A RETROSPECTIVE STUDY OF GESTATIONAL TROPHOBLASTIC NEOPLASIA IN A TERTIARY CARE CENTRE

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ABSTRACT: INTRODUCTION: Gestational trophoblastic neoplasia refers to the malignant spectrum of gestational trophoblastic diseases which include the invasive mole, choriocarcinoma and the very rare placental site trophoblastic tumour**.** It occurs when the normal regulatory mechanisms controlling the proliferation and invasiveness of trophoblastic tissue are lost. Chemotherapy is the best modality of treatment and response to treatment is monitored by hCG surveillance. **OBJECTIVES:** To study the characteristics of gestational trophoblastic neoplasia including high risk factors, its transformation and progression, response to chemotherapy and prognosis. **MATERIALS AND METHODS**: Case records of the patients with gestational trophoblastic neoplasia were analysed retrospectively. The study period was for 5 years from January 2006 to December 2010. **RESULTS:** There were 422 patients with gestational trophoblastic disease during the study period**.** Out of this 22.03% of patients progressed to GTN. 5 patients had metastatic disease.69.95% of the patients were between 20 and 35 years of age and 83.3% had an initial high levels of hCG. Majority of the patients with GTN were nulliparous or grand multiparous. 94.25% patients responded to single agent chemotherapy with methotrexate. Case fatality was 2.15%. **CONCLUSION:** Incidence of GTD was higher compared to international studies. If recognized in time and treated appropriately GTN is amenable to treatment with good cure rates.

KEY WORDS: Gestational trophoblastic neoplasia (GTN), Theca lutein cyst, Methotrexate, EMACO, remission.

INTRODUCTION: Gestational trophoblastic neoplasia (GTN) is the malignant counterpart of gestational trophoblastic disease (GTD) which is a group of pregnancy related disorders arising from abnormal placental trophoblast cells. The premalignant conditions of GTD are the complete and partial hydatidiform mole and the malignant GTN includes the invasive mole, choriocarcinoma, and the rare placental site trophoblastic tumour and epitheloid trophoblastic tumour.

GTN arises when the normal regulatory mechanisms controlling the proliferation and invasiveness of trophoblastic tissue are lost. Post hydatidiform mole gestational trophoblastic neoplasia is diagnosed by rising hCG and abnormal radiology suggesting the presence of molar tissue. Histological confirmation is not needed unless placental site trophoblastic tumour is suspected. According to Seckl et al, 16% of complete mole and 4% of partial mole undergo locally invasive disease and 4% of complete mole grow into metastatic disease.(1) Invasive mole is a complete or partial mole that invades the myometrium. Gestational choriocarcinoma develop from a molar pregnancy or can occur following any gestational experience such as a spontaneous or induced abortion, ectopic pregnancy, and preterm or term delivery. Incidence of choriocarcinoma is hard to calculate as most cases are labeled as post molar GTN, but the incidence of choriocarcinoma following nonmolar pregnancy is estimated to be 1 in 50,000. Differentiating between invasive mole

and choriocarcinoma following a molar pregnancy is not important as they respond to the same treatments.

Since GTN is one of the highly curable neoplasms, early diagnosis and prompt treatment is advocated. The majority of cases can be cured by chemotherapy with very low toxicity regimen. Unlike other gynaecological malignancies, fertility can be preserved and normal pregnancy outcome anticipated. (2)

MATERIALS AND METHODS: This was a cross sectional study conducted in the department of Obstetrics and Gynaecology, Govt. Medical College, Calicut in 2012. The hospital records of patients with malignant GTN during the five year period from January 2006 to December 2010 were analysed retrospectively.GTN was diagnosed on the basis of rising or persistent hCG after evacuation of a hydatidiform mole or histological evidence of choriocarcinoma or radiological findings suggestive of metastasis. Information regarding the age, parity, blood group, gestational age and uterine size at evacuation of molar pregnancy, type of antecedent pregnancy, hCG levels and treatment received including chemotherapy and surgery were recorded. Analysis done to assess the incidence and characteristics of GTN including high risk factors, transformation and progression of benign disease to malignant, and the response to chemotherapy. Analysed data was expressed as frequencies and means.

RESULTS: During the study period there were 88166 deliveries and 422 cases of molar pregnancy registered in the vesicular mole clinic with an incidence of 4.8/1000 deliveries. Of the 422 patients with GTD, 93 were diagnosed to have GTN during follow up, with an incidence of 22.03% of the trophoblastic diseases. Of these eighty eight (20.85% of GTD cases) had locally invasive disease and five (1.18%) had metastatic disease. There were 6 histologically proven cases of choriocarcinoma comprising 0.68/ 10000 deliveries. Five patients with choriocarcinoma presented with metastasis and one had disease confined to the uterus. Of the 93cases of GTN, 74 had evacuation of hydatidiform mole from our institution and the rest had evacuation outside and were referred for follow up.

