Original Article

Investigating the factors affecting the occurrence of gestational trophoblastic neoplasia following molar pregnancy

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ABSTRACT

This study investigates the factors affecting the occurrence of gestational trophoblastic neoplasia following molar pregnancy in women referring to the specialized clinic of Imam Khomeini Hospital in Ahvaz from 2018 to 2020. This descriptive-cross-sectional study was conducted using census sampling and checklists and medical records of women who were referred to the specialized clinic of Imam Khomeini Hospital in Ahvaz from 2018 to 2020. The sample size was equal to the entire population of women with molar pregnancy. Its size was considered to be 55 people. The data relating to each of the patients were collected through the checklist and by the researcher using the pathological findings and the patient's medical records.

Based on the results of the present study, the frequency of gestational trophoblastic neoplasia following molar pregnancy was 18.2% (10 cases) and the mean age of women with gestational trophoblastic neoplasia following molar pregnancy was 29.60 years. The frequency of previous abortion history in women with gestational trophoblastic neoplasia following molar pregnancy was 70% (7 people). Also, regarding the frequency of previous pregnancies in women with gestational trophoblastic neoplasia following molar pregnancy, 2 previous pregnancies with 30% (3 people) had the highest frequency. According to the results of the present study, the rate of gestational trophoblastic neoplasia following molar pregnancy is 18.2%. The factors affecting its occurrence include maternal age, gestational age, history of abortion, number of pregnancies, uterus height difference from fetal age, and vaginal bleeding.

Keywords: Gestational trophoblastic neoplasia, Molar pregnancy, Abortion, Gestational trophoblastic disease

Introduction

Gestational trophoblastic disease (GTD) is a group of tumors defined by abnormal trophoblastic proliferation. Trophoblast cells produce human chorionic gonadotropin (hCG). GTD is divided into hydatidiform moles (containing villi) and other trophoblastic neoplasms (lacking villi). The non-molar or malignant form of GTD is called gestational trophoblastic neoplasia (GTN). They include invasive mole, choriocarcinoma, placental trophoblastic tumor, and epithelioid trophoblastic tumor. These malignancies can occur weeks or years after any pregnancy. However, they mostly occur after molar pregnancies (1). In other words, these tumors start with pregnancy. Its origin is cytotrophoblast cells (tropho means nutrition and blast means primary growing cell) or placenta-forming cells (2). These cells normally first form a finger-like and thin protrusion called villi. These villi grow into the different layers of the uterus and eventually form the placenta (an organ that protects and nourishes the developing fetus) (3).

This disease includes a range of disorders related to pregnancy. They include disorders on the verge of cancer associated with complete and incomplete hydatidiform mole and cancerous disorders of invasive mole, choriocarcinoma, and rare trophoblastic tumors of the placenta (4). These forms of cancer are limited to gestational trophoblastic tumors. In other words, based on clinical, cytogenic, and histopathological findings, trophoblastic diseases caused by pregnancy include complete mole, incomplete mole, invasive mole, choriocarcinoma, placental trophoblastic tumor, and miscellaneous cases. These diseases have different potential for local invasion and metastasis (5). The prevalence of trophoblastic varies in different parts of the world. The overall prevalence of these disorders is 1 in 1,000 pregnancies in the United States. These disorders have a high prevalence in Asia and African countries (about 1 in 387) (6). The prevalence of this cancer is about 3 times that of Europe or

North America in some parts of Asia, such as Japan. In England, this prevalence is about 1 in 714 live births. Generally, 1% of women's reproductive system tumors are related to these disorders (7).

Also, choriocarcinoma occurs in approximately 1 in 20,000 to 40,000 pregnancies in the United States. In this regard, 50% occur after term pregnancies, 25% after molar pregnancies, and 25% after other pregnancy events. The rate of both hydatidiform mole and choriocarcinoma has decreased in all populations during the past 30 years (8). Some studies have been conducted in this area in Iran. However, they have reported different rates. Accordingly, 1 per 301 live births has been reported in Babol, 1 per 506 live births in Kashan, and 1 per 543 live births in Iran University of Medical Sciences (9). These differences may be related to geographical differences, food consumption, economic and social factors, and genetic factors of different people. Some studies have reported the increasing age of the mother as one of the risk factors associated with complete mole. Some others have reported that the probability of this disease is higher for younger mothers (10).

