

Does COVID-19 Affect the Course of Trophoblastic Gestational Disease in Partial Hydatidiform Moles; Is It A Viral or A Pandemic?

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ABSTRACT

Objective: Hydatiform mole (HM) is a non-malignant form of gestational trophoblastic disease (GTD) characterized by failure of normal fetal development and overgrowth of trophoblasts. With this retrospective cohort study, we planned to determine the incidence of PHM, etiology and progression rates to Gestational trophoblastic neoplasia (GTN) during the COVID-19 epidemic.

Materials and Method: This retrospective cohort study was conducted in Ankara Etlik Zübeyde Hanım Women's Health Training and Research Hospital Early Pregnancy Assessment Unit between March 2016 and February 2022. Patients who underwent therapeutic curettage (T/C) with the diagnosis of missed abortion, intrauterine exitus (IUEX), molar pregnancy or incomplete abortion after single spontaneous pregnancy were included in the study. The study group consisted of 138 patients who were diagnosed with partial hydatiform mole as a result of pathological examination in this process. There were 135 patients in the control group.

Results: The number of patients who applied during the pandemic period and were diagnosed with PHM was 62 (44.92%). The mean age of the patients in the study group was 31.97 ± 8.26 years. The mean body mass index of these patients was 26.38 ± 5.13 m²/kg. The mean paternal age in the study group was 34.95 ± 8.32 years, and it was higher than the paternal age of the patients in the control group ($p=0.028$). While the incidence of PHM was 1.22/1000 births in our hospital in 2019, this figure was calculated as 3.79/1000 births in 2020. The incidence of progression to GTN at 4 years before the pandemic was 0.02/1000 births; In 2020-2021, this rate was calculated as 0.25/1000 births.

Conclusion: During the pandemic period, along with the increase in the incidence of PHM compared to the pre-pandemic period, an increase in the incidence of progression to GTN disease was detected.

Keywords: COVID-19, pandemic, partial hydatiform mole, gestational trophoblastic neoplasia

INTRODUCTION

Hydatiform mole (HM) is a nonmalignant form of gestational trophoblastic disease (GTD) characterized by disruption of normal fetal development and trophoblast overgrowth [1]. However, it is considered a premalignant disease because it can transform into cancer with local invasion and distant metastasis [2]. Numerous risk factors have been identified for GTD: failed pregnancies in the past, such as miscarriages, folic acid deficiency, excessive maternal age (more than 35 years or less than 20 years), previous molar pregnancy history, use of oral contraceptives, advanced paternal age, use of beta-carotene or animal fats, and smoking [2].

Partial hydatiform mole (PHM); The presence of embryonic or fetal tissue, focal edema, and focal trophoblastic hyperplasia with or without atypia is the hydatiform type in which most 69XXY chromosomes are detectable. Complications are usually less than with complete hydatiform moles and are unlikely to persist (2-4%) [3]. The patient usually reports to the clinic with a missed abortion or incomplete abortion. The incidence of intrauterine growth retardation (IUGR) and fetal malformations is increased in partial mole [4]. PHM is most commonly diagnosed by pathological examination after evacuation of an unsuccessful pregnancy. Previous studies have shown that decidual immune cell infiltrates, particularly FoxP3+ regulatory T cells and CD3+ T cells, are significantly higher in molar pregnancy than in healthy pregnancy [5, 6]. Proinflammatory serum levels are also significantly increased [7]. Similar changes observed in viral infections have already attracted the attention of other researchers. In particular, a study was published suggesting an association between human papillomavirus (HPV) infection and complete molar pregnancy, indicating that the increase in proinflammatory markers was due to a viral etiology [8].

Coronaviruses (CoV) belong to the Coronaviridae family within the Nidovirales [9]. Human CoV infections mainly belong to the α - and β -subgroups and cause the following clinical conditions: severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) [10]. At COVID-19, both T cells and NK

cells are reduced. In addition, increased activity of molecules such as cytotoxic perforin and granulysin was found in CD8+ T cells [11]. During pregnancy and the puerperium, infection with COVID-19 can occur through aerosols or direct transmission from mother to fetus [12]. The effects of COVID-19 on the course and outcome of pregnancy are particularly important to pay more attention to this issue. SARS-Cov2 infection during pregnancy has been shown to be associated with spontaneous abortions, preterm births, and intrauterine growth retardation [13].

