

# Recurrent Hydatiform Mole, Clinical Features and Reproductive Outcome

Original Article

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## ABSTRACT

**Purpose:** Hydatidiform mole (HM) is the commonest type of gestational trophoblastic disease (GTD), a human pregnancy characterized by excessive trophoblastic proliferation and abnormal embryonic development. Recurrent hydatidiform mole (RHM) is a rare genetic disorder defined by the occurrence of at least two molar pregnancies in the same patient. The frequency of RHMs is very variable between different ethnicities and countries.

**Materials and Methods:** An observational prospective study to investigate risk factors, reproductive history and reproductive outcome in RHM patients at GTD clinic, Mansoura university hospital.

**Results:** Twenty-five cases of RHM were reported. Mean age of the studied cases was 29.56 years  $\pm$ 4.60 SD. Nineteen cases (76%) were nulliparous. Medical history of hypertension was observed in four cases (16%). Four cases of familial RHM with a history of consanguinity between the patients' parents were reported. Recurrent complete hydatidiform moles (CHM) were reported in 13 cases (52%) while recurrent partial hydatidiform moles (PHM) were reported in 3 cases (12%). Rate of GTN progression after complete and partial moles was 28% and 4% respectively. Viable term pregnancy was achieved in five cases (20%) during follow up while 11 cases (44%) resulted in molar pregnancy.

**Conclusion:** Recurrent molar pregnancy in Egypt appears to involve about 10% for a second or more molar pregnancies. For two consecutive episodes of molar pregnancy, subsequent molar pregnancy risk rises to 44%. Prior molar pregnancy, type of the preceding mole (CHM), nulliparity, parent consanguinity and family history of similar conditions are considered risk factors implicated in the causation of RHM.

**Key Words:** Gestational trophoblastic disease, molar pregnancy in Egypt, recurrent hydatiform mole.

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## INTRODUCTION

Conception after a complete or partial mole pregnancy has an increased risk of repeat HM. After one molar pregnancy, the risk of a HM in a subsequent pregnancy increases only to 1–2%. However, this risk depends on the type of the mole. Following a complete and partial molar pregnancy, the risk of HM in the following pregnancy has been reported as 0.91 and 0.28 percent, respectively. After two consecutive molar pregnancies, the risk increases to 23 percent<sup>[1]</sup>.

RHM is a rare genetic disorder defined by the occurrence of at least two molar pregnancies in the same patient. The frequency of RHMs in women with two or more molar pregnancy in England has been reported by Sebire *et al*<sup>[2]</sup> to be 1% to 2%. However, higher frequencies of RHMs have

been reported from the Middle and Far East, where it ranges from 2.5% to 9.4%<sup>[3]</sup>. At the clinical level, patients with RHMs do not have any significant feature that distinguishes them from those with non-recurrent sporadic moles. RHMs have been seen in related women from the same family, and these cases are termed familial cases of RHMs (FRHM). FRHM is a rare autosomal recessive condition where CHMs are diploid and biparental (BiCHM) in contrast to sporadic CHMs, which are androgenetic CHM<sup>[4]</sup>. These cases are considered very rare. Which represent 0.6–2.6% of all hydatidiform moles<sup>[5]</sup>. More than 31 families with FRHM have been reported<sup>[6-9]</sup>.

Suggestions of intracytoplasmic sperm injection and ovum donation in preventing recurrent molar pregnancies have been considered<sup>[10]</sup>, the latest is prohibited in Islamic countries.

## MATERIALS AND METHODS

### Study design

This study was carried out as a prospective observational study.

### Setting

GTD clinic, Obstetrics and gynecology department, Mansoura university hospitals, Mansoura University, Egypt.

### Inclusion criteria

Patients who attended GTD clinic with current recurrent molar pregnancy or history of 2 or more molar pregnancies (complete or partial) who accepted to participate in the study. The molar pregnancies should be histologically confirmed.

### Exclusion criteria

Patients with non-molar pregnancies, or patients with one molar pregnancy and recurrent miscarriages without histologic diagnosis.

