

Original Research Article

CLINICAL PROFILE OF HYDATIDIFORM MOLE - A COHORT STUDY

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ABSTRACT

Background: The incidence of molar pregnancy has demonstrated marked geographic and ethnic differences. This difference in the prevalence across various countries perhaps may depend upon the socioeconomic, genetic, nutritional and other cultural factors. In spite of having a higher prevalence among Asians, still epidemiological characteristics of Gestational Trophoblastic Disease (GTD) or Gestational Trophoblastic Neoplasia (GTN) are difficult to determine secondary to inconsistencies in case definitions and lack of centralised databases. Hence, this study was undertaken to determine the proportion and the clinical profile of women with hydatidiform mole from a South Indian population, where as of now there is limited data to enable us to detect and provide the standard of care for patients with GTN.

Materials and Methods: A prospective cohort study between August 2014 to December 2015 and a retrospective review of medical records for the preceding 2 years from the year 2012 to 2014 was conducted in JIPMER to determine the proportion of women with molar pregnancy as well as to study the clinico-epidemiologic profile of hydatidiform mole. The study population comprised of a total of 116 cases, of which, 68 cases belonged to the prospective group and 48 cases to the retrospective group. The patients belonging to the prospective group (68) were followed up for a period of 6 months to note the trend of the β HCG and to detect the occurrence of GTN. The patients in the retrospective group (48) were considered only for analysing the clinical profile of hydatidiform mole, as follow up was not possible for this group of patients.

Results: The proportion of molar pregnancy was calculated to be 2.07 per 1000 live births. Majority (59%) of the study population belonged to the age group of 18-23 years. Almost all the patients (98%) belonged to lower socio-economic group. More than one-third (48%) of the patients were nulliparous. It was observed that, greater than half of the patients (56%) presented between 11-15 weeks of amenorrhoea. Majority (76%) of the patients had no previous abortions in their obstetric history. Only 4 (3.45%) patients had previous history of molar pregnancy. Abnormal uterine bleeding was the most common complaint noted in 79% of patients. Nausea and vomiting were noted in 62 patients, out of which 25 (40%) presented with hyperemesis requiring fluid and electrolyte correction. Anaemia was the most common medical complication noted in 55% of patients, followed by hyperthyroidism in 33% and hypertension in 2% patients. Among the 116 patients, 74(64%) had pre-evacuation HCG level more than 2,00,000mIU/ml. Suction evacuation was done in all the cases and 9 (8%) patients required re-evacuation in view of residual vesicular mole on a check scan. Among the 116 patients, histopathology revealed complete mole in 88% patients and partial mole in

12%. In the prospective group, following suction evacuation, 79% of the patients attained remission by the end of 6 months whereas in 13 patients (21%), hCG continued to either plateau or increase following the primary evacuation and they further developed GTN requiring chemotherapy. Out of the 13 cases of GTN, 7 patients attained remission with chemotherapy, whereas 6 patients failed to achieve remission during the 6 months' study period.

Conclusion: Young, nulliparous women belonging to low socio-economic status had a higher proportion of hydatidiform mole. Improving the literacy rates, creating awareness among the women, early registration of pregnancy, prompt referral to higher centres and early administration of appropriate treatment, with a vigilant follow up would help in early detection of GTN. There is also a need for studies at country level which will give us a national figure on molar pregnancies. Thus, a standardized clinico-epidemiological profile of molar pregnancy in India can be created.

Keywords: Hydatidiform mole, Molar pregnancy, Gestational Trophoblastic Disease, Gestational Trophoblastic Neoplasia.

INTRODUCTION

Gestational Trophoblastic Disease (GTD) is a broad spectrum of tumors and tumor-like conditions arising from the products of conception within the uterus comprising of the most benign hydatidiform mole at one end to the most malignant choriocarcinoma at the other extreme.

