Gynecologic Oncology xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Multiple pregnancies with complete mole and coexisting normal fetus in North and South America: A retrospective multicenter cohort and literature review

Lawrence H. Lin [a], Izildinha Maestá [b], Antonio Braga [c], Sue Y. Sun [d], Koji Fushida [a], Rossana P.V. Francisco [a], Kevin M. Elias [e,f,g,h], Neil Horowitz [e,f,g,h], Donald P. Goldstein [e,f,g,h], Ross S. Berkowitz [e,f,g,h,*]

[a] University of Sao Paulo Trophoblastic Disease Center, University of Sao Paulo Medical School, Sao Paulo, Sao Paulo, Brazil
[b] Botucatu Trophoblastic Disease Center, Clinical Hospital of Botucatu Medical School, Sao Paulo State University, Botucatu, Sao Paulo, Brazil
[c] Rio de Janeiro Trophoblastic Disease Center, (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), Rio de Janeiro, Rio de Janeiro, Brazil
[d] Sao Paulo Hospital Trophoblastic Disease Center, Paulista School of Medicine, Sao Paulo Federal University, Sao Paulo, Sao Paulo, Brazil
[e] New England Trophoblastic Disease Center, Donald P. Goldstein MD, Trophoblastic Tumor Registry, Boston, MA, USA
[f] Division of Gynecologic Oncology, Brigham and Women's Hospital, Boston, MA, USA
[g] Department of Obstetrics, Gynecology and Reproductive Biology, Harvard Medical School, Boston, MA, USA
[h] Dana Farber Cancer Institute, Boston, MA, USA

HIGHLIGHTS

- Pregnancies with mole and fetus in South America presented with more complications.
- Pregnancies with mole and fetus were at high risk for persistent disease.
- Elective termination did not influence risk of persistent disease.

ARTICLE INFO

Article history:
Received 28 December 2016
Received in revised form 12 January 2017
Accepted 19 January 2017
Available online xxxx

Keywords:
Gestational trophoblastic disease
Hydatidiform mole
Pregnancy, Twin
Multiple, Pregnancy
Trophoblastic neoplasms
Near miss, healthcare

ABSTRACT

Objective. To determine the clinical characteristics of multiple gestation with complete mole and coexisting fetus (CHMCF) in North and South America.

Methods. Retrospective non-concurrent cohorts compromised of CHMCF from New England Trophoblastic Disease Center (NETDC) (1966–2015) and four Brazilian Trophoblastic Disease Centers (BTDC) (1990–2015).

Results. From a total of 12,455 cases of gestational trophoblastic disease seen, 72 CHMCF were identified. Clinical characteristics were similar between BTDC (n = 46) and NETDC (n = 13) from 1990 to 2015, apart from a much higher frequency of potentially life-threatening conditions in Brazil ($p = 0.046$). There were no significant changes in the clinical presentation or outcomes over the past 5 decades in NETDC (13 cases in 1966–1989 vs 13 cases in 1990–2015). Ten pregnancies were electively terminated and 35 cases resulted in viable live births (60% of 60 continued pregnancies). The overall rate of gestational trophoblastic neoplasia (GTN) was 46%; the cases which progressed to GTN presented with higher chorionic gonadotropin levels ($p = 0.026$) and higher frequency of termination of pregnancy due to medical complications ($p = 0.006$) when compared to those with spontaneous remission.

Conclusions. The main regional difference in CHMCF presentation is related to a higher rate of potentially life-threatening conditions in South America. Sixty percent of the expectantly managed CHMCF delivered a viable infant, and the overall rate of GTN in this study was 46%. Elective termination of pregnancy did not influence the risk for GTN; however the need for termination due to complications and higher hCG levels were associated with development of GTN in CHMCF.

* Corresponding author at: Brigham and Womens' Hospital, 75 Francis Street, Boston, MA 02115, USA.
E-mail address: rberkowitz@partners.org (R.S. Berkowitz).

http://dx.doi.org/10.1016/j.ygyno.2017.01.021
0090-8258/

1. Introduction

Multiple gestation with a complete mole and coexisting fetus (CHMCF) is a rare event, with an estimated incidence of 1 case for 20,000–100,000 pregnancies [1–3]. These pregnancies are characterized by the coexistence of a complete mole and a potentially viable fetus with a normal placenta, in contrast to partial moles, which are composed of a single triploid conceptus with an abnormal placenta [4]. The differential diagnosis is important due to the fact that a partial mole's fetus is nonviable and the gestational trophoblastic neoplasia (GTN) risk is <5% [5]. There is still controversy on the rate of GTN progression in CHMCF, with varying rates of GTN being reported [1,6–9].

CHMCF are classically associated with several pregnancy complications, such as spontaneous abortions, intrauterine deaths, preeclampsia and hyperthyroidism [2,6,7]. In the past, due to the uncertain behavior of these pregnancies, they were commonly advised to be terminated, leaving little information on the natural history of this condition. One large study on CHMCF has shown that there is no association between elective pregnancy termination and the rate of GTN; similarly in single moles, gestational age of evacuation does not influence the progression to GTN [1,10].

A recent collaborative study described different characteristics of complete molar pregnancy in adolescents in North and South America, showing that regional differences may play a role in the clinical presentation of complete mole [11]. The reports around the globe describing clinical presentation and GTN risk of CHMCF are conflicting, either due to differences in hospital-based versus population-based data or actual regional differences on disease behavior. The aim of this study was to determine the clinical characteristics of CHMCF in North and South America and provide additional information on the natural history of this condition.

