

Geographical, Clinical and Morphological Features of Molar Pregnancy in Pakistan

Kanwal Babar,¹ Saira Rathore,² Madiha Arshad,³ Shahida Niazi,⁴ Namra Mahmood,⁵ A.S Chughtai⁶

Abstract

Objective: To determine the association of molar pregnancy with age, geographical distribution, clinical presentation and morphological features in our population.

Method: It is a 5-years retrospective cross sectional study commencing from 1st January 2015 to 31st December 2019 on uterine evacuation samples submitted for histopathology at Chughtai's Institute of Pathology (CIP) and Central Park Teaching Hospital (CPTH), Lahore, Pakistan. Case records of all reported molar pregnancies during the study period were retrieved from computer files.

Results: A total of 462 cases of hydatidiform mole were diagnosed during this period. These constituted of 313 cases (67.74%) of complete hydatidiform mole (CHM) and 149 cases (32.25%) of partial hydatidiform mole (PHM). Maximum number of cases were received from the province of Punjab constituting of 242 cases (52.38%) followed by 132 cases (28.57%) from Khyber Pakhtunkhwa (KPK). However, maximum cases of complete moles were reported from the province of KPK constituting of 110 cases (83.33%) out 132 submitted samples. Geographical distribution of molar pregnancy was observed as a statistically significant associated factor regarding morphological features ($X^2 = 23.732$, p -value=0.000). Females ranging in age from 16 to 58 years were included in the present study. Maximum cases were reported in the 21-30 years age group comprising of 272 cases (58.87%) of which CHM constituting a maximum figure of 200 cases i.e 73.52% (p -value=0.004). Maximum specimens comprising of 265 cases (57.35%) showed grape like clusters on gross. The most common clinical presentation was vaginal bleeding constituting of 395 cases (85.49%). Incidental molar pregnancy was seen in 79 cases (17.09%).

Conclusion: Females with molar pregnancy can be cured and their reproductive function preserved provided their initial treatment and follow-up is timely and appropriate. Histopathological examination of molar tissue is the gold standard for its definite diagnosis & categorization as CHM & PHM.

Keywords: Hydatidiform mole, histopathology, trophoblast, chorionic villi, vesicles.

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Introduction

Gestational trophoblastic disease (GTD) constitutes a heterogeneous group of interrelated diseases

1,2,4-5. Department of Pathology, Central Park Medical College Lahore.

3. Department of Pathology, King Edward Medical University of Lahore.

6. Department of Pathology Central Park Medical College Lahore/ Chughtai Institute of Pathology Lahore

Correspondence:

Dr. Kanwal Babar, Assistant Professor, Pathology Department, Central Park Medical College, Lahore, Pakistan.

E-mail: drsalahkanwal@hotmail.com

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arising from tissues of placental origin which includes partial hydatidiform mole (PHM) and complete hydatidiform mole (CHM), invasive mole, choriocarcinoma and placental site trophoblastic tumor (PSTT).¹ Molar pregnancy represents the maximum burden of disease in the spectrum of GTD. The word “hydatid” is a Greek word meaning droplet and the word “mole” indicates the burrowing nature of the trophoblastic tissue into the uterine wall.²

The incidence of GTD varies in different regions of the world with the highest figures reported in the South-East Asian countries as compared to the western nations.

In Europe, the incidence of molar pregnancy is 1/1000 pregnancies, in Japan and South East Asia it is 2/1000 deliveries and in Taiwan it is 1/125 pregnancies.³ The highest incidence of molar pregnancy is reported in Turkey with an incidence of 12.1/1000 deliveries.⁴ The malignant potential of this disease is also highest in South East Asia ranging from 10-15% whereas in the Western nations it ranges from 2-4%. The reasons for these geographical variations are indefinite.⁵ The incidence of GTD in Pakistan is not known, however in one study the reported frequency is estimated as 28 per 1000 live births.⁶

The etiology of the disease is uncertain, however cytogenetic studies indicate a strong genetic association. CHM is characterized by having 46 chromosomes (46XX karyotype) all of paternal origin whereas the PHM is triploid, having a 69 XXX or 69 XXY karyotype.⁷

