A five-year review of the clinicopathologic profile of patients with hydatidiform mole at the Philippine General Hospital

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ABSTRACT

Background: The clinical presentation of patients with hydatidiform mole have changed in recent years due to earlier diagnosis as a result of widespread use of ultrasonography and availability of assays for human chorionic gonadotrophin.

Objective: To determine the clinicopathologic profile of patients diagnosed with hydatidiform mole at the Philippine General Hospital from January 2013 to August 2018.

Methods: This retrospective cross-sectional study included all patients with histologically confirmed diagnosis of hydatidiform mole managed at the Philippine General Hospital from January 2013 to August 2018. Medical records of patients were retrieved. All abstracted variables were analyzed retrospectively. The level of significance for all sets of analysis was set at p-value < 0.05 using two-tailed comparisons.

Results: From January 2013 to August 2018, a total of 435 patients diagnosed with hydatidiform mole were managed at the Philippine General Hospital with a prevalence rate of 15.7/1,000 pregnancies. Diagnosis was made in the first trimester in 52% of patients. A quarter of the patients had pre-evacuation B-hCG levels of more than 1 million mIU/mL. Vaginal bleeding was the most frequent presenting symptom but only 59% of the patients had anemia requiring blood transfusion. Majority (90.57%) had a histopathologic diagnosis of complete hydatidiform mole.

Conclusion: The prevalence and clinicopathologic profile of patients with hydatidiform mole in the Philippine General Hospital have remained largely unchanged.

Keywords: hydatidiform mole, gestational trophoblastic diseases, B-hCG, clinicopathologic profile

INTRODUCTION

Hydatidiform mole (HM) refers to an abnormal pregnancy characterized by varying degrees of trophoblastic proliferation and vesicular swelling of placental villi associated with an absent or an abnormal fetus/embryo.[1] HMs may be partial (PHM) or complete (CHM) depending on their gross appearance, histopathology and karyotype.[2]

Epidemiologic studies have reported wide regional variations in the incidence of HM, with the highest incidence in the Southeast Asian region. This may be due to discrepancies in hospital- and population-based data, availability of central pathological review or may reflect dietary and genetic influences.[3] Currently, there have been numerous reports of declining incidence rates in various Asian countries such as Japan, Korea, and Malaysia.[4-5] Additionally, the advent of ultrasonography and availability of reliable assays for the determination of the human chorionic gonadotropin (hCG) levels have made the diagnosis of HM easier and at an earlier age of gestation. As a consequence, the classic signs and symptoms associated with HM are less seen.

The reported national prevalence rate of HM in the country from 2002 to 2008 was 2.4/1,000 pregnancies.[6] The Philippine General Hospital (PGH), the largest tertiary government hospital with the only Trophoblastic Disease Center in the country, had an incidence of 13/1,000 pregnancies in 2008-2012, which has not changed since the 1990s.[4] Although imaging studies as well as assays for B-hCG have become more available, the diagnosis and management of patients with HM have remained challenging for variety of reasons.

OBJECTIVES

General Objective

To determine the clinicopathologic profile of patients with HM admitted to the PGH from January 2013 to August 2018.

Specific Objectives

1. To determine the prevalence rate of HM from January 2013 to August 2018
2. To describe the clinical profile of HM patients in terms of:
   a. mean age
   b. mean gravidity
   c. mean parity
   d. mean age of gestation (AOG) in weeks at diagnosis
   e. mean uterine size
   g. mean pre-evacuation B-hCG levels (mIU/mL)
   f. proportion of those patients with a history of molar pregnancy
   h. proportion of the medical complications encountered
3. To determine the methods of evacuation of molar pregnancy employed in HM patients
4. To determine the proportion of the types of histopathologic diagnosis of HM patients
5. To determine the percentage of patients given chemoprophylaxis
6. To determine the indications for giving chemoprophylaxis

MATERIALS AND METHODS

Study Design and Population

This was a retrospective cross-sectional study approved by the institution's technical and ethical review board, involving all patients with a histopathologically confirmed diagnosis of HM admitted at the PGH from January 2013 to August 2018. Patients with known medical co-morbidities prior to the molar pregnancy were excluded so as not to confound the actual proportion of patients with medical complications caused by HM alone.

