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Original Research Article

Gestational trophoblastic diseases: an observational study at a tertiary care teaching hospital in Jharkhand, India

Archana Kumari*, Nikita Chauhan

Department of Obstetrics and Gynecology, RIMS, Ranchi, Jharkhand, India

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***Correspondence:**

Dr. Archana Kumari,

E-mail: dr_karchana@yahoo.co.in

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ABSTRACT

Background: Gestational Trophoblastic Diseases (GTD) encompass a wide spectrum of proliferative disorders of trophoblast tissue, which hold a good prognosis if diagnosed and treated on time. A close understanding of the disease spectrum is therefore needed to reduce morbidity and mortality.

Methods: This is an observational study (both prospective and retrospective analysis) conducted in Rajendra Institute of Medical Sciences, a tertiary care teaching hospital in Ranchi, Jharkhand over a period of 2 years from 1st January 2017 to 31st December 2018.

Results: A total of 162 cases of GTD were identified during the study period. Disease spectrum comprised of complete molar pregnancy in 146 (90.12%) and partial molar pregnancy in 7 (4.3%), GTN in 9 out of 162 cases (5.5%). Bleeding per vaginum preceded by amenorrhea was the most common symptom, observed in 95.4% of the cases. Uterine size was more than period of amenorrhea in almost 50% of the cases. Theca lutein cysts were found in 39.8% of the cases, hypertension in 21.5%, hyperthyroidism in 6.5% cases. Overall, there were nine (5.56%) cases of choriocarcinoma and six (3.7%) cases of Invasive mole. Remission rate in GTN was 86.7% with chemotherapy.

Conclusions: Women complaining of vaginal bleeding in first half of pregnancy with uterine size more than period of amenorrhea must be evaluated for GTD by ultrasound and serum beta HCG. For cases of molar pregnancies, suction and evacuation remains the treatment of choice but need for regular follow-up and strict compliance to contraception during entire follow up has to be emphasized. Cases of GTN have excellent remission with chemotherapy.

Keywords: Choriocarcinoma, Gestational trophoblastic neoplasia, Gestational trophoblastic disease, Hydatidiform mole, Invasive mole, Molar pregnancy

INTRODUCTION

The term gestational trophoblastic disease (GTD), is used to refer to a group of tumors which involve abnormal trophoblastic proliferation.¹ GTDs are characterised by aberrant growth and development of the trophoblasts of placenta that may continue even after the end of pregnancy.² They can be benign (complete hydatidiform mole or partial hydatidiform mole) or malignant (invasive mole, placental site trophoblastic tumor, epithelioid tumor, choriocarcinoma).³ The malignant forms of GTD are known as gestational trophoblastic neoplasia (GTN).

They can occur weeks or years following any pregnancy, but are most commonly seen after a hydatidiform mole.⁴

GTN are of great interest as unlike other malignancies, they can be cured completely despite widespread metastasis if diagnosed accurately and treated on time. Potential of childbearing can be preserved and normal pregnancy outcome anticipated. There is significant morbidity and mortality from complications without timely management and proper follow-up. The most sensitive and specific marker for diagnosis and follow-up is the hormone, β -hCG which is produced by trophoblasts.⁵

To reduce mortality and morbidity from gestational trophoblastic disease, it is therefore important to understand the disease prevalence, clinical signs and symptoms, risk factors, diagnosis, proper management and need for follow-up for better outcome of the disease spectrum. With this background, the present study was done to determine the incidence and prevalence of GTD and to analyse presenting signs, symptoms, management options and disease outcome.

METHODS

This is an observational study (both prospective and retrospective analysis) conducted in Rajendra Institute of Medical Sciences, a tertiary care teaching hospital in Ranchi, Jharkhand, India over a period of 2 years from 1st January 2017 to 31st December 2018.

Inclusion criteria

- Newly diagnosed cases of gestational trophoblastic diseases coming to gynecology OPD or emergency of the study institution
- Cases of GTD on follow-up visits to the study institution
- Cases of GTN coming to the study institution.

