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Original Article

The Spectrum of Clinical Presentations of Gestational Trophoblastic Disease from a Tertiary Care Center

Jyothis P Jose[1], K V S Latha[2]

[1]Senior Resident, Department of Medical Oncology, Madras Medical College, Chennai, Tamil Nadu, India, [2]Professor and Head, Department of Medical Oncology, Madras Medical College, Chennai, Tamil Nadu, India

Abstract

Introduction: Gestational trophoblastic disease (GTD) is a disease of pregnancy and therefore a disease of women. GTD comprises the heterogeneous group of related lesions arising from abnormal proliferation of trophoblast of the placenta with a spectrum of disorders ranging from benign to malignant disease. The malignant form of GTD collectively called gestational trophoblastic neoplasia (GTN).

Aim: The aim of this study was to analyze the clinical characteristics, outcomes, and factors affecting response to treatment.

Materials and Methods: We undertook a retrospective review of GTD cases treated at our center from 2017 to 2019, in which patients demographic profile and clinical information were identified including age, gravidity, symptoms, gestational age, consanguinity, pathologic diagnosis, investigations, treatment, and follow-up data, and subsequently, statistical analysis was done.

Results: During the 3-year period, 78 cases of GTD were reviewed. Complete and partial molar pregnancies were diagnosed in 49 (68%) and 29 (32%) cases, respectively. According to the International Federation of Gynecology and Obstetrics anatomical staging, the most GTN patients were assessed as Stage I and Stage III, at 80.0% and 11.4%, respectively. Post-molar GTN developed more frequently in women who had a pathologic diagnosis of complete mole, uterus larger than 14-week size, and pretreatment human chorionic gonadotropin levels more than 150,000 mIU/mL. Our study demonstrated a superior response to single-agent actinomycin D (90%). The overall cure rate at our center approached 96% during the study period.

Conclusion: GTD results in significant maternal morbidity, which leads to mortality if not detected early. The patients should be risk stratified for proper management and referred to experienced centers that have capabilities for adequate supportive care and consequent treatment.

Key words: Beta-human chorionic gonadotropin, Gestational trophoblastic disease, Gestational trophoblastic neoplasia, Hydatidiform mole

INTRODUCTION

Gestational trophoblastic disease (GTD) is a disease of pregnancy and therefore a disease of women. GTD comprises a heterogeneous group of related lesions arising from abnormal proliferation of trophoblast of the placenta with a spectrum of disorders ranging from benign to malignant disease.[1] The malignant form of GTD collectively called gestational trophoblastic neoplasia (GTN). It includes benign non-neoplastic lesions, hydatidiform mole (HM), and GTN. GTD is more common in extremes of reproductive age; women in early age or perimenopausal are at higher risk.

Asian ethnicity[2] is an important risk factor for GTD, and risk assessment can be estimated by a modified World Health Organization (WHO) scoring system and International Federation of Gynecology and Obstetrics (FIGO) staging system. Overall, GTD carries a good prognosis.[3]

The incidence of HM is difficult to establish with certainty due to the low frequency of the disease and regional

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Corresponding Author: Dr. K V S Latha, Department of Medical Oncology, Madras Medical College, Chennai, Tamil Nadu, India.

variation in reported rates. The hormone beta-human chorionic gonadotropin (HCG) is essential for diagnosis, the management, or subsequent surveillance of GTD. The introduction of routine ultrasonography in early pregnancy is diagnostically reliable to confirm GTD and follow-up with them. Since GTD is a histologic diagnosis, it is essential to have an accurate histopathology examination and subsequently with adequate treatment based on staging.

Aim

The aim of this study was to analyze the clinical characteristics, outcomes, and factors affecting response to treatment.

