Incidence and outcome of gestational trophoblastic disease in lower Egypt

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Abstract

Background. Gestational trophoblastic disease (GTD) defines a spectrum of proliferative disorders of trophoblastic epithelium of the placenta. Incidence, risk factors, and outcome may differ from one country to another.

Objective. To describe incidence, patient characteristics, treatment modalities, and outcome of GTD at Mansoura University which is a referral center of Lower Egypt.

Methods. An observational prospective study was conducted at the GTD Clinic of Mansoura University. The patients were recruited for 12 months from September 2015 to August 2016. The patients' characteristics, management, and outcome were reported.

Results. We reported 71 clinically diagnosed GTD cases, 62 of them were histologically confirmed, 58 molar (33 CM and 25 PM) in addition to 4 initially presented GTN cases. Mean age of the studied cases was 26.22 years ± 9.30SD. Mean pre-evacuation hCG was 136170 m.i.u/ml ±175880 SD. Most of the cases diagnosed accidentally after abnormal sonographic findings (53.2%). Rate of progression of CM and PM to GTN was 24.2% and 8%, respectively.

Conclusion. The incidence of molar pregnancy and GTN in our locality was estimated to be 13.1 and 3.2 per 1000 live births respectively. We found no significance between CM and PM regarding hCG level, time to hCG normalization, and progression rate to GTN.

Keywords. Molar pregnancy; incidence; outcome.

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Introduction

Gestational trophoblastic disease (GTD) defines a spectrum of proliferative disorders of trophoblastic epithelium of the placenta[1]. GTD was classified histologically into benign forms of complete and partial hydatidiform moles and malignant forms of invasive moles, gestational choriocarcinoma, placental site trophpoblastic tumors (PSTT), and epithelioid trophoblastic tumors[2]. The incidence of gestational trophoblastic disease differs according to geographic distribution. The highest reported incidence was 1/125 live births in Taiwan, while 2/1000 pregnancies in Japan and South East Asia, 1/1500 in United States and 1/1000 in Europe[3]. However, underestimation of the molar pregnancy incidence may occur if the products oconception are not routinely subjected to histological examination and if the registry system is not developed[4]. Risk factors of molar pregnancy include genetic, racial[5], extremes of maternal age[6,7], dietary and nutritional factors[8].

Hydatidiform moles typically are diagnosed during the first trimester[9]. Abnormal vaginal bleeding is the commonest symptom. Other signs and symptoms include hyperemesis gravidarum, oversized uterus, absent fetal heart pulsations, pregnancy induced hypertension and abnormally high levels of hCG[10]. By ultrasound, molar tissue is usually identified as a diffuse mixed echogenic pattern replacing the placenta (snowstorm), produced by villi with intervening intrauterine blood clots[11]. Treatment of molar pregnancy is by suction evacuation with a soft plastic cannula[12] with ultrasound control. Following evacuation, it is mandatory to monitor all patients to diagnose and treat malignant progression.

Post-molar GTN is typically diagnosed in patients with serum B-hCG raised, plateau, or persistent beyond 6 months of molar evacuation[13]. GTN are categorized into

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low or high risk according to the International Federation of Gynaecology and Obstetrics (FIGO) staging and modified World Health Organization (WHO) risk-factor scoring system[14]. Patients with FIGO stages I–III with a score of 0–6 are categorized as low-risk GTN while either FIGO stage IV or any stage with WHO score ≥7 are classified as high risk[15]. GTN is well known to be highly responsive to chemotherapy. Low-risk GTN is cured with single-agent chemotherapy with either methotrexate or actinomycin-D in 90% of the cases[16]. High-risk GTN is treated with combination chemotherapy to optimize outcome[17,18].

Since the incidence, patients, characteristics, treatment modalities, and outcome of gestational trophoblastic disease may differ from country to another; we conducted this prospective study to describe our early experience in Gestational Trophoblastic Clinic, Mansoura University, Egypt.

Methods

An observational prospective study was conducted at the GTD Clinic of Mansoura University Hospitals, Mansoura, Egypt. Mansoura University Hospital provides tertiary healthcare for most of the Delta region of Egypt, with a population of about 12 millions. The patients were recruited for 12 months (from September 2015 to August 2016), followed by 6 months so that the follow up was at least 6 months for all patients.

Participants.