In the present study, we hypothesize that there is a possible association between the COVID-19 pandemic and the increased incidence of hydatiform mole. With this retrospective cohort study, we aimed to determine the incidence, etiology, and progression rates to GTN of PHM during the epidemic COVID-19 and compare the data with those from 4 years before the pandemic.

MATERIALS and METHOD

The study protocol was approved by the Ethics Committee (28/01/2022, #2022/02). The principles of the Declaration of Helsinki were followed.

This study was a retrospective cohort study. Patients with a singleton or spontaneous pregnancy who underwent dilatation curettage (D/C) with diagnoses of miscarriage, intrauterine exitus (IUEX), molar pregnancy, or incomplete abortion between March 2016 and February 2022 at a tertiary hospital early pregnancy assessment unit were included in the study. The study group consisted of patients diagnosed with partial hydatiform mole based on pathologic examination. The control group consisted of patients who had undergone therapeutic curettage after a single spontaneous pregnancy during the same period and whose pathological findings showed a normal villous structure. During this study period, the first 3 patients with D/C were randomly assigned to the control group on the first day of each month (Figure 1). COVID 19 Polymerase chain reaction tests were not routinely performed on all patients during the study period. Exclusion criteria for

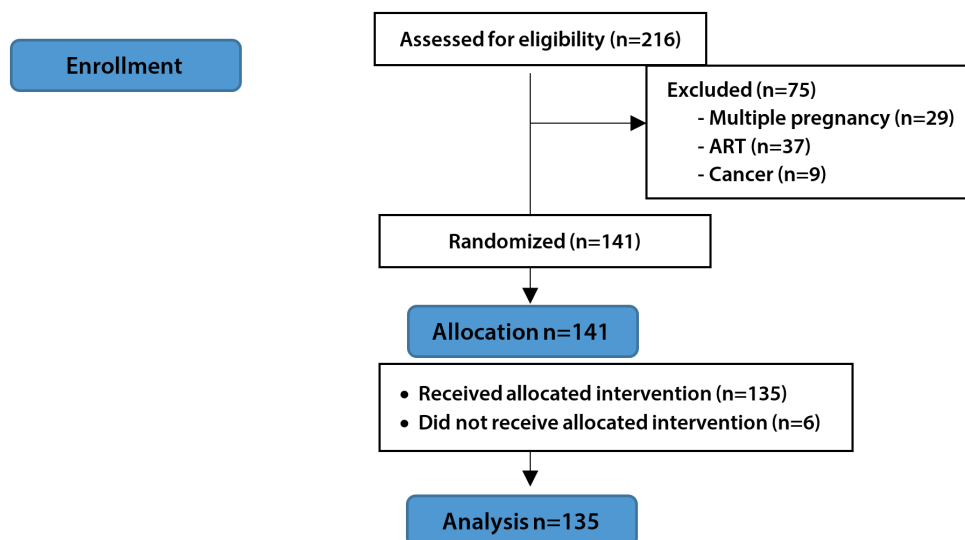


Figure 1. Flow Chart of the Control Groups

the study were maternal history of malignancy, pregnancy by assisted reproductive techniques, patients whose medical records were not available, and multiple pregnancy. Patients’ medical records (admission diagnoses, admission status during COVID-19), maternal age, number of births, pre-abortion symptoms, and last menstrual period were reviewed. The period between the pathology reporting date after curettage and the patient’s entry in the progress chart was calculated in days. Birth dates in our hospital were broken down by year. Follow-up of patients diagnosed with PHM was examined to determine whether or not GTN status developed.