In this regard, 80% of gestational trophoblastic diseases include hydatidiform mole, which is divided into two categories: complete mole and incomplete mole. A complete mole often manifests during the 11th to 25th weeks of pregnancy with vaginal bleeding or excessive size of the uterus according to the gestational age. The clinical manifestations of complete molar pregnancy have changed significantly in the past two decades (11). Hydatidiform mole (HM) is associated with abnormal fertilization and or gametogenesis. Risk factors include age, ethnicity, and previous history of HM, indicating a genetic basis for its etiology. Compared to women aged 21 to 35, the risk of complete mole is higher in women older than 35 and younger than 21 years, and 7.5 times higher in women older than 40 years. The risk of recurrent molar pregnancy in women with a history of molar pregnancy is about 1%, which is 10 to 20 times the risk for the general population. Reports suggest that a history of previous spontaneous abortion causes a two- to three-fold increase in molar pregnancy in women compared to a woman without a history of spontaneous abortion (8).

Hydatidiform mole is mostly diagnosed in the first trimester of pregnancy. The most common manifestation is abnormal bleeding. Other symptoms include uterine enlargement greater than expected for gestational age, absence of fetal heart sounds, cystic ovarian enlargement, vomiting of pregnancy, and abnormal hCG levels for gestational age. Molar pregnancy was mostly diagnosed in the second trimester of pregnancy in the 1990s. However, early diagnosis (first trimester) is nowadays possible thanks to the widespread use of ultrasonography during the first trimester and young ages of pregnancy. It has caused a change in the incidence of clinical manifestations and pathological findings of the disease (12).

Ultrasound is the gold standard in non-invasive techniques. The most common manifestation of a molar pregnancy on ultrasound is a "blizzard" or "bunches of grapes" pattern of the uterus. However, it is not commonly seen in the first trimester due to early diagnosis. Most complete first-trimester moles have the sonographic appearance of a complex, echogenic, intrauterine mass containing multiple small cystic spaces. These spaces correspond to hydropic villi in gross pathology. Despite the usefulness of ultrasound in this diagnosis, molar pregnancy is diagnosed only after pathological evaluation of the uterine curettage specimen in patients assumed to have spontaneous abortions. It often occurs in those with incomplete molars (13-15).

Surgical evacuation of the uterus (dilation and evacuation, suction curettage) is the primary treatment for complete or incomplete moles. Hysterectomy is an option for patients who have had enough childbearing experience. Medical management is controversial and has not been investigated well. There are concerns that induction of uterine contractions with uterotonics may increase the risk of metastatic disease (16-17). Some studies have been conducted in this area. The results of a study by Khosravi Rad (2017) showed that repeated measurements of β-hCG concentration have high predictive accuracy for early diagnosis of GTN. Thus, monitoring the three-week process of this marker is recommended for early diagnosis of this cancer for women who suffer from molar pregnancy (18). In a study entitled "Overview of the management of gestational trophoblastic neoplasia", Yousefi (2020) found that although GTN patients are treated with conventional surgical treatments or chemotherapy, these treatments may not be effective in some patients with the resistant disease and patients may die in some patients. Some new therapeutic drugs are needed to reduce the level of toxicity caused by conventional chemotherapy and to treat patients suffering from resistant disease.

The progression of hydatidiform to GTN and the issue of GTN drug resistance are the most recent issues related to the diagnosis of GTN (19). Albright (2020) reported that the prevalence of gestational trophoblastic neoplasia was estimated at 15.7%. Development of gestational trophoblastic neoplasia after normal hCG levels following molar pregnancy is rare. Gestational trophoblastic neoplasia after normal hCG levels following a complete mole in 89.6% of cases occurred when the evacuation time to normalization was 56 days or more, and for 60.7% than the usual, 6 months of care was recommended (20). In a study entitled "Diagnosis and treatment challenges of gestational trophoblastic neoplasia worldwide", Braga (2019) stated that according to the criterion proposed by the International Federation of Gynecology and Obstetrics, gestational trophoblastic neoplasia occurs when four or more concentrations of human chorionic gonadotropin exist during three weeks, hCG is elevated for three consecutive weekly measurements for at least 2 weeks or more, and hCG concentrations decrease six months or longer after molar evacuation. Early diagnosis of this disease and appropriate treatment are necessary to prevent maternal death and improve and maintain the reproductive ability of these women (22). It is possible to prevent the complications caused by this disease by knowing the effective factors in the occurrence of gestational trophoblastic neoplasia after molar pregnancy in women and even taking the necessary measures to treat the patients. Hence, the present study examined women with molar pregnancy referring to the

specialized clinic of Imam Khomeini Hospital in Ahvaz from 2019 to 2020.

