Original Article

Molar Pregnancy and Its Associated Risk Factors: A Case-Control Study in Qazvin, Iran

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Abstract

Background & Objective: Hydatidiform Mole (HM) is a type of gestational trophoblastic disease which causes serious complications and recognizing risk factors can play an important role in reducing the incidence. The aim of this study is to evaluate HM risk factors in Kowsar hospital in Qazvin, Iran.

Materials & Methods: In this case-control study, 77 pregnant women, by complete enumeration method with sonographic and pathological diagnosis of molar pregnancy in Qazvin Kowsar hospital in 2016-2017, were assigned to the case group and 77 pregnant women with no delivery problems were assigned to the control group. All demographic and midwifery data were extracted from the records in the hospital archive. Before patients were enrolled in this study, written consent was obtained. Data were analyzed by t-test and chi-square in SPSS software version 22. $P<0.05$ was considered significant.

Results: Mean age in both case and control groups was 27.16 ± 7.26. There was no significant difference in preeclampsia, multiple pregnancy, blood groups, Rhesus (Rh) and contraceptive methods in case and group groups ($P>0.05$). There was a significant relationship between HM and history of molar pregnancy and multiparity (OR: 2.1; CI: 1.77-2.48; p=0.01, OR: 1.85; CI: 1.07-3.6: p=0.04).

Conclusion: The present study also showed that HM was more likely to occur in multipara patients and patients with history of molar pregnancy. Therefore, it is recommended that women should undergo health care before pregnancy and further studies are required to provide solutions to reduce the cases of HM.

Keywords: hydatidiform mole, risk factors, pregnant women

Introduction

Hydatidiform mole (known as molar pregnancy) is a kind of gestational trophoblastic disease. Gestational trophoblastic disease (GTD) is a spectrum of benign and malignant tumors including moles and neoplasms (GTN) and is a product of an abnormal pregnancy (1, 2). The tumor originates from gestational tissue rather than maternal tissue and it is unique in gynecology. The gestational choriocarcinoma which might be highly invasive, is the form of GTD (3, 4).

Hydatidiform mole is a result of genetic problems of the sperm or the egg. By cytogenetic and morphologic analysis, HM is divided into at least two syndromes: complete (classical) mole (CM) and partial (incomplete) mole (PM). A

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complete mole has a diploid karyotype (usually 46XX). It is without any ascertainable embryo/fetus and has swollen villi. The partial moles have triploid karyotype (69, XXX or 69, XXY). It has a fetus (alive or dead) and normal villus (5, 6). An enucleated egg is fertilized by two sperm or haploid sperm to produce a single sperm, which can endure duplicates. This process in complete moles only results in the expression of paternal DNA (6, 7).

The Frequency of HM is low. In Europe and North America, the frequency is reported 60 to 120/100,000 pregnancies for HM (8). In other studies, this rate has estimated to be 3.3/1000 worldwide which can be the result of development in detecting methods specially increase in detection of partial moles. Cytogenetic and molecular genotyping evidence indicates that PM is almost as double common as CM (9).

The incidence of HM was 1.2 per 1,000 pregnancies in Sweden, 1 in 591 pregnancies in UK, 4.3 per 1,000 pregnancies in Morocco and one per 276 births in Nepal (10-13). In our country, Iran, the incidence of HM was seven per 1,000 pregnancies from 2012 to 2013 which is more than the incidence reported in the USA and European countries (14).

Maternal age (greater than 35 years old and early teenage years less than 20 years old), previous infertility problems (like pregnancies due to ovulation induction), spontaneous abortion, previous molar pregnancy, blood type A, lack of carotene (vitamin A) and smoking are reported as risk factors of HM in different studies (5, 8, 15).

Hydatidiform mole can present with vaginal bleeding and hyperemesis and these presentations are more common in CM (16).

To check vaginal bleeding in the pregnant women, a serum quantitative hCG level is needed. The hCG levels in the hydatiform moles are higher than normal pregnancy or ectopic pregnancy. These amounts are typically more than 100,000 in complete moles. The best imaging option for evaluation of the hydatiform moles is pelvic ultrasound. The pathognomonic findings include a snowstorm appearance which is a mass in the uterine cavity with multiple spaces. These spaces are the hydropic villi in the histology section. The complete mole has no embryo or fetus but in the partial mole, there is a viable fetus with amniotic fluid and placenta. The next step in management of HM is a computed tomography (CT) scan and positron emission tomography (PET) scan for staging the disease (17, 18).