MATERIALS AND METHODS

The medical records of all GTD patients who were diagnosed at the Institute of Obstetrics and Gynaecology, Egmore, Chennai, from January 2017 to December 2019 were retrospectively analyzed. For patients with a molar pregnancy, demographic profile and clinical information were identified including age, gravidity, symptoms, gestational age, consanguinity, pathologic diagnosis, investigations, treatment, and follow-up data. The biochemical profile includes complete blood counts, renal function, liver function tests, and serum beta-HCG estimation which were done. Measurement of serum beta-HCG levels was performed by chemiluminescent enzyme immunoassay. The normal level of serum beta-HCG was defined as lower than 5 mIU/Ml. Suction curettage was the recommended method of molar pregnancy treatment for most patients who were then monitored with weekly serum HCG measurements until the levels were normal for 3 consecutive weeks and then with monthly measurements for at least 12 months. Contraception was recommended, preferably with combined oral contraceptive pills. Post-molar GTN was diagnosed using the following criteria:[4]

1. Rise of serum HCG levels of 10% or greater for three values over 2 consecutive weeks
2. Plateau of serum HCG levels (rise or decline of <10%) for four values over 3 consecutive weeks
3. Histological diagnosis of choriocarcinoma
4. Presence of metastatic disease and
5. Persistence of serum HCG level in the 6 months after termination of pregnancy.

In the case of GTN patients, clinical information including age, parity, antecedent pregnancy, symptoms, pre-treatment serum HCG levels, treatment, and follow-up data were identified. The extent of disease was evaluated by chest radiography, ultrasonography, and/or magnetic resonance imaging. Planning the management of GTD patients was assigned based on the FIGO anatomic staging system and the modified WHO prognostic scoring system.[5] All GTN patients were categorized as follows:

1. Low-risk disease if Stage I or Stages II–III, score <7 and
2. High-risk disease if Stages II–III, score equal or more than 7, or Stage IV.

Single-agent chemotherapy (methotrexate or actinomycin D) was the treatment of choice for patients with low-risk disease, whereas combination chemotherapy was considered in patients with high-risk disease. The preferred combination regimen consisted of etoposide, methotrexate, actinomycin D, cyclophosphamide, and vincristine. During treatment, patients were monitored with weekly serum HCG measurements until normal, after which additional consolidation therapy was utilized (low risk: 1 cycle and high risk: 3 cycles). Patients were considered to be in remission when 3 consecutive weekly serum HCG measurements were at normal levels. The resistant disease was indicated when the following occurred:[6]

1. Rising of serum HCG levels over a cycle
2. Plateau of serum HCG levels for 2 consecutive cycles or
3. Presence of new metastasis.

After HCG remission was achieved, the patients were scheduled for monthly serum HCG measurements and ultrasonography abdomen for at least 12 months in Stages I–IV. Contraception was also recommended preferably with combined oral contraceptive pills. The relapsed disease was diagnosed when the serum HCG levels rose after achieving an initial remission. Patients with the resistant or relapsed disease received second-line chemotherapy. Statistical analysis of the data was carried out and demographic data were determined using percentage, mean, and standard deviation (SD). Comparisons between groups were performed using the Student's *t*-test and Chi-square test. $P < 0.05$ was considered statistically significant.

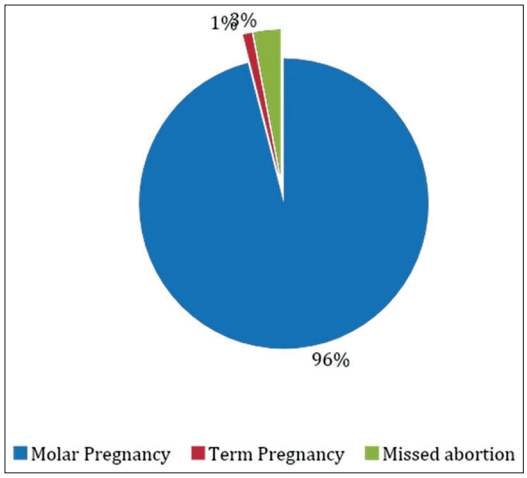

Figure 1: Antecedent pregnancy

RESULTS

During the 3-year period, 78 cases of GTD were reviewed, of which 45 HM and 33 cases of GTN were identified. Two patients of HM and two GTN patients were lost to follow-up. The mean age at diagnosis was 24.03 ± 6.6 years. The median gestation age was 11.04 weeks (range 3.20) and 59 cases (75%) were diagnosed in the first trimester. Seven patients had a history of previous molar pregnancy.

