

# A Prospective Study of Gestational Trophoblastic Disease in Al-Mosul City

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## ABSTRACT:

### BACKGROUND:

Gestational trophoblastic tumors comprise a wide spectrum of neoplastic disorders that arise from placental trophoblastic epithelium after abnormal fertilization which is characterized by trophoblastic hyperplasia and overgrowth of placental villi. There are several histologically distinct types of gestational trophoblastic diseases GTD: hydatiform mole (complete or partial), persistent/invasive gestational trophoblastic neoplasia (GTN), choriocarcinoma and placenta site trophoblastic tumors.

### OBJECTIVE:

Of the present study is to determine the incidence, clinical presentation and some of its relevant factors among women admitted to Al-Batool Hospital in Mosul- Iraq.

### METHODS:

The study was conducted in Al-Batool Hospital, Department of Gynecology and Obstetrics, Iraq, Mosul city, from April 2009 to January 2011 as prospective study 9500 patients were analyzed regarding their history, clinical examination, investigations, risk factor.

### RESULTS:

During the analysis, the peak incidence of age is between 21– 25 years (31.2%). The most common clinical presentation bleeding per vaginal (100%). The peak incidence of the disease is with para two (36%). Complete hydatidiform mole forming (80%). Partial hydatidiform mole forming (18.4%). Invasive mole forming (1.6%). The mean level of B-hCG in partial mole before evacuation is between 3000-4000 mIU/ml. the mean level of B-hCG in complete mole before evacuation is between 7000-10000 mIU/ml.

### CONCLUSION:

Frequency of GTD was higher compared to national and international studies. The disease was common in young ages, low para and grand multiparous women. Hydatidiform mole was the commonest type of trophoblastic disease in these patients. Most common presenting complaint was bleeding per vagina followed by pain in lower abdomen. It appears that the ultrasound is moderately sensitive in the diagnosis of hydatiform mole pregnancy

**KEYWORDS:** gestational trophoblastic disease, hydatidiform mole.

## INTRODUCTION:

Gestational trophoblastic disease (GTD) is one of several related disorders of fertilization. From histological point of view, it is specified by disorders of chorionic villi including trophoblastic proliferation and villous stromal swelling. GTD consists of a group of related tumors including complete and partial mole, placental site trophoblastic tumor and choriocarcinoma which are inclined in to local invasion and metastasis.<sup>(1)</sup> A study done by Rozina et al., (2011) revealed that broad variations in the incidence of gestational trophoblastic diseases have been reported in

different parts of the world.<sup>(2)</sup> The chromosome arrangement in 85% of molar pregnancies is in the form of 46xx and they have paternal origin. Description and division of moles into complete and partial is used on the basis of the presence or absence of fetus or foetal parts which in many cases this division is difficult<sup>(3)</sup>.

Maternal age and history of hydatiform mole have been established as strong risk factors for both hydatidiform mole and choriocacinoma. The evidence for the role of other factors, including diet, ethnicity, endogenous estrogen level, ABO blood group and environmental toxins, is weaker<sup>(4)</sup>. The role of high parity in the GTD is unclear, some authors said that the hydatidiform mole is more common in

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primigravida.<sup>(5,6)</sup> A few studies suggest that increase of maternal age causes the risk to be increased. It is likely that the oocytes of the older women are more apt to unnatural fertilization.<sup>(7)</sup> While other studies suggested that the incidence of hydatiform mole in younger or teenage mothers is more. Schrage, et al.,(2008) say in this regard: maternal age is connected with higher risk of gestational trophoblastic disease, in such a way that this risk among teenage women and those with 36-40 years age is nearly two times as much as among the women more than 40 years .Similarly, high paternal age may also increase the risk of GTD. Besides age, history of failed pregnancy increases the incidence of GTD. For Example, elective abortion and miscarriage are connected with increasing risk of molar pregnancy<sup>(8)</sup>

Symptoms are more likely to be dramatic with complete mole than with a partial mole<sup>(9)</sup>. In early stages of pregnancy, the symptoms of the pregnancy are exaggerated, for example the uterus may grow more rapidly than usual. The first obvious symptom is vaginal bleeding and lower abdominal cramps. The blood may contain hydatid vesicles, hyperemesis is possible and signs and symptoms of preeclampsia are also possible. Other complications of GTD may include anemia, infection, trophoblastic embolism uterine perforation and choriocarcinoma<sup>(10)</sup>