On morphology, CHM appears as grossly visible grape like vesicles and histologically is characterized by dilated chorionic villi surrounded by circumferential trophoblastic proliferation. Fetal parts, blood vessels and nucleated red blood cells (RBCs) are not seen in complete moles whereas the PHM grossly shows an admixture of some hydropically dilated villi and some normal villi with polar trophoblastic proliferation. Fetal parts with blood vessels containing nucleated RBCs are a prominent and diagnostic feature of PHM.⁸ Presenting complains include vaginal bleeding and increased uterine volume during the 1st trimester of pregnancy with the disease ultimately ending in a miscarriage.⁹

Well documented risk factors for molar pregnancies include extremes of maternal age, previous molar pregnancy and a history of spontaneous abortions having a 2-3 fold increased risk of molar pregnancy compared with normal pregnancies. Women with a previous molar pregnancy have a risk of 1-2% in the next pregnancy.⁹ Other risk factors includes low socio-economic status, dietary deficiency of protein, vitamin A, folic acid and iron. A nutritional deficiency during the 1st trimester may lead to the formation of a hydatidiform mole.¹⁰

The diagnosis of hydatidiform mole is greatly facilitated in the first trimester of pregnancy with ultrasound findings typically showing a “snow storm” appearance. The combination of ultrasound and markedly elevated serum β -HCG levels as expected for the gestational age is highly suggestive of molar pregnancy.⁷ However

histopathological examination of the evacuated uterine contents remains the ultimate gold standard for accurate diagnosis of molar pregnancy.⁹ A hydatidiform mole is considered benign, but is premalignant having a definite potential to become malignant and invasive.¹¹ The risk of malignant potential is approximately 15% in CHM, while it is much lower in PHM reported as 0.5- 1%.¹⁰

An important diagnostic immunohistochemical marker differentiating between partial and complete mole is p57, which is a paternally imprinted inhibitor gene. Its absence supports the diagnosis of complete mole. In contrast partial mole which has a maternal contribution is p57 positive.¹¹

The treatment of hydatidiform mole includes evacuation of the uterine contents by suction dilatation & curettage under ultrasound guidance in young females who desire fertility. However, hysterectomy is a preferred option in females older than 40 years of age and those who do not desire child bearing options.¹²

The objective of this study is to determine the occurrence of molar pregnancy in the different provinces of Pakistan and its relationship with different age groups and morphological features.

Materials and Methods

The present study is a 5-years descriptive cross – sectional study conducted from 1st January 2015 to 31st December 2019 on uterine evacuation samples received at Chughtai’s Institute of Pathology (CIP) and Central Park Teaching Hospital (CPTH), Lahore. Samples at CIP were received from the collection centers located in the different provinces of Pakistan.

Record and data of patients during this 5-year period was retrieved from computer files and entered in a proforma showing age, clinical features, gross and microscopic diagnosis alongwith address showing the province wise geographical location. Approval for the study was taken from the Ethical Review Board of CPMC (vide letter number CPMC/IRB-No/1312, dated February 09, 2022). Specimens with suspected molar tissue on gross examination, ultrasound and elevated β -HCG levels were included in the study. Products of conception (POC’s) without molar change on gross examination and endometrial curettings of non-pregnant females were excluded.

Molar tissue fixed in 10% buffered formalin was processed using standard protocols: following fixation the entire specimen was transferred to tissue cassettes

and processed using an automatic tissue processor. Routine 5-micron sections were stained with hematoxylin and eosin, and prepared slides were evaluated by two consultant histopathologists.

Data obtained was analyzed using SPSS version 24 and frequencies and percentages were calculated. p-values were calculated by using a chi-square test to observe the association of molar pregnancy with age, geographical region, gross morphological features and clinical presentation. A 5% level of significance was used.

Result

A total of 462 cases of hydatidiform moles were diagnosed during a 5-year period commencing from January 2015 to December 2019. These constituted of 313 cases (67.74%) of CHM and 149 cases (32.25%) of PHM giving a ratio of 2.10:1. (Figure:1-3)

Females ranging from 16 to 58 years were included in the study and categorized in four age groups. Maximum cases were seen in the age range of 21-30 years which constituted 272 cases (58.87%). Among this age category of 21-30 years, a maximum of 200 cases (73.52%) were reported as CHM and 72 cases (26.47%) as PHM. There were 21 cases (4.54%) of molar pregnancy in females above 40 years of age. These constituted 9 cases of CHM and 12 cases of PHM (Table1). Age distri-

bution was significantly associated with molar pregnancy ($X^2 = 13.163$, p -value=0.004).

