Gestational trophoblastic disease: The Philippine experience*

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INTRODUCTION

The first documented description of hydatidiform mole dates back to 400 BC when Hippocrates (470–410 BC) explained its formation through the consumption of dirty water by the pregnant woman.[1] Interestingly, in 1276, the countess of Henneberg reportedly died after giving birth to "as many children as there were days in the year".[2] In 1752, William Smelie coined the terms mole and hydatidiform to describe the pathology as a bunch of grapes consisting of different sizes.[1] Indeed, this condition that we have come to recognize as a hydatidiform mole (HM) has fascinated humans for centuries. But, it was not until 1903 when it was formally recognized as a clinical entity.[3] Currently, HM is part of the general classification of clinical conditions known as gestational trophoblastic disease (GTD).

In the Philippines, Dr. Honoria Acosta-Sison, the first Filipino female doctor, is known for her pioneering researches on GTD. As early as the 1960's, she reported on her experiences in the diagnosis and management of GTDs at the Philippine General Hospital. She also proposed possible risk factors for the development of these diseases. Most of her articles were published in recognized local and international peer reviewed journals. As such, she is hailed as the mother of trophoblastic diseases in the country.

Gestational trophoblastic disease covers a spectrum of placental trophoblastic lesions that range in presentation from benign forms to malignant invasive entities. The incidence of GTD varies widely in different parts of the world. Reports have consistently shown that the incidence is significantly higher in the Southeast Asian region as compared to their Western counterpart. GTD remains to be a prevalent problem in the Philippines, despite reported decreasing trends in neighboring countries such as Japan, Taiwan, and Korea.[4,6,7] Researchers have tried to explain the discrepancy in reported statistics as a reflection of the healthcare system in the country and the presence of a national registry for GTDs. Developed countries are presumed to have better healthcare systems leading to better data sets that would approximate the true incidence of the disease. On the other hand, data from developing countries, may not reflect the true incidence due to inadequate health care facilities and the lack of a national registry. For such countries, data are primarily institution-based reports, which can disproportionately skew the statistics.

Factors such as age, parity, and prior molar pregnancies have been proven to increase the risk of developing GTD. However, the effect of race, location, and sociodemographic factors are not as clear. Some studies have linked higher rates of GTD in women of Asian descent, which may point to a possible genetic influence, but further research still needs to be done to prove this.[4,5]

In recent years, there has been an increasing demand to improve the quality of epidemiologic data of GTD in the Philippines. There are many factors that make it difficult to establish the true incidence of GTD in the country, and to document the effectiveness of the interventions that are currently being done to treat the disease. The establishment of the national trophoblastic disease registry in 1985 by the Philippine Obstetrical and Gynecological Society (POGS), aimed to create a uniform system for hospitals to report their data. Despite this effort, the true national incidence still cannot be reliably determined as only those hospitals under POGS are required to submit. This would mean that areas with no POGS accredited hospitals would not be able to report their data. Moreover, patients who consult at their local health centers or are seen by traditional healers would likewise not be included in the statistics.

The Philippine General Hospital (PGH) is the national referral center for the diagnosis and management of gestational trophoblastic diseases. As such, it is a rich source of data regarding the current state of GTD in the country. This manuscript aims to describe the prevalence, patients' clinicopathologic characteristics, management protocols and treatment outcomes of patients admitted at the Division of Trophoblastic Diseases of the Department of Obstetrics and Gynecology of the Philippine General Hospital from 2014 to 2018.

*Presented in the 26th AOFOG Congress, Manila, 2019

HYDATIDIFORM MOLE

In the Philippines, there has been an overall decreasing prevalence rate of HM from 7 in 1000 pregnancies in the 1980s to 2.4 in 1000 pregnancies from 2002-2008.[7] In PGH, there has been no significant change in the prevalence of HM since 1991. As a national referral center, the hospital continues to report numbers significantly higher than the supposed national incidence rate. From 2014-2018, out of 22,265 pregnancies, there were 401 reported HM cases giving a prevalence of 18.01 cases per 1000 pregnancies. Of the 401 cases of HM, 311 (77.6%) were complete moles, 27 (6.7%) were partial moles, 5 (1.2%) were invasive moles, and 57 (14.5%) were of uncertain histology. A total of 334 (83.3%) patients underwent suction curettage while 63 (15.7%) patients had hysterectomy with mole in-situ. There were four patients (1%) who underwent completion curettage after majority of the molar products were passed out spontaneously prior to admission. The demographic profile of patients remained similar to previous reports with most cases occurring in the 20-30 year age group. Of the 410 cases, 204 (50.9%) were 20-30 years old, 83 (20.7%) were in the 31-40 year age group, 58 (14.5%) were below 20 years of age, 48 (12.0%) were in the 41-50 year age group, and 8 (2.0%) were 50 years and above.

