Oncology Case Reports Journal

Research Article
Published: 28 Sep, 2021

Clinical Spectrum of Gestational Trophoblastic Disease in a Tertiary Care Centre: A Retrospective Analysis

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Abstract

Objectives: Gestational Trophoblastic Disease (GTD) spectrum includes a wide range of benign and malignant entities associated with abnormal trophoblastic tissue proliferation and hydropic degeneration. In this study, we retrospectively observed all the GTDs in last two and half years at our tertiary care institute and hereby, report our interesting and varied observations of this enigmatic disorder.

Material and Methods: All cases with suspected GTD were recruited in our study and divided into Molar group and GTN group after histopathology confirmation. The demographic profile, b-hCG values, WHO scoring and FIGO staging for GTN cases was noted.

Results: The total number of cases falling in molar pregnancy group was 6 (60%) while 4 (40%) patients had GTN. The mean age of patients in molar group and GTN group was 25 years and 23 years respectively. Majority (66.7%) of patients in molar group were primipara, while GTN patients were predominantly (75%) nulliparous women. 67% patients of molar patients required blood transfusion. 1/3rd of molar pregnancy patients were detected with hyperthyroidism. The most common presentation in a molar pregnancy was vaginal bleeding in 75% cases, followed by pain abdomen. In GTN group, half the patients did not have any complaint, while another 25% had symptoms due to metastasis like breathlessness, jaundice and vaginal bleeding. Among the molar group, 67% were complete mole and 16% were partial mole.

Discussion: In our study, we found a higher ratio of GTN patients at a younger age was noticed in comparison with molar pregnancies (60%:40%; Molar:GTN). Dietary deficiency of beta carotene, nutrients, early age of marriage and first conception, delay in seeking obstetric help contribute to this higher incidence of GTN cases with respect to molar pregnancies.

Conclusion: These are treatable gynecological entities requiring proper follow up and timely intervention for preventing life threatening complications.

Keywords: Complete mole; Gestational Trophoblastic Disease (GTD); Gestational Trophoblastic Neoplasia (GTN); Molar pregnancy; Partial mole

Introduction

Gestational Trophoblastic Disease (GTD) spectrum refers to a group of conditions characterized by abnormal trophoblastic tissue proliferation. They include both benign and malignant diseases. Most commonly encountered is molar pregnancy with an incidence of 1.05% in India, 0.09% in Uganda, 0.16% in Japan and 0.2% in Nigeria [1-3]. Less frequently encountered GTD includes the persistent molar or non-molar malignant conditions known as Gestational Trophoblastic Neoplasms (GTN). These include choriocarcinoma, invasive mole, Placental Site Trophoblastic Tumor (PSTT) and Epithelioid Trophoblastic Tumor (ETT). All these neoplastic diseases can arise after a term delivery, abortion, molar pregnancy or ectopic pregnancy. Also, the b-hCG levels rise exponentially in these malignant conditions except for PSTT in which only a moderate rise is noted on account of its origin from intermediate trophoblasts, while others arise from cytotrophoblasts and syncytiotrophoblasts.

Age, both above 40 and adolescent group is associated with risk of developing complete mole. While, partial moles are associated with the use of oral contraceptives and a history of irregular menstruation, but not with dietary factors [4].

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Received Date: *12 Jul 2021*
Accepted Date: *06 Aug 2021*
Published Date: *28 Sep 2021*

Citation:
Yadav G, Singh P, Saini A, Rao M, Kathuria P, Gothwal M, et al. Clinical Spectrum of Gestational Trophoblastic Disease in a Tertiary Care Centre: A Retrospective Analysis. Oncol Case Report J. 2021; 4(3): 1040.

ISSN: 2641-9173

Despite the development in both pathological and imaging diagnostic modalities, GTD still presents a great deal of diagnostic dilemmas to the treating clinician. Even in today's era, we do not have the full knowledge of risk factors which can predict a woman's chances of having a molar gestation, her chances of progressing to the malignant disease and response to single-agent chemotherapy in case GTN develops. In this study, we retrospectively observed all the GTDs in last two and half years at our tertiary care institute and hereby, report our interesting and varied observations of this enigmatic disorder.