GTD consists of a spectrum of tumors and tumor-like conditions characterized by abnormal proliferation of pregnancy associated trophoblastic tissues which have varying propensities for invasion and spread.^[1-4] They include complete and partial hydatidiform mole, invasive mole, placental-site trophoblastic tumor (PSTT), and choriocarcinoma. Hydatidiform mole is the most common GTD.^[3,4]

Hydatidiform mole (HM) commonly referred to as molar pregnancy is the most common form accounting for 80% of all gestational trophoblastic diseases. The two histological types of HM are partial hydatidiform mole (PHM) and complete hydatidiform mole (CHM).

Molar pregnancy is more common in some parts of Asia, with reported incidence rates being as high as 2 per 1000 pregnancies in comparison with Europe and North America, where the incidence is usually reported to be less than 1 per 1000 pregnancies.^[5] In a study conducted in South India, over a period of 15 years at Calicut, the incidence of GTN was found to be 20.4%.^[6] In a retrospective study done on 99 patients with gestational trophoblastic neoplasia between 1994 and 2003 in India, the incidence was found to be 0.29% of all births.^[7] Gestational trophoblastic neoplasia was also found to occur in 10% of women with molar pregnancy. In spite of having a higher prevalence among Asians, still epidemiological characteristics of GTD or Gestational Trophoblastic Neoplasia (GTN) are difficult to determine secondary to inconsistencies in case definitions and lack of centralised databases.

The established risk factors include extremes of maternal age, previous history of spontaneous abortion, previous molar pregnancy. History of usage

of oral contraceptive pills and ovulation induction drugs for infertility has been associated with an increase in the incidence of molar pregnancies.^[5] Several other factors such as parity, maternal A and AB blood groups, smoking, exposure to pesticides, herbicides, expression of oncogenes and mutations in tumour-suppressor genes have been variably attributed to increase the risk of GTD, though their association is still controversial.

The clinical features include amenorrhoea, painless vaginal bleeding, expulsion of grape-like vesicles, uterine height greater than period of gestation, doughy uterus, associated with high serum levels of β human chorionic gonadotrophin (β HCG), theca-lutein cysts. In severe cases there can be hyperemesis, hyperthyroidism, thyrotoxicosis, pre-eclampsia.^[8,9,10] Ultrasonography is the imaging modality for diagnosis though the final diagnosis would be established by histopathological examination. Suction evacuation is the treatment modality for hydatidiform mole, excluding some extreme circumstances, which may mandate hysterectomy. A standard follow-up involves regular physical examination, weekly HCG until normal levels are achieved and other imaging modalities, if there is a suspicion of GTN.

Considering the lack of proper epidemiological studies and increased incidence rates among Asian population, this study was undertaken to determine the proportion and the clinical profile of women with hydatidiform mole from a South Indian population, where as of now there is limited data to enable us to detect and provide the standard of care for patients with GTN.

Aims and Objectives

1. To study the proportion of women presenting with hydatidiform mole.
2. To study the clinical profile of hydatidiform mole.

MATERIAL AND METHODS

All patients with molar pregnancy diagnosed and undergoing suction evacuation during the study

period at JIPMER between August 2014 to December 2015 were included in the study as sample. A total of 68 patients, were included in the study which formed the prospective group and a retrospective group was formed by including the women diagnosed with hydatidiform mole during the preceding 2 years. The study population comprised of a total of 116 cases, of which, 68 cases belonged to the prospective group and 48 cases to the retrospective group. The patients belonging to the prospective group (68) were followed up for a period of 6 months to note the trend of the β HCG and to detect the occurrence of GTN. The patients in the retrospective group (48) were considered only for analysing the clinical profile of hydatidiform mole, as follow up was not possible for this group of patients.

The study was approved by the Institutional Ethical Committee, JIPMER. Permission from the hospital authorities was taken to access the medical records of the patients with molar pregnancy for the preceding 2 years. All information collected from the hospital records was kept confidential.

The clinical parameters studied were maternal age, socioeconomic status, parity, gestational age at presentation, obstetric history, clinical presentation, associated medical complications like anaemia, pre-eclampsia, thyrotoxicosis, blood group, pre-evacuation HCG values, treatment received, complications, histopathological examination of hydatidiform mole, progression to GTN, type of chemotherapy received were noted down.

