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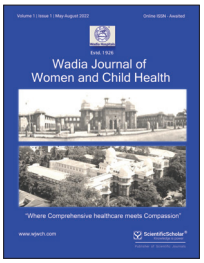

Original Article

Proportion of hydatidiform molar gestations among patients undergoing uterine evacuation for missed abortions, associated demographics and risk factors - Experience at a single center over 18 months

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ABSTRACT

Objectives: Gestational trophoblastic diseases represent a significant obstetric morbidity among women of reproductive age, with a potential to impact women's health substantially. Molar pregnancies present as clinical aberrations in embryogenesis and placentation during the first trimester of pregnancy. Cases with missed abortions and spontaneous incomplete abortions requiring uterine evacuation, could be an opportunity to look for molar pregnancies through histopathology which otherwise could be missed. We aim to study the proportion of hydatidiform molar gestations among patients undergoing uterine evacuation in cases of missed abortion and to evaluate the demographic and risk factors associated with hydatidiform molar gestations.

Material and Methods: A prospective observational, descriptive study was conducted at the Department of Obstetrics and Gynecology of a tertiary care teaching hospital over a period of 18 months. Data was collected using a pre-tested study questionnaire which included the objectives, besides the inclusion and exclusion criteria. The abortus and uterine evacuated tissue was sent for histopathologic examination by a single histopathologist. Analysis of various epidemiological characteristics and risk factors was done using the Statistical Package for the Social Sciences software version 21.

Results: Out of 67 patients presenting with missed abortions or incomplete abortions during the study period, five had hydatidiform molar gestations; an incidence of 7.5%. Upon histological examination 3 (4.5%) patients had a complete mole, 2 (3%) had a partial mole while 62 (92.5%) had non-molar histopathology. Eleven (16.4%) of the study participants had a history of previous spontaneous pregnancy loss/recurrent pregnancy losses. Three among five cases detected to have molar gestations had a history of prior spontaneous abortions (60%), and the difference observed was statistically significant (P = 0.019; Odds Ratio [95% Confidence interval] 10.25 [1.459–70.257]). Hyperthyroidism and high levels of serum beta-human chorionic gonadotrophin (β-HCG) were associated with molar gestations and this was statistically significant.

Conclusion: The risk of developing molar gestation is higher in patients who had previous first-trimester losses. Importantly, this should be a differential diagnosis in instances with elevated β-HCG and high thyroid hormone levels. Histopathological examination of products of conception should be considered as an essential assessment in all presentations of spontaneous abortions requiring uterine evacuation.

Keywords: Missed abortions, Molar pregnancy, Uterine evacuation, Thyroid disorders, Histopathology

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INTRODUCTION

Hydatidiform mole (HM), a rare yet significant gestational trophoblastic disease (GTD), manifests as an anomaly in embryonic development, characterized by abnormal placental growth. GTD encompasses a spectrum of pregnancy-related disorders, consisting of premalignant disorders namely complete HM (CHM) and partial HM (PHM), malignant disorders of invasive mole, choriocarcinoma, and the rare placental-site trophoblastic tumor.

In literature, the proportion of histologically confirmed HM, of those suspected on ultrasound in early pregnancy, ranged between 34.2 and 90.2% of all forms of HM, 57.8–95% for CHM, and 17.6–51.6% for PHM.[1,2] A recent meta-analysis by Memtsa *et al*. indicated substantial heterogeneity in the overall ultrasound diagnosis of HM and differentiation between CHM and PHM.[3]

These findings underline the fact that molar gestations may get missed during the first trimester if mainly diagnosed on ultrasonography (USG) which again is dependent on the availability of resources, quality of machines, and skills of the performer. Molar pregnancies fail to progress, and present with missed or incomplete abortions. It is important to identify such pregnancies and provide a histological diagnosis as these pregnancies put women at risk of repeat molar gestations and malignant trophoblastic disorders.[1]

Global observations have underscored these diverse clinical presentations of HM and the considerable risk of malignant transformation into choriocarcinoma. There are studies assessing the prevalence and other factors among missed abortions and incomplete abortions diagnosed as molar pregnancies.[4-8] However, comprehensive data pertaining to its prevalence and associated factors in the context of missed abortions are still insufficient and studies from India are lacking.