Materials and Methods

The study was descriptive and cross-sectional. Its statistical population included the medical records of women who were referred to the specialized clinic of Imam Khomeini Hospital in Ahvaz from 2018 to 2020. They were included in the study using a census method. The sample size was equal to the entire population of women with molar pregnancy, which was equal to 55 people. The exclusion criteria of the study were not completing the medical records of the patient and pregnant women who did not have a molar pregnancy. The data related to each of the patients were collected in the checklist and by the researcher using the pathological findings and the patient's medical record. To describe the data, mean and standard deviation were used for quantitative variables, and frequency and percentage were used for qualitative variables. Also, to analyze the data according to the normality of the data (by the Kolmogorov-Smirnov test), parametric and non-parametric tests were used in SPSS-22 software.

Results and Discussion

Table 1 presents the descriptive information of women suffering from gestational trophoblastic neoplasia after molar pregnancy referred to the specialized clinic of Imam Khomeini Hospital in Ahvaz from 2018 to 2020.

Table 1. Mean age of women with gestational trophoblastic neoplasia following molar pregnancy

Age	Mean	SD
Molar pregnancies	27.74	7.14
Women with gestational trophoblastic neoplasia	29.60	4.32
GTN (incidence of gestational trophoblastic neoplasia following molar pregnancy)	Frequency	Percentage of frequency
Yes	10	18.2
No	45	81.8
Number of pregnancies		
1	1	10
2	3	30
3	2	20
4	2	20
5	2	20
Mean B-HCG*		
Week 0	10.45	1.44
Week 1	9.67	1.30
Week 2	9.12	1.23
Week 3	8.81	1.41

*Weeks are based on curettage time. For example, week 3 B-HCG level is three weeks after the curettage time.

Table 2. Frequency and percentage of gestational age by week and GTN

Variable	Week	GTN		Total
		No	Yes	
Gestational age by week	5	Frequency	1	0	1
		Percentage of frequency	2.2%	0.0%	1.8%
	7	Frequency	3	0	3
		Percentage of frequency	6.7%	0.0%	5.5%
	8	Frequency	9	2	11
		Percentage of frequency	20.%	20.0%	20.0%
	9	Frequency	4	2	6
		Percentage of frequency	8.9%	20.0%	10.9%
	10	Frequency	7	2	9
		Percentage of frequency	15.6%	20.0%	16.4%
	11	Frequency	1	0	1
		Percentage of frequency	2.2%	0.0%	1.8%
	12	Frequency	5	3	8
		Percentage of frequency	11.1%	30.0%	14.5%
	14	Frequency	5	0	5
		Percentage of frequency	11.1%	0.0%	9.1%
	15	Frequency	4	0	4
		Percentage of frequency	8.9%	0.0%	7.3%
	16	Frequency	3	0	3
		Percentage of frequency	6.7%	0.0%	5.5%
	17	Frequency	0	1	1
		Percentage of frequency	0.0%	10.0%	1.8%
	18	Frequency	2	0	2

		Percentage of frequency	4.4%	0.0%	3.6%
	20	Frequency	1	0	1
		Percentage of frequency	2.2%	0.0%	1.8%
کل		Frequency	45	10	55
		Percentage of frequency	100.0%	100.0%	100.0%

Table 2 presents the frequency and percentage of gestational age by week and GTN. As seen, in the twelfth week, the highest frequency is 3 (30%) for GTN, and in the tenth week, the highest frequency is 7 (15.6%) for molar pregnancy. In this regard, 70.9% of molar pregnancies were diagnosed in the first three months of pregnancy.