Inclusion criteria

The current study included both molar pregnancies and GTN. Molar pregnancies were diagnosed clinically and based on ultrasound criteria with an abnormally high hCG levels. Patients presented by gestational trophoblastic neoplasia included postmolar GTN (with serum β-hCG raised, plateau, or persistent beyond 6 months of molar evacuation) or cases with histological evidence of choriocarcinoma, invasive mole, PSTT, and epithelioid trophoblastic tumors.

Exclusion criteria

Histologic confirmation of "products of conception" after suction evacuation and patients who refused to participate in the study.

Collected patient variables included the age, the body mass index, parity, gestational age, uterine size in weeks, sonographic findings, serum β-hCG, lung metastasis, and medical diseases were recorded. To get a rough estimate of prevalence of GTD in our Hospital; the included cases were compared to the whole number of live births in Mansoura University Hospitals.

Treatment of molar pregnancy

1. Pre-operative preparation: routine laboratory tests, β-hCG, chest X-ray and anaesthetic consultation were performed.
2. The patients were treated by suction evacuation using a soft plastic cannula, guided by ultrasonography under short acting general anaesthesia. After dilation of the cervix; Oxytocin 5 IU ampoule (Syntocinon, Novartis, Egypt) was given in 500 ml saline infusion in case of severe uterine bleeding during suction evacuation. After the procedure was completed; Ergometrine 0.2 mg ampoule (Methergine, Novartis, Egypt) was given intramuscular to reduce uterine bleeding. Prophylactic broad spectrum antibiotic was given. The patient was discharged 48 hours after evacuation.
3. Follow up. The patients were followed by serum β-hCG weakly till 3 negative results (below the reference range of 5 m.I.U/mL). Subsequently, hCG was checked monthly for 6 months to insure that the hCG levels remained undetectable. During the post evacuation management, the patients were under the umbrella of contraception; preferably combined oral contraception pills.

Diagnosis, staging, and risk factors for gestational trophoblastic neoplasia

Progression to GTN was diagnosed using the FIGO, 2002 criterion[15]: hCG levels rising (more than 10%) for three consecutive weeks, plateaued for four weeks or persistent beyond 6 months. Patients with a histological diagnosis of any of the malignant forms or metastases detected during post-molar follow-up were also classified as GTN cases. GTN was staged according to the FIGO, 2002 criteria and classified into low or high risk according to modified WHO scoring system. The diagnosed cases as GTN were discussed in the tumor board meetings to receive chemotherapy and possibility of surgical interference.

Ethical considerations

Oral and written consent was taken from the patients. The study was approved by the institutional review board

(IRB) of Faculty of Medicine, Mansoura University (number: MS/16.01.01).

Statistical analysis

Data were analyzed with SPSS version 21. The normality of data was first tested with one-sample Kolmogorov-Smirnov test. Qualitative data were described using number and percent. Association between categorical variables was tested using Chi-square and Fischer exact tests. Continuous variables were presented as mean ± SD (standard deviation) for parametric data and median (Min-Max) for non-parametric data. The two groups were compared with Student t test for parametric data and Mann Whitney test for non-parametric data. P values were considered statistically significant when $p < 0.05$.

Results

Between 1st of September 2015 till the 31st of August 2016, 71 clinically diagnosed patients as GTD were included in the study. Sixty-two were confirmed histologically to have GTD (58 cases of molar pregnancy and 4 cases of GTN). The total number of life births in MUH during the same period was 4398 thus the incidence of molar pregnancy and GTN in MUH is estimated to be 13.1 and 3.2 per 1000 live births respectively. In the same period of time, the number of live births in Dakahlia governorate was 155,962 representing a population-based incidence of molar pregnancy and GTN 0.37 and 0.09 per 1000 live birth respectively. The mean age of the cases with molar pregnancy was 26.22 ± 9.30 years with 16.1% of the cases are less than 18 years old and 12.9% are 40 years old or more. We reported one case with familial recurrent hydatidiform moles where CM was diagnosed in her 2 sisters. Genetic study was done for the sisters and revealed a mutation of NLRP7.Other socio-demographic criteria were shown in table 1. The clinical presentation of the studied cases is demonstrated in table 2, as can be noticed; thirty-three cases (53.2%) were accidentally diagnosed by ultrasound during routine antenatal care visits. Chest X-ray was free for all diagnosed cases. The sensitivity of ultrasound in diagnosis of molar pregnancy was calculated to be 87% while the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of ultrasound in differentiating complete and partial moles is presented in table 3 which were found to be 96.7%, 73.6%, 85.2%, 93.3%, and 87.7% respectively.