Majority of the GTN patients were between 21-35 years of age (69.89%) (Table -1) Age of the patients was between 16 and 45 yrs with mean age of 25.6 years .There were four patients above the age of 40 years. All the patients with choriocarcinoma were between 21 and 30 years. 45.16% were nulliparous and 24.73% were para 3 and above. (Table – 2). The common blood groups seen in the reviewed cases were O +ve (36.6%), followed by B+ve (34.4%). (Table -3).

Gestational age at evacuation of the molar pregnancy was between 6 and 21 wks with mean 11.8 weeks. 32.3% had evacuation of molar pregnancy at a gestational age more than 12 weeks. Only 28 cases (37.84%) of the 74 cases evacuated in our institution had uterine enlargement more than the gestational age. βhCG levels of 72 patients were known. 83.3% had pre evacuation βhCG level more than 1 lakh. 32.3% had persistent theca lutein cyst after evacuation. Irregular bleeding following evacuation occurred in 28% of cases.

Only one case of GTN had a history of recurrent molar pregnancy. All the non metastatic disease was following a molar pregnancy. 21.59% were following a partial mole and 78.41% were following a complete mole. Of the 6 choriocarcinomas, 50% were following complete mole, 2 were following a term delivery and one case followed a first trimester abortion. All the three case of

choriocarcinoma following non molar pregnancy presented with irregular vaginal bleeding following the gestational event. Five out of six choriocarcinomas, showed metastatic disease.

Transformation to neoplasia was diagnosed by plateauing or rise in hCG. 81.7% showed rise in βhCG and 15.1% showed plateauing. Increase in hCG noted from 2 weeks after evacuation. Longest period of transformation was seen in a case of choriocarcinoma where symptoms of malignant changes developed 34 weeks after an uneventful delivery. Mean duration of transformation to neoplasia after evacuation of the molar pregnancy was 7.8 weeks. 34 patients had ultrasound findings suggestive of invasive mole.

94.62% patients belonged to Stage 1 disease. 2 patients had vaginal metastasis, 1 had metastasis to lungs alone and 2 patients belonged to stage IV disease; one with liver metastasis and one with metastasis to brain and spleen. (Table - 4 and 5). Stage I and II patients (96.77%) had a FIGO prognostic score less than 6 (low risk) and Stage III and IV (3.23%) had score more than 6 (high risk).

All the patients in the low risk group including those with vaginal metastasis (89) were treated with Methotrexate- folinic acid regime. 2 patients took incomplete treatment and were lost to follow up. Of the patients who completed chemotherapy, 94.25% attained remission with methotrexate and 5.74% developed resistance. Overall, 95.29% with Stage I and 50% with Stage II disease attained complete remission with methotrexate folinic acid regime. Chemotherapy was given every 2 weeks with one more course after βhCG came to normal. Minimum number of courses of chemotherapy required was 2 and maximum was 10. (Table -6). Mean number of courses was 4.26. One patient with Stage II low risk disease and 4 patients with Stage I disease had methotrexate resistance and were changed to EMACO regime.

One patient with stage I disease who had abnormal liver function was given Actinomycin and recovered completely.

Combination chemotherapy with EMACO regime were given to 8 patients. One was having Stage III high risk disease, 2 were with stage IV disease and the rest 5 were with low risk disease who did not respond to single agent chemotherapy with Methotrexate. The patients in Stage I and II disease treated with EMACO achieved remission, while the patient with Stage III high risk disease was lost to follow up after one course of EMACO. Both the patients in Stage IV disease succumbed to death while on chemotherapy. (Table – 7)

Eight patients (8.6%) with GTN underwent hysterectomy. For three patients above the age of 40 years and two with histopathology report of choriocarcinoma, hysterectomy was done as a primary procedure. 3 of the total hysterectomies were performed as an emergency procedure, one for uterine perforation and intraperitoneal hemorrhage and two for intractable vaginal bleeding in spite of chemotherapy.(Table -8)

With complete chemotherapy, 94.62% of patients achieved remission. Mean duration of remission after the start of chemotherapy was 21.7 weeks. Three patients (3.22%) took incomplete treatment. Mortality occurred in 2.15%.

After remission, 72 patients completed one year follow up and 16 were lost to follow up. 22 patients (23.65%) had uneventful pregnancy and delivery after one year of completion of chemotherapy and 2.15% had missed abortion. None had a recurrent molar pregnancy.

DISCUSSION: Incidence of gestational trophoblastic disease was 4.8/1000 deliveries. This was higher compared to the 1 in 1000 pregnancies in Europe reported by Seckl MJ et al (1) and 2.5/1000

deliveries in North America as reported by Lara et al (3). Highest incidence of 12.1/10000 deliveries was reported in Turkey by Harma M et al. (4)

20.85% of trophoblastic diseases progressed to non metastatic GTN and 1.18% developed metastatic GTN. Studies by Berkowitz et al have shown that 15% of patients with molar pregnancy develop locally invasive tumour and 4% develop metastatic tumour. (5) 6.45% patients with trophoblastic neoplasia had choriocarcinoma; almost similar incidence reported by Khairuneesa et al (6)

Extremes of age are known risk factors of GTN (7), but most cases (69.89%) in this study were between 21 – 35 years. In their study Sakunthala Chabra et al cite that 24.4% of GTN patients were more than 25 years of age and 47.47% were between 20 and 25 years.(8) But other authors have reported age specific incidence to reveal a J shaped curve ; teenagers and women over 40 years old have higher incidence.(9) Transformation to GTN was seen to be high in nullipara and grand multipara (para 3 and above).