Statistical Analysis

Continuous variables such as age, gestational age and HCG values were expressed as mean and standard deviation. Categorical variables such as parity, socioeconomic status, previous abortions, previous molar pregnancies were expressed as percentage and range. The association of these variables and diagnosis of gestational trophoblastic neoplasia on follow up was studied using the Student-t test for continuous variables and Chi-square test/ Fischer exact test for categorical variables.

P value <0.05 was considered as significant.

RESULTS

The total number of pregnant women admitted during the study period for deliveries, abortions, MTP and ectopic management were 58,024, of which 116 were molar pregnancies. The proportion of molar pregnancy was 1.99 per 1000 pregnancies. The number of live births during the study period was 55,895, hence the proportion of molar pregnancy was 2.07 per 1000 live births.

Table 1 shows the clinical profile of patients admitted at our institute for treatment of molar pregnancy. A total of 116 cases of molar pregnancy

were included in this study. Majority (88%) of the patients were in the age group of 18- 30 years with a range of 18- 46 and mean age 22 years. Almost (98%) all the patients belonged to low socioeconomic status. One-half of the patients (48%) of the patients were nulliparous and 30% were primipara and about 4% gave a positive past history of molar pregnancy. Greater than half (56%) of the patients presented between 11-15 weeks of amenorrhoea. Table 2 shows the presenting complaints of which, amenorrhoea was the predominant symptom in all the women in the study group. Bleeding per vaginum and pelvic pain were noted in 79% and 69% of patients respectively. Nausea and vomiting were noted in 62 patients, out of which 25 (40%) presented with hyperemesis requiring fluid and electrolyte correction.

More than half (55%) of the patients had uterine height larger for gestational age. Anaemia was the most common medical complication noted in 55% patients, followed by hyperthyroidism in 33% and hypertension in 2% patients. The mean TSH value among the 38 patients with hyperthyroidism was 0.03mIU/ml. The blood grouping found B positive to be the most common blood group followed by O positive and A positive. 64% had pre-evacuation HCG level more than 2,00,000mIU/ml. Ultrasonography revealed theca lutein cysts in 20% of patients. Suction evacuation was the treatment method used in all the patients, 8% of the patients required re-evacuation in view of residual vesicular mole on a check scan, performed prior to discharge. Blood transfusion was required in 16.4% of the patients.

Histopathology revealed complete mole in 88% and partial mole in 12% of the cases. The ratio of complete to partial molar pregnancy was 7:1.

On following up the 68 patients in the prospective group for a period of 6 months post evacuation, 4 patients were lost to follow up, 2 had conceived within the follow up period of 6 months, so were excluded from the study. Out of the 62 patients under follow up, 79% of the patients showed a satisfactory falling trend of HCG with the values regressing to normal limits by the end of 6 months. The mean time taken to achieve remission (HCG <5 mIU/ml) was observed to be 14 weeks. By 20 weeks, 93.8% had attained normal HCG levels. Table 3 shows the management given for GTN cases during the follow up period of 6 months, wherein 21% of the patients, the HCG continued to either plateau or increase following the primary evacuation and they further developed GTN requiring chemotherapy. Of the GTN cases, single agent chemotherapy with Methotrexate was successful in inducing remission in 38% of cases, whereas 62% received EMA-CO therapy after failed single agent chemotherapy.

