Original Article

Journal of Iranian Medical Council, Volume 9, Issue no. 4
http://dx.doi.org/10.18502/jimc.v9i4.22465

Comprehensive Study on Patients with Molar Pregnancy Referred to Mahdieh Hospital in Tehran: A Descriptive and Retrospective Research

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Received: 11 Jun 2025
Accepted: 18 Oct 2025

Citation to this article
Parhizgar P, Moridi A, Esfidani T, Golmohammadi M, Farahmandi F, Akhtari K, *et al*. Comprehensive Study on Patients with Molar Pregnancy Referred to Mahdieh Hospital in Tehran: A Descriptive and Retrospective Research. *J Iran Med Counc.* 2026;9(4):962-72.

Abstract

Background: Hydatidiform mole is a rare but clinically significant pregnancy abnormality. This study was undertaken to improve understanding of molar pregnancy risk factors in the Iranian population and to develop strategies for early detection and management. It also aimed to evaluate the impact of Methotrexate (MTX) chemoprophylaxis on progression to Gestational Trophoblastic Neoplasia (GTN).

Methods: This single-center, retrospective descriptive study was conducted at Mahdieh Hospital in Tehran between 2011 and 2023. A total of 449 patients with histopathologically confirmed molar pregnancies were included. Detailed clinical and laboratory data were collected and analyzed using SPSS (version 26), with significance set at $p<0.05$. GTN was diagnosed according to FIGO criteria, based on serial β-hCG monitoring (rising or plateauing levels) and confirmed by histopathological examination.

Results: The incidence was 6.75 per 1,000 pregnancies. Anemia and vaginal bleeding were the most common presenting symptoms. Complete moles accounted for 66.6% of cases. Among 18 patients who received MTX prophylaxis, elevated β-hCG levels and larger uterine size were significantly associated with MTX administration ($p<0.001$). However, MTX prophylaxis did not significantly prevent progression to GTN ($p=0.365$). During follow-up, 11 patients developed GTN.

Conclusion: Molar pregnancies in Iran exhibited a higher incidence compared to developed countries. The limited benefit of prophylactic MTX in this small subgroup support the need for larger, multicenter studies to refine treatment protocols.

Keywords: Chemoprevention, Gestational trophoblastic diseases, Hydatidiform mole, Methotrexate

Introduction

Gestational Trophoblastic Disease (GTD) includes conditions ranging from benign Hydatidiform Mole (HM) to malignant Gestational Trophoblastic Neoplasia (GTN) (1). Molar pregnancies are categorized as complete or partial, both of which can progress to malignancies like choriocarcinoma, invasive mole, Placental Site Trophoblastic Tumor (PSTT), and Epithelioid Trophoblastic Tumor (ETT) (2). Post-molar GTN (PGTN) refers to neoplastic development after a molar pregnancy, with incidence influenced by factors such as maternal age and β-hCG levels (3-5). HM is characterized by abnormal trophoblastic growth and swollen placental villi, making it a rare yet clinically significant condition (6).

The global incidence of HM varies significantly, with rates in Europe and North America ranging from 0.6 to 1.2 per 1,000 pregnancies (7). Worldwide estimates suggest a higher rate of 3.3 per 1,000, likely due to better diagnostic tools and increased recognition of partial moles. Regions like Southeast Asia report even higher frequencies, possibly influenced by genetic factors, environmental conditions, and disparities in healthcare access and practices (8).

Advanced diagnostic tools like ultrasonography and β-hCG assays have significantly improved early detection of molar pregnancies, altering their clinical presentation (5). However, management remains challenging due to delayed consultations and vague symptoms. Research in Iran has provided important data on prevalence and characteristics, aiding the development of better healthcare strategies (9,10).

Several risk factors increase the likelihood of HM, including maternal age under 20 or over 35 years, infertility (especially after ovulation induction), spontaneous abortion, prior molar pregnancy, multiparity, blood group A, vitamin A deficiency, and smoking (7,9). Recognizing these factors is vital for early detection and prevention, particularly in Iranian women. In the Almasi *et al* study, 61 HM cases were found among 8,614 pregnancies (7 per 1,000). Women with HM were significantly more likely to have prior molar pregnancies, spontaneous abortions, lifetime oral contraceptive use, and ovulation induction history (11).