Description of the Study Procedure

The annual ward and admission reports, outpatient department census, and the computer database of the Trophoblastic Diseases Section of the Department of Obstetrics and Gynecology of the PGH were reviewed to identify all patients diagnosed with HM who were admitted during the study period. Medical records of eligible patients were retrieved and reviewed. Pertinent data abstracted and recorded in the patient data extraction form included the following: the patient's age, gravidity, parity, age of gestation (AOG) in weeks at the time of diagnosis, prior molar pregnancy, associated medical complications, uterine size, pre-evacuation serum B-hCG titer, presence of theca lutein cysts, method of molar evacuation, histopathologic diagnosis, whether chemoprophylaxis was given or not, and the indications for chemoprophylaxis.

Data Analysis

All extracted data were encoded using the Stata 13 software. Patient identity was not included in the electronic spreadsheet and replaced by a sequence number to ensure privacy and confidentiality. A master list of the patients' names with corresponding sequence number was kept in a separate password-protected electronic spreadsheet.

Data were analyzed using descriptive statistics. Continuous data were expressed as means and standard deviations, medians and ranges while categorical data were reported as frequency, percentages and proportions. Trend analysis of proportions was also performed to determine patterns of disease across the years indicated in the study duration. The level of significance for all sets of analysis was set at a p-value less than 0.05 using two-tailed comparisons.

RESULTS

There were 435 patients with histopathologically confirmed diagnosis of HM managed in PGH from January 2013 to August 2018, with a prevalence of 15.65 per 1,000 pregnancies (11.84-19.24 per 1,000 pregnancies per year). Figure 1 shows the yearly trend of HM cases. The highest number of HM admissions was in 2013. Trend analysis for proportions suggest a decreasing incidence proportion of the cases of HM seen in PGH over the years ($\chi 2$: 6.84, $p<0.01$).

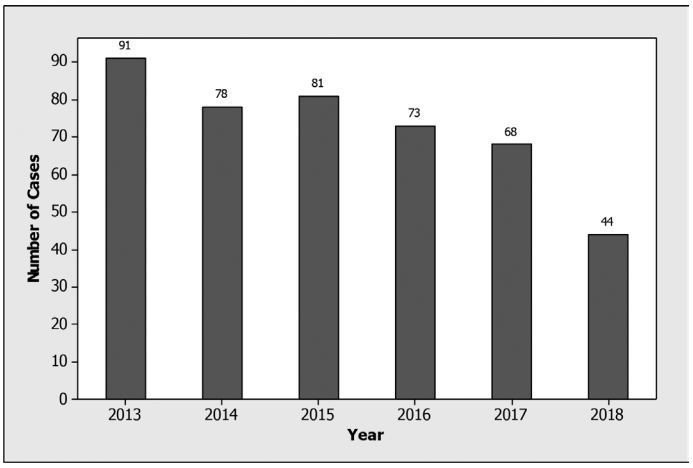

Figure 1. Incidence of Hydatidiform Mole from 2013 to August 2018

Table 1 summarizes the clinical profile of the study population. The mean age was 29 years (15-54 years) and more than half of patients were more than twenty-six years old. The mean gravidity was 3 (1-13) while the mean parity was 1 (0-12). The mean AOG at diagnosis was 14 5/7 weeks (4 4/7 to 31) with 52% of the patients (227/435) diagnosed during the first trimester. Uteri larger than dates were seen in 254 (58%) patients. Uterine size upon diagnosis ranged from 10 to 30 weeks with a mean of 19 weeks. The mean pre-evacuation serum B-hCG was 938,853 mIU/mL (23-126,200,000mIU/ml). Remarkably, a quarter of the study had pre-evacuation B-hCG levels of more than 1 million mIU/mL. Less than 2% (5/435) of the women reported a history of HM prior to the current one. One patient had a history of five molar pregnancies. All of the 5 patients with recurrent HM had a histopathologic diagnosis of CHM, except for one who had PHM. Vaginal bleeding was the most frequent symptom, accounting for 98% (427/435) of cases but only 257 (59%) of the patients had anemia requiring blood transfusion. There were 100 (23%) patients who had thyrotoxicosis and presented with tachycardia, palpitations, and tremors, but none of them had thyroid storm. Theca lutein cysts were seen on transvaginal ultrasound in 80 women, but only 35 had theca lutein cysts ≥6 cm. None required surgical intervention for complications. Less than 10% of them had hypertension with 4 (1%) having HELLP syndrome. Less common complications noticed were hyperemesis (1%), pulmonary embolism (0.5%), and pulmonary insufficiency (0.5%). None of the patients had sepsis or disseminated intravascular coagulation. One third of the women had multiple medical complications.