Table 3. Frequency and percentage of frequency of history of abortion, uterus difference from fetal age, and GTN

Variable			GTN	
			No	Yes
History of abortion	Yes	Frequency	33	7
		Percentage of frequency	73.3%	70%
	No	Frequency	12	3
		Percentage of frequency	26.7%	30%
Total		Frequency	45	10
		Percentage of frequency	100%	100%
Variable			GTN	
			No	Yes
uterus difference from fetal age	2<	Frequency	41	6
		Percentage of frequency	91.1%	60%
	>2	Frequency	4	4
		Percentage of frequency	8.9%	40.0%
Total		Frequency	45	10
		Percentage of frequency	100%	100%

Table 3 presents the frequency and percentage of history of abortion, the uterus difference from the fetal age, and GTN. As seen, out of 45 cases of molar pregnancy, 33 cases (73.3%) had a history of abortion and 7 cases (70%) of trophoblastic neoplasia had a history of abortion. Also, out of 45 cases of molar pregnancy, 41 cases had less than 2 (91.1%) and 4 cases had more than 2 (8.9%), and in trophoblastic neoplasia pregnancies, 6 cases had less than 2 (60%) and 4 cases had more than 2 (40%).

Table 4. Frequency and percentage of frequency of vaginal bleeding and GTN

Variable			GTN		Total
			No	Yes	
Vaginal bleeding	No	Frequency	9	3	12
		Percentage of frequency	20.0%	30%	21.9%
	Yes	Frequency	36	7	43
		Percentage of frequency	80%	70%	78.1%
Total		Frequency	45	10	55
		Percentage of frequency	100%	100%	100%

Table 4 presents the frequency and percentage of frequency of vaginal bleeding in molar pregnancy and GTN. As seen in molar pregnancy, 9 cases (20%) did not have vaginal bleeding and 36 cases (80%) had vaginal bleeding. In trophoblastic neoplasia pregnancies, 7 cases (70%) had vaginal bleeding and 3 cases (30%) did not have vaginal bleeding.

The relationship between factors affecting gestational trophoblastic neoplasia following molar pregnancy

Table 5- Logistic regression and relationship of factors affecting molar pregnancy

Variable	B	Exp(B)	Confidence interval		P-value
			Lower bound	Upper bound	
Age	0.71	1.073	0.915	1.258	0.384
History of pregnancy	-0.83	0.920	0.689	1.229	0.573
History of abortion	-0.331	0.718	0.201	2.570	0.611
Number of pregnancies	141	1.151	0.495	2.676	0.744
Uterus difference from the fetal age	2.590	13.335	2.154	82.566	0.005
Vaginal bleeding	113	1.120	154	8.121	0.911

Table 5 shows the effect of confounding variables on the pregnancy type variable. As seen, only the variable of the uterus difference from the fetal age in two types of pregnancy (molar and trophoblastic neoplasia) has a significant difference and no effect is observed for other cases. Based on the sample size, age, number of pregnancies, and vaginal bleeding also have a significant chance compared to other variables, but they are not statistically significant.

This study investigated the factors affecting the occurrence of gestational trophoblastic neoplasia following molar pregnancy in women referring to the specialized clinic of Imam Khomeini Hospital in Ahvaz from 2018 to 2020. The number of these women was 55. In the study by Almasi *et al*. (2012), between January 2012 and January 2013, all women who were referred to prenatal clinics immediately after a positive pregnancy test or after a delay in menstruation were examined. In this descriptive study, 8614 pregnant women with the mentioned criteria were included in the study and 61 cases of hydatidiform mole (0.7% or 7 cases in 1000 pregnancies) were diagnosed. Ten cases (16.4%) were patients with incomplete moles (22). In a cross-sectional study from November 2016 to February 2017, Mulisya *et al*. (2018) reported 20.180 (11.1%) incomplete moles and 3.180 (1.7%) complete moles (23). In a cross-sectional study entitled "Frequency of molar pregnancy in abortion cases diagnosed by histopathology samples at Nishtar Medical University Hospital, Multan, Pakistan", Shafiei *et al*. (2022) reported that molar pregnancy was observed in 7 patients (2.1%). Among them, 2 cases were complete moles and 5 cases were incomplete moles. The frequency of molar pregnancy among abortion cases before the 22nd week of pregnancy was 1.2% (24).