High-risk molar pregnancies typically stemming from complete moles are a major precursor to GTN. They are characterized by elevated β-hCG levels, large theca lutein cysts, advanced maternal age, and an enlarged uterus relative to gestational age. GTN is diagnosed using International Federation of Gynecology and Obstetrics (FIGO)/the World Health Organization (WHO) criteria, which include rising or plateauing β-hCG levels post-evacuation, persistent β-hCG elevation, histological confirmation of choriocarcinoma and/or radiologic evidence of metastases (12).

Some reports indicate that a single-dose prophylactic Methotrexate (MTX) regimen may lower the risk of GTN after suction evacuation; however, major guidelines [FIGO, European Society for Medical Oncology (ESMO)] do not recommend routine prophylactic chemotherapy except when reliable follow-up cannot be ensured (13,14). A randomized clinical trial in India found that a 100 *mg* intramuscular MTX dose significantly shortened β-hCG normalization time (15). Similarly, Aminimoghaddam *et al* reported reduced incidence of GTN in Iranian patients with high-risk features who received prophylactic MTX (16). However, more recent researches in 2021–22 from a Tehran hospital (22 patients receive single dose MTX *vs*. 58 controls) showed no significant benefit of MTX in remission rates, β-hCG normalization, or prevention of postmolar GTN, suggesting ongoing controversy regarding its effectiveness (17).

Further research is essential to clarify risk factors and improve early detection and management of molar pregnancies in Iran. This retrospective descriptive study, conducted at Mahdieh Hospital in Tehran during 2011–23, aimed to:

1. Assess the incidence and related sociodemographic and clinical risk factors, 2. Detail the main clinical presentations and outcomes, and 3. Evaluate the role of prophylactic MTX in preventing progression to GTN.

Materials and Methods

Study design and ethical consideration

This retrospective descriptive study was approved by the Institutional Review Board (IRB) of Shahid Beheshti University of Medical Sciences (Approval No. IR.SBMU.RETECH.REC.1402.718) and conducted at a tertiary care hospital in Tehran. For participants who

attended clinic visits during the study period or were contacted by telephone to complete missing data, verbal informed consent was obtained prior to data collection. For cases identified solely through our existing clinical database—into which patients are informed upon admission that their de-identified data may be used for research—the IRB granted a waiver of informed consent. All records were fully anonymized before analysis, and no personal identifiers were retained.

Eligibility and data collection

Women with pathologically confirmed molar pregnancies diagnosed within the defined study period were included. Histopathologic confirmation of molar pregnancy was performed according to the World Health Organization (WHO) classification criteria for GTD (14), including evaluation of villous size, trophoblastic proliferation, and stromal characteristics. All ultrasound examinations were conducted and interpreted following the American College of Obstetricians and Gynecologists (ACOG) guidelines (12), assessing features such as cystic villi and myometrial invasion. Records were included if they met the following criteria: no early pregnancy bleeding from other causes (such as ectopic pregnancy or incomplete miscarriage) and to have a definitive diagnosis of molar pregnancy. Computerized and paper-based Data were collected on sociodemographic history (age, parity, gestational age) and post pregnancy outcomes, including any previous molar pregnancies. Details on presenting complaints and physical examination findings were recorded. Investigations included blood tests, blood grouping, thyroid profile, serum β-hCG levels, and chest radiography. The uterine evacuation procedure and follow-up protocol-including histopathology reports and serial β-hCG monitoring- were documented.

Whenever the patient's medical information was incomplete, the data would be completed by calling and asking the patients. Diagnosis of GTN were tailored according to FIGO guidelines, including serum β-hCG trends, histopathology, and imaging findings.

Prophylactic MTX protocol

Adult patients were considered high-risk for PGTN if they met one or more of the following before uterine evacuation:

- Serum β-hCG > 100,000 *mIU/mL.*
- Maternal age > 40 years.
- Uterine size greater than expected for gestational age.
- Theca lutein ovarian cysts > 6 *cm.*
- Predicted poor adherence to follow-up (it is a condition for all the patients received MTX prophylaxis).

High risk patients who required or opted for hysterectomy were excluded from prophylaxis protocol. Patients who had received prophylactic MTX were administered the drug intramuscularly at a dose of 50 mg/m^2 as a single injection, given 6-12 *hrs* before evacuation or within 24 hours afterward for those who required or opted for suction evacuation.

Follow-up monitoring included: 1. Weekly serum β-hCG measurements until three consecutive values fell below 5 *mIU/mL*; 2. Monthly β-hCG assessments for 6 months thereafter; 3. Transvaginal ultrasound, complete blood count, liver and renal function tests if β-hCG levels plateaued or rose on two consecutive measurements.

