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Complete molar pregnancy in adolescents from North and South America: Clinical presentation and risk of gestational trophoblastic neoplasia

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HIGHLIGHTS

- A larger percentage of patients with molar pregnancy are adolescents in South America (31%) than in North American (13%).
- CHM complications and GTN risk factors are more frequent in South American than in North American adolescents.
- The percentage of adolescents treated for postmolar GTN did not differ between South American and North American sites.

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ABSTRACT

Objectives. To compare complete hydatidiform mole (CHM) clinical presentation and risk factors associated with GTN development between North American and South American adolescents.

Methods. This non-concurrent cohort study was undertaken including adolescents with CHM referred to centers in North America (New England Trophoblastic Disease Center, Harvard University, USA), and South America (Botucatu Trophoblastic Disease Center-São Paulo State University, Brazil; Trophoblastic Unit of Central University of Venezuela and Maternidad Concepcion Palacios of Caracas, Venezuela) between 1990 and 2012. Data were obtained from medical records and pathology reports. Study participants were allocated into 2 groups: North America (NA) and South America (SA).

Results. In NA and SA, 13.1% and 30.9% of patients with hydatidiform mole were adolescents, respectively. Of these, 77.6% in NA and 86.1% in SA had pathologic diagnosis of CHM ($p = 0.121$). Vaginal bleeding (SA = 69% vs NA = 51%; $p = 0.020$), anemia (SA = 48% vs NA = 18%; $p < 0.001$), and elevated serum hCG (SA = 232,860 mIU/mL vs NA = 136,412 mIU/mL; $p = 0.039$) were more frequent in SA than in NA. Median gestational age at diagnosis (SA = 12 weeks, NA = 11 weeks; $p = 0.030$) differed whereas GTN development rate (SA = 20%, NA = 27%; $p = 0.282$) showed no significant difference between groups. Compared to NA, medical complications and clinical factors associated with post-molar GTN were more frequent among SA adolescents.

Conclusions. Medical complications and clinical factors associated with GTN development were more frequent in SA than in NA adolescents with CHM, suggesting that, in South America, awareness about the importance of diagnosing molar pregnancy early and considering CHM in the differential diagnosis in adolescents suspected to be pregnant should be raised.

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1. Introduction

Hydatidiform mole (HM), or molar pregnancy, is an uncommon pathologic gestation characterized by abnormal development of both embryonic and extraembryonic tissues. Based on histopathology, clinical features, and chromosomal patterns, HM is characterized as either complete mole (CHM) or partial mole (PHM).

Maternal age has been reported as a significant risk factor for molar pregnancy across many countries including the United States, Asia, Europe and the Middle East [1,2]. Women < 16 or >40 years of age have a 4–10 times higher risk of developing a hydatidiform mole (HM) than those aged 20–30 [3–5]. In the U. K., the overall risk for women of reproductive age is <1: 500 [1]. However, risks are slightly higher for younger women (1:378–563 for teenagers aged 14–17), and significantly increased for those aged >40 (1:423 at 40, 1:101 at 45). At the extremes of the reproductive age range, the risk of HM for girls pregnant at the age of 13 is 1:208, and 1:8 for women aged ≥ 50 [1].

Although advanced maternal age is associated with a higher risk for molar pregnancy, HM patients > 40 years represent 4.5–5% [4,6], whereas adolescents with HM account for 10–34% of the cases in large trophoblastic diseases referral centers [5,7–9].

Adolescence has also been associated with increased risk of complete mole (CHM) [2,3,5], which increases the risk of developing postmolar gestational trophoblastic neoplasia (GTN) and, hence, the need for chemotherapy [10,11]. Studies assessing the risk of developing malignancy in adolescents have yielded conflicting results [5,12,13]; while some have reported increased risks [12], others have described a better prognosis for HM in this age group [5,13].

The clinical factors associated with risk of gestational trophoblastic neoplasia after CHM [14,15] remain uninvestigated in adolescents. Moreover, studies evaluating the different biological features and socioeconomic development levels found in different countries and regions are still lacking.