Statistical analysis

Data analysis was performed using SPSS (statistical package for social sciences, Chicago, IL, USA) 22.0 software. Analytical results were reported as mean ± standard deviation and median (minimum-maximum) for quantitative data and frequency (percent) for categorical variables. The distribution of parameters was assessed by Shapiro-Wilk normality tests. The difference between repeated measurements in independent groups was evaluated by the Wilcoxon test. For the normally distributed data, the independent-samples T test was used, and for the nonnormally distributed variables, the Mann Whitney U test was used. The Yates correction, Pearson Chi-square test, and Fisher’s exact test were used to examine the relationship between categorical variables by group. A type I error level of 5% overall was used to derive statistical significance.

RESULTS

Between 2016-2022, 138 patients with partial hydatiform moles who consulted the early pregnancy ward of our hospital were diagnosed by pathological examination. There were 135 female patients in the control group. The number of female patients who presented during the pandemic period and were diagnosed with PHM was 62 (44.92%). The mean age of patients diagnosed with PHM was 31.97±8.26 years. The median number of living children in these patients was 1 (0-5). The mean body mass index of these patients was 26.38±5.13 kg/m². When these data were compared with the control group, there was no statistical difference between the two groups (p=0.194/ p=0.294/ p=0.583). The mean paternal age in the study group was 34.95±8.32 years and was higher than the paternal age of the patients in the control group (p=0.028) (Table 1).

Table 1. Baseline characteristics of the groups

| | Control Group (n=135) | Study Group (n=138) | p |
|--------------------------------------|-----------------------|---------------------|--------|
| Age (year) | 30,55 ± 6,58 | 31,97 ± 8,26 | 0,194 |
| Number of living birth | 1 (0 - 5) | 1 (0 - 5) | 0,294 |
| Body Mass Index (m ² /kg) | 26,75 ± 5,30 | 26,38 ± 5,13 | 0,583 |
| Paternal age (year) | 32,56 ± 7,20 | 34,95 ± 8,32 | 0,028 |
| Time to get results (day) | 32,45 ± 46,64 | 18,75 ± 19,68 | <0,001 |

*Mann Whitney U test

p < 0.05 indicates significant difference. Data are expressed as mean ± standard deviation and median (maximum-minimum).

The mean time to undetectable beta-human chorionic gonadotropin level in the follow-up of patients diagnosed with PHM was 56.39±44.70 days. In patients whose diagnosis was confirmed PHM, the time to return to the hospital to learn the result of the biopsy was shorter (18.75±19.68/32.65±46.64) ($p < 0.001$).

The change in the number of patients diagnosed with PHM by year is shown in Figure 2. While the incidence of PHM in our hospital was 1.22/1000 births in 2019, this number was calculated to be 3.79/1000 births in 2020. In the PHM group, the number of patients whose previous pregnancies ended in cesarean section (CS) was 32 (23.2%), the number of patients with smoking habits was 51 (37%), and the number of patients who used oral contraceptives (OC) was 20 (14.5%). Active COVID 19 disease symptoms did not occur in any of the patients who presented during the pandemic period. In this group, the most common reason for hospitalization was a routine examination ($n= 70$ (50.7%)). The most common diagnosis on admission to the hospital was molar pregnancy ($n=52$ (37.7%)) (Table 2). In the PHM group, during the pandemic period, the most common reason for referral was routine examination ($n=32$ (51.6%)) and the most common diagnosis on admission to hospital ($n=25$ (40.4%)) was molar pregnancy. Missed abortion ($n=18$ (30.8%)); IUEX diagnosis ($n=10$ (15.4%)); incomplete abortion ($n=9$ (13.5%)) were the diagnoses at hospital admission. The difference between the two periods is shown in Figure 3. When the diagnoses and reasons for admission were examined, no statistically significant difference was found between the two time periods.

Progression to GTN disease was noted in 6 patients diagnosed with PHM, and 5 of them were patients diagnosed and followed up during the pandemic period. Before the pandemic, the rate of conversion of PHM disease to GTN was 17%. With the declaration of the pandemic, this rate increased to 83%. The incidence of progression to GTN was 0.02/1000 births 4 years before the pandemic; for 2020-2021, this rate was calculated to be 0.25/1000 births.