In the study by Jafari *et al*. on 137 patients admitted with the diagnosis of hydatidiform mole in the Imam Khomeini Teaching Hospital of Ahvaz, the mean age of the patients was 27.6 and there was a significant correlation between age over 40 years and complete mole and age over 40 years and persistent mole. In this study, 108 patients had complete moles and 24 patients had incomplete moles (25). In the study by Nankali *et al*. (2021), 237 molar pregnancies were investigated, of which complete molar pregnancies were observed in 181 cases and incomplete moles in 56 cases (26). Based on the results of the present study, the frequency of gestational trophoblastic neoplasia following molar pregnancy was 18.2% (10 cases) and the mean age of women with gestational trophoblastic neoplasia following molar pregnancy was 29.60 years. In a retrospective cohort study among 54 patients studied from 2000 to 2020, Capobianco *et al*. 2021 reported 46 (85.18%) HM cases, 8 (14.81%) GTN cases, with 6 cases of non-metastatic disease. Two out of 8 (25%) GTN cases were metastatic (27).

In a study entitled “Early diagnosis of gestational trophoblastic neoplasia based on serial measurement of human chorionic gonadotropin hormone in women with molar pregnancy”, Riahi *et al*. (2019) reported that GTN occurred in 14.9% of patients and the mean age of patients was 26.6 (6.55) years (28).

Homaei *et al*. (2011) reported the mean age of patients with placental trophoblastic tumors at 27±8.3 years (29), which is in line with the results of the present study. According to the results of the present study, the frequency of previous abortion history in women with gestational trophoblastic neoplasia following a molar pregnancy was 70% (7 people). Also, the frequency of the number of previous pregnancies in women with gestational trophoblastic neoplasia following a molar pregnancy is as follows. Two previous pregnancies had the highest frequency with 30% (3 people). The mean difference of uterine height from fetal age in women with gestational trophoblastic neoplasia following molar pregnancy was less than 2 cm in 60% (6 people) and 70% of women with gestational trophoblastic neoplasia following molar pregnancy (7 people) had vaginal bleeding. Previous history of spontaneous abortion is associated with an increased risk of molar pregnancy. Abortion more than or equal to 2 times also increases the risk of developing a mole by 1.3 times (30).

In a study by Hamaei, more than 25% of cases of mole and trophoblastic tumors had a history of previous abortion (29). In the study by Anyanwu *et al*. (2020), vaginal bleeding and abdominal pain were the most common symptoms (95%) (30). In the study by Nankali *et al*. (2021), 114 pregnant women (48.1%) were nulliparous and 123 cases (51.9%) were multiparous. Vaginal bleeding was also the most common symptom in women (26). It is consistent with the results of the present study. Based on the results of the present study, the mean hCG level in women with gestational trophoblastic neoplasia following molar pregnancy at week zero (the time of curettage) was the highest (44.1±10.45). In this study, the mean hCG had a mild decreasing slope. In a study by Homaei *et al*., the βHCG level was higher than normal in 100% of patients with placental trophoblastic tumors in the first 10 weeks. This study revealed that by comparing the regression curve of βHCG in gestational trophoblastic tumor patients with the regression curve of uncomplicated hydatidiform mole, patients with this tumor can be diagnosed earlier than the usual 8-10 weeks and treated more successfully (33). Capobianco *et al*. (2021) stated that the monitoring of serum hCG levels in the follow-up of patients with molar pathology is mandatory for the early diagnosis of persistent trophoblastic disease and the diagnosis of patients with resistance to first-line chemotherapy. Previous studies have shown that the relationship between hCG hormone concentration in molar pregnancies and the risk of permanent trophoblastic diseases changes linearly over time. Accordingly, the risk value is higher for higher values of the initial concentration (higher than 2000 mL/mIU). It also shows a decreasing trend after pregnancy (27), which is consistent with the results of the present study.

Conclusion

According to the results, the occurrence of gestational trophoblastic neoplasia following molar pregnancy was 18.2%. The factors affecting its occurrence included gestational age, abortion history, number of pregnancies, uterine height difference from fetal age, and vaginal bleeding. Further comparative studies are recommended in other provinces of the country.

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