Suction curettage remained the most common method of evacuation, being performed in 81.38% of cases, followed by hysterectomy with or without salpingo-oophorectomy with mole-in-situ, which was done in 16.32% of patients. Figure 2 shows that the number of cases of suction curettage and hysterectomy done were almost constant during the study period.

Majority of the patients (90.57%) had a histopathologic diagnosis of CHM. PHM was seen in only 5.06% (22/435) while 19 patients (4.37%) have uncategorized results. No immunostaining with p57kip2 was done to confirm the diagnosis.

Figure 3 shows that around three-fourths of the women underwent chemoprophylaxis (324/435) with a prevalence of 74.48%. Chemoprophylaxis was predominantly given for B-hCG levels ≥100,000 mIU/mL (72.18%) and uterine size larger than gestation by ≥6 weeks (27.59%) as seen in Table 2. There was no noted significant pattern of giving chemoprophylaxis and its indication.

Table 1. Clinical Characteristics of the Study Population

Characteristics	Summary Measures
Maternal Age in years	29 ± 9.35
Gravidity	3 (3)
Parity	1 (3)
Age of Gestation in weeks at Diagnosis	14.73 ± 4.35
Uterine Size in weeks at Diagnosis	19 ± 4.33
Pre-evacuation β-hCG levels in mIU/mL	938, 853 ± 421.76
History of Molar Pregnancy	5 (1.15%)
Medical Complications	
Vaginal bleeding	427 (98.16%)
Anemia	257 (59.08%)
Thyrotoxicosis	100 (22.99%)
Theca lutein cysts on sonogram	80 (18.39%)
Preeclampsia	38 (8.74%)
Preeclampsia with severe features	28 (6.44%)
Preeclampsia without severe features	6 (1.38%)
Preeclampsia with HELLP Syndrome	4 (0.92%)
Hyperemesis	4 (0.92%)
Pulmonary edema or embolism	4 (0.92%)
Amenorrhea	2 (0.46%)
Abdominal enlargement	1 (0.23%)
Dysuria	1 (0.23%)

**List of all known medical complications, patients may have one or more*

DISCUSSION

HM comprise the benign spectrum of gestational trophoblastic diseases (GTD). Ethnicity seems to play an important role in the incidence of HM, yet the exact underlying mechanism remains unknown. Investigations into possible ethnic and racial differences leading to an increased incidence of HM among American Indians, Eskimos, Hispanics, and African Americans as well as various Asian populations have not been able to attribute them to genetic traits, cultural factors, or simply differences in reporting.[7-9] In this study, the prevalence of HM in PGH is 15.7 per 1,000 pregnancies, which is higher than the figures reported by Isidro-Gutierrez et al of 10.6 per 1,000 pregnancies (1975-1983),[10] and by Cagayan of 13.4 per 1,000 pregnancies (2008-2012).[4] Over the years, trophoblastic diseases specialists have been educating health workers on the proper diagnosis of HM and the benefit of managing HM in a tertiary center. This may have caused the higher prevalence in this study owing to the higher rates of referral of HM cases to PGH due to the increased awareness of health providers across the country regarding HM and its sequelae. The prevalence reported in this study is in consonance with the reports in other Asian countries like Korea, Thailand, Indonesia, and Turkey, but different from most parts of the world which have a lower rate of 1 per 1,000 pregnancies.[11-14]

Despite the high over-all prevalence of HM in this research, a decreasing trend in its yearly values was observed. This may be ascribed to the decrease in the proportion of women that were in the extremes of the reproductive age, which are the age groups that have the highest risk of developing HM. A report supporting this asserted that HM appears to be caused by abnormal gametogenesis and fertilization more frequent at the extremes of reproductive age (<15 and >45 years) and pregnancies at these ages are a risk factor for HM. Teenagers have a two-fold risk of having HM.[15-17]