Pre-treatment serum HCG levels were assessed in 78 cases, with a mean level of 96,317. In our study only 2 cases had clinical hyperthyroidism. All molar pregnancies were terminated by suction curettage. Abnormal uterine bleeding was the most common presenting symptom (57.4%) [Table 1], while 33% of patients were asymptomatic. Theca lutein cysts were found in 3.8% of patients and only one patient developed GTD following term pregnancy.

Complete and partial molar pregnancies were diagnosed in 49 (63%) and 29 (37%) cases, respectively, whereas 45 molar pregnancy patients (59%) had the spontaneous achievement of remission [Tables 2 and 3 and Figure 1].

Among 78 GTD patients', molar pregnancy observed in 75 patients (96.10%) while terming pregnancy and missed abortion result in 1.30% and 2.60% of cases, respectively.

Among GTD patients, 49 (62%) were complete mole while partial mole in 29 (32%) cases. GTD developed following term pregnancy in 1 (1.3%) case while missed abortion observed in 2 (2.6%) patients. Consanguinity observed in 9 (11.5%) patients.

Most GTN patients (63.6%) had a serum HCG titer of <100,000 mIU/ml. According to the FIGO anatomical staging, most GTN patients were assessed as Stage I and Stage III, at 80.0% and 11.4%, respectively. Among seven metastatic patients, lung involved in four cases while vulvovaginal and brain metastasis observed in two and one cases, respectively. The GTN patients were divided into a low-risk and a high-risk group, comprising 77% and 23% of cases, respectively.

To determine the possible risk factors for developing post-molar GTN, comparisons were made between these two groups of patients. Post-molar GTN developed more frequently in women who had a pathologic diagnosis of complete mole, uterus larger than 14-week size, and pre-treatment HCG levels more than 150,000 mIU/mL. Table 3 displays the clinical characteristics of GTN pregnancy patients. The mean age at diagnosis was 25.24 years (SD, 5.8) Table 4. The median time interval from pregnancy events to treatment was 3 months.

Table 1: Study parameters of patients

Parameters	Number of patients	Percentage
Age in years		
<20	19	24.3
20–25	38	48.7
25–30	15	19.2
More than 30	6	7.6
Gravida		
Primi	37	47
Multi	41	53
Presenting complaints		
Abdominal pain	4	5
Asymptomatic	25	33
Bleeding	45	57
Hyperemesis	4	5

Table 2: Distribution of diagnosis and outcome

Parameters	Number of patients	Percentage
Diagnosis		
Complete	49	63
Partial	29	37
Outcome		
Invasive mole – Req. chemo	33	41
Non-invasive mole	45	59

Table 3: Symptoms (invasive mole)

Presenting complaints	Number of patients, *n* (33)
Bleeding	21
Asymptomatic	9
Abdominal pain	1
Hyperemesis	2

Table 4: Demographic characteristics (invasive mole)

Age in years (mean±SD)	25.24±5.89
GA at diagnosis in weeks (mean±SD)	12.33±1.85
Pre-treatment beta-HCG (mean±SD)	136,664±74,228

HCG: Human chorionic gonadotropin, SD: Standard deviation, GA: Gestational age

Table 5: Pre-treatment beta-HCG

Outcome	Mean	SD	*P*-value
Invasive mole	136,808	74,228	0.001
Non-invasive mole	96,317	9614	

HCG: Human chorionic gonadotropin, SD: Standard deviation

Table 6: Type of GTD versus histopathology

Type of GTD	Invasive	Non-invasive	*P*-value
Complete mole	26	21	0.007
Partial mole	7	22	