Detailed history of newly diagnosed cases including demographic profile, presenting symptoms, obstetric history and medical history were noted. For cases on follow-up, in addition to history, previous investigations, management and number of follow up visits were noted. Initial diagnostic workup of all cases of GTD included-routine blood investigations, thyroid profile, pre-evacuation serum β -hCG, ultrasound and chest X-ray PA view. All new cases of molar pregnancy were managed by suction and evacuation, irrespective of the gestational age and tissue was sent for histopathological examination. Once a falling trend of serum β -hCG post-evacuation was established, patients were discharged with advice to remain in strict follow-up. Follow-up was considered completed only when the patient came to OPD weekly till three consecutive normal β -hCG values followed by monthly till six normal β -hCG values. Contraception was advised for one year during the period of follow-up. If serum β -hCG showed rise or plateau during follow up, cases were re-admitted for further diagnostic work up. Diagnosis of post molar GTN was made in cases where women presented with continued vaginal bleeding, subinvolution, persistence of theca lutein cysts or if there were signs or symptoms of metastasis like cough, breathlessness, headache, convulsions or epigastric pain.

Cases of GTN were further evaluated in terms of metastases, response to previous treatment-chemotherapy and surgical management. Diagnostic workup of these cases included detailed history about symptoms, physical examination, pelvic examination to look for size of uterus, any vaginal metastasis or urethral nodules, serum

beta HCG, ultrasound and CT whole abdomen, CT chest, CT brain. These cases were managed in collaboration with oncology department after WHO GTN scoring and staging.

Statistical analysis

Descriptive statistics like percentage and mean calculations were used to interpret the data using Microsoft office 2007.

RESULTS

There was a total of 3,689 OPD and 18,121 emergency admissions over the study period. There were 13,741 deliveries (vaginal: 7849, caesarean: 5892) out of which 162 cases were identified to be GTD, thus the prevalence rate of GTD was 0.74% of all admissions.

There were 141 new cases of GTD in the study period and 21 were follow-up cases of GTD. Thus, the incidence of GTD turns out to be 1.02 in 100 deliveries. Sixty-eight cases (41.9%) were referred cases to the institution. Disease spectrum of GTD comprised of 153 cases of hydatidiform mole with complete molar pregnancy in 146 (90.12%) and partial molar pregnancy in 7 (4.3%), GTN in 9 out of 162 cases (5.5%). Out of 9 cases of GTN -3 were invasive mole, 6 were cases of choriocarcinoma. Six cases of GTN were further diagnosed during the period of follow up of molar pregnancy. Thus total 15 cases of GTN were identified during the study period of 2 years.

Table 1: Demographic profile.

Age group (years)	No (%) (n=162)
<20	46 (28.39%)
21-25	34 (20.9%)
26-30	24 (14.8%)
>30	58 (35.79%)
Parity	
Primigravida	44 (27%)
Second gravida	35 (22%)
Third gravida	40 (24.6%)
Multigravida	43 (27%)
Socioeconomic status	
High	7 (4.3%)
Middle	56 (34.56%)
Low	99 (61.11%)

Figure 1 shows a partial mole after expulsion. Table 1 shows the demographic profile - age, parity and socioeconomic status. A higher prevalence of GTD was seen in the extreme of ages with 28.39% less than 20 years old and 35.79% more than 30 years old. There was a higher prevalence noted in primigravida (27%) and in women who were grand multiparas (27%). Prevalence being 22% and 24% in second and third gravidas respectively.



Figure 1: Partial mole after expulsion.

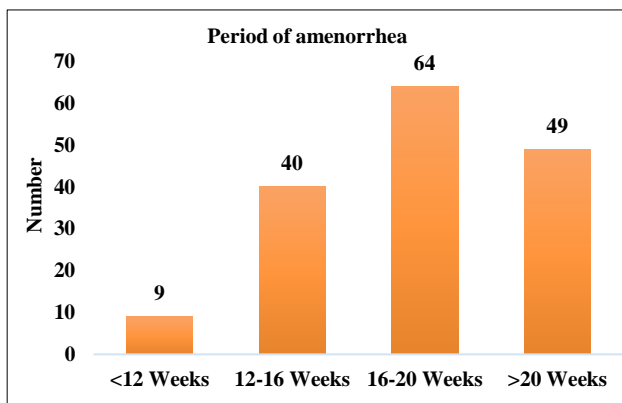


Figure 2: Period of amenorrhea.

