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A longitudinal study of Hydatidiform mole in a tertiary care centre of Manipur

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Introduction

Gestational trophoblastic disease (GTD) is defined as a neoplastic process that is derived from fetal chorion during pregnancy. It includes a spectrum of disease comprising molar pregnancies, persistent invasive moles, gestational choriocarcinomas and placental site trophoblastic tumours. Molar pregnancy is characterized histologically by abnormalities of the chorionic villi that consist of trophoblastic proliferation and oedema of villous stroma. The absence or presence of fetal or embryonic elements has been used to describe them as complete or partial mole.

The problem of the disease essentially remains an enigma. Probes into its mystery could not still unravel fully the complex nature of its etiopathogenesis, although various theory have been postulated. Even today there is no universally accepted classification of GTD. Indeed, several systems continue to be used for staging including WHO, FIGO scoring index, NIH classification & others.[1]

The incidence of GTD varies dramatically in different regions of the world. The reported incidence of molar pregnancies varies between 0.5 - 2.5 out of 1,000 pregnancies.[2] Asia has been known to have an elevated incidence of molar pregnancy that is 10 times higher than Europe and North America.[2,3] Besides, it is still more prodigious that even in the same region one particular segment of the community is far more affected than the other and also in the same individual more than one factor may be involved. For instance, women aged above 40 years are particularly susceptible to complete mole and are responsible for 1/3 of all the cases. There is increased risk in the 14 -16 years old primigravidas. Maternal age has been consistently identified as an important risk factor. Teenagers and women over 40 years old have higher rate. [4,5]

Thus, the diverse manifestations of the GTD provide a very fascinating area of research from the standpoints of identifying the prognostic factors for developing the disease. The crux of the present article is to assess the magnitude of the disease in terms of incidence rate per

1,000 pregnancies based on a hospital base sample of Manipuri women. Besides it also aims to identity risk factors associated with molar pregnancy and to evaluate the outcome following the termination of Molar pregnancy over a period of six months.

Methods

The present study was a prospective/longitudinal study conducted at the department of Obstetrics and Gynaecology, Regional Institute of Medical Sciences, Imphal from August 2009 to July 2011. All patients with Molar pregnancy admitted in the department were included for the study. The study was approved by the institutional ethical committee. Inclusion criteria was patients fulfilling the prementioned criteria and willing to participate in the study. Patients not willing to participate were excluded from the study. Informed consent was taken from all the participants and in case of minors, informed consent was taken from the parents with assent from the patient.

Identity of all the patients in relation to name, age, address, religion, socio-economic status, marital status, parity, literacy status, occupation were noted. It was followed by a relevant history and thorough clinical examination. Apart from the routine investigations of blood and urine examination, special investigations like serum b-hCG, ultrasonography, X-ray chest, thyroid profile and histopathological examination were done. All the above mentioned findings were incorporated in a pre-designed proforma. Termination/treatment was planned by suction evacuation and in selected cases by dilatation and evacuation. Injection oxytocin was given during the procedure to all patients to control vaginal bleeding. Serum β-hCG was repeated after 48 hours. If it was more than 1 lakh, plateau or rises over previous values, patients are kept for 1 week for observation. Serum β-hCG level was repeated till 3 consecutive values are normal.

The follow up was done for a period of 6 months after normalization of the serum β-hCG. Clinical examination, serum β-hCG level, USG etc were the criterions on which the patients were assessed. If in a patient, β-hCG was persistently high or rises again/plateaus in the follow up period or shows any other evidence of persistent disease, she was designated as case of GTN. Such type of cases in our institute was managed by a single agent methotrexate (MTX) or multidrug (EMACO) chemotherapy (for those patients who don't respond to single agent chemotherapy).

The incidence was calculated per 1000 pregnancies in our institution. Other data were in proportion and percentage. The final analysis was done by Chi-square test ($\chi 2$) using SPSS software.

Results

The present study is based on a sample of 48 molar pregnancy mothers screened out of the 24,524 pregnant women who were admitted in the department of Obstetric & Gynaecology, RIMS during August 2009 to December 2011. After informed consent all study subjects were identified having molar pregnancy through clinical assessment and ultrasound.

Detailed findings of clinical examination and routine investigations were elicited on the predesigned proforma. Patients were planned for suction evacuation or hysterectomy. Besides patients were follow up with β-hCG and clinical examination and USG if required on weekly basis till β-hCG becomes normal. Single agent chemotherapy in the form of Methotrexate (MTX) or combination chemotherapy (EMACO) was given for raising or plateau β-hCG levels depending upon the initial FIGO scoring. Chemotherapy was given till the β-hCG level becomes normal. Once β-

hCG becomes normal after chemotherapy, then patients were followed up on monthly basis. The data were processed through SPSS package using χ^2-test and P-value less than 0.05 is taken as cut off value of significance.