Molar pregnancies have long been recognized to have the potential for malignant transformation. Risk factors associated with the development of malignant degeneration include uterine size larger than 6 weeks age of gestation, a beta human chorionic gonadotropin (BhCG) titer of ≥100,000 mIU/mL, theca lutein cyst ≥ 6 cm in diameter, maternal age ≥ 40 years, severe trophoblastic proliferation, recurrent molar pregnancies, and medical complications associated with molar pregnancies.[8,9] High-risk molar pregnancies are important to identify as their risk of progression to GTN has been estimated to be 30-50%.[10]

One strategy to decrease the incidence of postmolar gestational trophoblastic neoplasia (PMGTN) is the administration of chemoprophylaxis soon after evacuation of HM. The use of chemoprophylaxis in the country was first reported by Dr. Honoria Acosta-Sison in 1964. In her article, 18 patients with HM who were managed at PGH, were given oral Methotrexate at a dose of 15mg in 3 divided doses for 5 days, for a total of 75 mg. None of these patients came back for malignant degeration.[11] In 1987, Isidro-Gutierrez et al reported on the incidence of PMGTN among HM patients admitted in PGH from 1969-1982 who received chemoprophylaxis compared to those who did not. Methotrexate was given either in the oral or intravenous route. Out of the 451 women with molar pregnancy who were admitted during the study period, only 44 did not receive chemoprophylaxis due to contraindications or patient delay. Results showed a significant decrease in the incidence of PMGTN among those who received chemoprophylaxis. However, there was one mortality due to drug toxicity between 1969-1975, and three deaths between 1975-1982. As a result, the authors recommended its use only for patients who are at greater risk of developing PMGTD based on certain prognostic criteria, which included the following: uterus significantly larger than AOG (> 6 weeks discrepancy in size), presence of lutein cysts, age ≥ 35 years old, parity ≥ G4, disturbing histopathology (post-operation), low socio-economic and literacy level, and geographic residence posing a problem to follow-up.[12]

The use of prophylactic chemotherapy has not yet been generally accepted by trophoblastic disease specialists all over the world. Main concerns with its use include unnecessary risks of toxicity to the patient, and the possibility of developing drug resistance.[10,13] A recent randomized controlled trial on the efficacy of prophylactic chemotherapy done at PGH involving 99 patients showed a lower incidence of PMGTN among patients who received chemoprophylaxis (16.67% or 5 out of 30) compared to the control group (38.71% or 12 out of 31). Although the results failed to reach statistical significance ($p = 0.07$), the authors concluded that the use of methotrexate chemotherapy may still be useful in preventing PMGTN particularly among high-risk HM and those who may have limitations that will prevent proper follow up and monitoring.[14] Currently, the Philippine Society for the Study of Trophoblastic Diseases (PSSTD) recommend the administration of chemoprophylaxis among high-risk HM and those with questionable ability to follow-up.[9] Indications include: advanced maternal age ≥ 40, uterine size larger than gestation by ≥ 6 weeks, serum BhCG titer ≥ 100,000 mIU/mL, theca lutein cyst ≥ 6 cm, recurrent hydatidiform mole, presence of any medical complication associated with increased trophoblastic proliferation such as preeclampsia, thyrotoxicosis, pulmonary insufficiency and disseminated intravascular coagulopathy and documented hydatidiform mole with a co-existent normal twin.[9] Following this recommendation, 292 of the 401 (71.2%) HM patients admitted at the Philippine General Hospital from 2014 to 2018, received chemoprophylaxis.

GESTATIONAL TROPHOBLASTIC NEOPLASIA

The national prevalence rate of gestational trophoblastic neoplasia was calculated at 0.56 per 1000 pregnancies from 2002-2008.[7] During the same time period, the prevalence in PGH was at 4.3 per 1000 pregnancies.[7] From 2014-2018, PGH had a higher

prevalence rate of 263 per 22,265 pregnancies or 11.8 per 1,000 pregnancies. This number is significantly higher than both the national prevalence rate as well as statistics obtained from PGH from 2002 to 2008. The recent increase in diagnosed GTN cases could be explained by the improvement and increased accessibility of diagnostic examinations available to our patients as well as better knowledge of the disease among general Obstetrician Gynecologists.

Demographic characteristics of patients during the period from 2014 to 2018 are listed in Table 1. Similar to molar pregnancies, most cases occurred in the 20-30 year age group. The antecedent pregnancy was a complete mole in majority of cases and most had 2-3 previous pregnancies.

The diagnosis of GTN is based on the patient's clinical presentation, serum BhCG level and typical findings on imaging studies. Histologic confirmation is not mandatory in order to start treatment. All patients are staged based on the FIGO 2000 staging system (Table 2) and classified as either low-risk or high-risk based on the WHO prognostic scoring system (Table 3). Patients are considered low-risk if their prognostic score is less than 7 and high-risk if the score is at least 7. Table 4 shows the clinical characteristics of the 263 GTN patients admitted in PGH from 2014-2018.