Presenting symptoms and signs of GTD are depicted in Table 2. Bleeding per vaginum preceded by amenorrhea was the most common symptom, observed in 95.4% of the cases. The incidence of classical signs was relatively low - hyperemesis was seen in 15.68% and passage of grape like vesicles was found in 22.8%. Pallor was associated with hydatidiform moles in 83% of the cases. Uterine size was more than period of amenorrhea in almost 50% of the cases. Theca lutein cysts were found in 39.8% of the cases, hypertension in 21.5%, hyperthyroidism in 6.5% cases.

Table 2: Presenting signs and symptoms.

Signs/symptoms	H. Mole (N=153)	GTN (n=9)
	No. (%)	No. (%)
Bleeding per vaginum preceded by amenorrhea	146 (95.4%)	6 (66.7%)
Pallor	127 (83%)	4 (44.45%)
Uterine size more than gestation age	76 (49.6%)	3 (33.34%)
Theca lutein cysts	61 (39.8%)	3 (33.34%)
Passage of grape like vesicles	35 (22.8%)	0 (0.00%)
Hypertension	33 (21.5%)	1 (11.1%)
Hyperemesis	24 (15.68%)	2 (22.23%)
Hyperthyroidism	10 (6.5%)	0 (0.00%)
Urethral nodule	0 (0.00%)	4 (44.45%)

Table 3: Pre-evacuation serum β-hCG levels.

Range (mIU/mL)	Complete H. Mole (n=146)	Partial H. Mole (n=7)	Invasive Mole (n=6)	Choriocarcinoma (n=9)
10,000-50,000	81 (55.47%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
50,000-1,00,000	36 (24.65%)	0 (0.00%)	1 (16.67%)	0 (0.00%)
1,00,000-5,00,000	29 (19.86%)	5 (71.4%)	3 (50%)	2 (22.23%)
5,00,000-10,00,000	0 (0.00%)	2 (28.5%)	2 (33.34%)	4 (44.45%)
>10,00,000	0 (0.00%)	0 (0.00%)	0 (0.00%)	4 (44.45%)

Table 4: Analysis of gestational trophoblastic neoplasia (n=15).

Serum β-hCG (mIU/ml) No. (%)	Signs and symptoms in follow-up No. (%)	Site of metastasis No. (%)
50,000-1,00,000: 1 (6.67%)	Continued vaginal bleeding: 8 (53.33%)	Lungs - 9 (60%)
1,00,000-5,00,000: 4 (26.67%)	Subinvolution: 8 (53.33%)	Vagina: 4 (26.67%)
5,00,000-10,00,000: 6 (40%)	Rising or plateau of β-hCG values: 10 (66.67%)	Liver - 2 (13%)
>10,00,000: 4 (26.67%)	Persistence of theca lutein cysts: 5 (33.34%) Metastasis: 4 (26.67%)	Brain - 1 (6.67%)

Figure 2 shows period of gestation, 64 (39.57%) cases presented with 16-20 weeks amenorrhea and 49 cases (30.24%) presented with amenorrhea of more than 20 weeks.

Table 3 shows pre-evacuation serum β-hCG values. It was found that β-hCG levels of range 10,000-50,000 were common in complete moles and a higher range of more than 5 lacs/mm³ was seen in cases of

choriocarcinoma. Four cases of invasive mole had β -hCG level between 50,000-5,00,000.

There was a total of 15 cases of GTN identified during the study period, nine cases on admission and six cases were diagnosed on follow up visits after molar evacuation. Out of 15 cases of GTN nine cases (60%) were choriocarcinoma and six (40%) cases were invasive mole.