The elucidation of prevalence rates, demographic patterns, and potential risk factors associated with HM in patients with a diagnosis of missed abortions and incomplete abortions requiring surgical evacuation holds paramount importance for refining clinical strategies, expediting early identification, and refining tailored management approaches for affected individuals.

This study aims to determine the proportion of hydatidiform molar gestations among patients undergoing uterine evacuation in cases of missed or incomplete abortion at a tertiary care teaching hospital and evaluate the demographics and risk factors associated.

MATERIAL AND METHODS

This is a prospective observational, descriptive study performed at the Department of Obstetrics and Gynecology of a tertiary care teaching hospital conducted over a period of 18 months.

Ethics committee permission from the Institutional Review Board (IRB) was obtained. Informed consent was obtained from the patients enrolled in the study. The sample size calculated as 67 based on appropriate biostatistic methods.

The inclusion criteria were (1) All patients admitted with non-viable pregnancies undergoing suction evacuation for missed abortions and spontaneous incomplete abortions. (2) Patients with USG suspicious of molar pregnancy. (3) Pregnant women with rising trend of serum beta-human chorionic gonadotrophin (β-HCG) levels on serial estimation. Exclusion criteria were as follows: (1) Patients going into spontaneous complete abortions. (2) Dilatation and evacuation in patients who opted for Medical Termination of Pregnancy (MTP)-surgical method.

Data were collected using a pre-tested, IRB-approved pro forma which included the objectives; inclusion and exclusion criteria of the study. Detailed history, physical examination, and necessary investigations including ultrasonography were conducted as per standard of care.

The evacuated tissue was placed in a plastic container containing 10% buffered neutral formalin immediately post evacuation and sent for a full gross and histopathologic examination. All the specimens were processed as per standard protocol to obtain tissue paraffin blocks; sections were taken and stained by hematoxylin and eosin stain and studied under the microscope.

Data were analyzed using the Statistical Package for the Social Sciences software Version 21 and appropriate tests of significance were used.

RESULTS

At presentation nearly half (49.2%) of the pregnant women were between 26 to 34 years of age, 44.8 % were less than 25 years and only 6% were above 35 years of age. Women with PHM presented at a younger age (28 ± 4.24 years) as compared to CHM (31.3 ± 6.8 years).

Hyperemesis gravidarum, vaginal bleeding, pain in abdomen, passage of grape-like cysts, and excessive uterine size were common symptoms observed in those who had HM [Table 1].

Table 2 describes the epidemiological profile and risk factors observed.

Out of 67, five patients were found to have molar gestations; an incidence of 7.5%. The histological examination revealed that 3 (4.5%) specimens had a complete mole and 2 (3%) had a partial mole, while 62 (92.5%) had non-molar histopathology.

Table 1: Symptoms at presentation (*n*=67).

Symptom	Hydatidiform mole (*n*=67)	
	Present (05)	Absent (62)
Vaginal bleeding during pregnancy	3 60.0%	22 35.48%
Pain in abdomen	3 60.0%	22 35.48%
Passage of grape-like cysts	3 60.0%	0 0.0%
Excessive uterine size	2 40.0%	0 0.0%
Hyperemesis gravidarum	4 80.0%	16 25.81%
Toxemia of pregnancy	2 40.0%	2 3.22%

Eleven (16.4%) of the study participants had a history of previous spontaneous pregnancy loss/recurrent pregnancy losses. Three participants among five detected as molar gestations had a history of prior spontaneous abortions (60%), this was statistically significant (odds ratio (OR) of 10.125; p = 0.019).

Various risk factors associated with HM are shown in Table 3. Among those with previous molar pregnancy, 1 (50%) had HM while among those who did not, four had HM. The difference was not statistically significant [Table 3].

Among the primigravida cases 6.8% had HM, and gravida 2 had none and one each of gravida 3 and gravida 4 had HM(14.3%, and 50%, respectively) had HM [Table 2].