Table 1: Demographic data of newly diagnosed cases of GTD in one year

Variables	The study group (n=62)	
	No	%
Age (years)		
<18	10	16.1%
18 to <40	44	71.0%
≥40	8	12.9%
Mean ± SD (Min.-Max.)	26.22±9.30 16-52	
BMI*		
Mean ± SD (Min.-Max.)	24.55±4.01 19-35	
Parity		
Nullipara & Primi para	33	53.2%
Multipara	29	46.8%
Mode of delivery (n=42)		
Cesarean section	24	57.1%
Vaginal delivery	18	42.9%
History of miscarriage	22	35.5%
Medical diseases	**n=23**	**37.1%**
Anemia	15	65.2
Asthma	2	8.7
Diabetes	2	8.7
Hypertension	1	4.3
Hyperthyrodism	1	4.3
Hypothyrodism	1	4.3
Deep venous thrombosis	1	4.3
Positive family history	1	1.6%

*BMI: Body Mass Index.

Positive family history**: Recurrent CHM was diagnosed in her 2 sisters.

Table 2: Clinical presentation of the studied cases

Clinical presentation (n=62)	No	%
Diagnosed by ultrasound	33	53.2
Vaginal bleeding	21	33.9
Hyperemesis gravidarum	4	6.5
Lower abdominal pain with pregnancy	2	3.2
Stoppage of menstrual cycle above 50 years old	1	1.6
Early onset Preeclampsia*	1	1.6

(*) One patient was admitted in the Neurology department because of convulsive fits and was diagnosed to have early onset preeclampsia with molar pregnancy.

Table 3: Accuracy of ultrasound in differentiating complete and partial moles.

		Histopathology		Total
		Complete mole	Partial mole	
U/S Diagnosis	Complete mole	29	5	34
	Partial mole	1	14	15
	Total	30	19	49

Sensitivity: 96.7% **Specificity:** 73.6% **PPV:** 85.2%
NPV: 93.3% **Accuracy:** 87.7%

In table 4, complete and partial mole were compared regarding the demographic and clinical data; the age and existence of bilateral theca lutein cysts were significantly different between two types of moles (P= 0.045 & 0.024 respectively), there were no significant differences regarding pre-evacuation hCG (P = 0.29), and mean time to hCG normalization (P = 0.16).The rate of hCG decline after complete and partial molar evacuation was shown in figure 1.The percentage of cases which transformed to GTN is 24.2% in complete mole and 8% in partial mole (P = 0.105).

Fourteen GTN cases were reported; ten cases resulted progression of molar cases during follow up and four cases initially presented as GTN. All cases were low-risk (FIGO score 1-5). One case of invasive mole aged 42 years was treated with upfront hysterectomy with one course of methotrexate. Thirteen cases received 8 days regimen of intramuscular methotrexate-folinic acid; two of them failed to respond and were shifted to EMA/CO (etoposide, methotrexate, actinomycine D, cyclophosphamide and vincristine combination). One of these two cases who failed to combination chemotherapy underwent local myometrial resection followed by 2 courses of EMA/EP (etoposide, methotrexate, actinomycin D, etoposide, cisplatin) followed by hCG normalization.

Table 4: Comparison between complete and partial mole regarding demographic and clinical data