Table 4 shows trend of β -hCG values, sign and symptoms and site of metastasis in 15 cases of GTN. Diagnosis of post molar GTN was made in cases where women presented with continued vaginal bleeding (8/15, 53.33%), subinvolution (8/15, 53.33%), rising or plateau of β -hCG values (10/15, 66.67%), persistence of theca lutein cysts (5/15, 33.34%) or there were signs or symptoms of metastasis like cough, breathlessness, headache, convulsions or epigastric pain (4/15, 26.67%). Most common site of metastasis was lungs (60%), followed by vagina (26.67%), liver (13%) and brain (6.67%).

Staging and GTN scoring was done for all cases of GTN as shown in Figure 3.

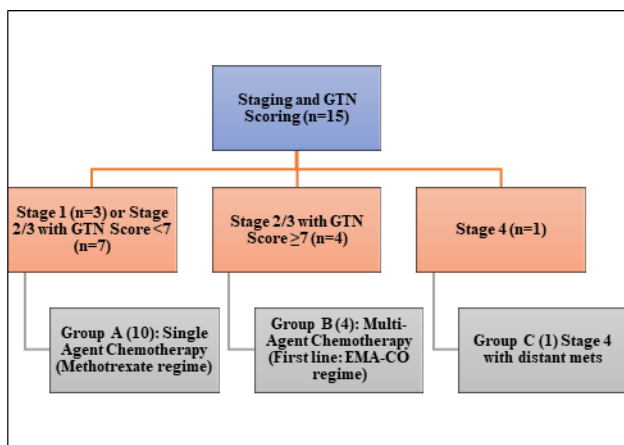


Figure 3: Staging and scoring of GTN.

Cases of GTN were managed in collaboration of the Oncology department. In Group A, eight cases showed complete remission with single agent chemotherapy while two cases had to be started on MAC (methotrexate, actinomycin, cyclophosphamide) regime due to chemoresistance. All patients of group A are in remission and follow-up. One of them presented with a rising β -hCG titre, amenorrhea and size of uterus being more than period of gestation. On further investigations, she was diagnosed with early twin pregnancy and she opted for termination of pregnancy.

In Group B, EMA-CO regime was given to all four cases. Total 4 to 6 cycles were required for complete remission. Hysterectomy was done for one patient after she showed remission. Two patients had to be started on EMA-EP regime due to chemoresistance. Hysterectomy was done

for both patients after they showed remission. However, despite hysterectomy, one of them presented with distant liver and brain metastasis two months later and couldn't survive. One patient in Group C presented in stage 4 with multiple episodes of convulsions, haemoptysis, vaginal bleeding with severe pallor. Before any intervention could be done for her, she died due to complications.

Thus, mortality from GTD in the present study was two out of 162 (1.2%), both belonging to stage 4 and case fatality rate for GTN was 2/15, 13.3%. Remission rate from GTN with chemotherapy was 13/15 (86.8%).

DISCUSSION

GTD encompass a wide spectrum of proliferative disorders of trophoblast tissue which hold a good prognosis if diagnosed and treated on time. Almost 98% of women with GTN recover without any long term sequelae. The incidence and prevalence of GTD shows a wide variation with respect to region.¹ In this study, prevalence of GTDs was found to be 0.74%. The incidence of GTD in the present study turns out to be 1.02 per 100 deliveries which is a slightly lower though comparable to results of other studies like Agarwal N et al (4.17), Koirala et al (3.94) or Sekharan P et al.⁵

Maternal age has been reported to influence the risk of GTD with the prevalence being higher in women less than 20 years and above 40 years of age as reported by other studies.⁹⁻¹¹ Similar observation was made in this study with higher prevalence in women of age group <20 years and in age group >30 years. The prevalence was more in extremes of parity in this study which is in accordance with other studies like Saraf et al and Brinton LA et al.^{12,13}

In present study, all patients (100%) had a period of amenorrhea. Most women presented with 16-20 weeks of amenorrhea (39.5%). In a study conducted by Kolawole et al, 100% cases presented with amenorrhea, while 92.2% cases presented with amenorrhea in a study by Jagtap S.^{2,3} This indicates that a molar pregnancy must be ruled out in a woman who suspects pregnancy and ultrasound scan should be done in all women at booking visit or at least in first trimester.