Regarding geographical distribution, specimens of molar tissue were received from the four major provinces of Pakistan (Baluchistan, KPK, Punjab and Sindh) as well as from Azad Jammu and Kashmir and Gilgit Baltistan. Maximum number of molar pregnancy cases were received from Punjab, constituting 242 specimens (52.38%) followed by 132 cases (28.57%) from KPK, of which complete molar cases constituted of 110 cases (83.33%). This figure represents the maximum number of cases reported as CHM from KPK followed by Punjab in which 150 cases (61.98%) out of 242 cases were categorized as CHM. In Sindh, 48 cases (58.53%) out of 82 cases were diagnosed as CHM. Very few cases were received from Baluchistan (2 cases), Gilgit Baltistan (2 cases) & Azad Jammu and Kashmir (2 cases) constituting a combined total of 6 cases of which 5 were reported as complete moles (Table1) Geographical distribution of molar pregnancy was observed as a statistically significant associated factor regarding morphological features ($X^2 = 23.732$, p -value=0.000).

Gross features included 265 cases (57.35%) with exclusive grape like vesicles, 141 cases (30.51%) showing a few grape like structures and 56 cases (12.12%) with no gross abnormality. Molar pregnancy was statistically significantly associated with these gross morphological

Table 1: Cross tabulation of molar pregnancy with age, province, morphological features and clinical presentation ($n=462$)

Factor	Category	Molar Pregnancy		Number of cases (Percentage) 462 (100%)
		Complete (313 cases) 67.74%	Partial (149 cases) 32.25%	
Age Distribution	< 20 years	46 (60.53%)	30 (39.47%)	76 (16.45%)
	21 – 30 years	200 (73.52%)	72 (26.47%)	272 (58.87%)
	31 – 40 years	58 (62.37%)	35 (37.63%)	93 (20.12%)
	> 40 years	09(42.86%)	12(57.14%)	21 (4.54%)
Province	Baluchistan	01(50%)	01(50%)	02 (0.43%)
	KPK	110 (83.33%)	22 (16.67%)	132 (28.57%)
	Punjab	150 (61.98%)	92 (38.02%)	242 (52.38%)
	Sindh	48 (58.53%)	34 (41.46%)	82 (17.74%)
	Gilgit Baltistan	02 (100%)	0 (0%)	02 (0.43%)
	Azad Jammu & Kashmir	02 (100 %)	0 (0%)	02 (0.43%)
Morphological Features	Exclusively grape like clusters	182 (68.68%)	83 (31.32%)	265 (57.35%)
	Few grape-like clusters	108 (76.60%)	33 (23.40%)	141 (30.51%)
	Normal products of conception	23(41.07%)	33 (58.93%)	56 (12.12%)
Clinical Presentation	Vaginal bleeding and increased uterine volume	294(74.43%)	101(25.57%)	395/85.49%
	Abdominal pain and hyperemesis	19(28.36%)	48 (71.64%)	67/14.50%

features ($X^2 = 23.395$, $p\text{-value} = 0.000$).

The commonest presenting feature was vaginal bleeding and increased uterine volume seen in 395 cases (85.49%). Other nonspecific symptoms included abdominal pain and hyperemesis seen in 67 cases (14.50%). Clinical suspicion of molar pregnancy was suspected in 383 cases (82.90%) whereas 79 cases (17.09%) were unsuspected incidental findings. Clinical presentation was significantly associated with morphological features ($X^2 = 55.649$, $p\text{-value} = 0.000$) (Table 1).



Figure. 1: Gross image showing numerous grape-like vesicles in a complete hydatidiform mole (CHM).

