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Original Article

The impact of the COVID-19 pandemic on ectopic pregnancy presentation and treatment: A retrospective cohort study

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\textbf{A B S T R A C T}

**Objective:** We examined ectopic pregnancy (EP) incidence, presentation, and management, before and during the COVID-19 pandemic, and following initiation of vaccination against COVID-19.

**Study design:** In a single-center retrospective cohort study, we compared incidence, presentation and management of EP, between 98 women who presented during the pandemic (March 1 2020 to August 31, 2021), and 94 women diagnosed earlier (March 1 2018 to August 31, 2019). Sub-periods before and after introduction of the vaccination were compared.

**Results:** Age and parity were similar between the periods. For the pandemic compared to the earlier period, the median gestational age at EP presentation was higher (6.24 ± 1.25 vs. 5.59 ± 1.24, P<0.001), and the proportions were higher of symptomatic women (42.9% vs. 27.7%, \(p = 0.035\)) and urgent laparoscopies (42.9% vs. 24.5%, \(p = 0.038\)). In a multivariable linear model, women who presented during the pandemic were more likely to undergo an urgent laparoscopy \([OR 2.30, 95\%CI (1.20–4.41)]\), \(P = 0.012\). In urgent surgeries performed during the pandemic compared to the earlier period, the proportion of women with a hemoglobin drop >2 gr/dL was greater (60% vs. 30%, \(p = 0.024\)). Statistically significant differences were not found in sonographic or laboratory findings, in rupture or massive hemoperitoneum rates, or in the need for blood transfusion in urgent laparoscopy. Outcomes were similar before and after introduction of vaccinations.

**Conclusion:** During the pandemic, and even after the introduction of vaccination, women with EP were more likely to undergo urgent surgery, and blood loss was greater. This is likely due to delayed diagnosis.

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**Introduction**

Ectopic pregnancy (EP) occurs in 1–2% of all pregnancies [1]. Since the implementation of earlier use testing of beta human chorionic gonadotropin (beta-HCG) and transvaginal ultrasound (TVS) in first-trimester pregnancy, about 85% of women with EP are diagnosed early, before the onset of symptoms [2]. Consequently, maternal mortality and morbidity have decreased significantly. Moreover, several clear benefits have been demonstrated for early diagnosis of EP, which enable conservative follow-up or medical treatment with methotrexate (MTX), without surgical intervention [3,4]. EP may be managed by watchful waiting, by MTX in hemodynamically stable patients, or by surgical intervention. Up to 50% of EP can be managed expectantly, without medical or surgical intervention [5,6]. The success rate of MTX treatment is estimated at 87–93% [6]. Nowadays, surgery remains the approach only for failed MTX treatment, EP with embryonic cardiac motion on ultrasound, recurrent EP in the same tube, contraindication for medical or expectant management, or suspected EP rupture and hemodynamic instability. Delayed diagnosis of EP can result in a life-threatening medical condition resulting from intra-abdominal bleeding and hypovolemic shock [7].

In late 2019, the first patients with COVID-19 were reported in China, and the World Health Organization declared a pandemic on March 11, 2020. On February 21, 2020, Israel reported the first cases of COVID-19, and restrictions began. Shortly afterward, the first lockdown was announced on March 23, 2020.

Since March 2020 and throughout the pandemic, several lockdowns and significant restrictions have been implemented, together with social distancing. Although restrictions regarding seeking pregnancy and emergent-related medical care have not been dictated, some individuals have distanced themselves to the extent of avoiding medical care due to the fear of contracting COVID-19.

The pandemic has affected the presentation and the incidences of several gynecological and non-gynecological medical conditions. We reported an increase in molar pregnancy incidence during the
pandemic, which was probably due to late diagnosis [8]. Others reported more urgent surgical intervention in EP during the first lockdown in Israel [9]. In addition, fewer urgent medical conditions such as appendicitis, stroke, and heart attacks were reported in emergency rooms in this period [10–13].

No studies examined the presentation and treatment of EP during the COVID-19, a long period of 18 months in addition to the examination of these parameters before and after introduction of the vaccination. The aim of this study was to examine EP incidence, presentation, and management during the COVID pandemic compared to previous years, and to examine a possible collateral effect of introduction of the vaccination in the presentation and the management of EP.

Materials and methods

This study was approved by the Institutional Review Board (Helsinki Committee) of Galilee Medical Center and the Israeli Ministry of Health before data collection (authorization number 0138–21–NHR, August 2021).