In the stable patients, dilation and curettage is necessary. In advanced maternal age and patients who have completed childbearing, hysterectomy is performed. The hysterectomy cannot eliminate the risk of metastasis so the evaluation for metastatic sites is needed. After extraction of the HM, the follow up with hCG levels should be obtained. If the hCG levels elevate, the invasive disease requires chemotherapy and gynecological oncologist consultation is needed (18, 19).

Early detection and treatment of HM are necessary for preserving fertility. It is also important because it can change into other types of GTD which are malignant (1, 14). Due to the importance of this issue and lack of enough information about HM, the present study was conducted to investigate the incidence and risk factors of HM in pregnant women referred to Kowsar Hospital in Qazvin, Iran in 2016-2017.

Material & Methods

Study population

This study was initially performed as a case-control study in 2016-2017 in Kowsar Hospital in Qazvin, Iran. For data collection, the maternity records available in the hospital archive were used. The sampling method in this study was based on complete enumeration and all the records in the hospital archive in 2016-2017 were evaluated. The incidence of HM was calculated, then in the form of a case-control study, 77 pregnant women, from 17116 birth records in two years, with no delivery problems were assigned to the control group as simple random samples (Random Number Table) and 77 pregnant women with sonographic and pathological diagnosis of molar pregnancy were assigned to the case group. The mean age

between the two groups will be equal due to the matching of case and control groups in the terms of age.

Inclusion and exclusion criteria

The inclusion criteria were all the molar pregnancies in 2016-2017. The exclusion criteria were women with other pregnancy and fetus complications such as IUFD and incomplete patient records. The data collection tool was a checklist including demographic characteristics such as maternal age, gravidity, blood group, Rhesus (Rh), type of contraceptive method and fetal heart existence, theca lutein cyst, vaginal bleeding, hyperemesis and hyperthyroidism. In addition, risk factors such as maternal records in previous pregnancies (preeclampsia, molar pregnancy, multiple pregnancies) were included in the checklist. The checklist was prepared by the researcher and approved by the board members who were obstetrician and gynecologist of the hospital.

Researchers obtained a code of ethics from the Ethics Committee of Qazvin University of Medical Sciences IR.QUMS.REC.1396.215 and referred to the Kowsar Hospital archive for sampling. The checklists were filled by the researchers based on the information in the records. Before patient was enrolled in this study, written participant consent was obtained. All of the principles and protocols were recommended by the Helsinki Convention for Ethics.

Statistical analysis

After data collection, data were entered into IBM SPSS Statistics software version 22.0 (IBM Corp., Armonk, NY, USA). They were analyzed by Kolmogorov-Smirnov test for normal distribution. T-test and chi-square parametric tests were used according to the distribution of samples in population. Logistic regression analysis was further clarified the role of confounding variables. $P<0.05$ was considered significant.

Results

Three patients were excluded from study. The mean age of the study population was 27.16 ± 7.262 and 75.3% of women with molar pregnancy were 19 to 34 years old. The mean gravidity in the case group was 2.48 ± 1.82 and in the control group it was 2.30 ± 1.80. The frequency of contraceptive use in case group were oral contraceptive pill (18.2%), intrauterine device (2.6%), withdrawal method of contraception (41.6%) and 37.7% of cases did not use contraceptive methods. The frequencies of contraceptive use in control group were oral contraceptive pill (9.1%), intrauterine device (2.6%), withdrawal method of contraception (44.2%) and 44.2% of cases did not use contraceptive methods. The most common type of contraception in case and control (41.6% and 44.2%) group was withdrawal method. There was no significant difference in contraceptive methods between two groups ($p= 0.4$).

In 9.1% of patients with HM, there was a positive history of molar pregnancy. Women with molar pregnancy had more vomiting and vaginal bleeding as these are some of the signs of molar pregnancy. Also, theca lutein cysts and hyperthyroidism were significantly more likely to happen in the case group. Table 1 showed these characteristics between case and control groups. There was a significant relationship between HM and occurring characteristics such as vaginal bleeding, hyperemesis, theca lutein cyst, and hyperthyroidism ($P<0.05$).

The frequency of blood group B in case group and frequency of blood group O in control group was higher than other blood groups, 33.8% and 40.2% respectively. Other blood groups in case group were A (27.2%), O (29.9%) and AB (9.1%). Blood groups in control group were A (18.2%), B (28.6%) and AB (13%). There was no significant difference in factors including blood groups, Rhesus (Rh) and contraceptive methods ($P>0.05$). There was no significant difference in factors including blood groups and Rhesus (Rh) between the two groups.