Statistical analysis

Data were analyzed using SPSS software (IBM SPSS Statistics, version 26.0). For descriptive statistics, frequencies and percentages were used for categorical variables, and means±standard deviations (SD) or medians [interquartile range, IQR] were used for continuous variables, as appropriate. For categorical variable comparisons, the chi-squared test was applied. Continuous variables were analyzed using the independent t-test or Mann–Whitney U test, depending on data distribution. Statistical significance was set at $p<0.05$. All analyses included sociodemographic characteristics, gestational age, clinical history, presenting complaints, findings from physical examinations and investigations, management procedures, histopathology reports, and follow-up outcomes. The effect of prophylactic MTX on progression to GTN was assessed by comparing two patient cohorts.

Results

Descriptive characteristics of the studied population

A total of 449 molar pregnancy cases were identified at

Mahdieh Hospital between March 2011 and June 2023. All 449 patients had at least one month of follow-up documented in the hospital's electronic health record. No patient was lost to follow-up; all 449 had complete outcome data. Of these, 89 patients (19.8 %) did not return for scheduled in-person follow-up beyond their initial visit. For those 89 patients, we conducted telephone interviews to ascertain clinical status and β-hCG results. While we could not verify the regularity of their assessments at external facilities, all reported laboratory confirmation of β-hCG normalization (<5 *mIU/mL*) or persistent were recruited (in these cases, they visit other hospitals). These cases represent a hospital-based frequency of approximately 6.75 per 1,000 pregnancies during the study period (2-13.7 per 1,000 cases of molar pregnancy annually). It is important to note that, since these cases were referred from various settings, this figure does not represent the true incidence of molar pregnancies in the general population, but rather the frequency observed among patients managed at our tertiary care center. Figure 1 showed the annual trend of molar pregnancies between March 2011 and June 2023.

Table 1 showed the summary of descriptive information for the studied population. The mean maternal age at diagnosis was 29.43 years (range, 14-55), and nearly half of the patients were aged 20-30 years. The majority (80.7%) were Iranian. A total of 109 patients (24.3%) had comorbidities, with hypothyroidism, heart disease and hypertension, diabetes, asthma, and depression being the most common. None of the patients had a history of alcohol consumption, and only three patients (0.7%) were smokers. A history of OCP use during their lifetime was reported by 148 patients (32.7%). The most common blood groups were A positive (31.3%) and O positive (31.1%). Seventeen patients had one previous molar pregnancy, and three had two previous molar pregnancies. A larger uterine size than dates was observed in 81.2%, equal size in 11.1%, and smaller size in 7.7% of patients.

Clinical features

As shown in table 2, One hundred ninety-five patients (43.8%) had anemia at diagnosis, but none required blood transfusion. Vaginal bleeding was the second most common manifestation at diagnosis (n=149). Four patients (0.8%) developed thyrotoxicosis, although no thyroid storm occurred. Four patients (0.8%) fulfilled the criteria for HELLP syndrome. On transvaginal ultrasound, theca lutein cysts were observed in only two patients (0.4%), and none required interventional surgery for this complication.

A variety of complications were documented among patients after GTD treatment. These included both complications that may be related to treatment and other health issues that developed during follow-up

