

RESEARCH ARTICLE

Risk Factors for Hydatidiform Mole: Is Husband's Job a Major Risk Factor?

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Abstract

Background: The hydatidiform mole (HM) is a precancerous placenta considered as a gestational trophoblastic disease (GTD). It may convert to more invasive forms of gestational trophoblastic neoplasia (GTN), endangering women's health by more severe complications. Most GTN cases originate from HM, which is associated with uterine bleeding, preeclampsia and thyroid problems. Its etiology has not been adequately explored, but some risk factors have been reported. The aim of the present study was to assess any relationships between molar pregnancy and factors including mothers' and husbands' occupations. **Methods:** In this case control study, seventy complete molar pregnancies (cases) were compared with 200 normal pregnancies (controls) in 5 educational hospitals affiliated to medical universities in Tehran, Iran. Data were analyzed using t-test, chi-square test, Fisher's exact test and logistic regression modeling. **Results:** There was no significant relationship between the risk of molar pregnancy and age, education, blood RH, parity, duration of OCP use, intra-uterine device usage, smoking, consanguinity of woman and husband, ethnicity, history of infertility, history of moles in the family, and dwelling ownership. The two groups were statistically different regarding husbands' jobs, history of abortion, use OCP, and ABO blood group. The odds ratio with a husband's physical job having exposure to dust and soil was 18.2 (CI: 8.26-43.03, PV<0.001). Logistic regression analysis only showed husband's job and husband's physical job exposure to dust and soil as predictors. **Conclusion:** Husband's jobs and especially exposure to dust and soil could be a major risk factor for molar pregnancy. More studies on the epidemiology, occupational health, microbiology and genetics are warranted to shed more light on this abnormal pregnancy.

Keywords: Hydatidiform mole- pregnancy- occupation- husband job- dust- women's health- GTD- GTN- placenta

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Introduction

Hydatidiform mole (HM) is a precancerous condition and is placed at the most benign position of a spectrum called Gestational Trophoblastic Disease (GTD). It occurs during conception and changes the process and outcome of pregnancy by developing abnormal fertilization and placenta. More importantly, it could convert to Gestational Trophoblastic Neoplasia (GTN). In fact most common (more than 50%) cause of GTN is HM (Suprasert et al., 2016). It is clear that management of disease including prevention, early diagnosis and follow up of HM are crucial for saving the mother's life (Berek and Hacker, 2015; Estevens et al., 2015; Jubilee et al., 2017). In the process of this kind of pregnancy the natural vascularization of the placenta does not develop and in some cases it progresses to form malignant disease such as invasive mole, trophoblastic tumor in the site of the placenta and choriocarcinoma. Choriocarcinoma could have influences on women's health even, years after

the primary HM and diagnosed by the brain metastatic signs and symptoms like convulsions, pain in the head and paralysis. Metastatic lesions could involve the lungs and demonstrate the lung involvements (Froeling and Seckl, 2014). According to Giorgione et al., (2017) study occurrence of GTN and amount of chemotherapy did not change after hysterectomy following HM. Women's health in poor regions could deeply be affected by HM complications, especially development of invasive forms. (Candelier, 2016).

Except converting to GTN, Hydatidiform mole affects women's health during her pregnancy and rest of her life. It even could induce maternal mortality (Iklaki et al., 2015). It induces uterine bleeding and as a result makes the mothers to be anemic and suffer from its consequences. Also, it is likely that the mother experience hyperemesis gravidarum, preeclampsia, hyperthyroidism, symptoms of lung function shortage (Buffetal et al., 2014; Cagayan, 2014) and acute abdominal manifestations (Escobar et al., 2013). The complications of HM are not limited to

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the physical health; it could deteriorate the mental health (Stafford et al., 2011). Fortunately, during last decades the mortality has been dropped due to early and better diagnosis, follow up and management of mole (Sekle et al., 2010). However, it imposes concerns, wasting time and cost to the patient, family and health system.

Molar pregnancy is distinguished by abnormal placenta. In terms of presence or absence of fetal organs partial and complete mole are differentiated. The most important point in HM is the reality that chromosomes usually have paternal origin and an empty or inactivated ovum is fertilized by a sperm which duplicates its chromosomes later. In other words; the chromatin of sperm reproduces in the empty ovum. It is not clear how it is happening (Gray et al., 2014; Candelier, 2016).

