Gynecologic Oncology xxx (xxxx) xxx

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

A possible association between hydatidiform mole and the COVID-19 pandemic: A retrospective cohort study

Ala Aiob, Karina Naskovica, Avishalom Sharon, Jacob Bornstein *

Department of Obstetrics and Gynecology, Galilee Medical Centre, Nahariya, Israel
Azrieli Faculty of Medicine, Bar-Ilan University, Safed, Israel

HIGHLIGHTS

- There was a statistically significant increase in the incidence of molar pregnancy during COVID-19 pandemic.
- The gestational age of the embryo at the time of diagnosis was smaller in the HM group than in the missed abortion group.
- The continuous provision of gynecological primary care during pandemics or crises is encouraged.

ARTICLE INFO

Article history:
Received 22 January 2021
Accepted 27 February 2021
Available online xxxx

Keywords:
Gestational trophoblastic disease
Hydatidiform mole
Covid-19

ABSTRACT

Objective. To confirm an increase in the number of women with molar pregnancy during the COVID-19 pandemic.

Methods. In this retrospective cohort study, all patients with complete or partial mole diagnosed at our institution between January 1, 2010 and October 31, 2020, were included. To verify whether there was an increase in the incidence of hydatidiform mole (HM) and deliveries in 2020, the incidences for each year from January 2010 to October 2020 were recorded. In addition, we identified all women who were diagnosed with HM from January to October 2020, and compared them with a control group who underwent uterine evacuation for missed abortion of a singleton pregnancy during the same period. We also documented the time taken to diagnose missed abortion or molar pregnancy to check if a delay in diagnosis can explain the increase in HM incidence.

Results. Between 2016 and 2019, there was a statistically significant increase in the incidence of molar pregnancy. A further increase occurred in 2020 (odds ratio = 2.071). The mean gestational age of the embryo at the time of diagnosis was smaller in the HM group than in the missed abortion group (6.3 ± 1.67–7.4 ± 2.4, one-sided $P = 0.034$), meaning that it took more time (days) to diagnose molar pregnancy than missed abortion (22.38 ± 10.32 vs. 15.83 ± 7.83 days, $P = 0.012$).

Conclusion. There was a significant increase in the incidence of molar pregnancy during the COVID-19 pandemic, possibly because of the delay in receiving medical care. We recommend providing gynecological primary care services during a crisis, such as a pandemic.

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1. Introduction

Hydatidiform mole (HM) is a non-malignant form of gestational trophoblastic disease (GTD) characterized by failure of normal fetal development and over-proliferation of the trophoblasts, which can present as a partial or complete mole; these depend on the chromosomal pattern, microscopic and gross histopathology, clinical presentation, and outcomes. However, it is considered a premalignant disease due to its ability to develop into a cancer with local invasion and distant metastases [1–4].

In complete moles, the genetic material is solely derived from the father, with the maternal genetic component lost either late in the oocyte development or at the time of conception [5]. Complete moles have no embryonic development and produce a characteristic appearance on ultrasound. They have a malignancy rate of approximately 15% [6,7]. In contrast, partial moles are triploid with two sets of chromosomes from the father and one from the mother [8]. Partial moles may have early embryonic development. Diagnosis is made most often by pathological examination after the evacuation of a failed pregnancy. The risk of malignancy is much lower for partial moles (approximately 0.5–1%) [7,9].

Some potential risk factors for molar pregnancies have been suggested, including vitamin deficiencies [10], maternal genetic translocations [11], and environmental toxins [12]. The incidence of HM is

* Corresponding author.
E-mail addresses: ala.aiob@gmail.com (A. Aiob), karina.naskovica@gmail.com (K. Naskovica), avishaloms@gmc.gov.il (A. Sharon), mdjacob@gmail.com (J. Bornstein).

https://doi.org/10.1016/j.ygyno.2021.02.035
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Please cite this article as: A. Aiob, K. Naskovica, A. Sharon, et al., A possible association between hydatidiform mole and the COVID-19 pandemic: A retrospective cohort s..., Gynecologic Oncology, https://doi.org/10.1016/j.ygyno.2021.02.035

difficult to ascertain due to its rarity and regional variation in existing reports [13,14]. The most significant risk factors for complete and partial moles are extreme maternal age and past molar disease [15,16].