Table 2. Risk factors for PHM

| | | n | % |
|---|---------------------|-----|------|
| Delivery Method | CS | 32 | 23.2 |
| | Normal Delivery | 48 | 34.8 |
| | Primigravida | 58 | 42.0 |
| Smoking | Yes | 51 | 37.0 |
| | No | 87 | 63.0 |
| Oral Contraceptive using | Yes | 20 | 14.5 |
| | No | 118 | 86.5 |
| Reason for admission to hospital | Control | 70 | 50.7 |
| | Bleeding | 40 | 29.0 |
| | Others | 28 | 20.3 |
| Preliminary diagnosis for hospitalization | IUEX | 17 | 12.3 |
| | Missed abortion | 49 | 35.5 |
| | Incomplete Abortion | 20 | 14.5 |
| | Molar Pregnancy | 52 | 37.7 |

Chi-square test (χ^2) was used for categorical variables.



Figure 2. Distribution of the number of PHMs by years

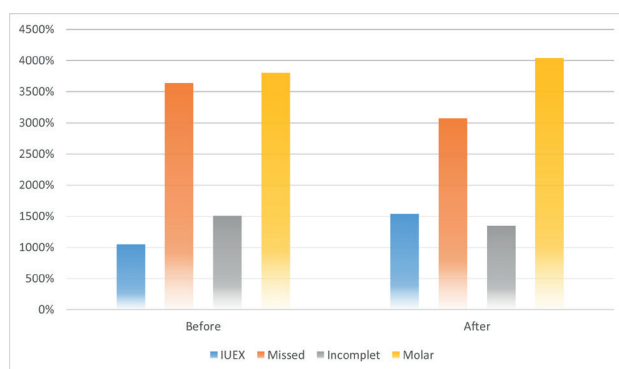


Figure 3. Diagnosis rates of the study group by pandemic

DISCUSSION

In this study, we found that there was an increase in patients diagnosed with partial hydatiform moles in our hospital because of the COVID-19 pandemic. Remarkably, we noted a significant increase in the rate of progression to GTN, particularly in this group of patients.

The pandemic COVID-19 put enormous pressure on health care systems around the world. Long quarantines made access to the health care system difficult, and the impact of the virus led to overcrowding in intensive care units. On the other hand, we did not have sufficient data on the impact of the virus on the fetus or mother during pregnancy from the beginning. Our hospital, which is a tertiary hospital, did not admit any patients with COVID-19 infection during this process and continued its normal service as a clean hospital. For this reason, unlike physicians working in other departments, we had the opportunity to independently assess the impact of the COVID-19 virus on pregnant women, its socioeconomic impact on society, and especially its impact on reproductive health. During this period, an increase in IUEX cases and pregnancy complications (such as preeclampsia, IUGR, threatened preterm labor) was observed in our hospital, whether the mother had COVID-19 infection or not [14, 15]. It is likely that the incidence of this patient group has increased due to a relative increase in density at our hospital as other hospitals in our region treat positive patients. While our total number of births in 2019 prior to the pandemic was 7334, this number increased to 7901 in 2020. The number of patients with suspected molar pregnancy during routine outpatient visits is higher than the number of patients coming to the emergency department with bleeding. A comparison of these hospitalization rates with the pre-pandemic period showed no difference between the two periods. In summary, therapeutic curettage was performed because an unhealthy pregnancy without active symptoms was detected during a routine examination, and the pathologic finding was eventually reported as PHM.

Studies conducted to determine the incidence of molar pregnancy worldwide have reported varying frequencies. Hayashi et al. reported that the incidence of HM in Southeast Asian countries is 2.5-3 times higher than in Europe and America [16]. While the incidence of HM for Turkey was 12.9/1000 births in 1997 [17], it was reported to be 6.60/1000 births in 2004 [18]. In another study by Gul et al, the incidence of gestational trophoblastic disease was reported to be 24.50/1000 births [19]. In these studies, both complete and partial molar pregnancies were reported, and there is no study on the change in incidence during the pandemic period. Abbas et al. published a study in which they stated that the increase in the incidence of HM with the pandemic in Egypt should be noted [20]. Another study conducted in Israel concluded that the incidence of molar pregnancies increased significantly during the pandemic COVID-19, possibly due to late visits to the physician [21]. Between 2016 and 2019, the number of births in our hospital and the number of registrations of pregnant women in the outpatient clinic decreased over the years. No change was observed in the incidence of PHM during the same period. However, during the announcement of the pandemic, the number of births and registrations in the outpatient clinic increased. However, an increase in PHM incidence was also noted.