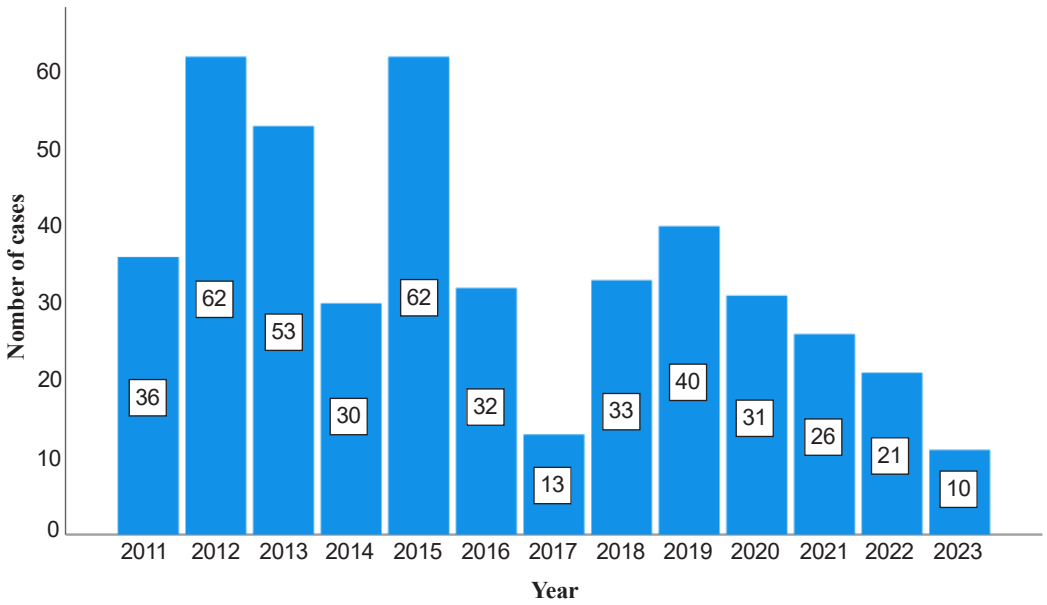

Figure 1. Yearly trend of molar pregnancy from March 2011 to June 2023.

Table 1. Descriptive information of the studied population

Variable	Summary measures (N=449)
Age	29.43±7.03
<20 years†	51(11.3%)
20-30 years†	212(47.3%)
30-40 years†	158(35.1%)
40-50 years†	26(5.8%)
Older than 50 years†	2(0.4%)
Comorbidity	
No†	340(75.6%)
Yes†	109(24.4%)
Hypothyroidism†	28(6.2%)
Cardiac disease and HTN†	16(3.2%)
GDM and DM†	12(2.6%)
Asthma†	3(0.7%)
Depression†	3(0.7%)
Nationality	
Iranian†	362(80.7%)
Afghan†	86(19.1%)
Pakistani†	1(0.2%)
Smoking	
No†	446(99.3%)
Yes†	3(0.7%)
OCP use	
No†	301(67.3%)
Yes†	148(32.7%)
Blood group	
A+†	141(31.3%)
B+†	100(22.2%)
AB+†	29(6.4%)
O+†	139(31.1%)
A-†	10(2.2%)
B-†	17(3.8%)
AB-†	2(0.4%)
O-†	11(2.4%)

Contd. table 1.

History of previous molar pregnancy	
No†	429(95.6%)
Yes†	20(4.4%)
Gravidity‡	2.52(median: 2; range:1-10)
Parity‡	1.16(median: 1; range: 0-8)
Living children‡	1.11(median: 1; range: 0-8)
Abortion‡	0.3(median: 0; range: 0-4)
Age of gestation in weeks at diagnosis‡	8.42±2.4 (range: 4-20)
Age of gestation in weeks at treatment‡	10.49±3.16 (range: 4-20)
Uterine size in weeks at diagnosis‡	10.35±2.78 (range: 6-24)
Serum β-hCG level at diagnosis‡	99,899.83 [median (IQR)]: 24,941.5 [4,995-141,784]) *mIU/ml*
Time to reach a normal serum β-hCG level‡	84.45(median [IQR]: 51 [36-101]) days
Follow-up*	6.18±3.6 years
Subsequent pregnancy	
No†	288(64.2%)
Yes†	164(35.8%)
One subsequent pregnancy†	109(24.2%)
Two subsequent pregnancies†	46(10.2%)
Three subsequent pregnancies†	6(1.3%)
Time from molar pregnancy to first subsequent pregnancy‡	2.01±1.58 (range: 0-8) years
Time from molar pregnancy to second subsequent pregnancy‡	5.15±2.18 (range: 2-12) years
Time from molar pregnancy to third subsequent pregnancy*	7.83±1.47 (range: 6-10) years
Result of first subsequent pregnancy†	87 children (79.9%), 12 abortions (11%), 10 molar pregnancies (9.1%)
Result of second subsequent pregnancy†	42 children (91.3%), 2 abortions (4.3%), 2 molar pregnancies (4.3%)
Result of third subsequent pregnancy†	5 children (71.4%),1 abortion (14.3%), 1 molar pregnancy (14.3%)

* Measures provided as mean±SD, † Measures provided as number (percentage), ‡ Measures provided as mean (median or [IQR]).

after surgery. For transparency, table 3 presents all complications observed in this cohort, without restricting them solely to treatment-related adverse effects. The most common complications after treatment were re-surgery (5.1%), hemorrhage (2.2%), nausea and vomiting (0.9), surgical site infection (0.7 %), headache (0.7%), and hypertension (0.7%) (Table 3). One patient suffered severe anemia due to massive hemorrhage and therefore received two units of packed red blood cells.