The study population was composed of young women with a mean age of 29 years old, a finding in agreement with other authors who credited it to the high fertility rate in this age group.[4, 10, 12,14,18]

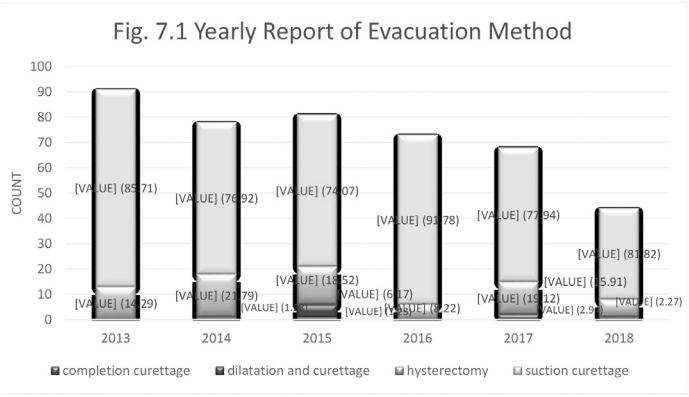

Figure 2. Evacuation Method of HM Patients from 2013 to August 2018

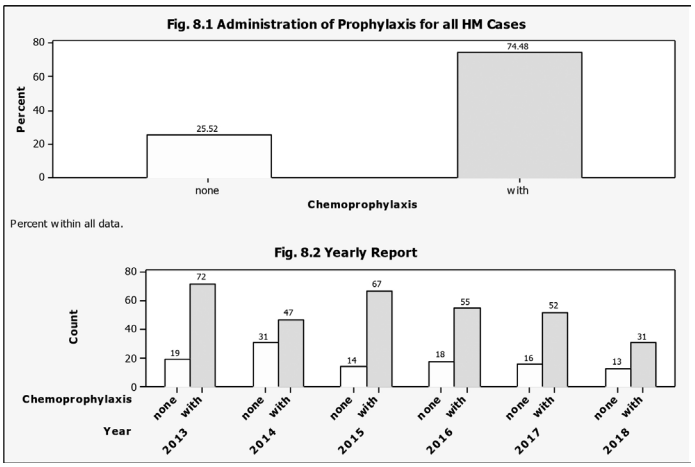

Figure 3. Administration of Chemoprophylaxis from 2013 to August 2018

Table 2. Indications for Administration of Prophylaxis among HM patients

Indications		
N=435	**n**	**%**
BhCG ≥100,000	314	72.18
uterine size larger than gestation by ≥6 weeks	120	27.59
thyrotoxicosis	77	17.70
advanced maternal age	47	10.80
theca lutein cyst/s ≥6 cm	39	8.97
preeclampsia	25	5.75
poor access to health care	3	0.69
no CPG indication	2	0.46
recurrent hydatidiform mole	2	0.46

**List of all known medical complications, patients may have one or more*

The gravidity and parity of the patient population remained the same when compared to the previous local studies.[4,10] One journal noted that there is insufficient evidence to imply a relationship between gravidity, parity and the risk of GTD, often due to the presence of confounding risk factors (e.g.: maternal age) within the analyses.[19]

In this report, more than half of the population were diagnosed with HM during the first trimester, as opposed to prior local studies which observed that patients managed in PGH were diagnosed during the second trimester of pregnancy.[4,10] This may be due to the increased availability of ultrasound and serum BhCG assays. However, compared to other countries where the diagnosis is made during the early first trimester,[3-19] the diagnosis in the PGH is still relatively late because patients come for their first prenatal check-up quite late and some just consult because of vaginal bleeding. The reason for the late consult is multifactorial and mostly driven by socioeconomic factors. As a result of the relatively late diagnosis, quite a number of the patients still present with the classic signs and symptoms of HM such as uterus larger than age of gestation, presence of theca lutein cysts on ultrasound, thyrotoxicosis, and anemia. In this paper, 26% of the study population had pre-evacuation B-hCG levels of more than 1 million mIU/mL. These represent the few patients diagnosed in the late trimester, when they already had complications of HM upon diagnosis. For developed countries, however, the classic clinical presentation of HM are seen less frequently because of earlier prenatal consultation, widespread use of ultrasonography and availability of accurate assay for hCG.[1,12, 17-18]