In a partial hydatiform mole (PHM), fetal tissue is present because the hydropic villi are vascular. The chromosome structure is of maternal origin, but the additional haploid chromosome is usually of paternal origin [22]. Generally, the oocyte is exposed to two sperm (dyspermy) [23]. Since the CDKN1C gene is of maternal origin, it can be detected as p57 positive and is located in the short arm of the 11th chromosome [5, 23]. Although the etiology of molar pregnancy is not clear, it is a disease associated with some changes in the implantation of trophoblastic tissue, and changes in the inflammatory response are observed in pathological examinations. The cellular immune response at the implantation site is higher in molar pregnancies than in the placenta of normal pregnant women. Studies have shown that the number of GrB- Tc cells and the number

of GrB+ NK cells in placental tissue are increased in molar pregnancies [24, 25]. On the other hand, the association between HM and the mutation in NLRP7 gene is clear, and this gene plays a role in the activation of inflammatory caspases [26]. These immunological changes and the response of placental tissue suggest viral infection. In 2002, Alex et al. published a study in which they suggested an association between human papillomavirus (HPV) infection and complete molar pregnancy and that the increase in proinflammatory markers was due to a viral etiology [8]. A common mechanism suggested was that infectious antigens activate endometrial lymphocytes and macrophages. However, other studies at HM have not demonstrated a clinical association with human immunodeficiency virus (HIV), cytomegalovirus (CMV), and herpes simplex virus (HSV) [8]. During the pandemic caused by COVID-19, Abbas et al. suspected a link between this virus and HM and that the possible pathophysiology is a low leukocyte count and an insufficient immunological response to cause molar pregnancy [20].

GTN, the invasive form of molar pregnancy that contains both benign and malignant components, belongs to a group of diseases that have an excellent prognosis and good clinical course when properly treated, unlike other malignancies [27]. Studies have also been conducted on the effects of viral infections on the progression of premalignant lesions to GTN. Of particular value is a study describing the association between human immunodeficiency virus (HIV) and GTN [27]. However, in such common viral infections, does this disease and its progression occur directly as an effect of the virus, or do the effects of medications, difficulties in the health care system, weakening of immunity, and increases in anxiety and stress trigger this situation indirectly? It is difficult to understand this and fully isolate the etiology.

This is the first study to examine in detail the association between COVID-19 and the incidence of PHM and progressive disease leading to GTN. The small sample size and retrospective design are the main limitations of our study. Another important

limitation is that complete molar pregnancies could not be included in this study. There is a need for larger studies examining tissue diagnoses. Because our study was a clean hospital study, we cannot say that the direct effect of a COVID-19 positive patient is molar pregnancy; however, we found that there was an increase in the incidence of PHM that was indirectly influenced by many factors.

Thus, we had the opportunity to compare the 4-year period before the pandemic with the 2 years after the pandemic. Along with the increase in PHM incidence, the incidence of progression to GTN disease also increased. This is a remarkable finding that needs to be explored. More comprehensive studies examining biochemical and clinical parameters and long-term outcomes are needed.

Author contribution

Study conception and design: MÇİ and YEÜ; data collection: MÇİ and YAR; analysis and interpretation of results: MÇİ, SYE, İÖÜ, KYY, Çİ, and YEÜ; draft manuscript preparation: MÇİ, SYE, BSÜ, KYY, Çİ, and YEÜ. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study protocol was approved by the Ethics Committee of Ankara Etlik Zubeyde Hanım Women's Health Training and Research Hospital (Protocol No. 02/28.01.2022).

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Conflict of interest

The authors declare that there is no conflict of interest.

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