Table 1. Demographic characteristics of the 263 GTN patients admitted at PGH from 2014 to 2018

Characteristic	Number	Percentage
Age		
< 20 years old	12	4.6%
20-30 years old	108	41.1%
31-40 years old	79	30.0%
41-50 years old	53	20.2%
> 50 years old	11	4.2%
Gravidity		
1	47	17.9%
2-3	114	43.3%
4-5	57	21.7%
> 5	45	17.1%
Antecedent Pregnancy		
Complete Mole	118	44.9%
Partial H. Mole	31	11.8%
Uncertain H. Mole	56	21.3%
Term	30	11.4%
Preterm	2	0.8%
Abortion	24	9.1%
Ectopic	2	0.8%

Table 2. FIGO 2000 Staging System

STAGE	DESCRIPTION
I	Disease confined to the uterus
II	GTN extends outside the uterus but is limited to the genital structures (adnexae, vagina, broad ligament)
III	GTN extends to the lungs with or without genital tract involvement
IV	All other metastatic sites

It is recommended that patients with low-risk GTN be given single agent chemotherapy in the form of either Methotrexate or Actinomycin. Currently, there is no consensus on which treatment regimen or agent is most effective.[15] In PGH, the 5-day Methotrexate Regimen is the first line agent and patients are shifted to Actinomycin D when resistance is noted. Out of the 120 low-risk GTN patients admitted from 2014-2018, all except one was started on Methotrexate. Patients classified as high-risk are started on combination chemotherapy in the form of Etoposide, Methotrexate, Actinomycin D, Cyclophosphamide, and Vincristine (EMACO). Patients who develop resistance to EMACO are given cisplatin-based regimens, the most common of which is the EP/EMA where the cyclophosphamide and vincristine part of the EMACO is replaced by Etoposide and Cisplatin. The EMACO regimen was used as first-line therapy in 90 patients with high-risk GTN disease. Of these, 7 patients necessitated salvage therapy in the form of EP/EMA. Ten patients who were diagnosed with stage IV disease due to brain metastasis were given high dose EMACO. Some patients succumbed to the disease prior to the institution of chemotherapy or did not consent to treatment.

Surgery and radiotherapy are considered adjunctive treatment modalities in the management of GTN. Table 5 shows the number of patients who underwent these forms of treatment.

Out of the 250 patients who underwent treatment in PGH from 2014-2018, 196 (78.4%) went into complete remission, 35 patients (14.0%) expired, 8 (3.25%) went home against medical advice, and 11 (4.4%) refused further treatment. Compared to the 2002-2008 census, majority (78.4% vs. 59.7%) of patients are now able to complete their treatment. The increase in patient compliance

Table 3. WHO Prognostic Scoring System

PROGNOSTIC FACTORS	SCORE			
	0	1	2	4
Age (years)	< 40	≥ 40		
Antecedent Pregnancy	Mole	Abortion	Term	
Interval months from index pregnancy	< 4	4 - < 7	7 - < 13	> 13
Pre-treatment hCG (mIU/ml)	< 1,000	1,000 - < 10,000	10,000 - < 100,000	> 100,000
Largest tumor size (including uterus) cm	< 3	3 to < 5	> 5	
Site of metastases	Lung	Spleen, kidney	Gastrointestinal	Liver, Brain
Number of metastases		1 - 4	5 - 8	> 8
Previous failed chemotherapy			Single drug	2 or more drugs

Table 4. Demographic characteristics of the 263 GTN patients admitted at PGH from 2014 to 2018

Characteristic	Number	Percentage
Diagnosis		
Clinical Diagnosis	186	70.7%
Persistent Trophoblastic Disease	6	2.3%
Invasive Mole	28	10.6%
Choriocarcinoma	38	14.4%
Placental Site Trophoblastic Tumor	4	1.5%
Epithelioid Tumor	1	0.4%
Stage		
I	72	28.1%
II	8	3.1%
III	135	52.7%
IV	41	16.0%
Prognostic Score		
Low risk	120	46.9%
High risk	136	53.1%

Table 5. Tabulation of adjunctive procedures done

Procedure	Number	Percentage
Total Hysterectomy +/- BSO	75	78.1%
Wedge Resection	1	1.0%
Thoracotomy	0	0.0%
Bilateral internal iliac artery ligation	5	5.2%
Craniectomy	0	0.0%
Whole brain irradiation	15	15.6%

is largely due to the subsidization of the government for patient treatment costs. Sustained remission rates remained high.

CURRENT CHALLENGES

Despite the recommendation of the International Federation of Gynecology and Obstetrics to use the Staging and Prognostic Scoring System as proposed in 2002, it is still not universally accepted. As of 2005, only 77% of centers worldwide have adopted its use. Additionally, some authorities have suggested further modification and improvement in the system due to challenges in the management of patients with prognostic score of 5-6 and those with a score of more than 12. Universal usage of the system and international collaboration are important to pave the way for a meaningful analysis of the system.

In the country, the creation of a national trophoblastic disease registry remains to be a challenge. While the POGS has taken the lead in initiating the creation of the registry, it is hoped that trophoblastic disease specialists, through the PSSTD, take an active part in its improvement and maintenance. It is only through this registry, will we have more information that will allow us, not only to have a better picture of the true prevalence of GTD in the Philippines, but more importantly, provide data that will pave the way for researches to help improve the diagnosis and management of the disease. ■

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