In present study, about 95% of women presented with bleeding per vaginum following a period of amenorrhea. Other common clinical presentations include pallor (83%), uterine size being more than period of amenorrhea (49.6%) and theca lutein cysts (39.8%). Similar observations were made in other studies Agrawal N et al (86.3%), Kolawole et al (97.6%) and Jagtap S et al (94.8%).^{2,3,6} In another study by Fatima et al, 97.78% cases presented as bleeding per vagina and 84.40% presented as amenorrhea.¹⁴ In this study, classical signs like passage of grape like vesicles (22.8%), hypertension (21.5%), hyperthyroidism (6.5%) and hyperemesis (15.68%) had lower incidence, probably due to advent of

ultrasonography which helps in an earlier diagnosis. Similar observations were made in other studies as well. The study done by Walkington L et al, reported 2% cases of hyperthyroidism while Singh N et al, reported 2.20% cases having hyperthyroidism.^{15,16}

A total 55.47% cases of complete molar pregnancies had a serum β -hCG level in the range of 10,000-50,000 mIU/mL. A level of more than 5,00,000 mIU/mL was found in cases of choriocarcinoma. However, in two cases of advanced partial moles, this level was more than 5 lacs mIU/mL. In the study by Jagtap S, most of the GTD cases showed β -hCG levels between 50,000-1,00,000 mIU/ml and they did not observe a level below 50,000 or above 10 lacs mIU/mL.³ Kolawole et al observed that more than 50% of the cases who got their β -hCG levels done, had levels greater than 12000 mIU/m.

All new cases of molar pregnancies were managed by suction and evacuation and discharged after a falling trend of β -hCG level was established post evacuation. In this study, total 15 cases were of GTN- three follow-up cases from before the study period, six new cases during study period and six new cases on follow-up after molar evacuation at the study institution itself, were diagnosed as GTN and managed with opinion from Oncology department. Overall, there were nine (5.56%) cases of choriocarcinoma and six (3.7%) cases of invasive mole in this study. This prevalence was relatively high as compared with other studies like Jagtap S et al (1.3% cases of Choriocarcinoma), unlike Kolawole et al who observed a higher prevalence.^{2,3} One case of GTN during follow up had conceived due to poor compliance with contraception. Therefore, proper counselling for compliance to contraception till the entire follow-up period is very essential to prevent pregnancy, as this can create confusion regarding prognosis and recurrence.

Remission rate with chemotherapy in GTN cases in this study was 13 /15 (86.7%). This finding reaffirms the fact that gestational trophoblastic neoplasia is one of the tumors which show excellent and complete remission with chemotherapy. All these patients are on follow-up and are doing well. Case fatality ratio of GTN was found to be 2/15 (13.3%) in this study, both had advanced stage 3 or 4 disease. Gueye M et al reported 21 deaths leading to a specific fatality of 12.8%.¹⁷

CONCLUSION

Gestational trophoblastic diseases need an early diagnosis and proper follow-up for effective management. An ultrasound is an important tool in diagnosis of GTD. Ultrasound should be made mandatory in all cases of suspected or confirmed pregnancy in the booking visit for early diagnosis of molar pregnancy. Also, women complaining of vaginal bleeding in first half of pregnancy with uterine size more than POG must be evaluated for GTD by ultrasound and serum beta HCG. For cases of molar pregnancies, suction and evacuation remains the

treatment of choice but need for regular follow-up has to be emphasized. Hysterectomy can be offered in cases where family is complete. For patients desirous of fertility, proper counselling for compliance to contraception till the entire follow-up period is very essential to prevent pregnancy, as this can create confusion regarding prognosis and recurrence. Poor compliance to follow up and contraceptive practice warrants the need for prophylactic chemotherapy in high risk cases. Authors recommend a need for maintaining a GTD registry in every state for proper reporting and follow-up of these cases.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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