Table 1. Comparison of characteristics between case and control groups*

Risk Factor		Case N (%)	Control N (%)	OR (95%CI)	P value
Vaginal Bleeding	Yes	42 (54.5)	2 (2.6)	45 (10.3-196.53)	0.01
	No	35 (45.5)	75 (97.4)		
Hyperemesis	Yes	15 (19.5)	1 (1.3)	18.38 (2.36-143.09)	0.01
	No	62 (80.5)	76 (98.7)		
Theca Lutein Cyst	Yes	13 (16.9)	2 (2.6)	7.61 (1.65-35.23)	0.01
	No	64 (83.1)	75 (97.4)		
RH	+	71 (92.2)	69 (89.6)	1.37 (0.45-4.16)	0.4
	-	6 (7.8)	8 (10.4)		
Hyperthyroidism	Yes	15 (19.5)	1 (1.3)	18.38 (2.36-143.09)	0.01
	No	62 (80.5)	76 (98.7)		

*Data are presented as n (%). OR = odds ratio; CI = confidence intervals

According to Table 2, history of molar pregnancy and multiparity was significantly higher in the case group.

Table 2. Comparison of the history of exposure to Hydatidiform Mole risk factors between case and control groups*

Risk Factor		Case N (%)	Control N (%)	OR (95%CI)	P value
Multiple Pregnancy	Yes	2 (2.6)	2 (2.6)	1 (0.13-7.28)	1
	No	75 (97.4)	75 (97.4)		
History of Molar Pregnancy	Yes	7 (9.1)	0 (0)	2.1 (1.77-2.48)	0.01
	No	70 (90.9)	77 (100)		
History of Preeclampsia	Yes	1 (1.3)	1 (1.3)	1 (0.61-16.28)	1
	No	76 (98.7)	76 (98.7)		
Gravidity	Multipara	54 (70.1)	43 (55.8)	1.85 (1.07-3.6)	0.04
	Primipara	23 (29.9)	34 (44.2)		
RH	+	71 (92.2)	69 (89.6)	1.37 (0.45-4.16)	0.57
	-	6 (7.8)	8 (10.4)		

*Data are presented as n (%) OR = odds ratio; CI = confidence intervals

Discussion

These studies have shown that HM is more frequent in Iran in comparison with European countries and the United States. In our study, 29.9% of molar pregnancy was for the first gestation.

In the present study, due to age matching of the case and control groups, we could not evaluate the effect of age on HM incidence in the two groups but the highest rate of HM was reported in women aged 19-34 years. The study of Milani et al. in 2017 reported that there was no significant relationship between the risk of molar pregnancy and age (p=0.29) (20).

The age of patients in their study was different in two groups but in this study, the mean of the age between case and control groups was the same due to matching of the case and control groups. The study of Karimi-Zarichi et al. in 2015 reported that 43.2% of patients were affected during the first gestation and the mean of age was 27 years with variation in age from 15-35 years.

In this study 54.5% of patients presented vaginal bleeding which is a common presentation of molar pregnancy. 19.5% of them experienced hyperemesis, 19.5% had hyperthyroidism and in 16.9% of the patients, theca lutein cysts were diagnosed. The most common symptom in that study was vaginal bleeding (90%) and the frequency of theca-lutein cyst was 54% (21). The most common symptom in the present study and Karimi-Zarichi et al. (21) study was same, which was vaginal bleeding. Another similarity between these two studies was the mean age of patients. In a cross-sectional study by Farzaneh in 2019, the mean age of patients with HM was 26.6 years and their most common clinical manifestation of hyperthyroidism was tachycardia. More than 50% of the patients had increased amounts of free T3 and free T4. They reported that there was no relationship between maternal age and gravidity with thyroid function tests (22). In the present study, the frequency of hyperthyroidism associated with HM was 19.5%. One of our limitations was the uncompleted thyroid function tests in some of the documents achieved so we cannot evaluate the hyperthyroidism with the levels of free T3 and free T4.

The prospective Indian study entitled "A Prospective Study on Clinico-epidemiological Profile of Molar Pregnancy in A Tertiary Care Hospital" was published in 2019 whose results can be compared with present study because both studies occurred in tertiary care hospital (in Qazvin province and in Odisha state in India). The incidence of HM was 2.85 in 1000 deliveries. Most of patients had low socioeconomic status and age group was 21-30 years. Primigravidae were more common in molar pregnancy and the past history of HM in prior pregnancy was negative. The most common symptom was vaginal bleeding after a period of amenorrhea (23). The race and genetics can explain the difference in molar pregnancy incidence but the other important points in our study were the history of molar pregnancy and the multigravidity in our cases compared with Odisha cases. We should evaluate the reason for refractory molar pregnancy in Iranian population with genetics and in vitro studies.

