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Original Research Article

Gestational tropoblastic disease: A prospective observational study of demography, clinical profile and outcome at tertiary care centre

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Abstract
Introduction: Gestational tropoblastic disease (GTD) comprises of heterogeneous group of pregnancy related disorders which occurs due to highly abnormal development and proliferation of tropoblastic tissue. The spectrum encompasses benign conditions like partial and complete hydatidiform mole, malignant condition like invasive mole, choriocarcinoma, placental-site trophoblastic tumor, and epithelioid trophoblastic tumor. The most common disease among the above is the complete mole. There is wide variation in the incidence and risk factors of occurrence of GTD in different geographic regions. In present study, we evaluate incidence, clinical profile and management of GTD at a tertiary care centre.
Material and Methods: The present study is prospective observational study done in department of obstetrics and gynecology at a tertiary care centre for duration of 2 years. All the cases diagnosed as gestational tropoblastic disease were included in study. The incidence, clinical presentation, management and six months follow up data were analyzed.
Observation and Results: There were 12,046 pregnancies, 11952 deliveries and 11620 live births during the present study. The total number of cases diagnosed to have GTD was 30, and they were included in study. This gave an incidence of 2.49 /1000 pregnancies, 2.51 /1000 deliveries and 2.58 /1000 live births. The most common presenting symptom was blood per vagina, noted in 21(70%) patients. Other symptoms were pain abdomen 11(37%), vomiting 4(13%). Only 2(7%) had classic symptom of passage of grape like vesicles. Histopathology examination showed 23 patients had complete hydatidiform mole, 6 had partial hydatidiform mole and one had invasive mole.
Conclusion: The incidence of hydatidiform mole and other forms of GTD were comparable to other reported studies in literature. Those pregnant patients, who are clinically or sonologically diagnosed as GTD should be evaluated properly and managed accordingly. These patients need proper follow up care to prevent complications and further, preserve fertility in them.

Keywords: Hydatidiform mole, partial mole, gestational tropoblastic disease, complete mole, epidemiology, outcome

Introduction

Gestational trophoblastic disease (GTD) includes a spectrum of pregnancy related placental disorders which are characterized by an abnormal proliferation of trophoblastic tissue. They are histologically distinct and can be benign/premalignant or malignant [1]. Premalignant forms of GTD includes Partial hydatidiform mole (PM) and complete hydatidiform mole (CM). Malignant forms of the disease are grouped together as gestational tropoblastic neoplasia (GTN) which includes invasive moles, choriocarcinoma, placental site tropoblastic tumour, epitheloid tropoblastic tumours [2]. Overall, Hydatidiform mole is most common form of GTD.

There is variation in worldwide incidence rates of GTD. Higher frequencies have been reported in Asia with rates ranging from 1 to 10 per 1000 pregnancies [3]. The incidence is less in European countries. High incidence of GTD in some populations is attributed to socioeconomic and dietary causes. Further genetic causes also influence incidence rates. In literature, the incidence rates reported are based on the total number of pregnancies, deliveries or live births, which further complicates the understanding of actual incidence rates. There is also under reporting of GTD, which may also occur in certain rural remote areas [4].

In the past recent years, hydatidiform moles have been diagnosed at younger gestational ages due to widespread use of human chorionic gonadotropin (hGC) measurement, routine first-trimester sonograph and ultrasound investigation of threatened miscarriage.

Majority of patients with complete hydatidiform mole patients are diagnosed coincidentally during routine first trimester ultrasound examination without any classical symptoms. However, the most common presenting symptom is bleeding per vagina. The clinical presentation of partial hydatidiform mole is less marked, with fewer clinical symptoms than complete hydatidiform moles.

GTD has a varying propensity for spontaneous remission or for local invasion and metastasis. Most of the hydatidiform mole (HM) regress spontaneously and simple surgical procedure with suction curettage remains the main stay of treatment. In about 15-20% of complete mole and 0.5-1% of partial mole, the tropoblastic elements remain active after evacuation with plateauing or rising human chorioninc gonadotropin levels in blood [5]. The above postmolar GTN is diagnosed according to the criteria descrined by the International Federation of Gynecology and Obstetrics (FIGO, Table 1), if one of the following is present: 1) A plateau of at least 4 persistently elevated hCG values during 3 weeks or longer, 2) A sequential rise of 3 consecutive weekly hCG value for two weeks or longer, and 3) the histological diagnosis of choriocarcinoma [6].

GTNs are generally cured with very low toxicity single agent chemotherapy regimen. However they require strict adherence to follow up procotcols. When compared to other gynecological malignancies, fertility can be preserved and normal pregnancy outcome anticipated. The curability of this condition is a milestone of success in the history of modern medicine.

