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Role of continuing regular follow-up of serial B-human chorionic gonadotropin measurements with health education following initial surgical management of complete molar pregnancy cases

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ABSTRACT

Objective: Our goal to confirm complete cure, early detection of persistent gestational trophoblastic disease and more effective and less complex treatment.

Methods: Fifty-one patients from 12,960 were admitted to the Department of Obstetrics and Gynecology at Tobruk Medical Center between August 2018 and July 2021 with complete molar pregnancy, the diagnosis was confirmed with histopathology after initial surgical management. Following identification of these patients, due to lack of registration centers, the patient's telephone was required to complete the data for continuing regular follow-ups over a period of time these patients were evaluated prospectively according to their age, number of deliveries, history of normal and abnormal pregnancy, the quantity of beta-human chorionic gonadotropin (B-HCG) at the time of diagnosis and follow-up and treatment type. Persistent gestational trophoblast disease was diagnosed on the basis of a rise of B-HCG after initial evacuation, and just one patient in our study diagnosed with invasive mole and underwent second evacuation and none of these patients developed choriocarcinoma during the follow-up period. Analysis was conducted by using the social package of statistical science (SPSS) version 25 software.

Results: 51 patients (0.39%) were diagnosed with complete molar pregnancy (CMP), the mean age was 31.90 (8.169) years range (17-47 years). Among 51 patients with CMP over three years, seventeen patients (33.3%) were diagnosed with persistent gestational trophoblast disease (PGTD), the incidence is about 1.3 per 1000 per deliveries, thirty-four patients (66.7%) reached spontaneous remission of molar gestation in a median time of 61 days and had a total follow-up time of 24 months.

Conclusion: Follow-up women with complete molar pregnancy especially after initial management is challenging task as the incidence of molar pregnancy increasing and exposed to the risk of developing

persistent gestational trophoblastic disease, and there are no specialist centres for documentation and surveillance programme. And due to wide geographical area in Libya and difficulty in the follow-up patients with molar pregnancies, especially after initial treatment has been performed. Therefore, we must create multiple centers throughout the country to cover all cases as much as possible and the communication between the patients and centers via internet, to ensure early detection of pregnancy complications.

Keywords: complete molar pregnancy, serial B-HCG and persistent trophoblast disease.

Abbreviation

PGTD: Persistent gestational trophoblastic disease; B-HCG: Beta-human chorionic gonadotropin; CMP: Complete molar pregnancy; GTN: Gestational trophoblastic neoplasia.

Introduction

Gestational trophoblastic disease (GTD) is a group of placental-related disorders derived from pregnancy. The World Health Organization classifies the trophoblast disease into premalignant hydatidiform mole (complete and partial moles) and malignant invasive mole, choriocarcinoma, placental site trophoblastic tumour (PSTT) and epithelioid trophoblast tumour (ETT). Malignant transformation can occur in both complete and partial moles; however, the probability of PGTD is higher in complete hydatidiform mole (15–20%) compared to partial hydatidiform mole (0.5–1%) [1,2]. The incidence of gestational trophoblast disease varies widely in different regions of the world [3] and geographic distribution greatly affects the incidence rates of persistent gestational trophoblast disease. The reported GTD incidence was 0.3-16 per 1000 pregnancies in Turkey, 0.61.2 in Europe and North America, 0.2-4.6 in Latin America, and 3.2-5.8 in Middle East countries [4,3], 7 per 1000 pregnancy in Iran [5]. In our study the reported GTD incidence was 3.9 per 1000 pregnancies in Tobruk Libya (no national study), this higher incidence has been attributed to lack of specialist centers for registration and follow-up programme. The majority of PGTD follow molar pregnancy (50%), although they can also follow any other gestational event, such as a miscarriage, ectopic (25%), term pregnancy (25%), or other gestational event. With cure rates that are almost 100%, gestational trophoblastic neoplasia (GTN) is the most treatable gynecological malignancy, even when metastatic disease is present [2]. Regardless of the malignant form of the disease in our study, beta-HCG is a good predictor for the development of persistent gestational trophoblast disease if compared to other risk factors, which were found to be a weak association. The treatment of molar pregnancy is suction aspiration, then confirmed with histopathology and once patients have been identified and the follow-up established, the beta-HCG level must be checked weekly to see if it has decreases or not. If her HCG levels remain elevated after treatment, further treatment will be given in the form of chemotherapy or surgery (hysterectomy), depending on the condition. Before starting chemotherapy, patients were evaluated using the International Federation of Gynecology and Obstetrics (FIGO) 2000 scoring system and classified as low risk (score < 6) or high risk (score >/= 7) [2] and will be treated accordingly.