Table 1: Clinico-epidemiological profile of patients with molar pregnancy

Variables	Categories	Number	Percentage
Age group in years	18-23	69	59%
	24-29	33	28%
	30-35	9	8%
	>35	5	5%
Parity	Nullipara	56	48%
	Para 1	35	30%
	Para 2	20	17%
	Para ≥3	5	5%
Previous history of molar pregnancy	Yes	4	3.5%
	No	112	96.5%
Period of gestation (POG)	<10 weeks	23	20%
	11-15 weeks	65	56%
	16-20 weeks	28	24%
Uterine size	Larger than POG	64	55%
	Equal to POG	40	35%
	Smaller than POG	12	10%
Previous history of abortions	0	88	76%
	1	22	18%
	2	4	3%
	≥3	2	3%
Pallor	Present	62	53.4%
	Absent	54	46.6%
Theca lutein cyst on USG	Yes	23	19.8%
	No	93	80.2%
Blood group	B positive	54	46.5%
	O positive	29	25%
	A positive	18	15.5%
	AB positive	8	6.9%

Table 2: Presenting complaints and subsequent management of molar pregnancies

	Number (116)	Percentage (%)
Symptoms		
Amenorrhoea	116	100%
Bleeding per vaginum	92	79.3%
Pelvic pain	80	69%
Nausea and vomiting	62	53.4%
Hyperemesis	25	21.5%
Tremors and palpitations	8	6.9%
Medical Complications		
Absent	14	12%
Present	102	88%
1. Anemia	62	55%
2. Hyperthyroidism	38	33%
3. Hypertension	2	2%
4. Blood transfusion	19	16%
Pre-evacuation HCG (mIU/ml)		
> 2 lakh	74	64%
1-2 lakh	22	19%
<1 lakh	20	17%
Treatment method		
Suction evacuation	116	100%
Re-evacuation	9	8%
Histopathology		
Complete mole	102	88%
Partial mole	14	12%
HCG Trend (Prospective group n=62)		
Falling titres	49	79%
Rising/ plateauing titres (GTN cases)	13	21%

Table 3: GTN cases and further management in the Prospective group

Chemotherapy received in GTN cases	Number of patients (n=13)	Percentage (%)
Single agent (Methotrexate)	5	38%
Methotrexate+ EMACO	8	62%
Remission rates in GTN cases		
Attained remission	7	54%
Not attained remission	6	46%
Remission based on Histopathological type		
Complete mole	5	56%
Partial mole	2	50%

Chemotherapy received	Total remission cases(n=7)	Percentage (%)
MTX (First line)	5	71
MTX + EMACO (Second line)	2	29

DISCUSSION

There is wide variation in incidence of GTD across the globe with higher proportion among Asian women. It was observed that the incidence of GTD was 2.1 per 1000 live births among Hispanics in the United States.^[11] High frequency of molar pregnancy has been reported in some parts of Asia and Middle East, with incidence rates ranging between 1 to 12 per 1000 pregnancies in comparison to western countries, where the incidence remains to be low as 1.54 per 1000 live births.^[12] In two studies from western Indian population, the incidence of GTD was 1.6 per 1000 deliveries and 1.2 per 1000 live births respectively.^[13,14] The present study from South India in a tertiary hospital revealed the proportion of hydatidiform mole to be 1.99 per 1000 pregnancies and 2.07 per 1000 live births respectively.

It was noted from most studies that GTD was observed commonly in women aged between 20-35 years.^[15,16] Other Indian studies also showed similar trend.^[17,18] Though there is a higher propensity for GTD to occur in extremes of age groups, in the present study, 88% of women with GTD belonged to the age group of 18-29 years. In one study from England and Wales done among Asian population living there, 80% of the women with molar pregnancy were aged between 20 and 34 years, though a subgroup analysis revealed that women in extremes of age such as less than 20 years and greater than 40 years had incidence of 4.2 and 5.5 per 1000 live births respectively. It showed that extremes of age groups were twice as likely to develop GTD in comparison with other women of reproductive age.^[15]

Literature across the globe shows that molar pregnancy rates have been higher among the underdeveloped countries and those belonging to low socioeconomic status. In studies done in Iraq and Pakistan, 65% and 82.4% of women with GTD belonged to low socioeconomic status respectively.^[16,19] Similarly a study from India showed that majority of the patients belonged to low and lower-middle socio economic classes.^[17] In the present study, 98% of patients with hydatidiform mole belonged to low socioeconomic group. The very high percentage could be attributed to the fact that the study had been conducted at a tertiary level hospital catering to the patients belonging to low socio economic group.