Therefore, this study was undertaken to assess and compare CHM clinical presentation and risk for gestational trophoblastic neoplasia in adolescents from a center in North America with centers in South America in order to investigate potential differences and their influence on GTN outcome.

2. Methods

This retrospective study included adolescents with complete hydatidiform mole (CHM) who were allocated into two nonconcurrent cohorts: North America - consisting of adolescents attending the New England Trophoblastic Disease Center (Brigham and Women's Hospital, USA); and South America (SA) - including adolescents treated in the Botucatu Trophoblastic Disease Center of São Paulo State University-Unesp (Brazil), the Trophoblastic Unit of the Central University of Venezuela, and the Maternidad Concepcion Palacios of Caracas (Venezuela), from 1990 to 2012. Adolescence was defined according to the definition of the World Health Organization as 10–19 years of age [16]. CHM was diagnosed based on classical histopathologic findings using the same criteria [17] in all centers.

The following data were collected by review of medical records: maternal age, gestational age at diagnosis, uterine size, pre-evacuation human chorionic gonadotropin (hCG) level, presence of theca lutein cysts > 6 cm, anemia (hemoglobin < 11 g/dL), vaginal bleeding, preeclampsia and hyperemesis. Gestational age was calculated on the basis of the date of the last menstrual period. Uterine size was considered excessive when the uterus was at least 4 weeks greater in size than expected for gestational age on clinical examination [15,18]. Theca lutein ovarian cysts > 6 cm were identified by pelvic ultrasound and bimanual pelvic examination under anesthesia prior to uterine evacuation [15]. Vaginal bleeding was defined as any bleeding either reported by the patient or detected during pelvic examination. Preeclampsia was determined as the presence of blood pressure ≥ 140/90 mm Hg with proteinuria [19]. Hyperemesis was defined as five or more episodes of nausea and vomiting per day requiring the use of antiemetics.

Serum hCG levels were measured before evacuation and every 1–2 weeks after evacuation for postmolar follow up [15]. According to the 2002 FIGO criteria [20], GTN was diagnosed as an hCG plateau of ±10% over the course of at least 3 weeks (days 1, 7, 14 and 21), or a rise of serum hCG > 10% over the course of 2 weeks (days 1, 7, and 14), or metastasis before hCG plateau or rise.

Statistical analyses were conducted using SPSS statistical software (version 21.0, SPSS Inc., Chicago, IL). The Chi-square test, Fisher's exact test, Student's *t*-test and Mann-Whitney test were used to compare CHM clinical characteristics between NA and SA adolescents. Linear regression analysis was used to assess the relationship between clinical factors and the development of postmolar GTN. Odds Ratio was calculated for a 95% confidence interval. Statistical significance was set at $p < 0.05$.

This study was approved by the Institutional Committees of Human Research Ethics (#2004-P-001372/13) at the Brigham and Women's Hospital, São Paulo State University, Botucatu Medical School (#04648312.0.1001.5411), Maternidad Concepción Palácios de Caracas, and University Hospital of Caracas, Central University of Venezuela (#CBE 26/2011).

3. Results

Of 510 patients diagnosed with hydatidiform mole at the New England Trophoblastic Disease Center (NA), 67 (13.1%) were adolescents, 52 (77.6%) of whom had histopathologic evidence of CHM. Of 955 women diagnosed with hydatidiform mole at the South American centers, 295 (30.9%) were adolescents, 254 (86.1%) of whom had histopathologic findings compatible with CHM. After all cases with missing data were excluded, 45 NA adolescents and 240 SA adolescents with CHM were included in the study (Fig. 1).