Methods

This is a prospective study to analyze data collected from medical records about gestational tropho-

blast disease. Fifty-one patients from 12,960 were admitted to the Department of Obstetrics and Gynecology at Tobruk Medical Center between August 2018 and July 2021 with complete hydatidiform mole, the diagnosis was confirmed with histopathology after initial surgical management, and as a result of the lack of the registration centers for molar pregnancies, we were forced to use the patient's telephone after they had been identified and follow-up programme had been coordinated for continuing regular follow-ups after personalised health information was given to the patient, about the risk of persistent gestational trophoblast disease and recurrence, which is manifested by persistent vaginal bleeding and confirmed with elevation in beta-HCG with a regular serial measurement over a period of time, and the patients were divided into two groups based on the complete remission of disease and persistent gestational trophoblast disease. These patients were evaluated according to covariates including age, number of deliveries, history of normal and abnormal pregnancy, gestational age at diagnosis (weeks), the quantity of beta-human chorionic gonadotropin (B-HCG) pre- and post-evacuation, treatment type and time to remission (months). And the persistent gestational trophoblast disease was diagnosed on the basis of a rise of B-HCG after initial evacuation, and just one patient in our study diagnosed with invasive mole and underwent second evacuation and none of these patients developed choriocarcinoma during the follow-up period. Analysis was conducted by using the social package of statistical science (SPSS) version 25 software.

Statistical analysis

Analysis was conducted by using the social package of statistical science (SPSS) version 25 software. Baseline characteristics were described using mean (standard deviation), median value (range), and proportion (%). The chi-square test (X2) was used for comparison between groups for qualitative variables. Linear Mixed Effect Model (LMM) was used to find the relationship between persistent trophoblast disease and other covariates. A P value of < 0.05 was considered significant.

Results

During the study period, 51 patients (0.39%) were diagnosed with a complete molar pregnancy, the mean age was 31.90 (8.169) years (range 17-47 years). Among 51 patients with complete molar pregnancy over three years, seventeen patients (33.3%) were diagnosed with persistent gestational trophoblast disease. The incidence is about 1.3 per 1000 pregnancies (17/12,960). Thirty-four patients (66.7%) reached spontaneous remission of molar gestation in a median time of 61 days. The mean follow-up for these patients was 3.8 months (range 1–24 months). The length (time) of follow-up will depend on the individual situation and whether the patient had a partial or a complete molar pregnancy. Reviewing the previously published articles in this field tells us that almost all research studies have applied a simple statistical methods, such as descriptive statistics, frequency and crosstab, and regression linear model analysis to find the relationship between persistent trophoblast disease as the dependent variable and other covariates as independent variables which include age, parity, gestational age at diagnosis, antecedent pregnancy, postevacuation persistent bleeding, pre- and post-evacuation serial B-HCG measurements, and treatment type. A P value of < 0.05 was considered statistically significant. Descriptive statistics tests were used to analyse all variables as shown in Table 1.

Table 1: The demographic characteristics of the study population

Variables	Mean	Std. Deviation
PGTD	1.67	0.476
Age	31.90	8.169
Parity	1.45	0.642
Persistent bleeding	1.63	0.488
Gestational age at diagnosis	1.88	0.325
Pre- evacuation	1.53	0.504
one week after evacuation	1.69	0.469
Two weeks after evacuation	1.82	0.385
Three weeks after evacuation	1.65	0.483
Four weeks after evacuation s	1.88	0.325
Two months after evacuation	1.80	0.401
Four months after evacuation	1.96	0.196
Return to normal/months	1.39	0.695
Antecedent pregnancy	1.20	0.448
Treatment type	1.02	0.140
chemotherapy	2.20	0.633

The average age was from 17-47, and most patients 31 (60.8%), diagnosed with complete molar pregnancy were in the age range 25-40 years, of which 11(21.6%) changed to a PGTD and 20(39.2%) had a spontaneous remission. The range of parity was from 0 to 8, most patients 32(62.7%) had a parity of less than three, 8(15.7%) with a PGTD, and 24 (47.1%) with spontaneous remission. Fisher's exact test showed there is no significant influence of age and parity on progression of disease at P value (0.304, 0.096) respectively. As well as with other covariates, there is no significant effect on progression of disease as shown in table 2. Therefore, the effects of age, parity, persistent uterine bleeding, antecedent pregnancy and treatment type on the occurrence of PGTD have weak associations and are considered predictors for PGTD without any statistical significance ($P > 0.05$). We used linear regression to identify the link between serial beta-HCG measurements pre- and post-evacuation and the risk of PGTD, which showed a positive statistically significant association between serial measurement of B-HCG and increased risk of occurrence of PGTD ($P < 0.05$) as shown in table 2.

Table 2: Shows the descriptive statistics for a total number of cases, and incidence, comparing patients with and without PGTD at different points as well as P values.