Patients with HM usually present with vaginal bleeding in the first or second trimester. However, more recently, it has been seen as a non-viable conception discovered during routine ultrasonography in early pregnancy [17]. Following the diagnosis, molar tissue is evacuated by surgical curettage, and the patient is followed up with serial serum or urine human chorionic gonadotropin (HCG) testing [18].

Following uterine evacuation, serum HCG levels return to normal in most cases, and no further treatment is needed. However, 15% of complete moles and < 1% of partial moles may develop into persistent trophoblastic disease requiring chemotherapy, and may rarely progress to locally invasive or metastatic gestational trophoblastic disease [19].

In our institution, we had an impression that the number of patients diagnosed with HM between January 1 and October 31, 2020 was higher than that in the previous 10 years. This increase coincided with the coronavirus disease (COVID-19), which was declared a global pandemic by the World Health Organization in March 2020 [20]. Consequently, we hypothesized that there is a possible association between the COVID-19 pandemic and the increasing incidence of hydatidiform moles. Abbas et al. attempted to explain the increase in HM incidence during the Covid 19 pandemic using the immunological and laboratory parameters of COVID-19. They suggested that non-reproductive tissue-specific antigens are one of the causative factors for the activation of endometrial lymphocytes and macrophages that can produce a negative environment, which can affect embryonic implantation and lead to the development of HM [21].

First, this retrospective cohort study aimed to confirm the increase in HM incidence during the COVID-19 pandemic and compare it with that of the previous 10 years in our department. Second, the study aimed to provide a possible explanation for this increase based on clinical and diagnostic features, or a delay in the diagnosis of HM or missed abortion.

We hypothesized that diagnostic delay leads to clearer sonographic findings and higher serum HCG levels, with increased suspicions of molar pregnancies and uterine evacuations, leading to an increased number of persons diagnosed with HM pathologically.

2. Materials and methods

This study was approved by the Institutional Review Board (Helsinki Committee) of the Galilee Medical Center of the Israeli Ministry of Health before the research began (authorization number 167-20-NJR) on September 10, 2020.

The study population consisted of all patients with a pathological diagnosis of complete or partial mole at the gynecology department of the Women's Health Wing at the Galilee Medical Center, Israel, between January 1, 2010 and October 31, 2020. The pathologist diagnosed all the cases by assessing the evacuated uterine contents at our institution. The diagnosis of molar pregnancy was made by a highly experienced Gyneco-pathologist, based on histopathologic features and P57 immunostaining in all cases.

There was no significant change in the demographics, the number of deliveries, or referrals to the emergency room (ER) in the past five years.

First, we identified the yearly incidence of HM (complete and partial moles) from January 2010 to October 2020. Additionally, we carried out a database search to identify the incidence of deliveries in our institution during the same period to determine the number of HM cases per the number of deliveries at this institution.

Second, we identified all the charts of patients with HM, with a final diagnosis of complete moles or partial moles, registered from January to November 2020. However, COVID-19 polymerase chain reaction test was not conducted on a routine basis during the study period.

Moreover, we recruited a control group that comprised randomly selected women who had undergone uterine evacuation for missed abortion of a singleton spontaneous pregnancy during the same period, with a final histological diagnosis of normal villi. In both groups, the diagnosis was made by a pathologist in our institution who evaluated the evacuated uterine contents.

The medical records of all patients (HM and missed abortion in the period of COVID-19) were reviewed to determine their age, gravidity, presenting symptoms, gestational age by the crown-rump length (CRL) or last menstrual period (LMP), indication of surgery, and ultrasound findings, including CRL at diagnosis.

In addition to the other characteristics, we evaluated the time taken to diagnose a missed abortion or molar pregnancy by measuring the time period between the original gestational age, which was determined by the LMP and/or first CRL measurement, and gestational age determined by the CRL at HM diagnosis or missed abortion in the control group. At the time of HM diagnosis or missed abortion, CRL was measured if the embryo was observed using transvaginal sonography (TVS). If we did not visualize an embryo, we assigned such pregnancy a gestational age of 5 weeks since the fetus cannot be seen by then on TVS.