Median patient age was 17 years (12–19 years) in SA and 18 years (14–19 years) in NA ($p = 0.189$). Table 1 shows the frequency of CHM clinical complications at admission. Vaginal bleeding (SA = 69%, NA = 51%; $p = 0.020$), anemia (SA = 48%, NA = 18%; $p < 0.001$), and high median serum hCG levels (SA = 232,860 mIU/mL, NA = 136,412 mIU/mL; $p = 0.039$) were more frequent in SA than in NA. Median gestational age at diagnosis (SA = 12 weeks, NA = 11 weeks; $p = 0.030$) differed between groups whereas rate of GTN development after CHM (SA = 20%, NA = 27%; $p = 0.282$) showed no significant difference between SA and NA adolescents.

Linear logistic regression revealed that, compared to NA adolescents, clinical factors associated with risk of post-molar GTN were greater in number and magnitude among SA adolescents (Table 2). Thus, anemia ($p < 0.001$, OR = 3.51, 95% CI = 1.73–7.08), preeclampsia ($p = 0.018$, OR = 3.98, 95% CI = 1.27–12.49), uterine size > gestational age ($p = 0.004$, OR = 2.60, 95% CI = 1.35–5.01), and theca lutein cysts > 6 cm ($p = 0.011$, OR = 3.07, 95% CI = 1.30–7.31) were associated with post-CHM GTN in SA, but not in NA adolescents.

4. Discussion

Our results show that median patient age did not significantly differ between NA and SA adolescents. However, although teen pregnancy rate in the United States is as high as that in developing countries [21], the percentage of adolescents with molar pregnancy found in this study was over two-fold higher in SA than in NA.

CHM rate was similar in both groups investigated, in agreement with several other studies demonstrating that risk of CHM, but not partial mole, is strongly associated with maternal age [1–3]. However, the exact mechanism leading to the increased incidence of molar pregnancy at the extremes of reproductive age remains unknown, especially among young women with CHM [2]. Strong correlations between

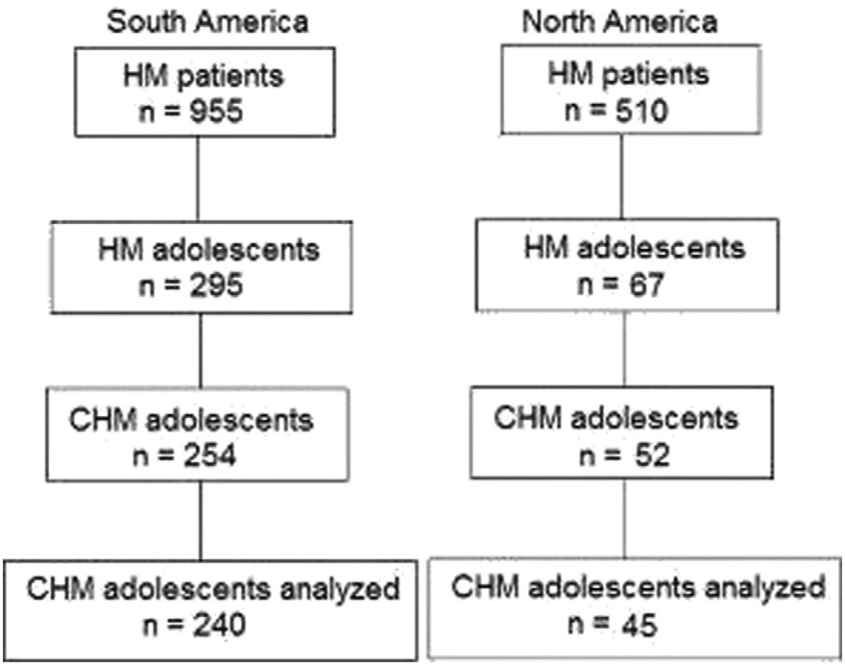

Fig. 1. Patient population flow chart.

chromosome abnormalities and advanced maternal age have been reported [22], but no chromosome defects have been found in oocytes of adolescents [23].

CHM clinical complications at admission, such as vaginal bleeding, anemia, and high hCG levels were more frequent in SA than in NA.

