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Incidence and clinicopathological profile of gestational trophoblastic disease in tertiary care centre

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ABSTRACT

Introduction: Gestational trophoblastic disease (GTD) arises from abnormal proliferation of placental trophoblastic tissue. The aim of this study was to determine the incidence and clinicopathological profiles with treatment outcome of gestational trophoblastic disease in Jigme Dorji Wangchuck National Referral Hospital, a tertiary hospital in Bhutan. **Method:** A prospective and retrospective observational study was conducted over a period of 18 months. **Results:** A total of 121 cases of gestational trophoblastic disease were diagnosed with an incidence rate of 19.7 per 1000 deliveries. Majority comprised hydatidiform moles (115);of which, 30 (26.1%) were complete and 85(73.9%) partial moles. The mean gestational age at diagnosis of hydatidiform mole was 9.8± 1.6 weeks and the most common symptom being vaginal bleeding (72.8%). Nine (7.8%) of these progressed to gestational trophoblastic neoplasia and was strongly associated with high pre-evacuation beta-hCG level (> 100,000 mIU/ml) and larger uterine size (> 14 weeks).**Conclusions:** This study revealed a high incidence of gestational trophoblastic disease in national referral hospital. Further in-depth research and instituting a GTD registry can be useful to validate these findings and find the true incidence. A substantial number of molar pregnancies can progress to GTN, and thus requires strict follow-up.

Keywords: Choriocarcinoma; Complete mole; Gestational trophoblastic disease; Molar pregnancy; Partial mole.

INTRODUCTION

Gestational Trophoblastic Disease (GTD) represents a heterogeneous group of disorders characterized by abnormal proliferation of placental trophoblastic cell. World Health Organisation (WHO) classifies it into benign and malignant lesions. The benign forms are hydatidiform mole (HM) and comprises complete and partial mole. Gestational trophoblastic neoplasia (GTN) or the malignant forms are invasive mole, choriocarcinoma, placental site trophoblastic tumour (PSTT) and epithelioid trophoblastic tumour.

Hydatidiform mole (HM) forms the majority (80%) of GTD with invasive moles (15%) and choriocarcinoma (5%). The incidence of HM in Japan and middle-east countries is twice as high; as compared to Europe or North America (1 per 1,000 pregnancies)[1,2]. Incidence of choriocarcinoma has been approximately 1 in 40,000 to 9 in 40,000 pregnancies[2]. The risk of molar pregnancy is higher in extreme of age; more so in elderly women[3]. While, overall risk of recurrence in subsequent pregnancies is 1.5-2%[4].

GTD is a significant problem among Bhutanese women resulting in higher inpatient admission-rate and greater morbidity in our referral hospital. This study was based in single institute, which aimed to determine the incidence and clinicopathological profile of GTD. The primary objective was to study the GTD incidence rate, and pathological types and treatment outcome.

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METHODS

This was a retrospective and prospective observational study of all newly diagnosed GTD cases among Bhutanese women in JDWNRH from 1st January, 2015 to 30th June, 2016. Complete mole patients were included with clinical diagnosis and histopathology (HPE) reports while partial moles were diagnosed from positive HPE reports; of specimens obtained from uterine evacuation of missed abortion or incomplete miscarriage. Choriocarcinoma cases were diagnosed with clinical criteria and HPE confirmation.

After obtaining ethical clearance from Research Ethical Board of Health (REBH/Approval/2015/034) and informed consent from patients, a data collection sheet was used to collect individual patient's information on present pregnancy like gravida, parity, gestational age calculated from last menstrual age; and past pregnancy details. Demographic data on home-town, ethnicity, education, occupation, socioeconomic class; and whether referred from district or not were also noted. Clinical presentations included the signs and symptoms, pre-evacuation beta-hCG, pelvic ultrasound findings, complications and treatment received. Follow-up of HM patients with weekly and monthly beta-hCG were done till the last case in June 2016 had

been declared cured as per the protocol for surveillance. For GTN and choriocarcinoma cases; details of antecedent pregnancy, beta-hCG levels, the risk categorization and staging; and type of chemotherapy regimen given were studied.

The data generated was used to calculate incidence, frequency of disease and treatment outcome rates. An assessment to know about the risk factors, common clinical presentation, and pathological types were also included. Data was entered into Microsoft Excel (Microsoft Corp.) and analysed using Statistical Package for Social Sciences Version 16 (SPSS Inc.USA). Descriptive analysis was done and findings were presented as percentages, mean, median and standard deviation. Inferential statistics such as Chi-square test and odds ratios (OR) with 95% confidence intervals (CI) were calculated to find significance. P value < 0.05 indicated statistical significance. For the incidence and frequency, the total number births (defined by birth after 28 weeks of gestation irrespective of outcomes) and total gynaecological patients admission in same period used in the denominator.

