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The Value of Ultrasonography in Predicting Invasive Mole

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Abstract

Background: Gestational trophoblastic neoplasm (GTN) during pregnancy includes an associated heterogeneous group of lesions that originates from abnormal proliferation of placenta. It includes invasive mole, choriocarcinoma, placental site trophoblastic tumor, and epithelioid trophoblastic tumor.
Objectives: The aim of this study was to predict the risk of invasive mole in patients with a molar pregnancy in association with β-hCG level after the evacuation of molar pregnancy.
Methods: The current study was a prospective cross-sectional cohort research conducted as a diagnostic study on 110 patients with molar pregnancy referring to Department of Gynecology and Oncology of Vali-Asr, Imam Khomeini Hospital of Tehran between the years of 2015 and 2016. Patients with molar pregnancy, who were hospitalized with a diagnosis of hydatidiform mole by transvaginal ultrasonography, were examined in the study. The ability to perform ultrasonography before and after evacuation as well as the consent to participate in the study was among the inclusion criteria for patients. The patients were studied for invasive mole followed by two ultrasonography examinations, one 48 hours and the other 21 days after evacuation. β-hCG levels were also measured in successive periods of one week to six months. The association of sonography findings 48 hours and 21 days after evacuation with post-evacuation β-hCG levels was investigated using Chi-square test and multinomial regression.
Results: In the current study conducted on 110 patients with hydatidiform mole, the results showed that 46 patients (41.8%) suffered from invasive mole. In 23 patients (50%) with invasive mole, the results of both ultrasonography 48 hours and 21 days after evacuation were positive. There was a significant correlation between ultrasonography after evacuation (positive and negative results) and the progress of β-hCG after evacuation in women with invasive mole (P = 0.001); this means that in 73% of women with invasive mole, the positive β-hCG results corresponded with positive 21-day sonography after evacuation, and in 41% cases, ultrasound results on day 21 were reported positive before the results of β-hCG.
Conclusions: Positive results of sonography accompanied with positive results of β-hCG have a high efficiency in the diagnosis of invasive mole; therefore, more definitive studies with a larger sample size are suggested to confirm this hypothesis.

Keywords: Hydatidiform Mole, Ultrasound Sonography, β-hCG, Invasive Mole

1. Background

Gestational trophoblastic disease (GTD) includes a heterogeneous group of related lesions resulted from abnormal proliferation of placenta. GTD may be either benign or malignant. Benign lesion includes complete and partial hydatidiform mole and its diagnosis is based on histological findings. Malignant lesion includes invasive mole, placental site trophoblastic tumors, and choriocarcinoma. Trophoblastic disease during pregnancy has the potential for local invasion and distant metastasis. This group of malignant lesions is called gestational trophoblastic neoplasia (GTN), which is a rare complication of pregnancy. GTN, occurs after normal delivery, spontaneous abortion or ectopic pregnancy. The risk of its occurrence increases by 2,000 times after the occurrence of hydatidiform mole (1-5).

Complete or partial mole that has invaded in the myometrium is defined as invasive mole (6). After evacuation of a complete mole, invasions to the uterus in 15% (7, 8) and metastasis in 4% of patients can occur although there is also the possibility of local invasion in 2 - 4% for partial mole (8). Currently, diagnosis of persistent invasive mole is based only on serum detection of β-hCG levels that are measured in consecutive weeks after the evacuation of molar pregnancy (9, 10).

This diagnosis is based on its stability for 3 weeks in 4 sessions of measurement or more than 10% increase in the serum β-hCG levels 3 times in 2 weeks (11). Ultrasonog-

raphy is the preferred method for early diagnosis of molar pregnancy, assessment of myometrial invasion before evacuation, diagnosis of molar residue, and also assessment of myometrial invasion after evacuation. Therefore, it is helpful as a predictive factor in assessing the recurrence of mole (12).

In the ultrasonography of molar pregnancy, the levels between abnormal trophoblast and normal myometrium are distinct in a high resolution and thus myometrial invasion is recognizable. This invasion could remain after evacuation, and ultrasonography can show the molar vesicles that are seen in multiple small spaces sized about 1 to 30 mm. In general, Doppler ultrasonography is useful in the diagnosis of invasive mole, mole recurrence, and evaluation of response to therapy (13).