Table 1: Age – wise incidence rate of Hydatidiform mole

Age (yr.)	No. of pregnancy	No. of Hydatidiform Mole	Incidence rate /1,000 pregnancies
Below 20	1344	6	4.46
20-30	15909	31	1.94
31-40	7041	7	0.99
40 and above	230	4	17.39
Total	24,524	48	1.95

$\chi^2 = 35.72$; df = 3, P < 0.001

Over all incidence rate of molar pregnancy per 1,000 pregnant women in the study sample is approximately 2 (1.95) and it varies according to age. The rate for the women having less 20 years is 4.46 and thereafter it decreases as age advances up to 31- 40 years (0.99) and then a sudden spurt of incidence rate (17.39) occurs in the age group of 40 years and above. These variation of rates over the age groups is found to be highly significant (P<0.001) that implies age is one of the significant risk factors for molar pregnancy especially in late and early ages.

Table 2: Parity –wise incidence rate of Hydatidiform mole

Parity	No. of pregnancy	No. of Hydatidiform mole	IR/1,000 pregnancy
P0000	13598	21	1.54
P0010	6758	4	0.59
P1001	2688	12	4.46
P2002	1002	5	4.99
P3003	374	2	5.34
P4004 and above	104	4	38.46
Total	24524	48	1.95

$\chi^2 = 94.15$; df =5; P <0.001

Table 2 show a positive association ship between parity and molar pregnancy as parity advances the corresponding incidence rate increases monotonically. A spurt pertains to P_{4004} which further entails the previous findings that late pregnancy attributes with higher parity. Further it is observed that parity has a certain link on the manifestation of molar pregnancy (P<0.001) especially at and after 4th parity.

Table 3: Distribution of Hydatidiform mole POG, Bleeding & Blood group

Parameters	No. of H/Mole (%)	χ^2	d.f.	P-value
POG (wk) :				
Below 12	22 (45.8)			
12-24	23 (47.9)	11.10	2	< 0.01
24 +	3 (6.3)			
Bleeding per Vaginum :				
Absent	8 (16.7)			
Mild	26 (54.1)	11.40	3	0.01
Moderate	11 (22.9)			
Severe	3 (6.3)			
Blood group :				
A +ve	14 (29.2)			
B +ve	11 (22.9)			
AB +ve	11 (22.9)	0.24	3	0.970
O +ve	12 (25.0)			

It is interesting to note from the table – 3 that percentages of H/Mole for the POG of below 12 weeks

and 12-24 weeks are almost akin to around 45% while sudden down fall to around 6% for POG of 24 weeks and above. The variation is found to be highly significant (P<0.01) that highlights higher POG, above 24 weeks, has less association with H/mole. Highly significant P-value (P<0.01) for bleeding per vaginum indicates the mild case has the most commonly occurred while the severe the least one.

At the same time, blood grouping of the patients doesn't have any association ship with the presence of molar pregnancy as evident by P=0.970.

Table 4: Distribution of Hemoglobin; β-hCG & blood transfusion

Parameters	No. of H/Mole (%)	χ^2	d.f.	P-value
Hb level : Below 6 gm 6-8 Gm% 8-11Gm % 11 + Gm %	 5 (10.4) 8 (16.7) 16 (33.3) 19 (39.6)	5.83	3	0.119
β-hCG : below 1,000 1,000 -10,000 10,000 – 1,00,000 >1,00,000 – 10,00,000 > 10,00,000 +	 3 (6.3) 2 (4.1) 9 (18.8) 26 (54.2) 8 (16.6)	16.45	4	< 0.01
Return of β-hCG to normal : 4 weeks 6 weeks 8 weeks 12 weeks 12 weeks + lost to follow	 2 (4.2) 5 (10.4) 10 (20.8) 15 (31.3) 12 (25.0) 4 (2.1)	8.78	5	0.118
Blood transfusion (unit) : 0 1-2 3-4 5 +	 8 (16.7) 34 (70.8) 3 (6.2) 3 (6.2)	22.12	3	< 0.01

A sharp positive correlation is witnessed, in table - 4, between Hb% level and H/Mole as the level rises, the percentage of H/mole cases increases dramatically from 10.4% for below 6 gm% Hb level to 39.6 % for 11gm% and above Hb level. Nevertheless variation of percentages over the Hb level is not significant enough statistically (P=0.119) and therefore Hb does not have significant impact on H/mole. However, β–hCG level has certain link with the occurrence of H/mole as evident by highly significant P-value (P < 0.01). Return of β-hCG to normal in terms of duration in weeks is not significant (P=0.118) but highest (31.3%) return within 12 weeks and lowest (4.2%) to 4 weeks. Highest percentage (70.8) of H/mole cases used 1-2 units of blood for transfusion as against the lowest (6.2%) each for 3-4 units, 5 units and above. The number of units used is varied significantly (P < 0.01).