Among those with hyperthyroidism, 50% had HM while among those without hyperthyroidism, 4.8% had it. The difference was statistically significant with $P = 0.001$ [Table 3].

Among those with raised serum β-HCG (above 100,000 mIU/mL) HM was observed in all of the cases whereas only 1 (1.6%) case with HM had normal β-HCG. The difference was statistically significant (p <0.001) [Table 3].

Serial beta HCG levels were monitored in all 5 cases of HM until the levels were undetectable.

DISCUSSION

The incidence of HM varies widely across different regions, ranging from 1 in 200 hospital deliveries in Southeast Asia to 2 in 1000 in Europe and North America, and it is higher in adolescents and elderly mothers.[1,2]

PHM is estimated to affect 1 in 700 births, with triploid PHMs accounting for almost 90% of occurrences. About 15–20% of patients with CHM experience gestational trophoblastic neoplasia (GTN), which necessitates chemotherapy, after uterine evacuation.[1-3]

A large North Indian study first reported and analyzed the incidence and epidemiologic factors in presentations of GTD in the Indian population to be 1 in 72 cases of spontaneous abortions and /or per 100 MTPs.[9] The incidence of GTD with respect to live births was 1.31/1000 live births and 1 GTD per 967 pregnancies (including live birth, stillbirth, spontaneous abortion, and MTPs).[9]

About 93.5% of the patients have moderate-to-severe vaginal bleeding as presenting symptom in the first trimester, while routine antenatal USG revealed GTD in 6.5% of completely

Table 2: Epidemiological characteristics and risk factors.

Factors	Proportion among total number of patients (*n*=67)	Percentage (%)
Age (years) Median (range minimum, maximum)	24 (range 22 to 38)	
Gravida (n) Mean ± SD	1.8±2.3	
History of abortions		
Nil (i.e., Primigravida)	44	65.7
Molar/ectopic pregnancy	02	03
Spontaneous abortions	11	16.4
Pre-treatment serum β-HCG level		
>100000 mIU/mL	04	06
<100000 mIU/mL	63	94
Serum TSH levels		
Below 0.5 mIU/mL	04	06
Above 0.5 mIU/mL	63	94
Molar pregnancies in this cohort	05	7.5
Complete mole (CHM)	03	4.5
Partial mole (PHM)	02	03

β-HCG: Beta-human chorionic gonadotrophin, TSH: Thyroid-stimulating hormone, CHM: Complete hydatidiform mole, PHM: Partial hydatidiform mole, SD: Standard deviation

Table 3: Risk factors and associations.

	Presence of hydatidiform mole (Total 05) (*n*=5/67)		*P*-value	
	Yes	No		
Diet				
Non-vegetarian	05		0.068	
Mixed	02			
Vegetarian	00			
Use of OC Pills	01	04	0.272	
Hyperthyroidism	02	03	0.025	Statistically significant
Previous H/o Molar pregnancy	01	04	0.145	
Previous H/o Spontaneous abortions	03	02	0.019	Statistically significant Odds ratio (95% CI) 10.25 (1.459–70.257)
Serum β-HCG >1,00,000 mIU/ml	04	01	<0.0001	Statistically significant
Serum TSH <0.5 mIU/mL	02	03	-0.025	Statistically significant

β-HCG: Beta-human chorionic gonadotrophin, TSH: Thyroid-stimulating hormone, CI: Confidence interval, OC: Oral contraceptive, H/o: History of

asymptomatic patients. Major risk factors were age over 30 years ($P < 0.01$, $P < 0.01$, Relative risk (RR)=2.7), history of previous abortion ($P < 0.001$, RR = 3.9), and multigravida ($P < 0.00001$, RR = 4.1). Early detection and treatment can help achieve 95.7% complete response. In a study by Kumar *et al.,* 17 out of 21 (80.9%) invasive moles were found in cases with multiple abortions and repeated mechanical interference in the form of check curettage is implicated in conversion of a mole to an invasive one.[9]

In the present study, 7.5% (n=5/67) cases of early pregnancy failure had HM. The prevalence rates in various studies range from 6 - 13%.[4,5,8,10] Mayun *et al*., in their study, observed the incidence of HM to be 7.5% similar to this study.[10]