3. Results

For the first aim, we included 107 patients with confirmed molar pregnancies between 2010 and 2020. As shown in Fig. 1, in synchronization with the onset of the COVID-19 pandemic [9], there was a significant increase in the number of molar pregnancies compared to that in the last 10 years (in the same period January–October). This increase was not related to an increase in the number of deliveries in our department.

As shown in Fig. 1, the incidence of molar pregnancy was stable from 2010 until 2016, which is the year we moved to a new modern facility, leading to an increase in the number of births in our department (Fig. 2). After 2016, the incidence of molar pregnancies was stable again until 2020, when we observed a significant increase in the number of molar pregnancies (0.59%).

In 2020, the risk of HM was significant and 6.274 times higher than that between 2010 and 2015.

Generally, from 2016 to 2019 and in 2020, there were significant increases in the incidence of molar pregnancy (odds ratio [OR] = 2.071).

For the second aim, we included 24 patients with confirmed molar pregnancies from January to October 2020: five (20.8%) with complete moles and 19 (79.2%) with partial moles. In addition, we recruited a control group of 32 patients with confirmed missed abortions of similar gestational ages, treated during the same period.

The comparison of maternal characteristics in both groups is presented in Table 1; the median maternal age was 30.2 (range 21–46) years and 33.4 (range 20–43) years in the HM and missed abortion groups, respectively. However, there was no significant difference in the body mass index, comorbidities, parity, rates of abortions, termination of pregnancy, ectopic pregnancy, in-vitro fertilization, and molar pregnancy in the past, or the gestational age according to the first CRL or/and the LMP.

We observed that patients in the HM group were younger than those in the missed abortion group, and most of them were smokers (16.7% vs. 9.4%, $P < 0.001$).

Although there was no significant difference between the gestational age by the first CRL and/or LMP in both groups, the mean gestational age by CRL at diagnosis was smaller in the HM group than in the missed abortion group (6.31 ± 1.67 weeks vs. 7.40 ± 2.4 weeks, 1-sided $P = 0.034$). This means that it took more time (days) to diagnose molar pregnancy than to diagnose missed abortion (22 ± 10.3 days vs. 15 ± 7.8 days, $P = 0.012$).

4. Discussion

From January to October 2020, there were 24 patients with confirmed molar pregnancies: five (20.8%) with complete moles and 19

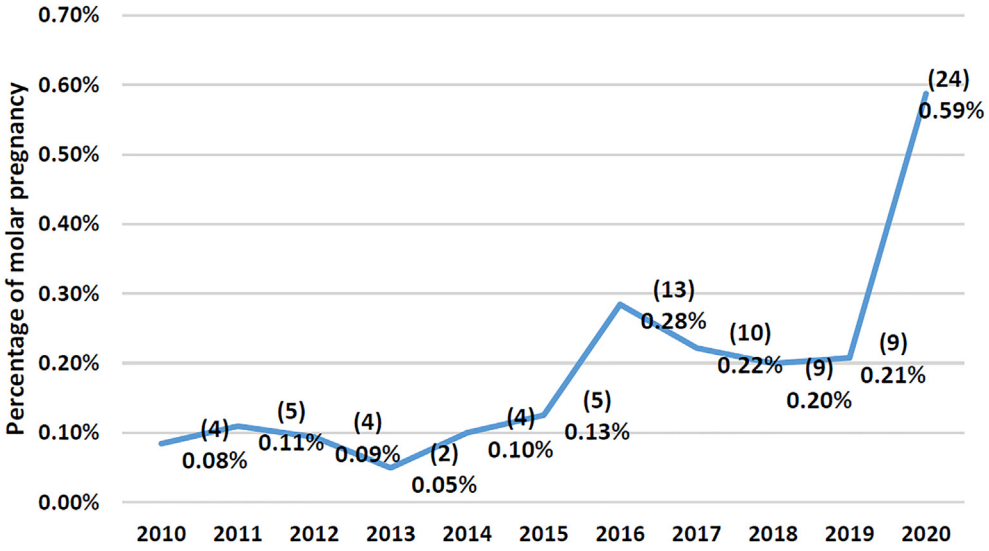

Fig. 1. The incidence of molar pregnancies at Galilee Medical Center (January–October, 2010–2020).