Table – 5: Profile of post-molar GTD requiring chemotherapy

Parameter	No. of patients		
Age	10(<30 yrs)	4 (31-40 yrs)	1 (> 40 yrs +)
Fundal Ht vs POG	11 (more)	4 (same)	
Theca lutein cyst	Present = 9	Absent = 6	
Blood group	A = 5	AB = 6	O = 3, B = 1
β-hCG (mlU/ml)	< 1 lakh = 2	1-10 lakhs = 8	> 10 lakhs =5
Chemotherapy	MTX = 10	EMACO = 5	

Table - 5 shows the profile of the 15 patients requiring chemotherapy i.e., out of 15 post molar GTD, 10 were below 30 years. Eleven patients had fundal height more than period of gestation. Theca lutein cysts were present in 9 patients. Thirteen patients had β-hCG > 1,00,000 mlU/ml. Single agent chemotherapy (Methotrexate and Leucovorin) was given in 10 patients and another 5 had EMACO.

Discussion

During August 2009 to July 2011, when the present study undergoing, the total number of pregnancies admitted was 24524 and there were 48 cases of molar pregnancies detecting the incidence rate of 1.95/1000 pregnancies. But three decades earlier, in this Institute the incidence was 1/133 (7.5 per 100 pregnancies).[6] A South Korean population-based study noted a drop in the incidence from 40/1000 deliveries to 2/1000 that was coincident with refinement in disease terminology and classification.[7] In Japan the incidence varies from 2.83 to 3.05/1000 live birth.[3] In the extremes of reproductive age below 20 years and above 40 years the disease is very common.[4,5] The present study also reveals the same findings. There is high association of molar pregnancy with elderly age group particularly more than 40 years. In the present study maximum number of H/mole is diagnosed before 14 weeks of pregnancy (93.7%). The use of ultrasound scanning in the early month of pregnancy when associated with vaginal bleeding (84.3%) helps in the diagnosis. However, in a study by Fowler et al. routine pre-evacuation ultrasound examination identifies less than 50% of hydatidiform moles, the majority of them appearing sonographically as missed or incomplete miscarriage.[8] Detection rates are, however, higher for complete compared to partial moles, and improve after 14 weeks gestation. Complete mole has a higher incidence of malignant sequel compared to partial mole. In most studies, 15-20 % of complete moles have evidence of persistent trophoblastic disease.[9,10] In the present study 15 (31.3%) patients have persistent GTD, for which they received chemotherapy. Schorge et al. have shown that earlier molar evacuation does not lower the risk of persistent GTD.[11]

Clinical factors that are associated with risk of post-molar GTD include 1) High β-hCG levels (>1,00,000mIU/ml), 2) Uterus large for the date, 3) Bilateral theca lutein cyst, 4) Respiratory distress syndrome after molar evacuation, 5) Eclampsia, 6) Hyperthyroidism, 7) Uterine subinvolution after post evacuation hemorrhage.

With any of these factors or a combination of many, the risk of post-molar GTN has ranged from 25% to 100% in some series.[12] In our study, 15/48 (31.3%) patients received chemotherapy for post molar GTD, of which 13/48 (27%) had β-hCG >1,00,000mIU/ml. Bilateral theca lutein cyst and uterine size more than gestational age were seen in 9/48 patients (18.8%) and 11/48 (22.9%) patients respectively. Two patients (4.2%) have evidence of hyperthyroidism, 1 have severe pre-eclampsia and 1 uterine subinvolution.

The risk factors for GTN noticed in the present study are age (below 20 yr & > 40 yr), fundal high more than POG, association of theca lutien cyst and β-hCG > 1,00,000 mlU/ml. These finding are more or less the same with the erstwhile reports.

The preferred method of treatment is suction evaluation regardless of uterine size.[13,14] Other surgical procedures like hysterectomy may be performed in very elderly patients above 40 year. Prophylactic chemotherapy is still a very controversial one. However, Kim et al. found the incidence of post molar GTD decreased from

47% to 14% among patients with high risk criteria by prophylactic chemotherapy with methotrexate during evacuation.[15] The same thing is reported for prophylactic chemotherapy with dactinomycin.[16] Weekly follow up with β-hCG till β-hCG come down to normal level at least for 3 consecutive time is the gold standard method. Several studies have evaluated and recent data support the safety of significantly shortening the duration of surveillance. It appears that a single blood sample demonstrating an undetectable of β-hCG following molar evacuation is sufficient to exclude the possibility of progression to GTN.[17,18] It needs an in depth study to recommend this modality of follow up.

Chemotherapy plays very important role in the management of GTD. This is the only group of neoplastic disease that can be cured. Out of 15 GTD 10 (66.6%) were managed with single agent chemotherapy of methotrexate (3 to 5 cycles) and 5 (33.4%) with EMACO (3 to 4 cycle). All 15 GTD achieved complete remission. Mungan et al. also reported the management of GTN with the same treatment modality with complete remission.[19]

Conclusion

The incidence of hydatidiform mole in our institute is approximately 2/1000 pregnancies. It is more common in extremes of reproductive age less than 20 years of age and above 40 years. Follow up with β-hCG is very essential in all cases to identify post molar GTD. Chemotherapy with Methotrexate and Leucovorin or EMACO is very effective with high cure rate. Presence of theca lutein cyst, uterine size more than gestation, β-hCG > 1,00,000 mIU/ml are the high risk factors for development of post molar GTD. The study outcome further confirms that all the complications including choriocarcinoma can be cured. Proper counseling and follow up of the patient are the key to successful management of GTD.

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