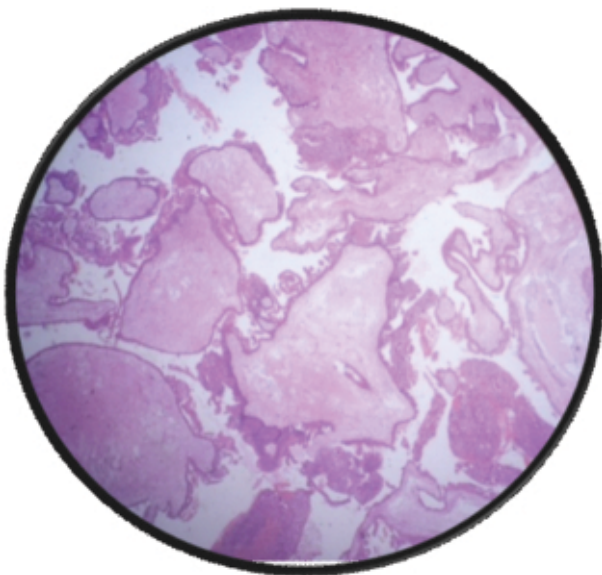


Figure. 2: Light microscopic view of complete hydatidiform mole (CHM) showing dilated chorionic villi with circumferential trophoblastic proliferation (Hematoxylin and Eosin x 200).

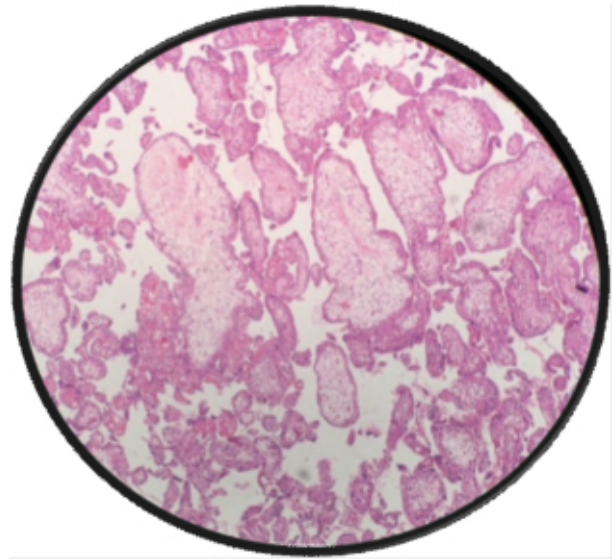


Figure 3: Light microscopic view of partial hydatidiform mole (PHM) showing intermixed population of large and small chorionic villi with polar trophoblastic proliferation (Hematoxylin and Eosin x 200).

Discussion

GTD is among the rare human tumors that can be cured despite the presence of metastatic disease.¹³ Complete and partial moles are genetically abnormal pregnancies and can be distinguished on the basis of morphological features, cytogenetic origin, clinical presentation and subsequent prognosis.¹⁴

Distinction between a molar conceptus from normal POC's by histopathology is extremely important as the patient's management and prognosis are based on this distinction. In addition, both entities have different potentials for clinical persistence, recurrence and malignant transformation.⁷

The diploid CHM is the premalignant form of gestational trophoblastic neoplasia¹⁴ whereas the triploid PHM has a reduced chance of malignant transformation, the risk being 1 in 200 pregnancies as compared to 1 in 12 for CHM.¹⁵

In the present study, CHM constituted 313 cases (67.74%) compared to PHM comprising of 149 cases (32.25%). A local study by Nousheen Aziz in 2012 quoted figures of 79.48% cases of CHM and 5.12% cases as PHM.¹ highlighting the increased frequency of CHM as compared to PHM.

In a study by Olivier Mulisya in 2018 on 181 patients, the prevalence of hydatidiform mole was 6.1 % (11 cases out of 181).¹⁶ All cases were CHM and there was no

PHM in his study. However, some other studies have reported contradictory figures in which PHM outnumber CHM. In a recent study by Talat Zehra in 2020 from Karachi all molar tissue were diagnosed as PHM⁴ and another study conducted in West Indies in 2013, PHMs constituted of 61.1% of molar pregnancies.¹⁷

Age is considered a significant risk factor for the development of molar pregnancy. The relative risk with odd ratio (OR) is quoted as 2.14 for females younger than 20 years and 7.39 for females above 35 years of age by Nargese J. Talati, Karachi.¹⁵ In the present study maximum number of 272 cases out of 462 cases (58.67%) diagnosed with GTD ranged from 21-30 years. Similarly, Talat Zehra also reported maximum number of GTD cases in 21-35 years of age.⁴ In their study no case was seen in females less than 20 years, while in our study 76 cases (16.45%) were seen in females less than 20 years of age with mean age of 25.5 years.