Gestational trophoblastic neoplasm (GTN) may follow molar pregnancy or normal pregnancy, or develop after abortive outcomes, including ectopic pregnancy. Approximately half of cases follow a hydatidiform mole, 25% follow an abortion, and 25% develop after an apparently normal pregnancy<sup>(11)</sup> Choriocarcinoma is an extremely malignant form of GTD.<sup>(12)</sup> The distinguishing features of invasive mole are excessive trophoblastic overgrowth and extensive penetration by the trophoblastic cells, including whole villi which penetrate into the depths of the myometrium,<sup>(13)</sup> Placental site trophoblastic tumors (PSTTs) rarely spread to distant sites. More often, they grow into the wall of the uterus<sup>(14)</sup>.

The clinical presentation of molar pregnancy has changed appreciably during the past 20 years. The availability of ultrasonography and quantitative measurement of HCG levels now allows earlier diagnosis. Ultrasonography is the criterion standard for identifying both complete and partial molar pregnancies. The classic image, using older ultrasonographic technology, is of snowstorm pattern representing the

hydropic chorionic villi while high resolution ultrasonography shows a complex intrauterine mass containing many small cyst<sup>(15)</sup> With available intrauterine pregnancy Beta hCG levels are found in 66% within 48hours . Excessively high serum B-hCG levels are found with GTDs (20 times the normal values).<sup>(4)</sup> Mohamed et al., 2011 demonstrated that a significantly raised serum B-hCG level was only associated with severe preeclampsia.<sup>(16)</sup> B-hCG levels greater than 100,000MIU/ml indicate exuberant trophoblastic growth and raise suspicion for a molar pregnancy, although levels with partial mole are only infrequently above the range of normal pregnancy<sup>(17)</sup> Furthermore, histological examination is a main tool in the diagnosis of molar pregnancy including the degree of trophoblastic hyperplasia, villous contours and scalloping, presence of distinct cisterns, trophoblastic inclusions, and the presence or absence of nucleated RBC in fetal vessels<sup>(18)</sup>.

The aims of the study were to identify:-

- (1) Incidence of gestational trophoblastic disease in al-Mosul city and the effect of maternal age on these rates.
- (2) The presenting sign and symptoms of the disease and common complications.
- (3) The probable associated factors

### **PATIENT AND METHODS:**

A descriptive observational study was done during two years from April 2009 till January 2011 on 9500 patients complaining from vaginal bleeding who referred to emergency care unit in AL-Batool Teaching Hospital. All patients gave a verbal consent; the study was approved by the scientific committee in the hospital. A specially designed questionnaire form was filled for each patient by direct interview. The data requested includes: age, last menstrual cycle, parity, socioeconomic status, obstetrics and gynaecological history, history of prior molar pregnancy, antecedent pregnancy, and clinical features like missed periods, vaginal bleeding, abdominal pain, excessive vomiting and inability to drink or eat any substance to the degree of dehydration (symptoms of hyperemesis gravidarum) then complete medical and gynaecological examination of the patient was done including abdominal examination for fundal height, vaginal examination was done to assess the uterine size and vaginal bleeding. Complete investigations were done for each patient, such as complete blood picture, blood group and Rh Ketone bodies and albumin in urine, HCG level, B-hCG examination done

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using minivida method-enzyme linked immuno flurecent assay. Pelvic and abdominal ultrasound examination. All patients complaining from vaginal bleeding undergo dilatation and curettage under general anesthesia. Patients who have B-hCG level higher than 1500 mIU/ml after dilatation and curettage send to histopathology to exclude GTD. Histopathological examination was done by using Microtome method using Hematoxiline and Eosine.

Analysis of data was done by SPSS version 13, aided by Excel. Two approaches were used; descriptive such as frequencies, percents, mean, S.D was done for some variables. While in the

second approach, Chi-square test was used for testing association between different variables. P value <0.05 was considered as statistically significant.