Vaginal bleeding was 69% in SA adolescents, which is in agreement with recent studies reporting a 70% rate [24,25]. In a study of NA adolescents conducted from 1970 to 2009 at the NETDC, vaginal bleeding rate was also 70% [5]. However, the rate of vaginal bleeding in NA adolescents participating in this present study was 51%. This decreased rate, may be explained by the fact that in the U.S., CHM has been diagnosed progressively earlier by pelvic ultrasound and hCG measurement in the first trimester. With earlier diagnosis, CHM signs and symptoms, such as vaginal bleeding, are less frequently observed [18,24,26].

Anemia was observed in 48% of the adolescents in SA, whereas only 18% of NA adolescents were anemic. This finding is consistent with the vaginal bleeding rates observed in each group. Anemia frequently complicates a complete molar pregnancy. As the visible bleeding may underrepresent the total amount of blood loss, which may be prolonged, considerable and occult in the endometrial cavity, patients might become anemic [15]. Thus, it is possible that the duration of bleeding before diagnosis was more prolonged in SA adolescents, and they might also have been malnourished before their molar pregnancy [27,28].

In comparison with NA study participants, SA adolescents showed higher serum hCG levels. These higher levels indicate marked trophoblastic proliferation, and increased trophoblastic volume which may be related to later diagnosis.

Median gestational age at diagnosis of complete molar pregnancy was 11 and 12 weeks in NA and SA study participants, respectively. While the percentage of patients diagnosed in the first trimester was 61% in South America it was 80% in North America ($p = 0.018$). Previous studies have shown that at the NEDTC median gestational age at diagnosis decreased from 12 weeks in 1995 [29] to 9 weeks in 2015 [18], whereas in one of the SA centers, it decreased from 15 weeks in 1988–1992 to 10 weeks in 2008–2012 [26]. Our findings in adolescents

Table 1
Demographic and clinical characteristics among adolescents with complete molar pregnancy from South America and North America.

Variable	South America (n = 240)	North America (n = 45)	p value
Median age (min-max), y	17 (12–19)	18 (14–19)	0.189(1)
Mean age (SD), y	16.8 (1.7)	17.2 (1.6)	0.179(4)
Median GA[a] (IQR, 25th; 75th)	12 (10; 16)	11 (9; 13)	0.030(1)
Gestational age ≤ 13 weeks	144/238 (61%)	32/40 (80%)	0.018(2)
Vaginal bleeding	165/239 (69%)	23/45 (51%)	0.020(2)
Anemia	114/239 (48%)	8/44 (18%)	<0.001(2)
Preeclampsia	13/239 (5%)	4/45 (9%)	0.323(3)
Hyperemesis	35/239 (15%)	6/40 (15%)	0.953(2)
Uterine size > GA[a]	81/239 (34%)	17/41 (42%)	0.348(2)
Theca lutein cysts	26/239 (11%)	3/44 (7%)	0.590(3)
hCG[b] (IQR, 25th; 75th)	232,860 (87,443;706,472)	136,412 (35,518;363,832)	0.039(1)
Postmolar GTN	47/240 (20%)	12/45 (27%)	0.282(2)

1. Mann-Whitney test
2. Chi-Square test.
3. Fisher's exact test.
4. Student's *t*-test.

[a] Gestational age.
[b] Median pre-evacuation hCG.

Table 2
Linear regression logistics of clinical factors associated with development of post-CHM GTN among adolescents from South America and North America.