Material and Methods

This was a single centre study over two and half years at All India Institute of Medical Sciences (AIIMS), Jodhpur. After seeking ethical approval, we conducted a retrospective study by recruiting all the cases that presented with suspected GTD and were further managed at our institute. These cases were histologically confirmed. We divided our patients into two groups; Molar group and GTN group. The demographic profile of these patients was noted along with their varied clinical presentation. Also, the imaging findings, b-hCG values, WHO scoring and FIGO staging for GTN cases was noted. Follow up for these cases was done and reviewed.

Results

All the patients were analyzed for the basic demographic profile. The total number of cases falling in molar pregnancy group was 6 (60%) while 4 (40%) patients had GTN. The mean age of patients in molar group and GTN group is 25 years and 23 years respectively (Table 1).

It was observed that majority (66.7%) of patients in molar group were primipara following term delivery, while GTN patients were predominantly (75%) nulliparous women, with 50% presenting with post molar GTN and rest of the GTN cases had antecedent abortion or term pregnancy. All the patients of molar pregnancy and 75% of GTN patients presented in 1st trimester, with each one first detected by imaging. None of the patients had history of Oral Contraceptive Pill (OCP) use or irregular menstrual cycles (Table 2).

Table 1: Age distribution of patients in each group.

Age group	Molar pregnancy group (n=6)	GTN group (n=4)
<20 years	1	1
20-25 years	3	2
25-30 years	2	1
Mean age	25 years	23 years

Table 2: Basic parameters and clinical profile in both the groups.

Basic Parameters		Molar pregnancy group (n=6)	GTN group (n=4)
Parity	0	2 (33.3%)	3 (75%)
	1	4 (66.7%)	0
	2	0	0
	3	0	1 (25%)
Antecedent pregnancy	Molar pregnancy	x	02 (50%)
	Abortion	02 (33.3%)	01 (25%)
	Term pregnancy	02 (33.3%)	01 (25%)
	None	02 (33.3%)	x
Trimester at presentation	1st trimester	06 (100%)	03 (75%)
	2nd trimester	X	01 (25%)
History	Oral contraceptive use	No	No
	Irregular menstruation	No	No
Diagnosis	Clinical	0	0
	Ultrasound	06 (100%)	04 (100%)

Table 3: Blood investigation profile in each group.

Investigation profile		Molar pregnancy group (n=6)		GTN group (n=4)	
Blood group	O+	x		02 (50%)	
	A+	01 (16.6%)		01 (25%)	
	B+	01 (16.6%)		01 (25%)	
	A-	01 (16.6%)		x	
	B-	01 (16.6%)		x	
	AB+	02 (33.3%)		x	
Anemia	<7.0 g	3 (75%)	4 (67%)	1 (33%)	3 (75%)
	07-09	1 (25%)		x	
	9-10.9	x		2 (66%)	
Thyroid profile	Hypothyroidism	1 (16.7%)		x	
	Hyperthyroidism	2 (33.3%)		2 (50%)	
	Euthyroid	3 (50%)		2(50%)	
B hcg	<50,000	4(67%)		01 (25%)	
	50,000-1 lac	x		x	
	>1 lac	02 (33.3%)		02 (50%)	

It was found that 50% patients with GTN had O+ as their blood group, and remaining 25% each had A+ and B+ grouping. While, in molar group, 1/3rd patients had AB+ as their blood group, and 1 patient each of A+, B+, A- and B-. 67% patients of molar pregnancy were anemic at the time of presentation to hospital requiring blood transfusion. 1/3rd of molar pregnancy patients were detected with hyperthyroidism. No clear association was observed in the incidence of GTD with respect to blood groups (Table 3).