Although, Gestational Trophoblastic Neoplasia (GTN) is highly curable, yet there are many patients succumbing to GTN in our country due to lack of proper organized follow up programs. It is important to have the regional registries and a central database for the proper understanding of this unique malignancy. This will help making decisions and optimizing management, and preventing treatment failure [7]. A lengthy timeframe for follow-up may result in poor compliance and an increased number of defaulters. Women are highly recommended to continue with follow-up for up to 6 months to enable detection of relapse or persistent gestational trophoblastic disease (pGTD). Unfortunately, in reality, women often default and do not complete the recommended protocol. This study was conducted to evaluate the incidence rate, management and followup of GTD in a tertiary care center.

Material and Methods

In the present ethically approved prospective observational study, all women who were diagnosed with gestational trophoblastic disease were included in the study. Written informed consent was taken from all patients who were enrolled in the study. The study was done for a period of 2 years. The inclusion criteria included women diagnosed with hydatidiform mole sonologically and histopathologically and women willing to give written consent to participate in the study.

Admission history of the patient included age, chief presenting complaint, gravidity, gestational age, outcome of previous pregnancies, menstrual history. The clinical examination included nutritional status, height, weight, BMI calculation, pallor, edema, pulse rate, BP, thyroid swelling. Size of the uterus per abdomen was noted to check if it corresponded to the weeks of gestation. A difference of atleast 4 weeks between uterine size and gestational age was considered significant. Blood samples collected for investigations which included Hb%, blood grouping and Rh typing, thyroid function test, serum beta-hCG. Cross matching samples were drawn if blood transfusion required. Urine samples collected for albumin, sugar and microscopy. The patients were subjected to USG if not previously done.

The primary mode of management was suction and evacuation for all patients followed by gentle curettage. Oxytocin infusion started at the end of the evacuation to minimize bleeding. The samples obtained sent for histopathological examination. Blood transfusions done if required before surgery, intraoperatively or in the post-operative period. Anti-D was given to Rh negative women. The serum β-hCG was repeated 48 hrs after evacuation. Post evacuation USG was done if the patient complained of excessive or irregular bleeding per vagina. Repeat evacuation was done if there was evidence of retained molar tissue on post evacuation USG.

They were followed up for duration of 6 months post-surgical evacuation for GTD. Then the patients were counseled regarding the need for follow up and use of contraception for the entire period of follow up. Follow up was done with weekly beta hCG until normal for 3 consecutive weeks followed by monthly determination until the levels were normal for 6 consecutive months. The normal level of beta hCG was taken as less than 10 mIU/L. At every follow up visit history regarding irregular vaginal bleeding, pain abdomen, headache, cough, hemoptysis, fever was taken and clinical examination which included cardiovascular, respiratory system, per abdomen, per speculum, per vaginal examination done to look for signs of GTN. The time to achieve the first normal beta hCG after evacuation was noted.

GTN was diagnosed during follow up either on the basis of a rise in serum beta hCG levels or histopathology or with evidence of metastasis. Those diagnosed as GTN were classified as low risk or high risk using FIGO scoring system for GTN and were treated with chemotherapy.

Statistical analysis

The data thus collected was analysed using various statistical methods like descriptive statistics (mean, median, range and standard deviation), chi square test, independent t test and paired t test. Statistical software SPSS Version 16.0 was employed for analysis.

Results

During the 2 year study period there were 12,046 pregnancies, 11952 deliveries and 11620 live births. A total of 30 cases were diagnosed to have GTD and were included in the study. The incidence was 2.49 /1000 pregnancies. The Mean age of patients was 28.67 years. Majority of the patients belonged to age group 20-25 years (46.6%). Majority of patients were primigravida (46.66%) (14 of 30). The antecedent pregnancy was full term delivery in 10(33.33%) patients and abortion in 6 (20%) patients.

The most common presenting symptom was bleeding per vagina which was present in 21(70%) patients. Other symptoms included pain abdomen, vomiting. Only 2 (7%) patients had classic symptoms of passage of grape like vesicles. Swelling of thyroid was seen in 3 patients (10%). All patients had history of variable duration of amenorrhea. One patient did not have any symptoms other than amenorrhea and was diagnosed on routine antenatal ultrasonography.