### RESULT:

During the period of the study, 9500 pregnant women were admitted to the Albatool teaching hospital. The total number of GTD cases were(125), its frequency was 1 in every 76 pregnant women. The incidence of GTD in our study is 13.8 per 1000 live births. The age incidence of GTD is illustrated in table (1) and shows that the highest incidence was at age group of 21 – 25 years (31.2%). The mean age of the pregnant woman in this study was 31.2% ranging from 15-50 year.

**Table 1: Age incidence of GTD out of 125 patients.**

Age distribution(years)	No. of patient	% out of 125 patient
Less than 20	33	26.4
21-25	39	31.2
26-30	21	16.8
31-35	15	12
36-40	12	9.6
Above 41	5	4
Total	125	100

Analysis of parity in hydatidform mole pregnancy two, 21.6% para four, 13.6% para three.19.2% of (Table 2) shows that 36% of patients were para patient were primigravida

**Table 2: Analysis of parity in hydatidiform mole pregnancy out of 125 cases.**

Parity in GTD	No. of patient	% out of 125
Primigravida	24	19.2
Para 2	45	36
Para 3	17	13.6
Para4	27	21.6
More than 4	12	9.6
Total	125	100

Table 3 shows that 65% of cases were of low socioeconomic state and the remainder of cases (35%) were of high socioeconomic state.

**Table 3: Distribution of cases according to socioeconomic state**

Socioeconomic state	No. of cases	Percentage
High Socioeconomic	42	35
Low Socioeconomic	78	65
Total	125	100

The mean gestational age was 11, ranging from 6-23 weeks. The GTD was most commonly (56.8%of cases) diagnosed at the first trimester while 43.2% of cases were diagnosis at second trimester(Table 4)

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**Table 4: Distribution of cases according to gestational age.**

Gestational Age	Frequency	Percentage
1 <sup>st</sup> trimester	71	56.8%
2 <sup>nd</sup> trimester	54	43.2%
Total	125	100%

Analysis of symptomology in patients with GTD presenting symptoms include abdominal cramps (68%), hyperemesis gravidarum (17.6) and with vaginal bleeding and 94.4 of patient presented with history of amenorrhea. Other

**Table 5: Analysis of symptomatology in patient with GTD.**

Syptomatology	No. of patient out of 125	%out of 125 patient
Bleeding per vaginal amenorrhoea	120	96
Pain abdomen	80	64
Hyperemesis gravidarum	22	17.6
Toxemia of pregnancy	13	10.4

The analysis of GTD cases through 2 years exhibited that there are 3 types: complete hydatidiform mole 80%, partial hydatidiform mole 18.4% and invasive mole(1.6%) (Table, 6)

**Table 6: Type of GTD.**

Types of GTD	No. of patient	%Out of 125patient
Complete hydatidiform mole	100	80
Partial hydatidiform mole	23	18.4
Invasive mole	2	1.6
Total	125	100

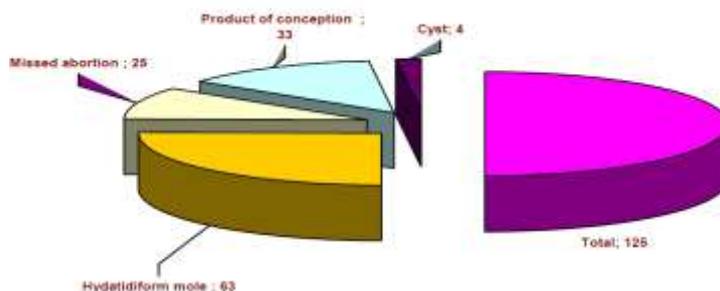
The mean level of B-hCG ranged from 3000-4000 mIU/ml in partial hydatidiform mole, 7000-10000 mIU/ml in complete hydatidiform mol and >10000 mIU/ml in invasive mole.(Table 7).