The most common presentation in a molar pregnancy was vaginal bleeding in 75% cases, followed by pain abdomen in 25% cases. One quarter of patients of molar pregnancy and half the patients of GTN had incidentally detected GTD, which signifies the importance of first trimester imaging. In GTN group, half the patients did not have any complaint, while another 25% had symptoms due to metastasis like breathlessness, jaundice and vaginal bleeding. Patients also had incidentally discovered hyperthyroidism, although thyroid storm, early onset pre eclampsia was not seen.

GTN cases included one patient each of choriocarcinoma, invasive mole, Placental Site Trophoblastic Tumor (PSTT) and persistent GTN. Among the molar group, 67% were complete mole and 16% were partial mole (Table 4).

Each of these groups had varied complications, with more life threatening manifestations in GTN group. We had four patients in GTN group, among which choriocarcinoma and invasive mole patients had metastasis. A respiratory complaint, jaundice was also noticed in GTN group. Vaginal bleeding was a common complaint in molar pregnancy group (75%) as compared to GTN group (25%). But, anemia was noticed in majority (75%) of patients in GTN group. Also, it must be stressed that severe anemia requiring blood transfusion was a result of acute bleeding in molar pregnancy group.

Table 4: Clinical presentation and histopathology.

Parameter		Molar pregnancy group (n=6)	GTN group (n=4)
Most common presentation	Vaginal bleed	04 (75%)	01 (25%)
	Pain abdomen	01 (25%)	x
	Breathlessness/Jaundice	x	01 (25%)
	None	01 (25%)	02 (50%)
Uterine size	>POA	04 (67%)	02 (50%)
	Same	02 (33%)	02 (50%)
Histopathology	Complete mole	4 (67%)	x
	Partial mole	2 (33%)	
	Invasive mole	x	1 (25%)
	Choriocarcinoma		1 (25%)
	PSTT		1 (25%)
	Persistent GTN		1 (25%)

Table 5: WHO prognostic scoring in GTN cases.

	Case 1 (Choriocarcinoma)	Case 2 (Invasive mole)	Case 3 (Persistent GTD)	Case 4 (PSTT)
Age	26	20	21	25
Antecedent pregnancy	Term delivery	Molar pregnancy	Partial mole	Abortion
Duration from antecedent pregnancy to start of chemotherapy	1.5 years	9 months	6 months	2 months
Blood group	A+	B+	O+	O+
B hcg values	3,36,131 mIU/ml	36,05,000 Miu/ml	10,000 Miu/ml	X
Size of tumor (Uterine) cm	10.1 × 9.8 × 6.4 cm	20.2 × 8.1 × 10 cm	2.9 × 3.6 × 1.5 cm	1.7 × 1.6 × 2.2 cm
No. of mets	X	X	X	X
Site of mets	Lung, Vagina	Lung	X	X
Prior Chemo	No	No	X	No
SCORE	12	8	4	1

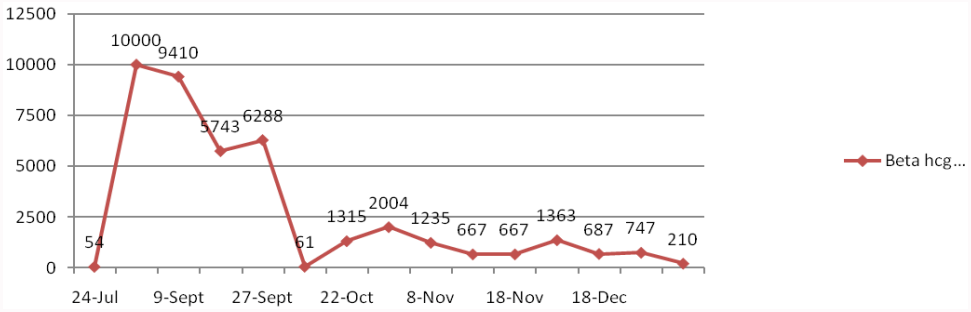

Figure 1: Beta-hcg levels in persistent GTD patient (Case 3).