RESULTS

In a one and half year period, 121 cases of GTD were diagnosed of which 115 (95%) cases were hydatidiform moles (HM). Eighty five (73.9%) of these cases were partial and 30 (26.1%) cases were complete moles. Five confirmed cases of choriocarcinoma and one placental site trophoblastic tumour were also seen. The total number of deliveries obtained from the birth register was 6149 and total gynaecological admission was 878 patients in the same period. The overall incidence rate was 19.7 per 1000 deliveries. GTD constituted 13.7% of the total gynaecological admitted cases in the maternity ward. Incidence of HM was 18.7 per 1000 deliveries and choriocarcinoma at 0.81 per 1000 deliveries. Table 1 illustrates the demographic characteristics of GTD.

Diagnosis of complete moles with clinical criteria alone was 33 cases. Of these, four cases were reported as retained products of conception, and five cases were reported as partial moles by histopathological examination. Histopathology of missed miscarriage, anembryonic pregnancy and incomplete miscarriage revealing partial mole were 22.6%, 22.6%, and 25.2% respectively. One tubal pregnancy and septic miscarriage also showed partial mole. Table 2 shows the age distribution of hydatidiform mole with 107(93%) patients within the age-group of 21 to 40 years. There was no significant association (p=0.67) between type of molar pregnancy and age.

The average gestational age at presentation of HM was 9.8 ± 1.6 weeks with range from 7 to 14 weeks. Partial moles were diagnosed earlier than complete moles (9.4 versus 11.2 weeks). The most common clinical symptom of HM was vaginal bleeding

Table 1. Incidence and demographic characteristics of GTD

Total GTD cases	121
Incidence rate	19.7 per 1000 deliveries
Age at diagnosis	
Mean ± SD	28.7 ± 5.8 years
Range	18 – 50 years
Parity	
Median	1
Range	0 – 6
Region	
North	73.6%
South	26.4%
Occupation	
Housewives	52.9%
Civil servants	26.4%
Private/business	20.7%
Percentage of referred patients	23.1%

Table 2. Age distribution of hydatidiform moles (n=115)

Age group	Complete moles n(%)	Partial moles n(%)	Significance
< 20	2 (6.7)	4 (4.7)	0.67
21-30 years	20 (66.7)	52 (61.2)	
31-40 years	7 (23.3)	28 (32.9)	
> 40 years	1 (3.3)	1 (1.2)	

Table 3. Clinical characteristics of complete and partial molar pregnancy

Clinical findings	Complete moles (%)	Partial mole (%)
Gestational age at diagnosis		
Average	11.2± 1.3	9.4± 1.4
Median	12.0	9.0
Range	8-14	7-12
Vaginal bleeding	21(70%)	62(72.9%)
Hyperemesis	09 (30%)	04 (4.7%)
Larger uterus	26 (86.7%)	06 (7.1%)
Anaemia and blood transfusion	18 (60%)	07 (8.2%)

(83 of 115 HM cases). Hyperemesis, anaemia requiring blood transfusion, and larger uterine size occurred more commonly in complete moles than partial moles. Table 3 depicts the clinical characteristics of hydatidiform mole.

Suction curettage and dilation & evacuation formed the treatment mode for hydatidiform mole. Complete mole required more than one evacuation, and repeat procedure was done in 19 (63.3%) patients. One partial mole in tubal ectopic pregnancy had laparotomy and right salphingectomy done. The cure rate of HM achieved was 89.9% after adjusting for the patients who were lost to follow up and those who progressed to GTN. The average period to achieve undetectable beta-hCGlevel was 5.2 ± 1.8 weeks with a range from 2 to 11 weeks. Complete moles took a longer time than partial moles (6.6± 1.6versus 4.8 ± 1.3week).

Fifteen cases of GTN were recognized. Nine (60%) cases were persistent GTD after a molar evacuation, five (33.3%) were gestational choriocarcinoma and one (6.7%) was a placental site trophoblastic tumour. Overall, 11 (73%) had occurred following molar pregnancy, 2 (13.5%) followed miscarriage and 2 (13.5%) occurred after a term pregnancy. The persistent GTD occurring after complete and partial mole were 26.7% and 1.2% respectively. Table 4 compares persistent GTD from cured GTD in terms of age, beta-hCG level and uterine size by using odds ratio. There was no significant difference in persistent GTD rates between patients aged <40 years and ≥ 40 years. However, beta-hCG level > 100,000 mIU/ml and larger uterine size (>14 weeks) were significantly associated with persistence of GTD.