### Study subject

The included patients were subjected to the following:

1. Complete history taking: including personal history of both couples, detailed Obstetric history including data of previous molar pregnancies (number, date, duration of pregnancies, suction curettage, biopsy result and follow up weekly  $\beta$ -hCG measurements), past medical and surgical history, and family history with focus on parent consanguinity, miscarriages, congenital fetal malformations and molar pregnancies.
2. Thorough clinical and ultrasound examination.
3. Follow-up for reproductive outcome for one year after treatment of molar pregnancy.
4. This study looked for risk factors, which included age, parity, and history of miscarriages, medical history, family history, parent consanguinity and type of preceding mole.
5. The patients were advised to use combined oral contraceptive pills for contraception at least for 6 months after  $\beta$ -hCG normalization following treatment of a molar pregnancy.

## RESULTS

This study included 25 cases of recurrent hydatidiform moles who were recruited at GTD clinic in Mansoura University hospital and the studied cases were followed up for further one year after treatment of molar pregnancy.

As can be seen from (Table 1), the Mean  $\pm$  SD age of the studied cases was 29.56 $\pm$ 4.60 years. Nineteen cases (76%) were nulliparous. History of abortion was also noticed in five cases (20.0 %). History of parent consanguinity was noticed in four cases (16%), medical history (hypertension) and family history was observed in four cases (16%), among the cases with family history; 75% sisters and 25% are cousins

**Table 1:** Socio-demographic & obstetric data among studied groups

	N=25	%
Age/years Mean $\pm$ SD	29.56 $\pm$ 4.60	
Parity Median (range)	2 (1-4)	
Nulli para	19	76.0
Primi para	3	12.0
Second para	2	8.0
4 <sup>th</sup> para	1	4.0
Abortion	5	20.0
Parent consanguinity		
-ve	21	84.0
+ve	4	16.0
Family history		
negative	21	84.0
Positive **	4	16.0
Medical history (Hypertension)		
-ve	21	84.0
+ve	4	16.0

The number of recurrence of molar pregnancies was variable, two in 7 cases (28%), three in another 7 cases (28%), four in 3 cases (12%), five in 4 cases (16%) and (six or more) in 4 cases (16%). The highest number was seen among the studied cases in one case was fourteen (Table 2). The commonest type of recurrent hydatidiform moles was recurrent complete mole as it was seen in 13 cases (52%) while recurrent partial mole was seen in 3 cases (12%) only, but recurrent mixed type was seen in 9 cases (36%). GTN progression was noticed in 8 cases (32%) among the studied cases.

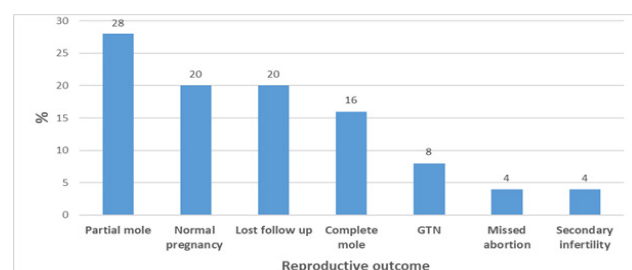
**Table 2:** Criteria of molar pregnancies

	N=25	%
Number of molar pregnancies		
2	7	28.0
3	7	28.0
4	3	12.0
5	4	16.0
6 or more	4	16.0
Types of mole		
Recurrent Complete mole	13	52.0
Recurrent Partial mole	3	12.0
Recurrent Mixed	9	36.0
Progression to GTN		
yes	8	32.0
no	17	68.0

As regard the reproductive outcome over a year of follow-up, As seen from (Table 3, Figure 1), 25 cases were reported, five cases resulted in normal pregnancy (20%), eleven cases resulted in molar pregnancy (four of them were CHM (16%) & seven cases were PHM (28%)), GTN progression occurred in two cases (8%), one case resulted in missed abortion (4.0%) and another one case suffered secondary infertility, lost follow up occurred in five cases (20%).

**Table 3:** Reproductive outcome over one year of follow-up

	N=25	%
Normal pregnancy	5	20.0
Recurrent Mole		
CM	4	16.0
PM	7	28.0
GTN	2	8.0
Missed abortion	1	4.0
Secondary infertility	1	4.0
lost follow up	5	20.0
Total	25	100



**Fig. 1:** Reproductive outcome of the studied cases

Only parity and medical history were significantly correlated to molar recurrence in subsequent pregnancies (*P value* = 0.04 & 0.02 respectively). (Table 4).