Vaginal sonography with high-resolution is not used routinely after evacuation although it is useful and its positive findings can be used as an indicator of invasion (14). Therefore, the aim of this study was to determine the positive sonography findings (cases of invasion) and its association with β-hCG progress in patients with hydatidiform mole (complete and partial) to evaluate the accuracy of ultrasonography in the diagnosis of invasive mole after evacuation.

2. Methods

The current study was a prospective, cross-sectional cohort research conducted as a diagnostic study on 110 patients with molar pregnancies referring to Department of Gynecology and Oncology of Vali-Asr, Imam Khomeini Hospital, Tehran between the years of 2015 and 2016. Patients diagnosed with molar pregnancy by ultrasonography who consented to the study were enrolled. Women who did not consent to participate in the study, those who diagnosed with non-molar pregnancy at the initial ultrasonography or remained deformed gestational sac, those having severe vaginal bleeding or any condition that required emergency intervention without the possibility of sonography, and individuals who went under hysterectomy were excluded from this research. Transvaginal color Doppler sonography using Medisone 20 device with dual-heads Curve Trans powered on C3-7 megahertz was carried out on patients with empty bladder in supine position (lithotomy position) by a radiologist. Positive results of ultrasonography included thinning of the myometrium, endometrial thickness as focal containing increased focal flow, lesion, or suspicious area of residue of a molar pregnancy, solid mass with hypervascular cystic spaces in the myometrium, a large spiral arteries in the uterus with low impedance vascular in cases with invasion into the myometrium, hypervascularity of endometrium and myometrium (development of low-resistance vessels in the myometrium), myometrium hyperechoic lesions and nodules ranging in a size from 15 to 40 mm, RI $\geq$ 0.4 of uterine artery and fading endometrial myometrium junction (EMJ). Observing any of the above mentioned conditions in ultrasonography before and after evacuation was considered as a positive result for invasion.

Follow-up was started 48 hours after suction curettage by conducting vaginal Doppler ultrasonography and serum β-hCG level measurement. Three weeks later, vaginal ultrasonography was repeated. Up to six months after the evacuation, all patients were controlled by measuring β-hCG levels. Evaluation of serum β-hCG was conducted weekly after evacuation until its level reached bellow 5 mIU/mL for three consecutive weeks. Then, the measurements were continued monthly for 6 months. The stability of the measurements for 3 weeks in 4 measuring sessions, or more than 10% increase in the measured β-hCG levels of serum 3 times in 2 weeks were considered as positive results (abnormal) for β-hCG level in invasive mole (15).

Necessary clinical information about the age of the mother, number of pregnancies, gestational age, history of previous molar pregnancies, β-hCG levels before evacuation, ultrasonography findings before and after evacuations, pathology as the gold standard, and β-hCG progress after evacuation was obtained. Not having any pathological samples, the existence of non-decidua in the pathology of sharp curettage, and non hydatidiform mole results were exclusion criteria from the study.

It should be noted that all ultrasonography, pathology, and laboratory examinations were performed at a same center.

After collecting the required information, with the use of SPSS version 19 (SPSS Inc., Chicago, IL, USA), the analysis of the collected data was performed. For qualitative variables, frequency, frequency percentage, mean, and standard deviation were calculated. In this context, independent t-test and Chi-square and Fisher and multinomial regression were used and the significance level was considered at 0.05 for interpreting the relationship among the variables.

3. Results

In 110 women with molar pregnancies, the mean age was 30.2 $\pm$ 6.8 years while the mean gestational age was 9.74 $\pm$ 2.9 weeks. Among patients with molar pregnancy, 46 patients (41.8%) were diagnosed with invasive mole. 42 patients (38.2%) were reported as complete mole and 68 cases (8.61%) as partial mole. Among 110 women with molar pregnancies, 62 cases (56.4%) were reported as positive in

ultrasonography 48 hours after evacuation and 61 patients (55.5%) were positive 21 days after evacuation (Table 1).

The findings in Table 2 did not show any significant association between positive/negative results of serial ultrasonography (48 hours and 21 days after evacuation) and the type of mole (P = 0.775). In other words, being negative or positive in ultrasonography after evacuation in patients with mole was not associated with the type of the mole (partial or complete).

The results in Table 3 show that the majority of participants, i.e. 23 patients (59%) out of 46 who were positive in both ultrasonography examinations, were diagnosed with invasive mole (P = 0.001); this means that the possibility of having invasive mole is higher in patients who are positive in both sonography examinations.