The majority of patients (N=337, 65.6%) had histopathology confirming Complete Hydatidiform Mole (CHM). Partial Hydatidiform Mole (PHM) was seen in 112 patients (24.9%), while 43 reports (9.5%)

Table 2. Clinical presentation and diagnostic findings at the time of diagnosis

Symptom	Number
Anemia	195
Vaginal bleeding	149
Abortion (missed or incomplete)	14
Abdominal pain	14
Nausea and vomiting	6
Thyrotoxicosis	4
Dyspnea	1
Mense retardation	21
Molar pregnancy sonography	124
Blighted ovum sonography	86
FHR negative sonography	66
Elevated β-hCG	6

Patients may have one or more.

Table 3. Complications observed among patients after GTD treatment

Complication	Number
Re-surgery	23
Hemorrhage	10
Nausea and vomiting	4
Surgical site infection	3
Headache	3
Hypertension	3
Back pain	2
Infertility	2
Urine incontinency	2
Relapse	2
Recurrent abortion	1
Tachycardia	1
Hypotension	1
Hernia	1

Patients may have one or more.

did not specify the HM subtype.

CXR was performed for all patients before treatment. One patient's CXR showed evidence of lung metastasis. Metastatic disease was also identified on brain CT in one patient, who was referred to an oncologist for treatment.

Treatment and follow-up

Suction curettage was the main treatment method, used alone in 92.2% of cases and with MTX chemoprophylaxis in 4%. Hysterectomy with or without salpingo-oophorectomy for moles *in situ* was performed in 1.1% of patients. Twelve patients (2.7%) sought treatment at other centers; no detailed information was available regarding the type of treatment they received.

Eighteen patients (4%) received prophylactic MTX prior to definitive surgical management. At our institution, definitive management consisted of suction curettage to evacuate molar tissue. These high-risk cases those who met the criteria described in the methods section, including advanced maternal age, markedly elevated β-hCG levels, excessive uterine enlargement, theca lutein cysts larger than 6 *cm*, or a history of prior molar pregnancy. Table 4 presents all comparisons—baseline β-hCG, uterine enlargement above gestational age, time to β-hCG

Table 4. Comparative outcomes by chemoprophylaxis status

Variable	Prophylaxis (n=18)	No prophylaxis (n=421)	p-value
Baseline serum β-hCG (*mIU/mL*), median (IQR)	223,361 [146,776-397,160]	22,410 [4,436.5-107,049.5]	p<0.001
Uterine enlargement above gestational age (*cm*), median (IQR)	15[12-18]	10[8-12]	p<0.001
Time to β-hCG normalization (days), median (IQR); n	77[44–141]	48[33–98]	0.180
Post-molar neoplasia, n(%)	1(0.22%)	10(2.27%)	0.365

normalization, and post-molar neoplasia with corresponding medians (IQRs), counts (percentages), and p-values between patients who did not receive MTX and those who did receive MTX.

During follow-up of the 449 patients, 11 (2.4%) developed PGTN. Among these, eight presented with invasive mole, two with choriocarcinoma, and one with PSTT. Of the 11 patients who developed GTN, one had received chemoprophylaxis with MTX prior to definitive surgical management, while the remaining 10 underwent definitive surgical management alone. All GTN cases were stratified using the FIGO risk scoring system and were classified as low risk, with scores ranging from 2 to 6.

Most patients were followed for at least one month after treatment. The mean follow-up duration was 6.18 years (range, 0-12 years). Six patients were excluded from the contraceptive-method follow-up because they had undergone hysterectomy and did not require contraception. Of the remaining patients, 22.3% did not use any contraceptive method; 53.9% used withdrawal; 11.5% used hormonal contraception; 9.3% used condoms; and 3.0% used an Intrauterine Device (IUD). A total of 164 patients conceived again after treatment of molar pregnancy; details are provided in table 1. A 49-year-old patient, gravida 6, para 1 (term), abortion 1, with one living child and four molar pregnancies experienced three consecutive post-molar pregnancies, all of which resulted in molar gestations.

Discussion

This study evaluated 449 confirmed molar pregnancy cases over a 12-year period at a tertiary center in Tehran, finding an incidence of 6.75 per 1,000 pregnancies. The majority of patients were young. Most presented with anemia and vaginal bleeding. Complete hydatidiform moles accounted for 66.6% of cases. Notably, 18 high-risk patients received prophylactic MTX based on elevated β-hCG levels and larger-than-expected uterine size. However, no significant reduction in progression to GTN was observed compared to the standard management group (p=0.365).