In the present study, histological examination revealed that 3 (4.5%) specimens had a complete HM, 2 (3%) had a partial HM, while 62 (2.5%) had non-molar histopathology. Kumar *et al*., in their study, observed that the majority of the lesions were of CHM similar to our study.[9] Mayun *et al.*[10] and Cheah *et al.*[11] also showed similar findings. Mulisya *et al*., in their study, observed that all the cases were that of CHM.[5]

In the present study, of the 11 cases with a history of previous spontaneous abortion, HM was seen in 3 (27.3%) cases and 2 (3.6%) out of 56 cases who did not have a previous history. The difference observed was statistically significant with logistic regression analysis revealing an OR of 10.125. Kumar *et al*., in their study, observed previous abortion to have a significant relationship with the presence of HM, similar findings were observed in the present study.[9] Mulisya *et al.*,[5] Acaia *et al.*,[6] Talati NJ,[12] Milani *et al.*[13] had similar findings suggesting significant association between presence of HM and history of previous abortions.

In this study, among all 5 cases with HM, 1 (20%) had history of previous molar pregnancy and 4 (80%) cases did not. This difference was not statistically significant. Interestingly, only 3% (n=2/67) of all cases had previous molar gestation. Kumar *et al*., in their study, observed that a history of previous molar pregnancy was observed among 35.1% of participants; HM cases.[9] Although Talati NJ,[12] Audu *et al.*[14] showed statistically significant association with presence of HM in subsequent pregnancy, we did not find the same.[12,14]

Association with risk factors such as hyperthyroidism and elevated β-HCG levels as seen in this study was also reported by others [Table 3].[9,15-17]

As far as malignant trophoblastic tumors are concerned, the diagnosis of invasive mole and choriocarcinoma can be challenging, particularly in patients who have had a previous HM. Such patients have about 10% chance of developing malignant transformation. Approximately 60% of choriocarcinomas occur without a prior molar pregnancy being clinically identified. Over the past few years, surgery and chemotherapy have achieved near 100% remission. The occurrence of choriocarcinoma seems to differ significantly depending on the geographical location and racial background. Data are scarce regarding the causes of choriocarcinoma, primarily due to the challenges associated with investigating a tumor that is uncommon. The only two confirmed risk factors for HM are maternal age and history of previous occurrences. However, studies have also suggested potential risks associated with the use of oral contraceptives and other hormones, consanguinity, blood group types, and other unknown factors.[18]

It is necessary for future epidemiologic research to categorize moles as either complete or partial, especially because complete moles seem to have a higher risk of developing choriocarcinoma and metastasis.

Limitations of this study include (1) the cytogenetic and molecular diagnostic markers such as p53 and p57kip markers not used in the diagnosis of molar disorders. p57kip immunohistochemistry has been shown to be the most specific for molar tissue and, thus, has been proven to be extremely useful, especially in the diagnosis of difficult cases of vesicular mole. However, due to limitations of cost and affordability, we could not include these in our study. (2) The study was conducted at a single center with a small sample size; therefore, the findings cannot be generalized and warrants a need for a multicentric study with a larger sample size.

CONCLUSION

Clinicians need to be vigilant about the diagnosis of GTDs while dealing with the first trimester of pregnancies; symptoms suggestive of missed abortion, incomplete abortion should arouse suspicions of HM. Importantly, this should be a differential diagnosis in instances with elevated β-HCG and thyroid hormone levels.

The risk of developing molar gestation is higher in patients who have had previous first-trimester losses.

Patients presenting with first-trimester failures are the potential windows of opportunity to detect molar gestations which would otherwise go undiagnosed. Histopathological examination of products of conception should be considered as an essential assessment in all presentations of spontaneous abortions requiring surgical evacuation.

It was discovered that there was no correlation between HMs and gravida state, nutrition, blood group, or history of prior molar pregnancy. It is necessary to conduct additional research to examine these variables for deriving further conclusions.

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Ethical approval

The research/study approved by the Institutional Review Board at Seth G.S. Medical College, Parel, Mumbai, number EC/16/2019, dated January 23, 2020.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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