The study population consisted of women diagnosed with EP in the Obstetrics and Gynecologic Department at the Galilee Medical Center, Israel, between March 2020 and August 2021 (during the COVID-19 pandemic) and women diagnosed in a parallel period before the pandemic, between March 2018 and August 2019. We compared between the periods, incidences of EP per number of deliveries at our institution, and the volume of urgent surgeries. In addition, we aimed to identify possible changes in presentation and treatment trends following the introduction of vaccination in January 2021. To this end, we divided the pandemic (COVID-19) period into two sub-periods, from March 2020 to December 2020, and from January 2021 to August 2021.

During the study period, EP was diagnosed, and managed according to current practice, based on the American College of Obstetricians and Gynecologists Practice Bulletin [14]. This included a combination of serial beta-HCG measurements and the absence of evidence of an intrauterine gestational sac, with or without sonographic suspicion of extrauterine pregnancy. When EP was suspected and the TVS was inconclusive, the diagnosis was confirmed during laparoscopic surgery and pathology assessment. The location of extra tubal EP was confirmed during laparoscopy. The pregnancy week at presentation was calculated by the date of the last menstrual period.

Urgent laparoscopy was performed when ruptured EP was suspected by hemodynamic instability, acute abdomen, sonographic evidence of large free fluid in the cul-de-sac, or acute anemia diagnosed by hemoglobin < 9 gr/dl [15]. The surgical modality was chosen according to the EP location: salpingectomy for tubal pregnancy [18], wedge resection for ovarian pregnancy [16], lesion excision for abdominal pregnancy [17], and cornual excision for interstitial pregnancy [18].

In women for whom urgent surgery was not indicated, three treatment modalities were possible: expectant management, MTX, and planned laparoscopy.

Expectant management (observation) was selected for early EP, asymptomatic and hemodynamically stable patients, with spontaneous beta-HCG decline [15].

MTX was selected for hemodynamically stable patients, with beta-HCG level < 5000 (IU/L), gestational sac <4 cm and the absence of embryonic cardiac motion detected on TVS [14].

Planned laparoscopy was selected for those who declined treatment by MTX and those with contraindications to MTX.

We searched the hospital’s database using the International Classification of Diseases, Ninth Revision (ICD-9) Codes 633, 633.90, and 633.9. After validating the data, we included those confirmed as EP. We included all women assessed for EP and excluded cervical and scar pregnancies due to the different guidelines for treatment modality [19,20].

We also accessed demographic characteristics, presenting symptoms (asymptomatic, abdominal pain, vaginal bleeding or both), indications of surgical management, ultrasonographic reports and laboratory data. The ultrasonographic reports included mass size, embryonic cardiac motion, and the presence of free fluid in the cul-de-sac. The laboratory data included hemoglobin (g/dl), beta-HCG at presentation, and treatment modality. Additional variables were intraoperative findings, estimated blood loss (mL), the administration of blood products, postoperative care, and the duration of hospitalization.

EP complications were defined as ruptured EP confirmed in laparoscopy, massive bleeding as either (hemoperitoneum >1000 ml), a hemoglobin decline greater than 2 gr/dl (admission-discharge) or the need for blood transfusion.

The primary outcome was the proportion of women with EP requiring urgent surgical intervention. Secondary outcomes were gestational age at presentation, symptoms at presentation (vaginal bleeding, abdominal pain, asymptomatic), the need for blood product transfusions, estimated blood loss, ectopic embryonic cardiac motion identified by TVS, and beta-HCG level at admission. Massive blood loss was defined as a >2 gr/dl decline in hemoglobin level from admission until discharge. Hemoperitoneum was defined as at least 1000 ml of blood as assessed by the surgeon.

Statistical analysis

We described the categorical data using frequencies and percentages. Continuous variables with normal distributions were presented as means ± standard deviations. Median values and ranges were used for variables that did not meet the normal distribution assumption.

For the inferential analysis, we compared categorical variables between the groups using the Chi-square test, or alternatively Fisher’s exact test (when expectancy <5).

We compared continuous variables between the groups using the independent t-test or Wilcoxon rank-sum test according to the variable distributions. Accordingly, if a normal distribution was found, the independent t-test was presented; a histogram determined the distribution shape.