The present study showed that just history of hydatidiform mole and multiparity may play a significant role in the incidence of hydatidiform mole. Another study by Mulisya et al. in Uganda reported the prevalence of hydatidiform mole was 6.1%. In this study, 24.3% of patients with molar pregnancy had the history of abortion and risk factors including maternal age more than 35 years (P=0.01) and history of previous abortion or molar pregnancy (P=0.05) had a significant relationship with hydatidiform mole (24). We could not evaluate the effect of age on HM incidence in the two groups but the history of molar pregnancy in prior pregnancy is consistent with present study. It can be due to the fact that the pathology of many abortions is not clear and HM may be one of the causes of these abortions.

The study of Eagles et al. in 2015 with 16000 pregnant women between 1990-2009 reported that the risk of next molar pregnancy was 0.91% and frequency of multiparity was 54% (25). These results are consistent with present study.

In the present study, there was no significant difference in factors including blood groups, Rhesus (Rh) and contraceptive methods. Different studies all around the world have shown many variations and different environmental risk factors in the incidence of HM: vitamin A deficiency and lack of carotene, history of previous moles, blood type A and history of OCP intake (5, 14, 15, 26, 27). Frequency of blood type A in our case group was lower than blood type O and there was no significant difference between two groups in blood groups risk factor.

In the similar study in Tehran, there was a significant increased risk of molar pregnancy in

patients with OCP use, history of molar pregnancy and history of abortion. However there was no significant difference between blood groups and molar pregnancy as well as this study (14). The reason of no relationship between blood groups and RH in Qazvin and Tehran populations can be attributed to the same environmental and genetics factors in these cities. No significant difference between OCP use and HM in our study can be the result of less use of OCP in Qazvin because of cultural differences between two cities (18.2% in molar group, 9.1% in non-molar).

One of the limitations of this study was uncompleted data based on the records in the hospital archive. Other limitations of the present study include failure to record history of smoking, maternal education and precise details of all pregnancy complications in previous pregnancies. Another limitation is that some women could not recall all of their past medical history so some histories were missed.

The strong point of the study is Kowsar Hospital of Qazvin which is an educational center with Level 3 Health Care Service, so almost all high-risk pregnancies in the province are referred to this hospital.

Conclusion

In the present study, there was a significant relationship between HM and history of molar pregnancy and multiparity. The incidence of molar pregnancy in Qazvin, like the many other Asian countries, is more than that of European countries and USA (9). There should be more attention and programming in Iran and other Asian countries to reduce modifiable risk factors.

It is recommended that women with risk factors receive extra clinical care and checkups before pregnancy. Also, more studies with greater populations should be done in order to decrease the incidence of HM in Iran associated with early diagnosis of molar pregnancy in high-risk patients and starting the treatment.

Conflict of Interests

The authors declared no conflict of interest.

Acknowledgments

Hereby, we would like to thank the Clinical Research Development Center of Kowsar Hospital and the Student Research Committee of Qazvin University of Medical Sciences, Qazvin, Iran. Researchers obtained a code of ethics from the Ethics Committee of Qazvin University of Medical Sciences IR.QUMS.REC.1396.215.

References

1.Shaaban AM, Rezvani M, Haroun RR, Kennedy AM, Elsayes KM, Olpin JD, et al. Gestational trophoblastic disease: clinical and imaging features. Radiographics. 2017;37(2):681-700.

2.Mittal S, Menon S. Interstitial pregnancy mimicking an invasive hydatidiform mole. American Journal of Obstetrics & Gynecology. 2019;220(5):501.

3.Sarmadi S, Izadi-Mood N, Sanii S, Motevalli D. Inter-observer variability in the histologic criteria of diagnosis of hydatidiform moles. The Malaysian journal of pathology. 2019;41(1):15-24.

4.Ning F, Hou H, Morse AN, Lash GE. Understanding and management of gestational trophoblastic disease. F1000Research. 2019;8.

5.Parazzini F, Mangili G, La CV, Negri E, Bocciolone L, Fasoli M. Risk factors for gestational trophoblastic disease: a separate analysis of complete and partial hydatidiform moles. Obstetrics and gynecology. 1991;78(6):1039-45.

6.Braga A, Mora P, de Melo AC, Nogueira-Rodrigues A, Amim-Junior J, Rezende-Filho J, et al. Challenges in the diagnosis and treatment of gestational trophoblastic neoplasia worldwide. World journal of clinical oncology. 2019;10(2):28.

7.Yuk J-S, Baek JC, Park JE, Jo HC, Park JK, Cho IA. Incidence of gestational trophoblastic disease in South Korea: a longitudinal, population-based study. PeerJ. 2019;7:e6490.