Variables	Complete mole (n=33) 57%	Partial mole (n=25) 43%	p-value
Age/years	27.66±10.71	23.20±5.53	0.045
<18 18-<40 ≥40	7 (21.2%) 21 (63.6%) 5 (15.2%)	3 (12.0%) 21 (84.0%) 1(4.0%)	0.199
BMI	25.00±4.07	23.88±3.51	0.276
Parity Null& Primi para Multipara	 19 (57.6%) 14 (42.4%)	 13 (52.0%) 12 (48.0%)	0.672
Gest. Age (weeks)	8.75±2.30	9.72±3.12	0.183
Mode of delivery Caesarean Section Vaginal Delivery	 12 (54.5%) 10 (45.5%)	 12 (66.7%) 6 (33.3%)	0.436
History of abortion	11 (33.3%)	9 (36.0%)	0.832
Med. Disease	7 (29.2%)	8 (33.3%)	
Complaint Vaginal Bleeding Hyperemesis diagnosed by U/S PET Pelvic Pain	 9 (27.3%) 3 (9.1%) 21 (63.6%) 0 (0.0%) 0 (0.0%)	 11 (44.0%) 1 (4.0%) 11 (44.0%) 1 (4.0%) 1 (4.0%)	0.324
Theca Leutin Cysts			
free	27 (81.8%)	25 (100%)	0.024
Bilateral and > 6 cm	6 (18.2%)	0 (0%)	
Blood transfusion need during evacuation	23 (69.7%)	12 (48.0%)	0.094
Mean pre-evacuation hCG (m.i.u/ml) Median (Min-Max) Mean ± SD	 88810 (3210-831000) 162970± 190737	 65109 (4300-780000) 107230± 161652	0.29
Mean time to hCG normalization(weeks) Median (Min-Max)	8.5 (5-60) 11.37±10.8	10 (5-16) 10.26±2.37	0.16
Progression to GTN	8/33 (24.2%)	2/25 (8%)	0.105

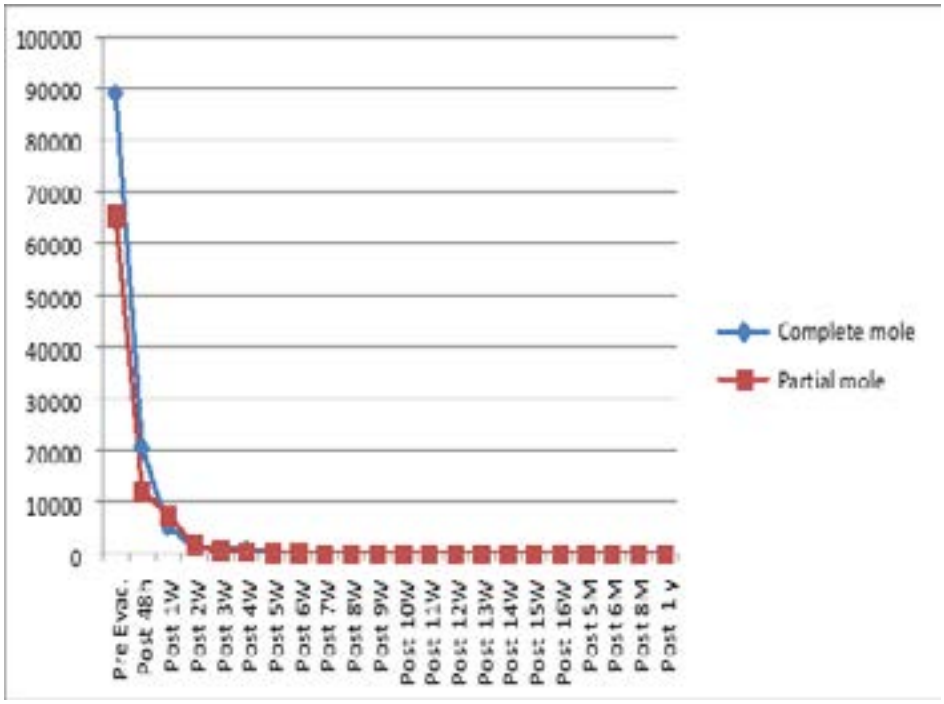

Figure 1: Comparison between complete and partial mole regarding different hCG levels before and after evacuation.

Discussion

We reported for first time hospital -based and population – based incidence of molar pregnancy in Lower-Egypt population of 13.1 and 0.37 per 1000 live births respectively. Since data on the total number of pregnancies are not available; the denominator is live births which underestimate the population at risk which may result in a small overestimation of the incidence rates observed in the current study. The hospital-based incidence is more than reported in Taiwan (8.0 per 1000 deliveries), Indonesia (9.9 per 1000 pregnancies). Furthermore, our population based incidence is less than reported in the Netherlands (0.68 per 1000), Japan (3.0 per 1000) and England (1.54 per 1000)[19]. However, in Egypt and many developing countries spontaneous abortions specimens are not routinely subjected to histopathologic review and registration.