67% patients required blood transfusion in molar pregnancy group, while only 25% required in GTN group. Early onset pre eclampsia, thyroid storm, theca lutein cysts were not found in either of the groups, although hiking b hCG levels were present in some of the patients. Uterine size greater than period of amenorrhea was seen in 67% of molar pregnancy cases, while 50% of GTN group patients manifested the same.

The primary treatment of molar pregnancies was suction evacuation, followed by beta-hCG estimations weekly till three negative values, followed by monthly b-hCG estimations for 6 months. All the six patients in molar group were under regular follow up with b-hCG estimation till three negative values. Thereafter, monthly b-hCG was done till 6 consecutive months. None of these patients developed persistent GTD during the course of follow up and followed the contraceptive advice for a year. None of the patient has conceived till date during their follow up, but are planning for the same and safe motherhood.

Among the GTN group, chemotherapy was given to ¾ patients. One patient with invasive mole was in high risk group, so received EMACO regimen, while the patient with choriocarcinoma received doxorubicin initially followed by EMACO. The persistent GTD patient received methotrexate regimen. Chemotherapy associated side effects in form of mucositis; gastrointestinal complaints were noted with EMACO candidates.

Choriocarcinoma patient was given alternative regimen in beginning (doxorubicin) due to highly raised serum bilirubin, followed by EMACO regimen. Repeat CECT Chest and pelvis was done for metastatic GTN patients after 6 months which showed significant reduction in size of pulmonary nodules, resolving pericardial effusion and uterine size. Patients did well with the multidose chemotherapy and are in regular follow up at present with monthly b-hCG estimations over a year. PSTT patient is also under regular follow up with our institute. As the patient had non metastatic disease, which was not confirmed on repeat biopsy at our institute, definitive treatment was deferred in our case (Table 5).

Persistent GTD patient showed presence of arteriovenous malformation, for which uterine artery embolisation was done at our institute. The fluctuating b-hCG values are depicted in Figure 1 (Case 3).

Discussion

In our study, the mean age of patients in molar pregnancy group and GTN group was 25 years and 23 years respectively. It was in concordance with other Indian studies showing 23.02 ± 2.96 years and 24.6 ± 4.4 years as the mean age [5-7]. One study from Nepal also showed mean age of 22 years, while Nigerian studies show a higher age of 30 years [8,9].

In our study, 67% patients with molar pregnancy had uterine size more than gestational age, while remaining 33% had corresponding size. This was bit higher than other Indian studies reporting 54.2% and 27.2% rates respectively [6,7].

Our study also showed the relation of GTD with gravidity and parity. The incidence of molar pregnancy in primiparous patients increased to 66%. GTN was mainly observed in nulliparous patients (75%) with history of prior abortion/mole in majority cases. A Nigerian study showed the increase in GTD risk in patients with parity four and above [10]. Lakra et al. [7] showed no correlation of these parameters on incidence of GTD.

As far as anemia and blood transfusion is concerned, our study showed 67% patients of molar pregnancy being anemic requiring blood transfusion, which was in great concordance with previous study by Thapa et al. [11] having 68% anemic patients.

Sometimes, their occurs persistent disease following both partial and complete molar pregnancy. After a complete mole, persistent disease may occur in elder age group of patients. In a study, it was shown to be 37% in patients aged more than 40 years, while other study showed an incidence of 60% in patients above 50 years [4,5].

In partial mole, the probability of persistent disease is quite low, ranging from 1% to 4% and is non metastatic in nature. After molar evacuation, persistent GTN may exhibit the histologic features of either hydatidiform moles or choriocarcinoma but after a non-molar pregnancy, persistent GTN always has the histologic pattern of choriocarcinoma.

Human Chorionic Gonadotropin (hCG) is a critical marker for GTD to diagnose the development of GTN, monitor response to chemotherapy, and occurrence of relapse. Metastases can occur after any type of GTD but, more common after non-molar pregnancies, mainly in the lung and vagina. The chances of invasion in complete mole are 15% and metastasis is 4%. If b-hCG level greater than 1,00,000 mIU/mL, excessive uterine enlargement or theca lutein cysts ≥ 6 cm in diameter, the chances of post molar tumor are more.