2. Methods

2.1. Study design and setting

This is a retrospective cohort study consisting of all multiple pregnancies with complete mole and coexisting fetus registered at the New England Trophoblast Disease Center (NETDC) from 1966 to 2015 and 4 Brazilian Trophoblastic Disease Reference Centers (Botucatu Trophoblastic Disease Center, Rio de Janeiro Trophoblastic Disease Center, Sao Paulo Hospital Trophoblastic Disease Center and University of Sao Paulo Trophoblastic Disease Center; all located in the southeast region of Brazil) from 1990 to 2015. This study was approved by the centers' respective institutional review boards and the manuscript was drafted in accordance with STROBE guidelines [12].

All electronic and paper charts for the patients were reviewed. The diagnosis of CHMCF was confirmed by histological evaluation by experienced pathologists in all cases. In cases with uncertain histological diagnosis, additional $p57^{KIP2}$ immunostaining, ploidy or/and cytogenetic analysis was also performed. Patients with a diagnosis of partial mole or placental mesenchymal dysplasia were excluded from this study.

The patients were compared regarding: regional location (NETDC vs Brazil) from 1990 to 2015; current cohort (1990–2015) vs historical cohort (1966–1989) in NETDC; GTN progression vs spontaneous regression (all cohorts' data). For temporally concurrent comparisons, a recently published NETDC cohort on single complete moles (1994–2013) was compared to the NETDC CHMCF cohort (1990–2015) and all CHMCF data in recent years (1990–2015) [10].

2.2. Variables and definitions

The following variables were abstracted: pregnancy presentation, medical complications, obstetric outcomes, GTN progression and treatment, potentially life-threatening conditions and maternal near miss complications. Due to the nature of referral centers, some patients were outside consults without complete follow-up; patients with missing information were included only in analyses of variables for which data were available. All patients followed in the referral centers were assisted during the course of pregnancy by maternal fetal medicine and trophoblastic disease team specialists.

Medical complications evaluated in this study included vaginal hemorrhage, preeclampsia, clinical hyperthyroidism and respiratory distress. Vaginal hemorrhage was defined as excessive vaginal bleeding leading to hospitalization, hemodynamic instability, blood transfusion or termination of pregnancy. Preeclampsia was defined as hypertension (systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg) associated with proteinuria on dipstick or at least 300 mg in 24 h. Clinical hyperthyroidism was characterized as suppressed thyroid-stimulating hormone (TSH) with elevated serum free thyroxine (T4) levels in the presence of classical symptoms (such as tachycardia, tremor or elevated body temperature) or the need to be treated with beta-blocker. Respiratory distress was defined when the patient presented with acute tachypnea or dyspnea with a radiographic pulmonary infiltrate or pleural effusion. World Health Organization (WHO) defines a maternal near miss as "a woman who nearly died but survived a complication that occurred during pregnancy, childbirth, or within 42 days of termination of pregnancy". Potentially life-threatening conditions and maternal near miss were established using the WHO criteria and classification [13]. According to the *WHO recommendations on interventions to improve preterm birth outcome* guideline, fetal viability depends on the local resources and before 24 weeks the chance of survival without considerable morbidity is low even in high-resource settings; therefore, viable pregnancies were considered the ones in which live infants were delivered at least at 24 weeks of gestational age [14].

After the end of pregnancy the patients were followed with weekly serum human chorionic gonadotropin (hCG) measurements until normal values were achieved and then with monthly values up to 6 months. All reference centers used hCG detection kits based on chemiluminescent methods with a sensitivity of at least 5 mIU/mL. In cases where the hCG was above the detection range of the method, the highest recorded value was identified. The patients were diagnosed with GTN if they presented with at least one of the following FIGO (2002) diagnostic criteria: (1) rise of at least 10% of hCG levels in 3 weekly measurements, (2) plateau (<10% variation) for 4 weekly values of hCG, (3) metastatic disease in the presence of positive hCG, (4) histological diagnosis of choriocarcinoma. Patients with GTN were staged according to the FIGO (2002) anatomic and prognostic system [15]. Remission was classified as the normalization of hCG levels for at least 3 consecutive weeks. Resistance was defined as a variation <10% in 3 consecutive weekly hCG levels or the rise of >10% in 2 weekly values of hCG during chemotherapy. Recurrence was characterized as hCG elevation after remission of disease after completion of chemotherapy in the absence of a new pregnancy.

2.3. Statistical methods

The results were analyzed in means ± standard deviation for quantitative variables and in proportions for qualitative variables. The means were compared using the unpaired Student's *t*-test for normally distributed variables and a Mann-Whitney test for variables with non-normal distribution, while proportions were analyzed using Fisher's exact test. A p value <0.05 was considered statistically significant. The results were all shown as medians in the tables of this manuscript because of the non-normal distribution they displayed.

2.4. Literature review

A literature review was performed by searching in Medline, Pubmed and EMBASE databases for cohort studies or case series related to CHMCF in the literature, using the following MeSH (Medical Subject

Please cite this article as: L.H. Lin, et al., Multiple pregnancies with complete mole and coexisting normal fetus in North and South America: A retrospective multicenter cohort..., Gynecol Oncol (2017), http://dx.doi.org/10.1016/j.ygyno.2017.01.021