**Table 7: Mean level of B-hCG in GTD before evacuation**

Partial hydatidiform mole		
Mean level of B-hCG (MIU/ml)	No. of patients out of 125	% Out of of 125 patients
3000	11	8.8
3500	8	6.4
4000	4	3.2
total	23	18.4
Complete hydatidiform mole		
Mean level of B-hCG (MIU/ml)	No. of patients out of 125	% Out of of 125 patients
10000	51	40.8
9000	20	16
8000	14	11.2
7000	10	8
total	100	80
Invasive mole		
Mean level of B-hCG (MIU/ml)	No. of patients out of 125	%Out of of 125 patients
>10000	2	1.6
Total	125	100

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The ultrasonic analysis of histologically confirmed GTD revealed hydatidiform mole (50.4%), product of conception (26.4%), missed abortion (20%) and finally cyst (3.2%), as shown in Figure 1:



**Figure 1: Pie Chart Of Ultrasonic Analysis Of Histological Confirm GTD**

Ultrasound analysis of 9500 patients presented with vaginal bleeding (Table 8) revealed 125 cases of hydatidiform mole, 4 patients threatened abortion (70%), missed abortion (12.89%), incomplete abortion (8.25%), complete abortion (5.79), haydatidiform mole (1.32%) and ectopic pregnancy (1.05%). Out of 125 cases of hydatidiform mole, 4 patients demonstrated theca lutein cysts, which had high risk of malignancy on subsequent observation.

**Table 8: Analysis of the vaginal bleeding out of 9500 patients**

Cysts findings	No. of patient out of 9500	% out of 9500 patients
Threatened abortion	660	7
Missed abortion	1220	12.89
Incomplete abortion	780	8.95
complete abortion	550	5.79
Hydatidiform mole	125	1.32
Ectopic pregnancy	100	1.05
total	9500	100

Results of screening test (Table 9) exhibited that prevalence was 0.01, sensitivity (52%), specificity (97%) and accuracy (97%). 65 cases (True +ve), 60 cases (False -ve), 250 cases (False +ve) and 9185 cases (True -ve). The

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	Present in hydatidiform mole (+ve)	Absent hydatidiform mole (-ve)	
Present in ultrasound	a 65(True +ve)	b 250(False+Ve)	315 Total test +ve
Absent in ultrasound	c False -Ve) (	d 9125(True-Ve)	9180 Total test-ve
total	125 Total disease +ve	9375 Total disease-ve	9500 Grand total

**Table 9: Results of Screening tests.**

Prevalence : 0.01  
 Sensitivity : 0.52  
 Specificity : 0.97  
 Accuracy : 0.97  
 Predictive value of +ve result : 0.21  
 Predictive value of -ve result : 0.99  
 McNemar Chi-square : 115.23

### DISCUSSION:

Worldwide, true estimates of the incidence of molar pregnancies are difficult to obtain owing to the vast variation in the presentation and management of normal and abnormal pregnancies. Early observations suggest a 5- to 15-fold higher incidence in the Far East and Southeast Asian countries compared to that in the United States.<sup>(19)</sup> The incidence of molar pregnancies has been reported to be as high as 1 in 120 pregnancies in the Far East. In Singapore, the incidence of molar pregnancy has been as high as 1 in 72 pregnancies<sup>(20,21,22)</sup> In another study carried out in Iran, the incidence of disease was seen in 1/314 pregnancies<sup>(23)</sup> and in Saudi Arabia it occurred 1/452 deliveries<sup>(24)</sup> In a study among women in Indonesia the incidence is 1/100 and 1/250 pregnancies in Philippines. Moreover, the highest incidence of 12.1/1000 deliveries is reported from Turkey.<sup>(25)</sup> In our study, frequency of GTD is 13.8 per 1000 which is quite significant. Perhaps the difference is related to nutrition, socio-economic, environmental, genetic factors, and sample volume and research methodology

Maternal reproductive age is the most consistent risk factor for GTD in every region and ethnic group. In the study done by Rozina (2011), stated that the disease was more common at extremes of reproductive ages. This is consistent with the findings of studies from Singapore, Karachi and Nawabshah<sup>(26)</sup>The available evidence suggests that molar pregnancy arises as a consequence of defective ova. It is premature in young and post mature in old

GTD is below 25 years, i.e in young age (57.6 %).

