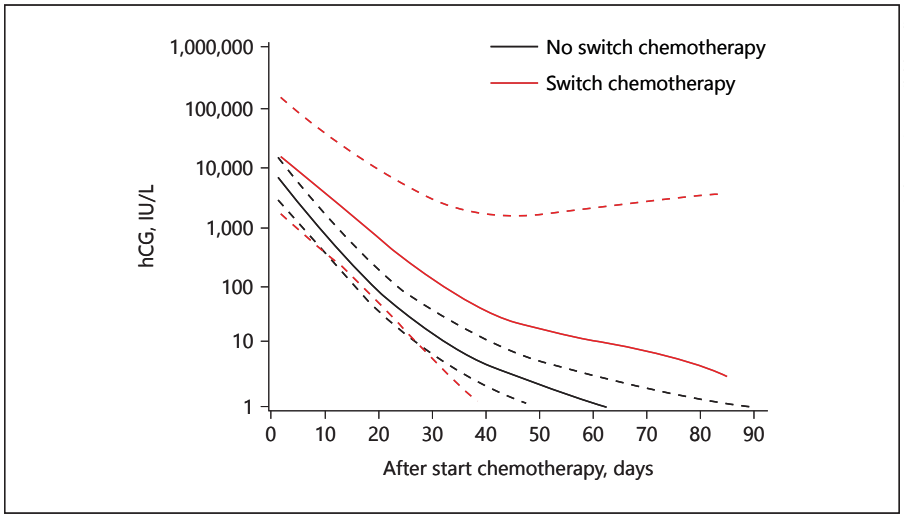

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Fig. 5. hCG regression curves of GTN patients. Black line with 95% CI: GTN patients responding well to first-line chemotherapy. Red line with 95% CI: 6 GTN patients in need of a switch of chemotherapy, before the essential switch.

In addition, hCG regression curves of GTN patients during first-line chemotherapy can also be used to evaluate response.

Our strength is that our total number of patients with this rare disease is higher than the number mentioned in the article of Schlaerth et al. [13]. In the latter, a spontaneous progressive fall was noted in 49 patients. A plateau or rise in the titers (according to the 95% confidence limits of the normal regression curve observed in the 49 patients) was seen in 28 patients and they all received therapy. Ten patients were diagnosed with metastases. They all plotted regression curves out of the 95% confidence limits of the curve created with the 49 patients. All together these are small numbers and no difference was made between CM or PM pregnancies. However, when we look to the CM subgroup and the GTN patients, the numbers are small, and therefore, it is impossible to make statistically significant statements.

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Disclosure Statement

All authors declare no conflicts of interest.

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