Of the numerous risk factors for HM that have been suggested, other studies disclosed that the only clear data related to it are maternal age and the previous occurrence of a prior molar pregnancy.[20-21] Women with CHM have a 1 in 100 and 1 in 4 risk of further CHM after one or two consecutive CHM, respectively, while women with PHM have only a small increase in risk (0.28%) for further molar pregnancies.[20] Some repeat molar pregnancy may be due to familial or sporadic biparental molar disease.[3] In this report, five patients had recurrent hydatidiform mole (RHM) with 1-2 prior molar pregnancies. One patient had 5 pregnancies that were all molar pregnancies for which she underwent suction curettage, and was given chemoprophylaxis after. Blood samples from the patient, her husband, mother, grandmother and sister were sent for genetic testing. Results revealed that the patient had NLRP7 mutation.[22]

Suction curettage is the preferred method of evacuation irrespective of uterine size in patients who want to preserve fertility. Given the young study population, it follows that a greater proportion of patients underwent suction curettage, which is in concordance with prior publications.[4,23] Hysterectomy with or without salpingo-oophorectomy for mole in situ followed next. It was done among patients with advanced age and completed family size with the additional benefit of providing permanent sterilization and eliminating the risk of local myometrial invasion. Hysterectomy has been reported to decrease the overall risk for postmolar GTN to approximately 3.5% from the anticipated 20% following suction curettage.[23] Because of the potential for metastatic disease even after hysterectomy, the importance of continued B-hCG monitoring was emphasized. Some patients in this research underwent dilatation and curettage and completion curettage because they either had small uterine size (12-14 weeks) or had passage of vesicular tissues upon consult.

In this paper, CHM was the more common histopathologic diagnosis, which is consistent with literature.[4,14] Less than 5% of HM patients had results that were unclassified into CHM or PHM because of the difficulty in the morphologic differentiation between the two entities. Although immunostaining with p57kip2 is recommended, patients in PGH usually are unable to comply due to financial constraints.

Current evidence in favor of chemoprophylaxis is limited by the poor methodological quality and small size of the included studies.[2] However, prophylactic administration of either Methotrexate (MTX) or Actinomycin D chemotherapy at the time of or immediately after evacuation of a hydatidiform mole has been shown to be associated with a reduction in incidence of postmolar GTN from approximately 15-20% to 3-8%, particularly in the high-risk population.[23] A marked difference in the incidence of postmolar GTN among those who received MTX for chemoprophylaxis (16.67%) compared to those who received placebo (38.71%) was shown by a research in PGH in 2015.[24] As a result, the Philippine Society for the Study of Trophoblastic Diseases (PSSTD) recommends administration of chemoprophylaxis for high risk patients in the presence of at least one of the criteria depicted in Table 3, because of their propensity to have poor follow-up and poor access to health care.[25] Following these guidelines, more than half of the study population received chemoprophylaxis.

CONCLUSION

For the past four decades, the prevalence of HM in PGH has remained unchanged. Although there seems to be a trend towards earlier diagnosis compared to earlier reports, a few of the study population are still diagnosed in the late first trimester with the classic signs and symptoms of HM such as uterus larger than age of gestation, presence of theca lutein cysts on ultrasound,

Table 3. PSSTD criteria for the administration of prophylaxis among HM patients

Advanced maternal age ≥40 years
Uterine size larger than gestation by ≥6 weeks
B-hCG titer ≥100,000 mIU/mL
Theca lutein cyst(s) ≥6 cm
Presence of any medical complications associated with increased trophoblastic proliferation (preeclampsia, thyrotoxicosis, pulmonary insufficiency and disseminated intravascular coagulopathy)
Recurrent hydatidiform mole
Documented hydatidiform mole with a coexisting normal twin

thyrotoxicosis, and anemia. Despite the increasing availability of ultrasound and B-hCG assay, patients still consult late leading to a diagnosis made during the later part of the first trimester. As such, health professionals must continue to reach out to the remotest regions of the country to be able to improve the healthcare-seeking attitude of patients and further educate all those involved in the care of women regarding the diagnosis and management of HM. ■

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