Demographic characteristics		Characteristics of women with persistent PGTD				
	Category	Number =51(%)	PGTD		correlation	P value
			Persistent 17 (33.3%)	Remission 34 (66.7%)		
Age (years)	< 25 25-40	10(19.6%) 31 (60.8%) 10(19.6%)	4(7.8%) 11(21.6%) 2 (3.9%)	6(11.8%) 20(39.2%) 8 (15.7%)	0.133	0.304
parity	< 3 3-5 >5	32(62.7%) 15(29.4%) 4(7.8%)	8(15.7%) 6(11.8%) 3(5.9%)	24(47.1%) 9(17.6%) 1(2%)	-0.283	0.096
GA at diagnoses (weeks)	Up to 8	6(11.8%) 45(88.2%)	3(5.9%) 14(27.5%)	3(5.9%) 31(60.8%)	0.129	0.183
Persistent bleeding postevacuation	Yes	19(37.3%) 32(62.7%)	8(15.7%) 9(17.6%)	11(21.6%) 23(45.1%)	0.143	0.158

B-HCG before evacuation	>100000 <100000	24(47.1%) 27(52.9%)	17(33.3%) 0%	7(13.7%) 27(52.9%)	0.750	0.000
One week post evacuation	>20000	16(31.4%) 35(68.6%)	14(27.5%) 3(5.9%)	2(3.9%) 32(62.7%)	0.777	0.000
3-week post evacuation	> 1000 < 1000	18(35.3%) 33(64.7%)	16(31.4%) 1(2%)	2(3.9%) 32(62.7%)	0.870	0.000
2-months post evacuation	> 500 < 500	11(21.6%) 40(78.4%)	11(21.6%) 6(11.8%)	0% 34(66.7%)	0.594	0.000
Return to normal (months)	2-4 5-8 9-12	37(72.5%) 8(15.7%) 6(11.8%)	3(5.9%) 8(15.7%) 6(11.8%)	34(66.7%) 0% 0%	-0.806	0.000
Antecedent pregnancy	Normal	42(82.4%) 8(15.7%) 1(2%)	12(23.5%) 4(7.8%) 1(2%)	30(58.8%) 4(7.8%) 0%	-0.250	0.038
Treatment type	Suction aspiration Second evacuation	50(98%) 1(2%)	16(31.4%) 1(2%)	34(66.7%) 0%	-0.200	0.080
Chemotherapy	No Single Multiple	6(11.8%) 29(56.9%) 16(31.4%)	2(3.9%) 10(19.6%) 5(9.8%)	4(7.8%) 19(37.3%) 11(21.6%)	0.022	0.439

According to the results of this study, the observed HCG serum levels at one week (0.777) and three weeks (0.870) after evacuation has positive correlation, and the return of HCG to normal level has negative correlation (-0.806), but their relationship with progression to PGTD are considered as strong statistically significant.

According to the receiving operator characteristic curve (ROC curve) the only predictors of persistent GTN were HCG levels at one and three weeks after evacuation, other factors were weak related to persistent GTN as shown in Figure 1.

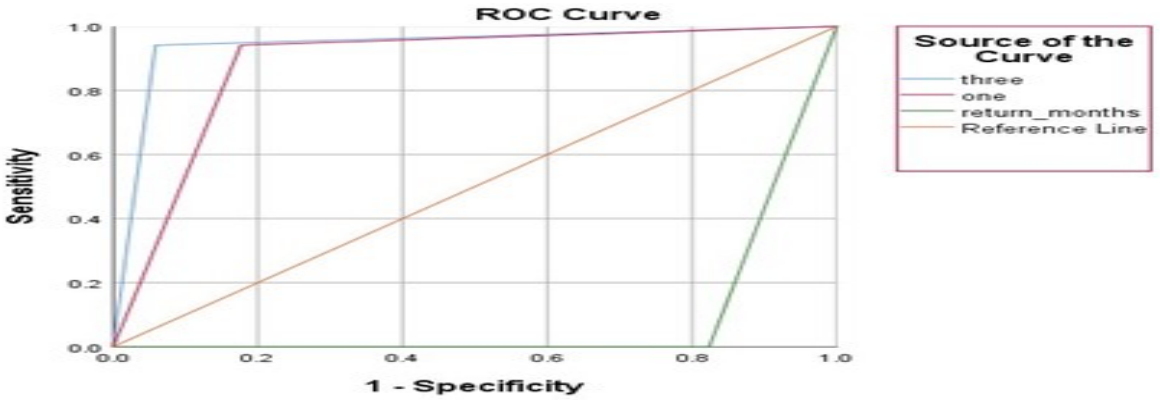

Figure 1: Diagnostic value of HCG and levels

after one and three weeks in patients with persistent GTN.