Majority of the women (16 out of 30, 53.34%) in the present study presented in the first trimester (<12 weeks). Thirteen patients out of 30 (43.3%) presented between 13-20 weeks and only 1(3.3%) after 20 weeks. The mean gestational age was 13.57 $\pm$ 3.71 weeks with the most advanced gestation being 22 weeks. Most of the patients, 63.33% (19 of 30) had uterine size

larger than the period of gestation. 26.66% (8 of 30) had uterine size corresponding to the period of gestation and 10% (3 of 30) had uterine size smaller than period of gestation. Most of the patients (70%) in the present study had Hb% more than 10 gm%. Only 1(3.33%) patient had severe anemia with Hb% less than 7 gm%. The mean Hb% was 10.46 ± 1.89gm% with range 4 to 13.6.

All patients underwent thyroid function tests. It was suggestive of hyperthyroidism in 10(33.33%) patients but none of the patients had symptoms of hyperthyroidism. Out of 10 who were hyperthyroid, only 4 had clinically enlarged thyroid gland. Twenty patients (66.6%) had TFT within normal limits.

Table 1: Baseline Beta hCG Levels

Baseline βhCG levels(IU/L)	Number of patients	Percentage %
1000 to <10,000	2	6.66
10,000 to <1,00,000	15	50
1,00,000 to <10,00,000	13	43.33

50% of the patients had pre evacuation beta hCG values between 10,000 to < 1,00,000 IU/L. 43.33% of the patients had beta hCG values between 1,00,000 - <10,00,000. (Table 1)

Table 2 shows a comparison of uterine size with the pre-evacuation beta hCG levels. The pre-evacuation beta hCG values in patients who had uterine size larger than the gestational age were significantly higher compared to patients who had uterine size equal or smaller than gestational age [2.18 ± 1.97 lakhs Vs 0.46 ± 0.40 lakhs; p=0.0083].

Table 2: Comparison of Pre-evacuation β hCG – Uterine Size

Statistics/category	Pre-evacuation hCG in Larger than Gestational Age Uterine Size(in lakhs)	Pre-evacuation hCG in Equal or Smaller than Gestational Age Uterine Size (in lakhs)
N	19	11
Mean ±SD	2.18 ± 1.97	0.46 ± 0.40
95%CI	0.4802 to 2.9598	
p -value(2-tailed)	0.0083	

On ultrasonography all patients has findings of molar pregnancy. Theca lutein cysts was present in only 17(56.66%) of patients.

In the present study suction evacuation was the primary mode of treatment which was done in 29(96.33%) patients. Two (6.66%) patients underwent hysterectomy. One patient had profuse bleeding PV at presentation and underwent hysterectomy for moribund status. The other had profuse persistent bleeding PV post suction evacuation and underwent hysterectomy.

Twenty patients attained normal β hCG during follow up period. The mean time for attaining first normal β hCG was 8.95 weeks**.** It ranged from 5 to 12 weeks. Complications were minimal in the present study. Two (6.66%) patients had profuse hemorrhage. One underwent hysterectomy for profuse post evacuation bleeding and the other case had excessive bleeding at presentation which was managed by hysterectomy. Complications like uterine perforation, tumor embolization, fever, sepsis were not seen in our study.

Table 3: Histopathology Diagnosis

Histopathology diagnosis	Number of patients	percentage
Partial mole	6	20
Complete mole	23	76.66
Invasive mole	1	3.33

The above table 3 summarizes the histopathological diagnosis. Six (20%) specimens were partial hydatiform mole giving incidence of 0.50 per 1,000 deliveries, 23(76.66%) were complete hydatidiform mole with incidence of 1.92 per 1,000 deliveries. The specimen of uterus of one patient who underwent hysterectomy showed hydropic villi invading myometrium suggestive of invasive mole. No cases of choriocarcinoma, PSTT or ETT were seen in the study.

In the present study 6 (20%) patients underwent repeat suction evacuation due to persistent bleeding after initial evacuation procedure and post evacuation USG suggestive of incomplete evacuation of uterus. Out of 6, 4 patients completed follow up of 6 months and had spontaneous regression, 2 patients developed invasive mole.

GTN

Out of 30 cases, 9(30%) cases were diagnosed as GTN. One patient underwent hysterectomy for profuse bleeding per vagina and histopathology of uterus showed hydropic villi invading myometrium suggestive of invasive mole. Eight patients were diagnosed as GTN on persistent rising levels of beta hCG after suction evacuation. All of them belonged to low risk according to FIGO score. Out of the above eight, six patients achieved regression with single drug (methotrexate) chemotherapy. One case was resistant to methotrexate and then treated with Actinomycin-D. One patient became pregnant before attaining normal βhCG and was lost to follow up.