According to the epidemiological and clinical studies, HM should be considered as a public health issue (Bufettal et al., 2011). The epidemiology of Gestational Trophoblastic Disease (GTD) and HM as the important topics in gynecology oncology has not been cleared exactly; but, different studies have been reported from different countries, cities and hospitals (Simms-Stewart et al., 2013). The incidence of molar pregnancy has been reported differently in various geographic areas and among different target populations. The frequency of GTD in a tertiary hospital in Sindh was 1 per 45 live births (Khaskheli et al., 2007). Study of all published data during 1932-2011 in Turkey showed that the HM incidence was 0.3-16 per 1000 pregnancies and 1-24.5 per 1000 deliveries. (Ozalp and Oge, 2013). The incidence of HM during 1975 till 2001 in Finland was reported as 984 per 10 (6) deliveries or 73 per 10 (6) women (Loukovaara et al., 2005).

Meanwhile, several rates have been reported from different parts of Iran. The incidence of GTN in a hospital during 10 years was reported as 2.02 per 1000 deliveries (Farhadifar et al., 2007) and 3.1 per 1,000 live birth was the frequency of HM in another city of Iran (Rezavand and Seyedzade, 2009). The frequency of molar pregnancy in a number of prenatal clinics in Tehran was 7 per 1,000 pregnancies (Almasi et al., 2014). Among 120 histopathology records in North of Iran, 4.2% was choriocarcinoma and 95.8% was Hydatidiform mole (Sharifi et al., 2014). The incidence of mole in Hamadan during 10 years was 3.34 per pregnancy and 3.7 per 1,000 deliveries (Aghababaie et al., 2015). For more accurate incidence of HM and GTN multicenter and population based studies are needed.

Mother's age, previous abortion, history of previous mole, ethnicity, history of OCP, IUD, blood group, radiation, socioeconomic status, infertility, artificial insemination, genes mutations have been reported as risk factors for occurrence of HM. Mother age and history of HM have been found as the more considerable risk factors (Talati, 1998; Parazini et al., 1991; Altman et al., 2008; Andreasen et al., 2013; Gray et al., 2014; Gockley et al., 2016). Relationship of mother's age and severity of signs has been reported. Mangili et al., (2014) found that the older mothers (≥ 40 years old) involved in more vigorous conditions. Meanwhile, nutritional (Berkowitz et al., 1985; Lurain, 2010 Gray et al., 2014; Parazini

et al., 2015; Candelier, 2016) and genetic factors role (Slim et al., 2007; Andreasen et al., 2013; Fallahian et al., 2013) has been mentioned as risk factors for HM. Despite our knowledge about the effects of environment and workplace condition on health and disease, a little is known about relationship between HM and environmental factors especially occupational risks (WHO, 2012; Roger et al., 2015; WHO, 2017). In the review of literature a few articles were found about relationship between the occurrence of molar pregnancy or GTN and the occupation especially the husband's occupation (Messerli et al., 1985; shamshiri, 2008; Reid et al., 2009).

The aim of this study was to determine related risk factors to HM and also, discover whether, there is any relationship between the occurrence of molar pregnancy and the women's and husbands' occupation and especially those who are exposed to soil and dust?

Materials and Methods

After approval of sub secretary for research of School of Medicine, through a case- control study, seventy eligible cases of complete molar pregnancies (cases) were compared with 200 term normal pregnancies (controls). Cases were recruited from 5 educational hospitals affiliated to Shahid Beheshti medical university in Tehran, Iran. For each case, 3 women were selected with normal pregnancy from the same clinic and same hospital and on the same day as controls. After describing the aim of study to the participants, their written consents were taken. They have been told that the any information will be confidential and will be used for research purposes. Each mother was interviewed by the trained interviewer. Data on demography, obstetric history, medical history and the general condition was recorded on the designed questionnaire. Inclusion criteria of the cases were pathologically proven complete molar pregnancy without any other serious underlying disease (i.e. blood pressure, preeclampsia, diabetes, thyroid problems, dislipidemia, malignancy, and autoimmune disorders). Participants were asked to give an exact description about own and the husbands' jobs, environments and relevant materials.