The area under the curve (AUC) and related data are shown in Table 3. There are significant relationships exist between persistent GTN and HCG levels at one and three weeks after evacuation. At one week after evacuation (AUC,0.882; sensitivity 94.1%, specificity 82.4%) and at three weeks after evacuation (AUC, 0.941; sensitivity 94.1%, specificity 94.1%). This finding indicates that the most reliable predictor of GTN is the serial HCG level at three weeks after evacuation (75.8%). The rate of decrease of HCG level at three weeks after surgical evacuation is the most reliable and the strongest predictive factor than the others for the progression of molar pregnancies to persistent GTN. In comparison this rate of our study which is consistent with a study in Lamis Misurata Clinic regarding early detection of molar pregnancy, the rate was 30% with PGTD and 70% with spontaneous remission.

Table 3: shows the HCG level in the prediction of PGTD

HCG level	AUC	sensitivity	specificity	PPV	NPV
One week	0.882	94.1%	82.4%	87.5 %	91.4%
Three weeks	0.941	94.1%	94.1%	88.9 %	94.1%

Discussion

In our study, among 51 patients 0.39% were diagnosed with a complete molar pregnancy over three years. The incidence of persistent gestational trophoblast disease is about 1.3 per 1000 pregnancies (17/12,960). The typical approach for diagnosing PGTD is beta HCG surveillance, beta HCG is produced by the placenta during pregnancy. In addition to pregnancy, abnormal fetal tissues and gestational trophoblastic disorders like GTN can also release beta-HCG [6]. Beta-HCG levels drop quickly following surgical suction aspiration of a molar pregnancy, particularly in patients whose trophoblast tissue is limited to the endometrium; however, if trophoblast tissue has invaded the uterine wall or has spread to other organs, beta-HCG levels decrease more slowly because there is still trophoblast tissue that can still produce beta-HCG. Indeed, the existence of invasive trophoblast tissue may be predicted by a gradual drop in beta-HCG levels following molar evacuation [7,8]. Patients with complete molar pregnancy are monitored for the development of gestational trophoblastic neoplasia (GTN) by monitoring beta-HCG levels in the blood or urine after undergoing initial therapy with uterine suction and careful sharp curettage. All published surveillance guidelines advise monitoring beta-HCG levels every one to two weeks until they reach normal (<5 IU/L) [9,10]. Traditionally, the monitoring was carried out for a minimum of six months after the initial normal reading, as advised by the Royal College of Obstetricians and Gynecologists [11]. According to the most recent FIGO guidelines, the partial moles should be monitored with HCG for one month, and complete moles for six months [10]. However, a recent study showed that daily beta-HCG measurements provide a better prediction of PGTD [12]. Monitoring serum betaHCG levels is essential and mandatory in the post-treatment phase of patients with molar pathology consistent with our previous studies which demonstrated that measurement of beta-HCG after treated molar pregnancy is an effective indicator to distinguish patients with spontaneous recovery from patients with PGTD [7,13,14]. To avoid PGTD after initial treatment, patients were classified into low-risk or high-risk categories using Goldstein's Mole prognostic scoring system [17]. Those in the high-risk category (score >4) received prophylactic single-agent chemotherapy

with methotrexate, prophylactic chemotherapy during molar evacuation has been reported by several researchers to reduce the incidence of post-molar tumors [15,16]. In a prospective randomized study, Kim and colleagues found that prophylaxis Methotrexate decreased the rate of post-molar tumors from 47% to 14% in high-risk patients with complete mole [17], in our study, the cure rate of molar pregnancy, with the use of prophylactic chemotherapy is 88.3%. After chemotherapy for gestational trophoblastic neoplasia, pregnancy should be avoided for at least 6 months to 1 year (depending on risk score) until HCG levels are normal. However, patients who become pregnant within 6 to 12 months of treatment are more likely to have a good outcome [18]. Women undergoing follow-up after molar pregnancy should receive reliable contraception (OCP or Depo-Provera) throughout the follow -up period [19]. In subsequent pregnancies in women with previous gestational trophoblastic tumors or recurrent molar pregnancies, follow-up care for subsequent pregnancies may include early ultrasound, postpartum examination of the placenta with HCG, and histological examination of all non-viable pregnancies should be included [19].

Conclusion

Follow-up women with complete molar pregnancy especially after initial management is challenging task as the incidence of molar pregnancy increasing and exposed to the risk of developing persistent gestational trophoblastic disease, and there are no specialist centres for documentation and surveillance programme. And due to wide geographical area in Libya and difficulty in the follow-up patients with molar pregnancies, especially after initial treatment has been performed. Therefore, we must create multiple centers throughout the country to cover all cases as much as possible and the communication between the patients and centers via internet, to ensure early detection of pregnancy complications.

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