Table 4: Patient Compliance to Follow-up

Patient compliance with hCG follow up	Number of patients	Percentage
Follow up for 6 months and more	29	90
Lost to follow up	1	3.33

A total of 29 (90%) patients completed the follow up for a period of 6 months or more. One patient who was diagnosed as invasive mole became pregnant and was lost to follow up.

Discussion

There is wide geographical variation in the incidence of gestational trophoblastic disease. This is partly due to differences in methodology, classifications of mole, case detection and definition of the denominator.[8] Hence comparison of incidences between countries becomes difficult. Standardization of histopathological and clinical nomenclature by the Scientific Group of the World Health Organization has improved uniformity in the different epidemiological studies across the world.[9] Asian women are at a higher risk of developing molar pregnancies than non-Asians. Many countries monitor incidence of gestational trophoblastic disease and produce epidemiological reports on their population, but India do not have such disease specific registry for gestational trophoblastic disease. In such a scenario institution based studies will provide some light on the epidemiological data. The current study is an effort towards understanding the incidence, demographics, treatment and outcome of hydatidiform mole patients in a tertiary care hospital.

Table 5: The following table shows the incidence of hydatidiform mole in other population/hospital based studies as published in literature.

Region/Institution	Authors (ref)	year	HM per1000 pregnancies	HM per 1000 live births	HM per 1000 deliveries
Population based studies					
Sweden	Flam *et al.* [10]	1992	0.9		
Japan	Hando *et al.* [11]	1998		2.23	
Denmark	Olsen *et al.* [12]	1999	1.1		
Japan	Matsui *et al.* [13]	2003		1.61	
USA(New Mexico)	Smith *et al.* [14]	2003	1.19	1.42	
Hospital based studies					
Netherlands	Chatlotte *et al.* [15]	2011			1.34
Katmandu (BPKIHS0	Koirala *et al.* [16]	2011			3.94
Dubai (al wasl hospital)	Tasneeem *et al.* [17]	2011		2.5	
New delhi(LHMC)	Neeta kumar *et al.* [18]	2003		1.31	
Malaysia	Nirmala CK *et al.* [7]	2013			2.6
Present study		2012-2014	2.49	2.51	2.58

The incidence of GTD in the present study is 2.49 per 1000 pregnancies, 2.51 per 1000 deliveries and 2.58 per 1000 live births. This is consistent with rates found in previous hospital based studies in Dubai (2.5 per 1000 live births), Malaysia (2.6 per 1000 deliveries). However a hospital based study in India by Neeta Kumar *et al.*, New Delhi in 2003 showed a lower incidence of 1.31 per 1000 live births. Again in the same year a study by Sekharan *et al*. showed a very high incidence of 5 per 1000 deliveries at Calicut Medical College, Kerala. Present study findings concur with many others that Asian women are more likely to develop molar pregnancies than non-Asians when compared with historical data [19].

Differences in reported incidence rates can be accounted for inaccurate ascertainment of the number of patients as a function of the number of gestational events. Different denominators, which represent the population at risk, are used in published studies. The preferred denominator for women at risk of GTD is 'all women who have conceived'. Since this number is unknown, ratios for GTD are presented in relation to the number of pregnancies, deliveries or live births.

In the present study majority (47%) of patients belonged to age group 20-25 years. Mean age of the patients was 28.67 ± 8 years with the age ranging from 20 to 45 years. The only other study in India by Neeta Kumar *et al*. had majority of their patients (66%) in the age group of 20-25 years with the mean age 24.6 ± 4.4 years [18].

WHO and FIGO criteria terms age more than 39 years as a high risk factor, in our study we had 4 patients more than 39 years. WHO does not consider age less than 20 years as a risk factor though some experts have found both extremes (<20 years and >35 years) to be at increased risk of disease [20, 21, 22].

In the present study all patients had presented with history of amenorrhea. Vaginal bleeding was a presenting symptom in 70% of patients. Fatima *et al*. noted bleeding per vagina to be the commonest symptom seen in 94.2% [23]. This was also noted to be the commonest symptom by a large series by Goldstein where it was present in 97% of their patients and also in a series from China were it was present in 83.2% of the patients with hydatidiform mole [24]. However, contrastingly a clinical study from Dubai reported incidence of vaginal bleeding only in 29% of patients [17].

The classic symptom of passage of grape like vesicles per vagina was seen in 60% of patients in a study by Ocheke AN *et al*. [25]. We found it in only 2 (7%) patient in our study. Routine antenatal USG detected symptomless GTD in 6.5% of study population in study by Neeta Kumar *et al*. in 2003 [18]. In our study USG detected 6.66% of patients without symptoms. This is mainly because of the early diagnosis during routine antenatal scans in first trimester as majority of patients in the current study presented during first trimester.