8.Ghassemzadeh S, Kang M. Hydatidiform Mole. StatPearls [Internet]. 2020.

9.Colgan TJ, Chang MC, Nanji S, Kolomietz E. A Reappraisal of the Incidence of Placental Hydatidiform Mole Using Selective Molecular Genotyping. International Journal of Gynecologic Cancer. 2016;26(7):1345-50.

10.Salehi S, Eloranta S, Johansson AL, Bergström M, Lambe M. Reporting and incidence trends of hydatidiform mole in Sweden 1973–2004. Acta oncologica. 2011;50(3):367-72.

11.Savage P, Williams J, Wong S-L, Short D, Casalboni S, Catalano K, et al. The demographics of molar pregnancies in England and Wales from 2000-2009. J Reprod Med. 2010;55(7-8):341-5.

12.Boufettal H, Coullin P, Mahdaoui S, Noun M, Hermas S, Samouh N. Complete hydatiforme mole in Morocco: epidemiological and clinical study. Journal de gynecologie,

obstetrique et biologie de la reproduction. 2011;40(5):419-29.
13.Thapa K, Shrestha M, Sharma S, Pandey S. Trend of complete hydatidiform mole. JNMA; journal of the Nepal Medical Association. 2010;49(177):10-3.
14.Almasi A, Almassinokiani F, Akbari P. Frequency of molar pregnancies in health care centers of Tehran, Iran. Journal of reproduction & infertility. 2014;15(3):157.
15.Sebire N, Fisher R, Foskett M, Rees H, Seckl M, Newlands E. Risk of recurrent hydatidiform mole and subsequent pregnancy outcome following complete or partial hydatidiform molar pregnancy. BJOG: An International Journal of Obstetrics & Gynaecology. 2003;110(1):22-6.
16.Sun SY, Melamed A, Joseph NT, Gockley AA, Goldstein DP, Bernstein MR, et al. Clinical presentation of complete Hydatidiform mole and partial Hydatidiform mole at a regional Trophoblastic disease Center in the United States over the past 2 decades. International Journal of Gynecologic Cancer. 2016;26(2):367-70.
17.Ross JA, Unipan A, Clarke J, Magee C, Johns J. Ultrasound diagnosis of molar pregnancy. Ultrasound. 2018;26(3):153-9.
18.Heller DS. Update on the pathology of gestational trophoblastic disease. Apmis. 2018;126(7):647-54.
19.Ling C, Zhao J, Qi X. Partial molar pregnancy in the cesarean scar: A case report and literature review. Medicine. 2018;97(26).
20.Milani HS, Abdollahi M, Torbati S, Asbaghi T, Azargashb E. Risk Factors for Hydatidiform Mole: Is Husband's Job a Major Risk Factor? Asian Pacific journal of cancer prevention: APJCP. 2017;18(10):2657.
21.Karimi-Zarchi M, Mortazavizadeh MR, Soltani-Gerdefaramrzi M, Rouhi M, Yazdian-Anari P, Ahmadiyeh MH. Investigation of risk factors, stage and outcome in patients with gestational trophoblastic disease since 2001 to 2011 in Iran-Yazd. International journal of biomedical science: IJBS. 2015;11(4):166.
22.Farzaneh F, Keikha R. Evaluation of Prevalence of Changes in Thyroid Functional Tests in Mole Hydatiforme. Prensa Med Argent. 2019;105(2):2.
23.Nayak AK, Hota S, Padhi M, Jain MK. A Prospective Study on Clinic Oepidemiological PROFILE of Molar Pregnancy in a Tertiary Care HOspital. International Journal of Medical and Biomedical Studies. 2019;3(9): 125.
24.Mulisya O, Roberts DJ, Sengupta ES, Agaba E, Laffita D, Tobias T, et al. Prevalence and Factors Associated with Hydatidiform Mole among Patients Undergoing Uterine Evacuation at Mbarara Regional Referral Hospital. Obstetrics and gynecology international. 2018;2018.
25.Eagles N, Sebire N, Short D, Savage P, Seckl M, Fisher R. Risk of recurrent molar pregnancies following complete and partial hydatidiform moles. Human reproduction. 2015;30(9):2055-63.
26.Berkowitz RS, Cramer DW, Bernstein MR, Cassells S, Driscoll SG, Goldstein DP. Risk factors for complete molar pregnancy from a case-control study. American journal of obstetrics and gynecology. 1985;152(8):1016-20.
27.Parazzini F, Vecchia CL, Pampallona S. Parental age and risk of complete and partial hydatidiform mole. BJOG: An International Journal of Obstetrics & Gynaecology. 1986;93(4):582-5.