(79.2%) with partial moles. We are aware that this is an unusual proportion of cases compared to previous reports. However, this proportion is so close to our general proportion of complete HM and partial HM over the last 10 years; 73% of the cases were partial HM, and 27% were complete HM. Further, it should be noted that there was no significant difference in this proportion in 2020.

On the other hand, we are aware that the relative incidence of complete HM versus partial HM is problematic because of the discrepancies between hospital-based and population-based data and the disparity in availability of expert pathology evaluation. Moreover, our proportion is similar to that of United Kingdom, in which the incidence of complete HM is approximately 1 per 1000 pregnancies compared to partial HM, which is 3 per 1000 pregnancies [22].

In synchrony with the onset of the COVID-19 pandemic, there was an approximately two-fold increase in the risk of molar pregnancy in 2020 from 2016 to 2019, and a six-fold increase from 2010 to 2015. This may be explained by the following immunological hypothesis [21]: compared to healthy pregnancy, patients with HM have a low white blood cell count as seen in patients with COVID-19 [23–25]. This reflects the association of HM with a poorer inflammatory function and could explain the causative association of COVID-19 in the pathogenesis of HM.

The non-reproductive tissue-specific antigens, such as those of infectious organisms, are one of the causative factors for the activation of endometrial lymphocytes and macrophages that can produce a negative environment, which affects embryo implantation [26]. This activation of endometrial lymphocytes and macrophages will lead to the release of variable cytokines, as seen in COVID-19 [25], which may affect the normal implantation and lead to HM development.

Previous studies have documented an association between recurrent molar disease and a mutation in the NLRP7 gene. The NLRP7 gene is implicated in the activation of proinflammatory caspases via their involvement in multi-protein complexes called inflammasomes. They play a role in the activation of inflammation and apoptosis, thereby increasing the risk of bacterial, parasitic, or viral disease that may result in HM [27]. Furthermore, Abbas et al. observed an increasing incidence of patients diagnosed with HM in synchrony with the onset of the COVID-19 pandemic; they offered a possible explanation for this condition based on the COVID-19 immunological and laboratory parameters [21].

Another possible explanation for this increase could be the delay in diagnosing missed abortion and/or molar pregnancy due to the lock-downs during the COVID-19 pandemic. Hence, it can lead to clearer ultrasonographic and laboratory features, which will result in more uterine evacuations for suspected molar pregnancies. However, the time taken (days) to diagnose HM in the HM group was higher than that in the missed abortion group (22 ± 10.3 vs. 15 ± 7.8, $P = 0.012$). This can justify our hypothesis that the increase in the incidence of molar pregnancy was caused by a delay in the diagnosis of missed abortion or molar pregnancy.

Furthermore, in our cohort, 40% of the patients had a pre-evacuation suspicion of molar pregnancy, compared to 91% with a pre-evacuation

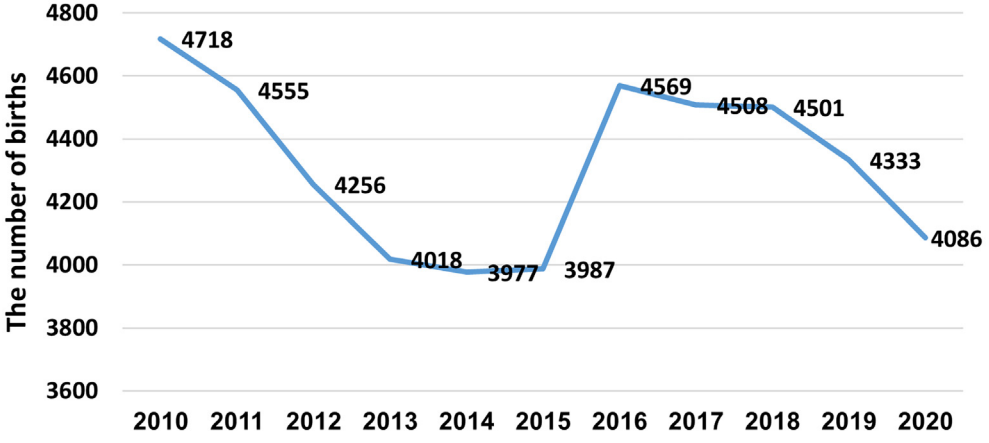

Fig. 2. The number of birth per year at Galilee Medical Center (January–October, 2010–2020).