It is evident from most of the studies that greater than 50% of GTD patients presented at gestational age less than 20 weeks. In other studies, 64%, 61%, 57.5%, 57% and 55% of molar pregnancies presented below 20 weeks of gestation respectively.^[16,18,20,21,22] In the present study, we observed that 79.3% of hydatidiform mole patients presented between 11-20 weeks of gestation, with

mean gestational age at presentation being 13 weeks.

On analysing the relationship between GTD and parity, it was observed from different studies that 81%, 81%, 80% and 78% of GTD to occur in multiparous women respectively.^[16,18,13,7] In the present study, 51.7% of GTD was observed in multiparous women among this 30% were of low parity (≤ 1) with the proportion of women with GTD in high parity being low. In a retrospective study by Aziz et al, the frequency of molar pregnancy was 42.4% among nulliparous and in primiparous women.^[21]

In a retrospective study from India, bad obstetric history was noted in 18% of their patients¹⁸. In comparison, other studies from Iraq and India, history of previous abortion was noted in 30.4%, 36.9% and 30% of women with GTD respectively.^[17,13,22]

In the present study, out of the total 116 patients, 28(24%) had previous history of abortions and among the 13 patients of GTN, 4(31%) had previous history of abortion.

A study showed that women with 2 consecutive spontaneous abortions were 32 times more likely to develop a complete mole than women who had previously delivered term babies.^[23]

Studies have shown that the risk of subsequent molar pregnancy increases by 1% to 2% after diagnosis of one molar pregnancy and by 15% to 20% after two molar pregnancies.^[24] In a retrospective study from Nepal, it was observed that 8.8% of patients had a prior history of molar pregnancy, whereas another study from Germany noted 2.9% of recurrent molar pregnancy in their study during their follow up of 139 cases of complete molar pregnancies.^[25] In the present study, 4(3.5%) patients presented with a history of previous molar pregnancy with the recurrence rate similar to other studies.

In the present study, vaginal bleeding was the most common presenting symptom followed by hyperemesis which was observed in 79% and 40% of cases. Several studies have quoted the frequency of hyperemesis to be 19%, 17.6%, 17%, 12% in women with molar pregnancy.^[16,13] Abdominal pain, which may be secondary to presence of theca lutein cysts was ranging between 20% to 38% in various studies, whereas in our study, 69% of the patients presented with pelvic pain.

Various studies have shown that uterine size to be greater than gestational age in 70%, 57.5% and 56.7% of patients with GTD respectively.^[19,13,21] In the present study, 55% patients presented with uterine height larger than the period of gestation. Low socioeconomic conditions, poor literacy rate and lack of awareness could be the major contributory factors for late presentation in the present study.

In an Indian study from Mumbai, 84.8% of patients presented with anaemia.^[17] In the present study, 53% of the patients were found to be anaemic, revealing that anaemia was the most common medical complication. The need for blood transfusion in the perioperative period was noted in 18 (29%) patients because of their underlying anaemic status. Hyperthyroidism was observed in 33% of cases, a slightly higher result in comparison to another Indian study, which was 21%.^[13]

Hypertension was noted in 2(1.7%) patients in the present study. This was similar to that reported in an Indian study, consisting of 92 patients of GTD, where hypertension was noted only in 1 patient.¹³ Studies conducted in Iraq and Pakistan revealed that 10.4% and 11.8% patients had preeclampsia respectively.^[16,19]

In 2 studies from Nepal and Iran, there was a significant association between blood groups O, blood group A and complete mole.^[23,14] In the present study, 47% and 25% of women with molar pregnancy had B and O grouping respectively, whereas another Indian study revealed no significant association between hydatidiform mole and blood groups.^[17] The present study also did not show any significant association between blood group and molar pregnancy.