In a positive 21-day ultrasonography the number of cases with invasive mole was higher (P = 0.02), so that in the positive cases of 21-day sonography, 16 cases (73%) were reported with invasive mole against 6 patients (27%) without invasive mole. In cases with negative ultrasonography results after evacuation, no significant relationship was found with invasive mole (P > 0.05).

Only 3 patients (13%) who had positive 48-hour ultrasonography were diagnosed with invasive mole versus 20 patients (31%) who did not have invasive mole. Fisher test showed the significance of this relationship (P = 0.02). In other words, the role of positive sonography 21 days after evacuation seems effective in the diagnosis of invasive mole. In other words, positive 21-day sonography is effective in predicting the development of invasive mole.

The results of Table 4 show that there is a significant relationship between serial sonography results (positive or negative) and β-hCG progress after evacuation (P = 0.001); so that among all cases that had positive 48-hour sonography, 20 cases (87%) had a decline in β-hCG progress and not diagnosed with invasive mole while only 3 patients (13%) were diagnosed with invasive mole. In other words, it seems that in 87% of cases, despite a true positive 48-hour sonography, no association was observed with β-hCG progress (i.e. a declined f β-hCG was reported) and false positive diagnoses of 48-hour sonography after evacuation were reported.

In patient having only 21-day sonography after evacuation, 6 patients (27%) had a declining β-hCG progress and no invasive mole while 16 patients (73%) in this group were diagnosed with invasive mole. It should be noted that 7 patients (32%) after 21-day sonography. This means that 21 β-hCG before the 21-day sonography and 9 individuals (41%) had ascending or fixed β-hCG after 21-day sonography. This means that 21-day sonography was antecedent to the β-hCG progress in predicting invasive mole in 41%.

In other words, ultrasonography on day 21 have shown the occurrence of invasion in 41% before β-hCG that in fact suggested a predicting power of 41% for sonography on day 21 before the positive results of β-hCG.

4. Discussion

Due to the fact that in complete and partial moles there is also a possibility of malignant transformation, early diagnosis and timely treatment regimens is important. To this end, ultrasonography can play an important role, which in addition to the diagnosis of invasive mole, it can detect hydatidiform mole (16).

In the present study, among 110 women with molar pregnancies, 38.2% had complete mole and 61.8% partial mole.

In a study by Sebire et al. 41% of participants had complete mole and 59% partial mole (17). A study by Johns et al. showed that 25% had complete mole and 75% partial mole (18). Another study showed 29% with complete mole and 71% with partial mole (10). A study by Kirk et al. showed 33% cases of complete mole and 67% of partial mole (6).

The results of the current study are similar to those of other studies, indicating more prevalence of complete mole. In the current study, the results showed that there is a significant relationship between serial sonography examinations after evacuation (positive and negative) with the progress of β-hCG after evacuation. Among the cases that had sonography 48 hours after evacuation, 20 individuals (87%) had declining β-hCG without any invading mole. It seems that the role of sonography 48 hours after evacuation is not very efficient in predicting the course of the disease. It can be due to that 48 hours after evacuation, myometrium and endometrium conditions have not return back to their natural condition and therefore, it might not be a good time for sonography for predicting invading mole.

Also, in 73% of women with invasive mole, the positive results of β-hCG are consistent with positive results of sonography on day 21; in other words, predicting the course of the disease can be reliable up to 73% based on the 21-day sonography results after evacuation with regard to β-hCG results. It must be noted that in 41% of cases, the results of sonography on day 21 have been reported to become positive before β-hCG became positive; this result alone can confirm the predicting power of sonography on day 21 for early diagnosis of disease when compared to β-hCG.

In a study by Garavaglia et al. that has been published in AJOG, sonography has been introduced as a major method for identifying patients with invasive mole; among 186 individuals with molar pregnancies, 14 cases (7%) have had invasive mole, and 54% of the patients with

Table 1. Demographic Characteristics (Qualitative and Quantitative Variables) in Studied Patients[a]

Variable	
Age, year, mean ± SD	30.2 ± 6.8
Gestational Age, w, mean ± SD	9.74 ± 2.9
History of Mole	
1. have	11 (10)
2. don't have	99 (90)
Positive results from diagnosis of invasive mole in sonography before evacuation	
1. have	19 (17.3)
2. don't have	91 (82.7)
Invasive Mole	
1. have	46 (41.8)
2. don't have	64 (58.2)
Mole type	
1. complete	42 (41.8)
2. partial	68 (43.6)
Positive results from sonography 48 hours after evacuation	
1. have	62 (564)
2. don't have	48 (43.6)
Positive results from sonography 21 days after evacuation	
1. have	61 (55.5)
2. don't have	49 (44.5)

[a]Values are expressed as No. (%) unless otherwise indicated.