In the present study majority of the patients presented in the first trimester (46.6%). Ocheke *et al*. in a study in Nigeria observed 44% presented in first trimester [25]. Whereas, study by Fatima *et al*. showed that only 31.6% presented in first trimester. The mean gestational age during diagnosis in the present study was 13.57± 3.71 weeks. This is comparable with many other recent studies like Nirmala *et al*. [7] where it was observed a mean gestational age of 11±3 weeks during presentation. This is probably because, routine use of ultrasonography for the evaluation of early pregnancy has led to earlier diagnosis and the mean gestational age at presentation has decreased.

In the present study a total of 19 (63.33%) women had a uterus larger than dates which was similar to another study from Pakistan where the authors Fatima *et al*. [23] found 70.6% of patients had uterus larger than dates. Other studies had varied proportion of patients having uterus larger than gestational age. C K Nirmala *et al*. observed it only in 17.6% [7]. Tasneem *et al*. observed it in 34% of their patients [17].

Table 6: Showing percentage of patients who had uterine size larger than gestational age

Authors	Uterus larger than gestational age (%)
Fatima *et al.*	70.6
Nirmala CK *et al.*	17.6
Tasneem *et al.*	34
Present study	63.33

In our study the pre-evacuation β-hCG level was higher in complete mole group (1.62 ± 1.76 lakhs IU/l) compared to partial mole group (1.25±2.18 lakhs IU/L), however the difference did not meet statistical significance (p=0.67), probably because of small sample size. The number of weeks until the serum β-hCG level became undetectable was statistically not significant (p=0.0.64) between complete and partial mole in this study though it was numerically higher in complete mole group. Similar observations were made by C K Nirmala *et al*. [7].

However some studies have noted that the mean pre-evacuation serum β-hCG level was significantly higher in the complete mole as compared with the partial mole [26, 27]. Feltmate *et al*. (2003), observed that the number of weeks taken until serum β-hCG level became undetectable was significantly higher in complete mole group.

In the present study histopathology examination (HPE) of 20% of the patients showed partial mole, and in 76.66% HPE showed complete mole. In a study from Malaysia, 46.1% observed to

have CHM compared to 53.9% having PHM.[7] Charlotte Lybol *et al*. observed 30.2% having CHM, 44.5% of patients having PHM and in rest 11.6%the HPE was unspecified [15].

Table 7: Showing histopathology of GTD in different studies

Authors	Partial mole in %	Complete mole in %
Nirmala CK *et al.*	53.9	46.1
Charlotte lybol *et al.*	44.5	30.2
Present study	20	76.66

Complications usually associated with GTN include hemorrhage, tumour embolization, uterine perforation, and sepsis. These were minimal in our study. 3.8% patients had haemorrhage. One was managed with blood and blood components, the other underwent hysterectomy.

In the present study 9 (30%) developed GTN, 6 being persistent trophoblastic disease, 3 being invasive mole and none choriocarcinoma. Similar proportions were reported in a Malaysian study where 3.9% patients developed persistent trophoblastic disease [7] However in a study from northern part of India by Kumar *et al*., 23% of the patients developed invasive mole and 14% developed choriocarcinoma [18].

In the present study only 93.33% of patients completed the 6 months follow up. 3.33% of the patients were lost to follow up after first normal beta hCG and 3.33% even before attaining a single normal beta hCG level.

Limitations of the study

This was a tertiary centre data; all measurements and results reflect the situation in our centre at that particular time. The available data may not reflect the true incidence in the population.

Conclusion

Asian women are at increased risk of having molar pregnancies. The findings of the present study were consistent with majority of the published literature and differed with some of the published reports. The prevalence of gestational trophoblastic disease was higher than the published reports from non-Asian population which is consistent with earlier epidemiology studies from Asian population. Routine use of ultrasonography leads to diagnosis of molar pregnancy in the first rather than late second trimester. Appropriate diagnosis and treatment leads to a near 100% cure. Majority of cases are cured by simple surgical intervention. Follow up of the patients remains a challenging task. Uncomplicated molar pregnancy should have shorter duration of follow up not exceeding 6 months after attaining one undetectable serum beta hCG level. Longer follow up protocol do not pose additional benefit but rather increases financial and emotional burdens on to the women and also health providers both of which attribute to poor compliance.

A multi-centered study is essential in India to determine the true incidence and overall outcome of molar pregnancy that will help in the understanding of the burden of the disease. Also there is a need to establish a centralized disease specific registry to ensure unbiased and non-selected data because of paucity of epidemiological studies from India.

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