**Table 4:** Correlation between the socio-demographic characteristics and the reproductive outcome of patients as regard molar recurrence and normal pregnancy

	Normal pregnancy N=5(%)	Recurrent Mole N=11(%)	Test of significance
Age/years Mean±SD	29.60±1.34	30.38±4.52	t=0.451 p=0.659
Parity			
Nulli para	2(40.0)	10(90.9)	MC P=0.04*
Primi para	2(40.0)	0(0.0)	
Second para	0(0.0)	1(9.1)	
4 <sup>th</sup> para	1(20.0)	0(0.0)	
Consanguinity			
-ve	5(100.0)	7(63.6)	FET P=0.245
+ve	0(0.0)	4(36.4)	
family history			
Negative	4(80.0)	9(81.8)	MC P=0.676
positive in Sisters	1(20.0)	1(9.1)	
Positive in Cousin	0(0.0)	1(9.1)	
Medical history (hypertension)			
-ve	3(60.0)	11(100.0)	FET P=0.02*
+ve	2(40.0)	0(0.0)	

MC: Monte Carlo test FET: Fischer exact test p: probability of error

## DISCUSSION

The incidence of molar pregnancy was reported by Eysbouts *et al* as 0.5-1 per 1000 pregnancies in North America and Europe, 2 per 1000 pregnancies in Southeast Asia, 1 per 250 pregnancies in Philippines, and much higher in Taiwan, 1 per 125 pregnancies<sup>[11]</sup>. A recent study conducted in Egypt reported that the hospital-based and population-based incidence of molar pregnancy in Mansoura were 13.1 and 0.37 per 1000 live births respectively<sup>[12]</sup>. However, this incidence may be underestimated as some molar cases were managed in private clinics without referral to Mansoura university hospital. The most important risk factors for the development of HM are maternal age, geographical factors including ethnicity, and a previous molar pregnancy<sup>[2]</sup>.

Recurrent hydatidiform mole is a rare genetic disorder defined by the occurrence of at least two molar pregnancies in the same patient<sup>[13]</sup>. The hospital-based incidence of RHM in Mansoura, Egypt is estimated to be 10% per HM as 250 patients diagnosed as hydatidiform moles at GTD clinic in Mansoura University Hospital and Twenty-five cases of RHM patients were recruited in the same period while incidence of RHMs have been reported from the Middle and Far East; as it ranges from 2.5 to 9.4%<sup>[3]</sup>.

This prospective observational study was conducted to investigate risk factors, reproductive history and reproductive outcome in RHM patients.

Twenty-five cases of recurrent hydatidiform mole patients were recruited at GTD clinic in Mansoura University Hospital. The Mean±SD age of the studied cases was 29.56±4.60 years with majority of cases between 18 and 40 years old which is quiet understandable as this is the child bearing age period for women with the maximum number of pregnancies which reported also by other authors<sup>[2,12]</sup>. Another study reported by Sebire *et al*<sup>[14]</sup> that the risk of molar pregnancy is strongly associated with extremes of maternal age, for women over 40 years of age there is a 10-fold increase, much greater than the 1.3-fold increased risk seen in teenagers.

This study found that, for patients with RHM, nineteen cases (76%) were nulliparous. Others reported that there was no significant relationship between parity and risks of molar pregnancy<sup>[15,16]</sup>.

In this study the percentage of the cases with previous history of miscarriage was 20.0%. A history of spontaneous miscarriage, giving women a 2- to 3-fold increased risk of a molar pregnancy compared to women without a history of miscarriage<sup>[17]</sup>.

Also in the present study history of parent consanguinity was noticed in four case (16%), familial cases with evidence for consanguinity in the parents of affected women, have been also described<sup>[18-20]</sup>.

The current study reports four cases of FRHM with a history of consanguinity between the patients' parents but no consanguinity between the patients and her husbands with family history of a similar condition, although more than 31 families with FRHM have been reported<sup>[21-24]</sup>. Thus, strong family history and consignors' marriages considered a great risk factors for recurrent molar pregnancy which also reported<sup>[25]</sup>.