In our study, the molar pregnancies constituted 60% of cases, while GTN constituted 40%. Another study done by Singh A et al. [12] showed a ratio of 75%:25%.

Diagnosis of GTN is based on the following criteria:

- Serum βhCG>20,000 mIU/mL 4 weeks after evacuation
- Plateauing of βhCG - 4 measurements over a period of 3 weeks - [Day 1, 7, 14, 21]
- Rise of βhCG - 3 measurements over a period of 2 weeks - [Day 1, 7, 14]
- Level of βhCG - Remain elevated 6 months after
- Histological evidence of choriocarcinoma

WHO risk stratification for GTN classifies the patients into low risk (<6) and high risk (>/=7). Low risk metastatic and non-metastatic cases are managed with single drug regimen i.e. Methotrexate + Folinic acid or Actinomycin D, while the high risk cases are given EMACO regimen, and if needed surgery to treating complications/ drug resistant sites or radiation therapy. Except for PSTT and ETT, all forms of GTN respond well to chemotherapy treatment. In all patients of non metastatic PSTT and ETT, definitive treatment in the form of hysterectomy is done. For metastatic disease, remission can be achieved but they are less responded by chemotherapy [10].

For diagnostic imaging, ultrasonography is reliable modality for both complete and partial mole. Vesicular cystic spaces and diffuse hydropic swelling is seen in complete mole, while focal vesicular areas are visualized in placenta with increased transverse diameter of sac in case of a partial mole. Uterine Arteriovenous Malformation (AVM) following Gestational Trophoblastic Neoplasia (GTN) is a rare condition. Sometimes, irregular persistent bleeding is noticed during follow up of a GTN patient. As in our case, ultrasound showed a probability of AVM, which was later confirmed by MRI. Possibility of AVM must be kept in mind as few cases have been seen in literature where 49 AVM cases have been seen following GTN. Complete molar pregnancy was the most common initial gestational trophoblastic diagnosis (48%). Hypo-echoic space in the myometrium is the most relevant finding on USG, but the gold standard for diagnosing AVM is angiographic examination. Uterine Artery Embolization (UAE) is the most common treatment option as it controls bleeding in 85% cases [13].

In our study, we found a higher incidence of GTN. This could be probably due to dietary factors, early age at marriage and conception. The patients were found non-compliant and less aware for their nutrition. Diet deficient in carotene and folic acid contributes to developing molar pregnancy and most of the women included in this study were malnourished and vegetarian by diet. But, to our surprise, we did not encounter good number of molar pregnancy cases. Although the percentage of GTN was relatively high in proportion with molar disease. This can be largely attributed to patient's awareness and delay in seeking medical care. Despite advancements in medical care, better imaging facilities, ongoing awareness programs and accessible medical health options, the patients are still hesitant and ignorant towards their health. The mindset of some sectors of our population still remains dormant. The females do not present to hospital at earliest and majority of females give a history of missed abortions, spontaneous bleeding at earlier gestations for which they did not seek any obstetric help and consultation. This largely misses the chance of early diagnosis. As far as diagnosis is concerned,

ultrasound at earlier gestation had detected most of our cases which reported to us either with pain abdomen or vaginal bleeding.

It is a need to spread awareness in the general population at least in our sector of western Rajasthan, so that we detect these cases at the earliest. As each woman matters, not a single patient should miss from being diagnosed and treated for this treatable gynecological condition.

Conclusion

Gestational trophoblastic diseases are double edged sword. They need to be monitored and follow up is essential. To pick the development of neoplasia on time proves essential, as they are curable conditions. Steps should be taken to ensure good nutrition and create awareness in pregnant females, as it is neglected by some sections of society.

Acknowledgement

I would like to thank all my co authors for their significant contribution in preparation of this manuscript, and making it possible to evaluate the content by joint team effort.

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