Table 4. Comparison of patients with persistent and cured GTD

Odds ratio	Persistent GTD (n=9) n (%)	HM cured (n=106) n (%)	*p*- value
Age (years)			OR-2.08
≥ 40	1 (11.1)	6 (5.6)	*p*-0.52
< 40	8 (88.9)	100 (94.4)	(95% CI 0.22-19.49)
b-hCG(mIU/ml)			OR-23.0
≥100,000	7 (77.8)	14 (13.2)	*p*-0.0002
<100,000	2 (12.2)	92 (86.8)	(95% CI 4.33-1222)
Uterine size			OR-89.2
≥ 14 weeks	7 (77.8)	4 (3.8)	*p*-< 0.0001
< 14 weeks	2 (12.2)	102 (96.2)	(95% CI 13.5-574.5)

Out of fifteen, eleven cases were in stage I, and four cases were in stage III with lung metastasis. Nine (60%) of them classified as low-risk and five (40%) were high-risk according to FIGO-WHO risk classification. Most (66.7%) low-risk GTN responded to single agent methotrexate regimen as first line and 33.3% received multi-agent EMACO regimen due to resistance.

DISCUSSION

Our study revealed incidence of GTD at 19.7 per 1000 deliveries in JDWNRH which seemed very high for a country with low population density. Earlier studies viewed that Asian populations are at increased risk of developing GTD, but subsequent reports and reviews revealed a decreasing incidence possibly due to inconsistencies in reporting system or improvements in the socio-economy[5,6]. Recent studies from Asian countries have shown incidence rate ranging from 1.3 to 4.2 per 1000 deliveries which is at similar rate to developed countries[7,8]. The high incidence could be a true burden of GTD in our population or higher cases could be due to many referrals from other districts. Establishing a GTD registry or further multi-centred studies would be able to determine the true incidence.

Our finding of hydatidiform mole (95%) cases followed by choriocarcinoma (4.1%) diagnosis was similar to clinicopathological studies conducted by Wairachpanich et al. and Sharifi et al[8,9]. A higher number of partial moles and therefore high incidence could also suggest a pathological diagnostic challenge of hydropic changes of failed pregnancies from true moles. An increasing number of molar pregnancies are diagnosed earlier; adding further challenge to diagnosis[10].

Risk factor such as extremes of maternal age (≤ 15 and ≥ 45years) is associated especially older maternal age with molar pregnancy[11]. In our findings, majority (93%) of cases were aged between 21 to 40 years. Studies have shown, the risk of progression to GTN after complete and partial moles was 15-20% and 1-5% respectively which was similar to our study; 26.7% and 1.2%[12]. One of the complete moles reported negative for molar tissues had also progressed to GTN. A false negative could be due to inappropriate tissue selection and processing for histopathological examination. Thus, the importance of appropriate and adequate tissue selection; as well as following up patients diagnosed by clinical criteria is emphasized here.

A rare case of partial mole was seen in ectopic pregnancy. Study shows it's incidence to be about 1 in 100,000 pregnancies[13]. We suggest tissues from all early pregnancy complications to be subjected to histopathology for appropriate diagnosis.

Patients with complete molar pregnancy had a larger uterus than estimated gestational age, higher rates of anaemia requiring blood transfusion and higher beta-hCG levels at presentation than patients with partial molar pregnancy which are very much consistent with other studies[7,8]. Like in other studies, ultrasound has played a major role in early diagnosis and has better detection rate of complete moles than partial moles[14,15]. Suction evacuation was the primary mode of treatment of molar pregnancy; and achieved cured in about 90 percent of all molar pregnancies[2,5,8].

More than half of the patients with low-risk GTN responded well to single agent methotrexate regimen as first line and 33.7% of them received multi-agent EMACO regimen due to resistance. Actinomycin-D in these resistant patients was not tried due to toxicity, although higher cure rates have been proclaimed in a Cochrane review by Alazzam et al. for low- risk GTN[16].

A significant association between pre-evacuation beta-hCG level > 100,000 mIU/ml and larger uterus more than 14 weeks; and persistence of GTD was found as in other studies[4,8,17]. It is emphasized that patients with high serum hCG and larger size uterus are strictly monitored during surveillance to detect early progression to GTN and institute timely intervention.

The average week to achieve undetectable beta-hCG level after evacuation was about 5.2 ± 1.8 weeks with complete moles taking longer time than partial moles (6.6 versus 4.8 weeks). The fall of beta-hCG levels were seen earlier or similar to other studies[8,9].

CONCLUSIONS

From this study, it is evident that a high burden of GTD is existing in JDWNRH. Molar pregnancies can occur from any type of gestations and a substantial number of them progress into GTN which necessitate a strict follow up for early intervention and management.

The finding of high incidence could have been confounded by high number of referrals to our centre which was limited by a retrospective analysis. The outcome of GTN and choriocarcinoma could not be followed up due to long follow up period and limited time. However, this study being the first of its kind in our population will serve as a baseline data for future studies**.** We recommend on instituting a GTD registry and further studies to validate our study findings and find true incidence.

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AUTHORS CONTRIBUTION

Following authors have made substantial contributions to the manuscript as under:

TT: concept, analysis of data, study design, manuscript drafting and critical reviews

UT: concept, analysis of data, study design, manuscript drafting and revisions

Authors agree to be accountable for all respects of the work in ensuring that questions related to the accuracy and integrity of any part of the work are appropriately investigated and resolved.

CONFLICT OF INTEREST

None

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