Table 2. The Relationship Between Serial Ultrasonography Findings (Positive and Negative) After Evacuation and Mole Type in Patients[a,b]

Sonography	Total Mole Number, (N = 42)	Partial Mole Number, (N = 68)	Total Number	P-Value
Positive results of both Sonography examinations	15 (38.46)	24 (61.54)	39 (100)	0.5259
Negative results of both Sonography examinations	8 (30.77)	18 (69.23)	26 (100)	0.5402
Only positive in the sonography of 48 hours after evacuation	9 (39.13)	14 (60.87)	23 (100)	0.6679
Only positive in the sonography of 21 days after evacuation	10 (45.45)	12 (54.55)	22 (100)	0.5943

[a]Values are expressed as No. (%).
[b]Serial means twice sonography on 48 hours and 21 days after evacuation.

positive results of sonography on day 21 after evacuation developed invasive mole (15).

The difference between the percentage of positive sonography on day 21 in individuals who developed invasive mole in two studies (54% in Garavaglia study versus 73% in this study), might be due to the number of patients with invasive mole which was 42% in the current study and 7% in the study of Garavaglia.

It must be noted that in both studies, the size of uterus, engagement of myometrium and endometrium, volume of uterus and hyper vascularity of myometrium and endometrium, residue of trophoblastic tissue, myometrial nodule, and the size of the tumor were used to determine positive sonography results. However, the statistical difference between the two studies can be due to the sample size, number of individuals with invasive mole, and serial sonography examinations in 2 stages in the current study.

Since there has been no study with similar aim and scopes, we can point out to the strengths of this study which are: confirmation of sonography before evacuation

Table 3. The Relationship Between the Results of Serial Ultrasonography (Positive and Negative) after Evacuation in Patients With Invasive Mole[a,b]

Sonography Results	Having Invasive Mole 66 Individuals	Not Having Invasive Mole 64 Individuals	Total Number	P-Value
Positive results of both Sonography examinations	(23) 59	(16) 41	39 (100)	0.0011
Negative results of both Sonography examinations	(4) 15	(22) 85	26 (100)	0.03
Only positive in the sonography of 48 hours after evacuation	(3) 13	(20) 87	23 (100)	0.0002
Only positive in the sonography of 21 days after evacuation	(16) 73	(6) 27	22 (100)	0.02

[a]Values are expressed as No. (%).
[b]Serial means twice sonography on 48 hours and 21 days after evacuation.

Table 4 . The Results of Serial Ultrasonography (Positive and Negative) After Evacuation and β-hCG Progress After Evacuation in all Patients[a]

β-hCG Progress	Negative β-hCG[b]	Negative β-hCG[c]	Cases that Became Positive in β-hCG After Second Sonography	Number = 100 Individuals	P-Value
Positive in both sonography examinations	(16) 41.03	(12) 30.77	(11) 28.21	39 (100)	0.001
Negative in both sonography examinations	(22) 84.62	(4) 15.38	(0) 0.00	26 (100)	
Only positive in sonography of 48 hours after evacuation (Sono 1)	(20) 86.96	(3) 13.04	(0) 0.00	23 (100)	
Only positive in sonography of 21 days after evacuation (Sono 2)	(6) 27.27	(7) 31.82	9 (40.91)	22 (100)	

[a]Values are expressed as No. (%).
[b]cases of β-hCG with a declining progress (After evacuation).
[c]cases of β-hCG with ascending progress after abortion and before sonography of 21 days.

with pathological results, serial sonography examinations 24 hours before evacuation, and 48 hours and 21 days after evacuation and their correspondence with serum level of β-hCG after evacuation, complete following up of the patients by β-hCG for 6 months, using a specialist radiologist and laboratory, having a singular strategy for measuring β-hCG, and provident methods of evaluation. Therefore, by looking at the results of the study based on sonography examination 21 days after evacuation for predicting GTN, it might be possible to use it for diagnosing and treating patients with invasive mole. Therefore, for confirming more persistent results, it is recommended to conduct a comparative study on non-molar pregnancies with a larger sample size.

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