In this study the most frequency was seen in the women who were experiencing their second pregnancy 36%. In Altieri and Moodley studies, hydatidiform mole pregnancy was seen more among nulliparous women,<sup>(27,28)</sup> while in the Kabouze,<sup>(29)</sup> Nowak<sup>(30)</sup> and pang<sup>(31)</sup> studies, hydatidiform mole incidence among multiparous women was more. In Harma study there was not clear correlation between parity and hydatidiform mole incidence<sup>(32)</sup>. Sixty five percent of cases were of low socioeconomic state, while 35% of the cases were of high socioeconomic status. Nutritional and socioeconomic factors appear to be important risk factors for molar pregnancy in some populations.<sup>(33)</sup> Another study conducted by Tham stated that the high incidence in Asia is generally attributed to low socioeconomic status and malnutrition<sup>(34)</sup> In a study done in Saudi Arabia by Felemban et al., (2003) revealed that; the mean gestational age at molar evacuation was 13.3weeks and 54.4% of patient were diagnosed in the first trimester<sup>(35)</sup> which coincide with the result of the current study. In a study done in Malaysia by aye and karali (2009) revealed that 75% of cases of GDT were diagnosed at first trimester<sup>(36)</sup> which mean that their facility for early detection and diagnosis of GTD were better.

Vaginal bleeding of varying severity occurred in all the patients. Abdominal pain and vomiting

ages.<sup>(2)</sup> In this series more than the half cases of

other important presenting symptoms, thus indicating the importance of these symptoms in

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the diagnosis of molar pregnancy. Rozina in 2011 stated that the most common classical symptom of a complete mole is vaginal bleeding due to early separation of molar tissue from the deciduas. The uterus may become distended by large amount of blood, and dark fluid may leak into the vagina. This symptom occurs in 50% of cases. Patients may also report severe nausea and vomiting. This is due to extremely high levels of HCG. (2) Another study done by Liliana (2011) revealed that the vaginal bleeding was found in (39.13%) of cases. (37) Histological examination is the main tool in the diagnosis of molar pregnancy including the degree of trophoblastic hyperplasia, villous contours and scalloping, presence of distinct cisterns, trophoblastic inclusions and presence or absence of nucleated RBC in fetal vessels. (38,39)

Khairunnisa (2009) found that the Hydatidiform mole was diagnosed in 21(70%) patients, invasive mole in 7 (23.3%) and choriocarcinoma in 2 (6.6%) patients. No patient had placental site trophoblastic tumour. (10) Chhabra and Qureshi, 2007 stated that out of 99 cases of the gestational trophoblastic neoplasm (GTN) managed in 10 years, there were 88.88% cases of hydatidiform mole, 8.08% of partial mole and 3.03% of invasive (40). The author Chawla, 2006 confirmed that Partial mole constitutes 15-25% of the molar pregnancies (41). In this series the incidence of complete mole percentage is (80 %), partial mole (18.4 %) and invasive mole is (1.6 %). This result was more or less parallel to the result of the above mentioned authors. No patient had placental site trophoblastic tumour.

Regarding B-hCG levels, Al-Alaf and Ibrahim Omer 2010 stated that B-hCG level in partial mole was less than 2000 mIU/ml, in complete mole was more than 10000 mIU/ml and in invasive was more than 10000 mIU/ml. (42) Furthermore Muller and Cole (2008) confirmed that hydatidiform mole often presents with much higher hCG levels and can reach > 10000 mIU/ml (43). In this sequence the highest level of B-hCG in partial mole is up to 4000 mIU/ml, and in complete mole is 10000 mIU/ml and more, and in invasive mole is more than 10000 mIU/ml. This result was more or less parallel to the results of the authors above.

ultrasonography was very useful in the diagnosis of GTN specially in the diagnosis of asymptomatic cases (57%), in detection of theca lutein cysts (20.20%) and in detecting invasive disease (8.08%) (40). Robert et al., (2008) found that ultrasounds were 68% diagnostic for molar pregnancy. (44) In our study, ultrasounds were (52%) diagnostic for molar pregnancy, 20% for missed abortion, (26.4%) for product of conception and 3.2% for cyst. This was more or less parallel to the result of the above authors.

### CONCLUSION:

Frequency of GTD was higher compared to national and international studies. The disease was common in young ages, low para and grand multiparous women. Hydatidiform mole was the commonest type of trophoblastic disease in these patients. Most common presenting complaint was bleeding per vagina followed by pain in lower abdomen. It appears that the ultrasound is moderately sensitive in the diagnosis of GDT and hydatiform mole

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