The proposed predictors of development of neoplasia in GTD are evacuation of the vesicular mole at gestational age more than 12 weeks, uterine size more than the gestational age, pre evacuation βhCG more than one lakh and persistent theca lutein cysts. There was a significant relation between hCG levels over 100,000 mIU/ml and persistence of disease. (10) In our study, 83.3% patients had βhCG more than one lakh. Other risk factors were found in about one-third of cases. Nermis Kosus reported excessive uterine enlargement in 36.8% of invasive mole βhCG, more than one lakh in 78.9 % of invasive mole and all patients with choriocarcinoma, theca lutein cyst in 57.9% of invasive mole and 33.3% of choriocarcinoma (10).

The antecedent pregnancy was complete mole in majority of the cases, but partial moles also were found to turn malignant. A study on invasive mole reported that seventy and three tenth percents were preceeded by complete mole, 18.5% by partial mole and 11.2% by uncertain pathology. (11). In this study non molar pregnancies progressed to choriocarcinoma with metastasis. Antecedent pregnancy was hydatidiform mole in 40% and spontaneous abortion in 60% cases of choriocarcinoma. (12)

Mean duration of transformation to malignancy as detected by hCG levels and imaging was 7.8 weeks after termination of antecedent pregnancy. Average transformation period was 2.6 months in a study of invasive mole in Indonesia. (11) Time interval between end of antecedent pregnancy and onset of chemotherapy was 4 – 7 months in 60% of the patients in a study of choriocarcinoma. (12)

All Stage I patients were low risk and all Stage IV patients were high risk. 95.29% patients with Stage I and 50% with Stage II disease recovered with methotrexate folinic acid regime. Recent studies on chemotherapy for GTN showed 83.5% remission in Stage I, 80% in Stage II low risk and 81.8% in Stage III low risk patients treated with methotrexate. (13) In an earlier study in our institution, 92.9% with post molar GTD was found to have complete remission with Methotrexate – folinic acid regimen. (14)

There was 100% remission in Stage I and Stage II patients (with methotrexate resistance) treated with combination chemotherapy. Total remission with EMACO was 62.5%. Combination chemotherapy was found to induce complete remission in 100% with high-risk stage II GTN and in 97.3% with high-risk stage III GTN. (13)

Hysterectomy either as primary treatment or after a diagnosis of drug resistance is clearly beneficial in women whose lesions are still confined to the uterus. (15). Stage I patients who underwent hysterectomy had 100% remission with methotrexate.

Both the patients (2.15%) who died in spite of chemotherapy had Stage IV disease. Other studies showed case fatality of 2.02% (8) and 3.3% (6)

CONCLUSION: Incidence of GTD was higher compared to international studies. Trophoblastic disease with initial βhCG levels more than 1 lakh are at risk of progression to neoplasia and transformation is mainly detected by rising hCG values. Malignant GTN has good prognosis with single agent chemotherapy with methotrexate and the subsequent uneventful pregnancy is more than 20% after one year of completion of chemotherapy. Hence continued patient education, social awareness, and strict surveillance is required; so that neoplasia developing after molar pregnancy can be detected as early as possible, thereby reducing complications and mortality and preserving future fertility.

Table -1: Age wise distribution

Age (yrs)	Frequency	Percentage
< / = 20	19	20.43%
21 - 35	65	69.89%
>35	9	9.68%

Table -2: Parity

Parity	Frequency	Percentage
Nullipara	42	45.16%
Para one	16	17.2%
Para 2	12	12.9%
Para 3 and more	23	24.73%

Table -3: Blood group

Blood group	Frequency	Percentage
O+	34	36.6%
B+	32	34.4%
A+	19	20.43%
B-	5	5.38%
O-	2	2.15%
AB+	1	1.08%

Table -4: Stage of disease

Stage of disease	Frequency	Percentage
Stage I	**88**	**94.62%**
Stage II	Stage II	Stage II
Stage III	Stage III	Stage III
Stage IV	Stage IV	Stage IV

Table -5: Metastatic sites

Metastasis	Frequency	Percentage
brain, lung, spleen	1	1.1%
liver, lung	1	1.1%
lung	1	1.1%
vag	2	2.2%

Table -6: No. of chemotherapy courses

No: of courses of Methotrexate	Frequency	Percentage
<= 4 doses	58	62.4%
> 4 doses	33	35.5%
Incomplete chemo	2	2.2%

Table – 7: Response to chemotherapy

Chemotherapy regime	No: of patients treated	Remission	Resistance	Incomplete treatment
Methotrexate – folinic acid	89	82 (94.25%)	5 (5.74%)	2
Actinomycin	1	1 (100%)		
EMACO	8	5 (62.5%)		1

Table – 8: Hysterectomy

Stage of disease	No: of patients who required hysterectomy
Stage I	6
Stage II	0
Stage III	1
Stage IV	1

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