In this study, the mean age was 26.22±9.30 years with 71.0% of the 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[20-22]. The mode of delivery of the studied cases was; 57.1% caesarean deliveries and 42.9% vaginal deliveries which is compatible with the increasing trend in caesarean section rates in Egypt[23]. The percentage of the cases with previous history of abortion was 35.5%, a history of prior spontaneous abortion has been reported to give women a two to three-fold increase in molar pregnancy compared to a woman without such a history[24]. Anemia was the most common medical disease affecting 65.2% of the studied cases which goes with the previous studies concerning anemia among pregnant women in Egypt[25].

In this study, we found that 53.2% of molar pregnancies were asymptomatic and accidentally discovered by ultrasonography which agreed with Joneborg et al[26] who reported that patients with vesicular mole were diagnosed before the onset of symptoms in 42.5% of cases, while Sun SY et al[27] reported that the most common presentation was vaginal bleeding in 46% compared with 33.9% in the current study. The sensitivity of ultrasound forccurately diagnosing hydatidiform mole was 87%, though Fowler et al and Kirk et al[28] reported that the sensitivity of ultrasound for accurately predicting hydatidiform mole was 44%. This discrepancy may be attributed to small sample size of our study.

The median level of hCG decline after molar evacuation for any type of GTD was 9 weeks which is earlier than reported by Delattre et al which was 12.3 weeks[29] which

may explained by different patient criteria. Furthermore, we found that the GTN sequel during follow up was 10 cases (16.1%). Joneborg et al[30] reported that the risk of post-molar GTN was 8% in his study, though Schmitt et al[31] found that GTN developed in 12.1% of his cohort study. The variation of molar progression to GTN in different studies may reflect different outcome among different countries.

In literature a wide range of ratios of complete mole to partial mole incidence has been reported ranging from 0.3 to 3.032. In the present study; 33 complete mole case to 25 partial mole cases of total 58 cases with a ratio of 1.3. Morphologically, both complete mole and partial mole have distinct histopathological features; however, the subjective nature of the morphological characters may give rise to variation in diagnosis[33]. In particular when earlier evacuation is performed in the present ultrasound era, classic morphological features may be less distinct[34]. The differentiation between molar and non-molar gestations is usually clear in cases showing typical histological features, and in cases of complete mole this is confirmed by p57 immunohistochemistry[35]. However, the diagnosis of partial mole can still be confusing, even to specialized gynecological pathologists[36] and this is important clinically in view of the risk of GTN progression in these patients. Moreover, hydropic abortion has traditionally been considered the major differential diagnosis of partial mole[37].

The trend toward earlier diagnosis for both complete mole and partial mole observed in our center is consistent with the global trends as the median gestational age at evacuation was 8.75±2.30 weeks for complete mole and 9.72±3.12 weeks for partial mole. Sun et al reported The median gestational age at evacuation was 9 weeks for complete mole and 12 weeks for partial mole[38] and reported in another study[29] that the median gestational age at diagnosis continued to decrease in two non-concurrent cohorts (1988-1993 versus 1994-2013) of patients from the New England Trophoblastic Disease Center; 9 weeks versus 12 weeks. Blood transfusion was required during evacuation of 69.7% of cases of complete moles and 48.0% of partial moles. This figure is much more than reported by authors at the New England Trophoblastic Disease Center[39]. The high rate of blood transfusion in our study may be attributed to higher incidence of anemia in Egyptian pregnant women which was reported by some authors[25] and correlated to high prevalence of anemia among the studied cases that was 65.2%.

The current study has limitations that Mansoura University Hospital is a regional referral center, and, therefore, our patient population may not be representative of the entire patient population. The reported data could be influenced by referral bias. Furthermore, immunohistochemical staining with P57 is not used routinely to differentiate between partial and early complete moles which may result in relatively higher incidence of partial moles. Centralization of GTD work allows proper estimation of incidence, sharing expertise at the national level, and help implementation of clear guidelines of diagnosis and treatment of GTD cases[40].

Conclusion

The incidence of molar pregnancy and GTN at Mansoura University Hospitals is estimated to be 13.1 and 3.2 per 1000 live births respectively. Ratio of complete to partial moles was 1.3. Fifty-three percent of the cases were accidentally discovered by ultrasound. We found no significance between CM and PM regarding mean pre-evacuation hCG level, mean time to hCG normalization, and rate of progression to GTN which need to be verified in future studies.

Conflict of interest

The authors declare that there are no conflicts of interest.

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