Variable	South America	North America
	OR (95% CI) p-value	OR (95% CI) p-value
Age at diagnosis, y	0.92 (0.77–1.10) 0.373	1.12 (0.73–1.70) 0.591
Gestational age, wk	1.03 (0.95–1.12) 0.390	1.32 (0.97–1.79) 0.069
Vaginal bleeding	1.54 (0.73–3.23) 0.252	1.48 (0.39–5.65) 0.560
Anemia	3.51 (1.73–7.08) <0.001	3.50 (0.71–17.21) 0.123
Preeclampsia	3.98 (1.27–12.49) 0.018	[a]
Hyperemesis	2.21 (0.99–4.93) 0.052	1.62 (0.25–10.57) 0.611
Uterine size > GA[b]	2,60 (1.35–5.01) 0.004	2.72 (0.63–11.78) 0.179
Theca lutein cysts	3.07 (1.30–7.31) 0.011	6.20 (0.50–75.8) 0.153
Pre-evacuation hCG	1.00 (1.00–1.00) 0.005	1.00 (0.99–1.00) 0.204

[a] GTN rate in North American adolescents with preeclampsia = 0.
[b] Gestational age.

are consistent with a global trend towards decline in median gestational age at diagnosis of complete molar pregnancy over the past years with the widespread use of ultrasound and hCG measurement. While earlier diagnosis of CHM has been reported to be associated with a decrease in classical presenting symptoms such as bleeding, anemia, and excessive uterine size, it has not been associated with any decrease in the development of postmolar GTN, as was seen in the current study.

Complete molar pregnancy has been diagnosed progressively earlier in recent years across the globe [18,24,26]. While earlier diagnosis has been associated with a decrease in the classical presenting symptoms, this has not been associated with a change in the development of GTN [18]. The differences between the development of postmolar GTN in NA vs SA were not statistically significant in this study. While some of the classic presenting symptoms for CHM were significantly associated with the development of GTN in SA, this was not found in the patients with complete molar pregnancy in NA. This may be partly related to the fact that NA patients with complete molar pregnancy were diagnosed significantly earlier and showed the classic presenting symptoms significantly less frequently. However, earlier diagnosis and less frequent classic presenting symptoms have not been associated with a decrease in the development of GTN. It is quite possible that with early diagnosis the classic presenting symptoms for complete molar pregnancy may be less predictive of developing GTN. Furthermore, it is important to acknowledge that the database from North America represents a small patient population with differing healthcare systems and differing referral patterns which may potentially contribute to a distortion in statistical comparison. It is also important to point out that the definition of the development of postmolar GTN followed the 2002 FIGO criteria [20] in both the patients from North America and South America.

Overall, our findings suggest that, although not specifically evaluated in this study, geographic, cultural and economical conditions most probably contributed to the differences observed between NA and SA adolescents with CHM. All centers participating in this study are regional. However, the NA center, NETDC, is a very well resourced center where the great majority of patients have health insurance and the ready availability of routine ultrasound favors the early diagnosis of molar pregnancy. On the other hand, in SA centers, patients more frequently have no health insurance, and resources are limited with ultrasound scanning not always available in early pregnancy. Moreover, many women in developing countries do not consult a health-care worker for early antenatal care [30]. Among SA adolescents, this picture may be aggravated by lack of knowledge about sex and family planning, and the severe social consequences of pregnancy, particularly for unmarried girls [31]. Denial or even fear of telling others about the pregnancy may lead to delayed pregnancy testing, and reporting problems leading to unreliable menstrual dates [32] or unreported bleeding events. Thus, it is possible that in some of the SA cases included in this study gestational age was underestimated and that diagnosis was actually delayed as reported in other developing countries such as the Philippines [33] and El Salvador [34]. As a complete molar pregnancy advances, trophoblastic proliferation may become more marked increasing hCG levels, and vaginal bleeding may be more commonly present, which can result in anemia [29]. Additionally, adolescents in SA have been reported to have higher rates of malnutrition and iron-deficiency anemia during pregnancy [35].

In conclusion, medical complications and clinical factors associated with GTN development were more frequent in SA than in NA adolescents, with CHM likely due to later diagnosis. Our results suggest that, in South America, awareness about the importance of diagnosing molar pregnancy early and considering CHM in the differential diagnosis in adolescents suspected to be pregnant should be raised among healthcare policymakers and those involved in medical care and education.

Conflict of interests

The authors declare no conflict of interest.

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