After data collection and quality control, it was processed using SPSS16, and was analyzed using t-test, chi-square test and fisher's exact test.

Job data was analyzed in two phases. At first phase jobs were divided in two categories: physical and nonphysical. Physical jobs included the jobs that needed involvement of body and physical force like cook, agricultural and constructive workers. Nonphysical jobs included the jobs which did not usually done by physical force like; clerk, manager, and secretary. At the second phase the jobs in physical category divided into two groups; those had exposure to dust and soil and those had not such exposure.

Since the majority of mothers were housewives, so, we analyzed mother's jobs in 2 steps. At first step we compared housekeeping between case and control groups. Then comparison was done between the remaining jobs as physical and nonphysical.

We first analyzed the relationship between mothers' age (mean age and age groups), level of mothers'

Table 1. The Association between Mothers' Characteristics and Risk of Molar Pregnancy

	Mole	Control	OR	CI _{95%}		P-value
				Low	Upper	
Mother age group, n (%)						0.295
<20	11 (15.9)	20 (10)	0.96	0.22	4.03	0.958
20-29	37 (35.6)	131 (65.5)	0.49	0.14	1.78	0.467
30-39	17 (24.6)	42 (21)	0.7	0.18	2.73	0.886
< 40	4 (5.8)	7 (3.5)	Reference			
Mother education, n (%)						0.899
Illiterate	5 (7.1)	10 (5)	1.27	0.34	4.79	0.982
Primary school	8 (11.4)	24 (12)	0.85	0.28	2.58	0.777
High school	48 (68.6)	143 (71.5)	0.86	0.37	1.98	0.888
university	9 (12.9)	23 (11.5)	Reference			
Type of household, n (%)						0.251
Owner	15 (21.4)	59 (29.5)	0.65	0.34	1.24	0.251
Tenant	55 (78.6)	141 (70.5)	Reference			
Mother smoking, n (%)						0.569
Positive	5 (7.1)	11 (5.5)	1.32	0.44	3.94	0.569
Negative	65 (92.9)	189 (94.5)	Reference			
Mother and husband consanguinity, n(%)						0.196
Positive	13 (18.6)	23 (11.5)	1.75	0.83	3.68	0.196
Negative	57 (81.4)	177 (88.5)	Reference			
Mother ethnicity, n (%)						0.937
Turk	14 (20)	44 (22)	0.91	0.33	2.49	0.862
Fars	48 (68.6)	133 (66.5)	1.03	0.43	2.47	0.933
Afghan	8 (11.4)	23 (11.5)	Reference			
Mother Blood group, n (%)						0.013
A	29 (41.4)	43 (21.5)	2.52	1.37	4.66	0.004
AB	3 (4.3)	9 (4.5)	1.25	0.32	4.88	0.748
B	6 (8.6)	28 (14)	0.8	0.3	2.1	0.833
0.833O	32 (45.7)	120 (60)	Reference			
Mother blood group(Rh), n (%)						0.281
Rh +	63 (90)	188 (94)	0.57	0.21	1.52	0.281
Rh-	7 (10)	12 (6)	Reference			
Parity						0.372
< 2	56 (80)	171 (85.5)	0.68	0.34	1.37	0.372
> 2	14 (20)	29 (14.5)	Reference			
History of mole, n (%)						0.055
Positive	3 (4.3)	1 (0.5)	8.91	0.91	87.16	0.055
Negative	67 (95.7)	199 (99.5)	Reference			
History of mole in family						0.067
Positive	2 (2.9)	0 (0)	14.63	0.69	308.7	0.067
Negative	68 (97.1)	200 (100)	Reference			
Abortion, n(%)						0.001
Yes	19 (27.1)	21 (10.5)	3.17	1.57	6.36	0.001
No	51 (72.9)	179 (89.5)	Reference			
OCP history, n(%)						0.044
Yes	27 (38.6)	50 (25)	1.88	1.05	3.35	0.044
No	43 (61.4)	150 (75)	Reference			
Duration of OCP, n (%)						0.345
< 4 years	17 (63)	38 (76)	0.54	0.19	1.48	0.345
> 4 years	10 (37)	12 (24)	Reference			