GTD: Gestational trophoblastic disease

Table 7: WHO score

WHO score	GA at diagnosis		*P*-value
	Mean	SD	
<7	10.67	3.2	0.012
More than or equal to 7	14.57	3.5	

GA: Gestational age, WHO: World Health Organization, SD: Standard deviation

Table 8: Disease category/chemotherapy

Chemotherapy	Number of patients (*n*)	Complete remission (%)
Single-agent methotrexate	18	13 (74)
Single-agent actinomycin D	7	6 (90)

Pre-treatment beta-HCG versus outcome [Table 5], type of GTD versus histopathology [Table 6], and WHO score versus gestational age at diagnosis [Table 7] showed a statistically significant correlation in our study.

All GTN patients received chemotherapy, the overall complete remission rate to the initial regimen was 79%; we observed a complete remission rate of 74% in patients treated with single-agent methotrexate, while the remission rate was 90% in patients treated with single-agent actinomycin D [Table 8]. Higher WHO score (5–6) associated with increased resistance to single-agent chemotherapy. Eventually, the cure rate of the low-risk patients approached 100% excluding lost follow-up cases, but two cases in the high-risk group are in salvage chemotherapy.

DISCUSSION

The incidence[7] of GTD varies widely in different regions and ethnicities of the world. The incidence of HM appears to be about 0.5–1/1000 deliveries in most parts of the world. The majority of women diagnosed with GTN can be cured with an overall worldwide survival rate of the low-risk group approaching 100% and 80–90% for high-risk group.[8-13] However, these tumors are rare in any individual hospital and most treatment recommendations are based on observational studies from larger series. Our Institute of Obstetrics and Gynaecology, Egmore, Chennai, has become a referral center and many patients were directed to our center from all across Northern Tamil Nadu. In this series of 78 patients spanning over 3 years of period, we confirm the previously reported highly curable rates of GTN when therapeutic decisions are based on the FIGO anatomic stage and the WHO prognostic scoring index. The overall survival rate for patients with GTN treated at our center approached 96%.

In the present study, a history of the previous molar pregnancy, extremes of maternal age, and consanguinity were found to have risk factors associated with molar pregnancy. This is in accordance with the previous studies. In our study, especially younger maternal age is more commonly observed as a risk factor.

The median gestational age at diagnosis of molar pregnancy of 12[8,14,15] weeks found in the present study was consistent with other studies in centers with routine first-trimester ultrasound. In the present study, abnormal uterine bleeding was the most common presenting symptom[8,15] (60%) of molar pregnancy; on the other hand, the identification of asymptomatic patients was 25%, which was also in accordance with the previous studies (29–41%). The frequency of theca lutein cysts (3.8%)[16,17] in this study was lower than that found in other studies, in which the rates were 20–46%.

Post-molar GTN developed more frequently in women who had a pathologic diagnosis of complete mole, uterus larger than 14-week size,[18] and pre-treatment HCG levels more than 150,000 mIU/mL. Higher WHO score (5–6) even it is considered as the low-risk associated with increased resistance to single-agent chemotherapy.

Patients with low-risk GTN can usually be treated successfully with single-agent chemotherapy. In our series of 27 low-risk patients, we observed a complete remission rate of 74% to single-agent methotrexate and 90% to single-agent actinomycin D.[19] In keeping with our results, other peer-reviewed studies have also reported the superiority of single-agent actinomycin D over methotrexate as frontline therapy in low-risk patients. A randomized clinical trial comparing biweekly actinomycin D to weekly IM methotrexate has demonstrated a superior response rate for actinomycin D over methotrexate.

CONCLUSION

Clinical characteristics and outcome are comparable with other studies happened in developing countries. Histological diagnosis of complete mole, higher gestational age, and pre-evacuation beta-HCG of higher than 150,000 mIU/mL was significant factors for developing post-molar GTN. The patients should be risk stratified for proper management and referred to experienced centers that have capabilities for adequate supportive care and consequent treatment.

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