Table 1
Maternal and pregnancy characteristics.

	HM 2020 $N = 24$	Missed Abortion 2020 $N = 32$	P 2/1 sided
Age (Mean)	30.2 ± 6.08	33.4 ± 5.74	0.040*
Age (Range)	30.2 (21–46)	33.4 (20–43)	
Thrombophilia (n%)	(1) 4.2%	(2) 6.3%	0.504+
BMI (Mean)	24.7 ± 4.9	25.4 ± 5.8	0.994*
Smoking (n%)	(4) 16.7%	(3) 9.4%	0.001 < P+
Regular menstruation (n%)	(23) 95.8%	(32) 00%	0.429+
Consanguinity (n%)	(1) 4.2%	(1) 3.1%	0.678+
Gestational age by first CRL/LMP (Mean)	9.55 ± 1.546	10.08 ± 2.53	0.889*
Gestational age at diagnosis by CRL (Mean)	6.31 ± 1.67	7.40 ± 2.42	0.034** 0.068*
Days for diagnosis (Mean)	22.38 ± 10.32	15.83 ± 7.83	0.012*
Gravidity (Mean)	3.17 ± 1.71	4.06 ± 1.68	0.046*
Deliveries (Mean)	1.75 ± 1.19	1.94 ± 1.16	0.474*
Spontaneous Abortion (Mean)	0.33 ± 0.76	0.84 ± 1.29	0.075*
Termination of pregnancy (n%)	(2) 8.3%	(3) 9.4%	0.749*
Ectopic pregnancy (n%)	0	(1) 3.1%	
Recurrent HM	0	0	
IUFD	0	0	
IVF	0	(1) 3.1%	
Last pregnancy before (Mean)	46.22 ± 8.73	44.93 ± 7.5	
D&C because Susp. HM (n%)	(10) 41.7%	(1) 3.1%	P < 0.001+
Oral Contraceptive	0	0	
Blood typing A+ (n%)	(13) 54.2%	(7) 21.9%	0.023*

HM- Hydatidiform mole, BMI- Body mass index, CRL-Crown-rump length, LMP- Last menstrual period, IUFD-Intrauterine fetal death, IVF- In vitro fertilization, D&C- dilatation and curettage, Susp- Suspected.
* 2-Sided Wilcoxon Rank-Sum Exact Test.
** 1-Sided Wilcoxon Rank-Sum Exact Test.
+ Fisher's Exact Test 2-Sided.

clinical diagnosis of missed or incomplete abortion in another study [28]; this difference can support our hypothesis.

5. Strengths and limitations

This study is the first to provide a detailed description of the relationship between COVID-19 and the frequency of HM, which should serve as a basis for patient counseling and future studies, including the GTN. The main limitations of our study were its small sample size and retrospective design. Furthermore, the reported rate is an approximation of the incidence of HM, though reasonable. However, the ideal incidence of HM should be calculated as a percentage of pregnancies, not just deliveries.

Additionally, when we did not visualize an embryo by TVS, we assigned such pregnancy a gestational age of 5 weeks also in complete HM, despite there was no embryo. However, we think that this cannot affect the delayed diagnosis reported.

6. Conclusion

There was a two-fold significant increase in the incidence of molar pregnancy during the COVID-19 pandemic compared to that in the previous 10 years.

We discussed other possible explanations for this condition based on clinical and diagnostic features. Delay in the diagnosis of missed abortion or molar pregnancy (which can be due to the hesitancy in keeping clinic appointments in early pregnancy because of the COVID-19 pandemic) can cause clearer sonographic findings and higher serum B-hCG levels, which could lead to more diagnosed molar pregnancies and uterine evacuations for suspected molar pregnancies. Moreover, in women diagnosed with missed abortion, early termination can lead to less clinical features of molar pregnancy, less surgical interventions, and more medical interventions (Cytotec), resulting in misdiagnosis of molar pregnancy.

Our findings encourage the continuous provision of gynecological primary care during pandemics or crises.

Authors' contributions

All authors contributed equally to the conceptualization, data curation, analysis, draft preparation and review, and final acceptance of the manuscript.

Declaration of competing interest

None.

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