Table 1. Continued

	Mole	Control	OR	CI _{95%}		P-value
				Low	Upper	
IUD history, n (%)						0.75
Positive	9 (12.9)	21 (10.5)	1.25	0.54	2.89	0.75
Negative	61 (87.1)	179 (89.5)	Reference			
History of infertility, n (%)						0.776
Positive	5(7.1)	12 (6)	1.2	0.41	3.55	0.776
Negative	65(92.9)	188 (94)	Reference			
Mother housekeeping, n (%), n (%)						0.583
Yes	58 (82.5)	173 (86.5)	0.75	0.36	1.58	0.583
No	12 (17.2)	27 (13.5)	Reference			
Mother physical job, n (%)						0.954
Yes	5 (41.7)	10 (37)	1.21	0.3	4.86	0.954
No	7 (58.3)	17 (63)	Reference			

education, husbands' age and level of husbands education, mothers' blood group (ABO and RH), parity, history of OCP usage and its duration, history of intra uterine device, smoking of mothers and husbands, consanguinity of the woman and her husband, ethnicity, history of infertility, history of mole in family, dwelling ownership with the risk of molar pregnancy. Next we used logistic regression modeling to indicate the predictors of the molar pregnancy.

Results

We studied 70 cases and 200 controls. The mean age of mothers was 26.38±6.59 (14 – 51 years). The husbands' mean age was 30.62±6.91 (20 – 60 years).

Table 1 shows the risk factors of mother regarding molar pregnancy. There were only significant association between occurrence of molar pregnancy and mothers' blood group ABO and OCP usage.

Table 2 indicates the husbands' characteristics. There were significant associations between molar pregnancy and husbands' jobs (physical and nonphysical) and husband's physical jobs exposure to dust and soil and without exposure to dust and soil.

In order to find out the predictors and risk of molar pregnancy, we ran a logistic regression model by four covariates (significant risk factors shown at Table 1 and Table 2; husband's job (physical and nonphysical), husbands' physical job exposure, OCP history and Blood group ABO. The husband physical job (OR= 4.66, PV

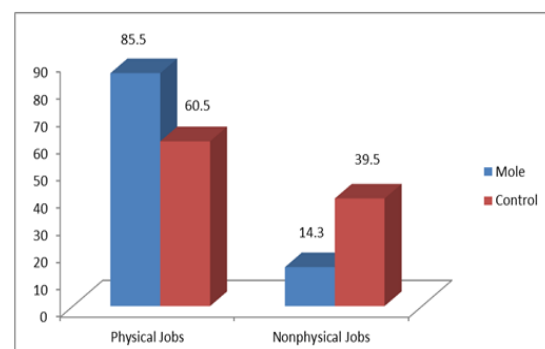


Figure 1. Distribution of the Job Type of the Husbands in Moles and Controls

Table 2. The Association between Husbands' Characteristics and Risk of Molar Pregnancy

	Mole	Control	OR	CI _{95%}		P-value
				Low	Upper	
Husband age group, n (%)						0.086
20-29	35 (50.7)	96 (48)	0.54	0.24	1.25	0.182
30-39	22 (31.9)	86 (43)	0.38	0.16	0.91	0.033
>40	12 (17.4)	18 (9)	Reference			
Husband smoking, n (%)						0.141
Positive	31 (44.3)	67 (33.5)	1.57	0.9	2.57	
Negative	39 (55.7)	133 (66.5)	Reference			
Husband job, n (%)						<0.012
physical	60 (85.7)	121 (60.5)	3.91	1.89	8.1	
Non-physical	10 (14.3)	79 (39.5)	Reference			
Physical husband job exposure, n(%)						< 0.001
soil and dust	34 (56.6)	10 (8.3)	14.51	6.36	33.1	
Without dust and soil	26 (43.4)	111 (91.7)	Reference			

Table 3. Logistic Regression Modeling to Predict Risk Factors on Molar Pregnancy

	OR (crude)	CI95%		P-value	OR (adjusted)	CI95%		P-value
		Low	Upper			Low	Upper	
Husband's job								
Physical	3.91	1.89	8.1	0.012	4.69	2.26	9.72	0.009
Non-Physical	Reference				Reference			
Husband physical job exposure								
Physical with soil and dust	14.51	6.36	33.1	<0.001	18.2	8.26	43.03	<0.001
Physical without soil and dust	Reference				Reference			

<0.001) and exposure to dust and soil (OR=18.2, PV <0.001) were identified as predictors for mole.