A study in India (2019) by Jyoti R Chandran shows a mean age of 24.65 years for molar pregnancies.¹⁸ Similarly, a study by Saleem Sadiq at JPMC, Karachi reported maximum of 111 cases (45.5%) in 21-30 years of age with mean of 27 years,¹⁹ which is in accordance to our study.

According to a study in 2013 by Savage PM regarding age distribution, higher frequency of molar pregnancies was observed in females younger than 20 years and older than 45-50 years.²⁰ In our study maximum number of 272 cases (58.87%) were observed in the 21-30 years age range followed by 31-40 years age group which constituted of 93 cases (20.12%). However, 76 cases (16.45%) were also reported in females less than 20 years. Three cases of CHM were reported in females aged 16 years, all reported from KPK. At the other extreme, 21 cases (4.54%) were reported in females more than 40 years of age. The maximum age reported was 58 years diagnosed as CHM from KPK and a case of a 50-year female was reported from Punjab.

The global prevalence of molar pregnancy is almost 1 for 4 abortions (24.7%).²¹ Its incidence varies by geographical region, being high in developing countries, females younger than 20 years and older than 40 years of age. It is more common in patients of low socioeconomic status with its associated dietary deficiency of protein, folic acid and carotene. A history of abortion is associated with increasing chances of developing a subsequent molar pregnancy.²²

Out of a total 462 cases, 454 cases were diagnosed and

treated with suction curettage, 6 cases were diagnosed and treated with hysterectomy and two placentae were received. All hysterectomies were reported as CHM with an age range of 25-45 years reported from Punjab and KPK. Both placentae were received with a fetus and diagnosed as PHM.

In present study 85.49% cases presented with vaginal bleeding during the first trimester and 14.50% had other symptoms of increased uterine fundal height, abdominal pain, distention and hyperemesis. A study in 2021 from Italy by Giampiero reported 87% cases with abnormal vaginal bleeding.⁹ These findings are in accordance to our study.

In this study pre-evacuation clinical suspicion of molar pregnancy was seen in 383 cases (82.90%) whereas 79 cases (17.09%) were unsuspected of being molar pregnancies. They were assumed to be normal POC's but on histology were reported as hydatidiform moles highlighting the importance of histopathological examination being the gold standard for the diagnosis of molar pregnancy. In the study by Olivier Mulisya in Uganda, clinical diagnosis of molar pregnancy was suspected in 13 patients, of which 9/13 cases were confirmed as CHM histologically. Two cases were clinically unsuspected and diagnosed after surgical evacuation for abortion.¹⁶

A rare and interesting occurrence consisting of a twin pregnancy with a normal fetus and a coexistent associated mole is estimated to occur in 1 in 22,000 – 100,000 pregnancies. This occurrence can be seen with both CHM and PHM.²³ The diagnosis can be established antepartum by ultrasound and such patients with a twin pregnancy having a normal fetus with a concomitant molar pregnancy should be warned about a high risk of hemorrhage, hypertension and other complications including persistent GTN.²³ Such patients also have higher chances of metastatic disease requiring multidrug chemotherapy.²³

In our study there were two twin pregnancies both with fetuses and the second sac was associated with CHM. In some cases, these types of twin pregnancies are incidentally discovered on examination of the placentae after delivery.

As this is a retrospective study, we could not get the post-treatment radiological features, serum β -HCG level and subsequent follow-up of these cases of molar pregnancy as regards their further progression towards malignant change or subsequent normal pregnancies.

Conclusion

Of the two types of molar disease, CHM has a greater propensity for being persistent and recurrent with a subsequent progression to choriocarcinoma in 2.5% cases, whereas only less than 0.2% of partial moles will undergo this complication.

It is strongly suggested that all products of conception whether suspected or not of being molar pregnancy should be evaluated by histopathological examination especially if there is a strong clinical suspicion and if relevant risk factors like history of previous molar pregnancy or recurrent abortions are present. In addition, early diagnosis with subsequent follow-up helps in management and treatment of such patients with a subsequent decrease in complications and mortality associated with this entity.

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Authors Contribution

SR, KB, SN: Conceptualization of Project

SR, KB, SN: Data Collection

MA, NM: Literature Search

SN, KB: Statistical Analysis

MA, SN, ASC: Drafting, Revision

KB, SN: Writing of Manuscript