In addition, this study showed that medical history of hypertension was observed in four cases only one of them developed preeclampsia, other studies reported that RHM considered risk factor to develop early onset preeclampsia<sup>[26, 2]</sup>.

Also the present study revealed that among the studied cases seven cases had 2 consecutive hydatidiform moles (28%), another seven cases had 3 consecutive hydatidiform moles (28%), three cases had 4 consecutive hydatidiform moles (12%), and four cases had 5 consecutive hydatidiform moles (16%) and six or more consecutive hydatidiform moles were observed in 4 cases (16%). The highest number was seen among the studied cases in one case (4%) was 14 consecutive hydatidiform moles. The highest number of molar gestations in a single patient was 18 and was reported in 1912 by Essen-Moeller<sup>[13]</sup>.

Where recurrent molar pregnancies have been defined as CM or PM, the second molar pregnancy may be of either type but is more usually of the same type as the index mole<sup>[2,4]</sup>, which also reported here as 64% of the studied cases were the same type of the preceding mole, however the commonest type of recurrent hydatidiform moles reported here was complete one as it was seen in 13 cases (52%) followed by recurrent mixed type as it was seen in 9 cases(36%) but recurrent partial moles were the least common type as it was seen in 3 cases(12%) only. This is in accordance with previous results from studies which have reported cases with recurrent partial hydatidiform moles<sup>[27,28]</sup>.

This study has demonstrated that in women conceiving following a pregnancy affected by complete or partial mole, there is an increased risk of gestational trophoblastic neoplasia as GTN progression was noticed in 8 cases (32%) and GTN progression after complete moles is higher than that in partial moles as 7 cases (28%) followed complete mole and 1 case (4%) followed partial mole. This is also in accordance with previous results from studies which have reported that CHM has a higher risk of GTN than PHM as it has been estimated that 10–30% of CHM develops GTN whereas 5% of PHM develops GTN<sup>[29,30]</sup>.

Reproductive outcome after recurrent complete and partial hydatidiform moles was evaluated in the current study. Five cases out of 25 resulted in normal pregnancy (20%) during follow up, eleven cases (44%) resulted in molar pregnancy (four of them were CHM (16%) & seven

cases were PHM (28%)), GTN occurred in two cases (8%), one case resulted in missed abortion (4.0%) and another one case suffered secondary infertility, lost follow up occurred in five cases (20%).

So that the present study assessed the reproductive outcome after RHM and has demonstrated that there is an increased risk of repeat hydatidiform mole as 11 cases (44%) of the studied cases resulted in molar pregnancy, However it was reported that after two consecutive molar pregnancies, the risk to another molar pregnancy increases to 20 to 23 percent<sup>[31,32]</sup>.

Among the 25 patients with recurrent hydatidiform mole, viable term pregnancy was achieved in 5 (20%). Moreover, some studies reported that cases with RHMs may be reassured in terms of normal subsequent pregnancy outcome and a considerable percentage of cases with recurrent molar pregnancies can anticipate a normal future reproductive outcome<sup>[33,34]</sup> as Yapar *et al* reported 4 viable term pregnancies out of 9 patients with recurrent hydatidiform moles (44.4%).

Also this study shows that nulliparity was significantly correlated to molar recurrence in subsequent pregnancies (*P value* = 0.04) as ten cases out of eleven in whom hydatidiform mole recurred during follow up were nulliparous while other studied reported that was no significant relationship between the parity and molar recurrence<sup>[15,16]</sup>.

This study also shows that medical history (negative) was significantly correlated to molar recurrence in subsequent pregnancies (*P value* = 0.02) as negative medical history was observed in the eleven cases in whom hydatidiform mole recurred during follow up. Correlation between medical history and recurrent mole not reported by other authors.

The point of strength of this study is being first prospective study in Egypt that investigated the clinical aspects of recurrent mole.

#### **ETHICAL APPROVAL**

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The study was approved by the Mansoura Faculty of Medicine Institutional Research Board (MFM-IRB).

#### **CONFLICT OF INTERESTS**

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There are no conflicts of interest.

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