Ultrasound was the diagnostic modality used in all the study cases and theca lutein cysts were noted in 20% of patients in the present study, similar to another study from Nepal.^[20] In another study from India, 20.2% of GTN cases had concomitant theca lutein cysts.^[7] There was a slightly higher percentage of women with theca lutein cysts in 2 studies from India and Pakistan respectively.^[19,17] It was also observed that patients with theca lutein cysts in the present study had a significant progression to GTN ($p < 0.05$).

The pre-evacuation HCG was more than 50,000mIU/ml in 86% of patients with hydatidiform mole in a study from Pakistan. In various other studies, 60-75% of patients had HCG value > 1 lakh. The present study had a higher mean value of 1,49,086 mIU/ml. It was also observed that in 65% of the patients, total HCG values was > 2 lakhs, but still on follow up almost 93.8% regressed by end of 6 months. On further analysis, we did not find any significant association between pre-evacuation HCG values and GTN.

The present study revealed a higher frequency of complete molar pregnancy, which was observed to be 88%. The ratio of complete and partial molar pregnancy in the present study was 7:1. The results were similar to that of a study conducted in Iraq which showed complete molar pregnancy in 80% and partial molar pregnancy in 18.4% of cases.¹⁶ In a study from India, the complete and partial moles accounted for 78% and 22% respectively.^[21] One study showed that out of 77 cases of molar pregnancy, 52 cases were complete moles and 25 cases were partial molar pregnancy. Persistent GTD

occurred in 20 (26%) out of 77 cases diagnosed in their study centre.^[12]

Studies reveal the incidence of GTN to be 0.6 to 1.1 per 1000 pregnancies in Europe and North America, whereas it was 2 per 1000 pregnancies in Japan. In India and Middle East countries, the incidence is 1 in 160 pregnancies. Two retrospective studies from Nepal showed the incidence of GTN to be 0.24 per 1000 livebirths, whereas other studies from Germany and Saudi Arabia have shown the incidence of GTN to be 0.33 and 0.35 per 1000 deliveries respectively.^[12,20,25,23] A retrospective study from Western part of India depicted a higher incidence of GTN, which was 2.9 per 1000 livebirths and 2.7 per 1000 admissions respectively.^[7] An Indian study done on 92 patients of GTD, showed the rate of GTN to be 37%.^[17] In the present study, 79% of patients had a satisfactory falling trend of HCG levels following the primary evacuation, whereas 21% (13 cases) progressed to GTN. The incidence of GTN was found to be 0.61 per 1000 live births in the present study.

Chemotherapy was successful in achieving remission in 53.8% (7 out of 13) of patients within the short follow up period of 6 months. In a study from Egypt, among 51 patients of GTN, remission rate observed was 71%.²⁶ Similarly, another prospective study from India, among 25 patients with high risk GTN, EMACO (Etoposide, Methotrexate, Actinomycin D, Cyclophosphamide, Oncovin) chemotherapy showed remission in 77% and resistance in 23% of patients.^[27]

Methotrexate alone as a single agent was successful in achieving remission in 5 out of the 7(71%) patients. In other study from Egypt, methotrexate as a single agent was successful in attaining remission in 84.8% of cases.²⁶ Methotrexate followed by EMACO was successful in achieving remission in 29% of patients in the present study. In remaining 6 patients despite receiving EMACO, did not achieve remission within 6 months follow up period. In a study done by Priyanka et al from India on 25 patients with high risk GTN, EMACO therapy showed remission in 77% of cases.^[27]

In another study from Egypt, among 51 patients of GTN, 15.2% of patients achieved remission with EMACO.^[26]

CONCLUSION

In the present study, the proportion of hydatidiform mole was observed to be 1.99 per 1000 pregnancies and 2.07 per 1000 livebirths, with recurrence occurring in 3.5% of the patients. The incidence of GTN was 0.61 per 1000 live births during follow up. Improving the literacy rates, creating awareness among the women, early registration of pregnancy, prompt referral to higher centres and early administration of appropriate treatment, with a vigilant follow up would help in early detection of GTN.

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