Based on the present study, the mean maternal age was 29.43 years, reflecting a young patient population. This finding aligns with a retrospective cross-sectional study in the Philippines, which reported a mean age of 29 years among molar pregnancy cases (18). Similarly, studies from Asia, Europe, and North America found that most patients with molar pregnancy were aged 20-30 years (19-22). The higher fertility rate in this age group may account for the increased incidence of molar pregnancy observed (23).

Incidence rates of molar pregnancy vary globally, with our study reporting 6.75 per 1,000 pregnancies comparable to rates in Iran (7 per 1,000) (11) and Pakistan (5.1 per 1,000) (20). Other Asian and African countries show wide variation, such as Japan (2.02 per 1,000 live births), Malaysia (2.6 per 1,000 pregnancies), Egypt (13.1 per 1,000 pregnancies), and Turkey (7 per 1,000 pregnancies) (22,24-26), while lower rates are noted in the USA and parts of Europe (27,28). These disparities may stem from nutritional deficiencies like folate and vitamin A (29), but comparisons should be cautious due to differences in study design, population type (community *vs*. hospital-based) (20), center scale (18,24,25), methodology (retrospective *vs*. prospective) (25,27), and diagnostic criteria (20,30,31). Tertiary centers, including the present study, often capture more severe cases (20,24), whereas registry-based studies offer broader population insights (22,28).

Vaginal bleeding was the most common presenting symptom in molar pregnancy, followed by abdominal pain, nausea, vomiting, and delayed menses consistent with findings from other population-based studies (32,33). Over 40% of patients were anemic at diagnosis, though only one required transfusion for severe anemia, contrasting with earlier reports of higher transfusion rates (34).

Uterine enlargement beyond gestational age was observed in approximately 81% of cases in our study, consistent with previous reports of frequent overgrowth in molar pregnancies (34,35). In contrast, fewer than 10% of patients with partial moles in a European cohort exhibited this feature (36).

This study assessed whether single-dose prophylactic MTX could reduce the risk of PGTN. Although early trials suggested potential benefit, major guidelines (FIGO, RCOG) advise against routine prophylaxis unless follow-up is unreliable (14). MTX was given to patients with larger uterine size and elevated β-hCG, but no significant reduction in GTN incidence was

observed (p=0.365), possibly due to small sample size and selection bias. A trend toward faster β-hCG remission was noted, indicating possible clinical relevance in high-risk cases. These findings contrast with earlier studies showing protective effects (16,31,37,38), though differences in methodology, sample size, and use of folinic acid may explain the discrepancy. Notably, a recent Iranian study in 2024 also found single-dose MTX ineffective as a prophylactic strategy (17). Beyond regional data, randomized trials and systematic reviews have shown mixed results regarding prophylactic MTX for GTN. One meta-analysis found MTX had fewer toxicities in low-risk patients but was less effective than actinomycin-D (39). A multicenter trial confirmed MTX's tolerability but noted limited efficacy (40), while another review suggested MTX-based protocols may benefit high-risk patients (41). Overall, the effectiveness of prophylactic MTX appears to depend on methodological factors such as sample size, patient selection, and treatment regimen. This study benefits from a relatively large cohort and extended follow-up, enhancing the reliability of its findings. As this was a retrospective, single-center study, there is potential for selection and recall bias, particularly in cases where data were supplemented by phone interviews. Conducted at a single tertiary referral center with 449 cases remains modest, the results may not be widely generalizable. Additionally, the inclusion of ethnically diverse participants, not limited to Iranians, may have influenced outcomes.

Conclusion

In summary, this study revealed a notably high incidence of molar pregnancies in Iran and underscored variability in clinical presentation, with vaginal bleeding being the most prevalent symptom. Although MTX prophylaxis was administered to high-risk patients, we did not observe a significant reduction in GTN incidence, which may be influenced by the relatively small number of patients receiving prophylaxis. From a policy perspective, the development of regional guidelines for molar pregnancy management and investment in patient education programs could enhance adherence to surveillance protocols and ultimately reduce progression to GTN. These findings support the need for further research to optimize diagnostic and management protocols tailored to regional practices.

Acknowledgement

This study, approved by the technical and ethical review board with ethics code: IR.SBMU.RETECH.REC.1402.718.

Conflict of Interest

There was no conflict of interest in this manuscript.

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