Discussion

Our study demonstrated that husbands' of women with complete molar pregnancies were significantly more involved in physical jobs vs. nonphysical jobs. Husbands physical jobs increases molar pregnancy by 4 folds on comparison to normal pregnancies. This association was true for physical jobs that would cause exposure to dust and soil compared to those do not exposed to soil and dust. Exposure to dust and soil in some jobs increased the occurrence of mole by 18 folds. This relationship was

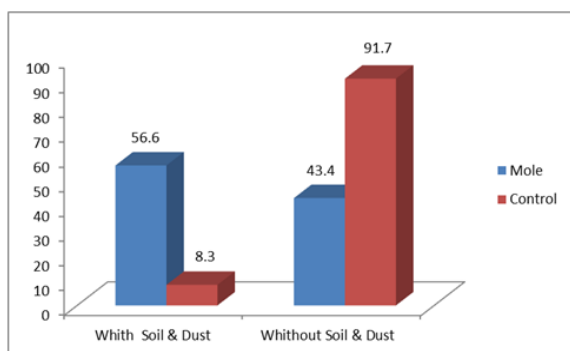


Figure 2. Distribution of the Husbands' Physical Jobs with and without Exposure to Dust and Soil in Moles and Controls

found in another study done by the first author (Shamshiri, 2008). Boufettal (2011) found that 85% of mothers who involved in hydatidiform mole lived in cultivation regions (Boufettal et al., 2011). Although, Boufettal did not study the husbands' jobs but it is probable that husbands were exposed to dust and soil more than other districts.

Messerli and colleagues (1985) did not report any relationship between molar pregnancies and husbands' jobs. A reason for this difference could be the different classifications of jobs.

Meanwhile, in current study no significant association was found between molar pregnancy and mothers' age and parity. In other studies there were found relations between mole with mother's age especially age-groups of less than 20 and more than 35, multiparity, low parity, nuliparity (Parazzini, 1991; Honda et al., 1992; Talati, 1998; Morphy et al., 2008 ; Audu et al., 2009; Aziz, 2012).

Considering the ABO blood groups, in our study the blood group A was more frequent in women with molar pregnancies compared to other types of blood groups. This is similar or dissimilar to the results of other studies (Parazini et al., 1985; koirala et al., 2011).

However, we did not found relationship between mother's job and molar pregnancy.

In addition, our study showed that there was a significant association between molar pregnancy and histories of abortion. Talati (1998) found the same result (Talati, 1998).

At present study there was significant association

between molar pregnancy and history of OCP usage. Palmer (1991), found not significant but slightly elevation of HM occurrence by OCP using (Palmer, 1991). Also, we did not found statistical association between HM and previous molar pregnancy however study of Talati (1991) found a statistically association (Talati, 1998).

The socioeconomic situation may have a role in developing molar pregnancy (Ekanem et al., 2005; Aziz et al., 2012), we did not find any significant differences among mothers' and husbands' educational level, mothers' jobs and ownership in case and control groups. We could conclude that the case and control groups in our study were similar in regarding to socioeconomic situation; in addition all of the mothers in case and control groups had referred to the same hospitals. So, we conclude that probably there was not any difference between case and control groups from the standpoint of socioeconomic condition.

Although, the partner may have a role on the health of her/his partner like STDs, but there is a few knowledge on the process and mechanism of other diseases specially molar pregnancy. It is clear that sperm has a role in the process of fertilization and pregnancy, but it has not been focused so far. According to the findings of present study we can hypothesize that husband physical job especially being exposed to soil and dust could alter the spermatogenesis which causes the abnormal fertilization like mole hydatidiform.

This study showed that the husband's job especially exposure to dust and soil could be a major risk factor for hydatidiform mole.

We suggest more community based studies in this field in different countries. In addition, further studies in epidemiology, occupational health, microbiology, immunology and genetic aspects of molar pregnancies are proposed to respond to the more important question: what does trigger the abnormal fertilization?

Conflict of disclosure

This study was performed of our own will and without any organizational support. There was any conflict of interest.

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