A multivariable linear model was adapted to examine the correlation between the pandemic period and urgent laparoscopy in EP. The dependent variable was urgent laparoscopy. Women’s age, gravidity, and the pandemic period were included as independent variables.

P <0.05 was considered to be significant. SPSS Version 27.0 statistical software was used for the statistical analysis.

Results

We identified 102 women with an EP during March 2020 – August 2021 (the pandemic period) and 100 women during the same months of 2018–2019 (the earlier period). These included four cervical or scar pregnancies in the pandemic period, and six in the earlier period. After excluding these, the pandemic period comprised 98 women with confirmed EP, and the earlier period included 94. The ectopic to delivery rate was similar between the pandemic and earlier period (1.37% and 1.18%, respectively, p = 0.344) (Fig. 1).

The baseline characteristics of all the patients are presented in Table 1. The median gestational age of the EP at presentation was significantly higher in the pandemic than the earlier period (6.24 ± 1.25 vs. 5.59 ± 1.24, P<0.001). No difference was found in age, gravidity, parity, EP history, and EP location between the two periods.

The clinical, laboratory and sonographic presentation are presented in Table 2. In the pandemic compared to the earlier period, a larger proportion of women presented with abdominal pain (42.9% vs. 27.7%, P = 0.035), and a smaller proportion was asymptomatic.
However, in the pandemic compared to the earlier period, a higher proportion of women underwent urgent laparoscopy (42.9% vs. 24.5%, \(P = 0.038\)), and a lower proportion underwent planned laparoscopy (5.1% vs. 14.9%, \(P = 0.029\)). Similar proportions of women in the two periods were treated by expectant management and MTX (Fig. 2).

The multivariable linear model showed that during the pandemic period, women with EP were more likely to undergo urgent laparoscopy than women before the pandemic; the OR (95% confidence interval) was 2.30 (1.20–4.41), \(P = 0.012\). Correlations of the remaining variables (age and parity) with the need for urgent laparoscopy were not statistically significant.

Table 3 presents a sub-analysis of the 42 women in the pandemic period and the 23 in the earlier period who underwent urgent surgery for treatment of EP. Statistically significant differences were not found between the two periods in surgical findings such as EP rupture rate and massive intra-abdominal bleeding above 1000 ml; and in laboratory findings such as postoperative hemoglobin level and anemia rate (defined as hemoglobin <9 gr/dL). A hemoglobin drop of more than 2 gr/dL was twice as common in the pandemic than the earlier period (60% vs. 30%, \(P = 0.009\)). A smaller proportion of women in the pandemic period, received blood product transfusion, though the difference was not statistically significant. The median post-surgery hospitalization length was longer in the earlier than the later period (1.54 (range: 1–5) vs. 2 (range: 1–5), \(P = 0.036\). No complications were reported in any of the urgent surgeries.

In a sub-analysis of the pandemic period, statistically significant differences were not found between the pre- and post-vaccination sub-periods, in any of the parameters examined (Table 4). These included features of EP presentation such as presenting week, symptoms (asymptomatic, abdominal pain or vaginal bleeding), and hemoglobin and beta-HCG levels at admission; sonographic details such as EP size (cm); or embryonic cardiac motion. The rate of urgent laparoscopy was equal, 46%, in the pre- and post-vaccination periods. Surgical findings in urgent laparoscopy, including intra-abdominal bleeding, ruptured EP, and massive hemoperitoneum >1000 ml, were also similar.

### Discussion

In this study, we showed that women who presented with EP during the COVID-19 pandemic period were more likely to undergo urgent laparoscopy than women in an earlier period. Additionally, we showed that during the pandemic compared to the same months in a previous year, women with EP presented later (6.24±1.25 vs. 5.59±1.24, \(P<0.001\)), and the proportion with blood loss >2 gr/L was higher. Moreover, for the respective periods, a greater proportion of women with EP presented with abdominal pain, and a smaller proportion were asymptomatic at presentation. (35.7% vs. 57.4%, \(P = 0.004\)). Statistically significant differences were not found between the groups in vaginal bleeding, or in hemoglobin or beta-HCG level at presentation. Sonographic details such as EP size and embryonic cardiac motion were similar in the two groups.

**Table 1**

Baseline characteristics of women with ectopic pregnancy in the pandemic period (March 2020 to August 2021) and an earlier period (March 2018 to August 2019).

| Location                        | Pandemic period      | Earlier period   | P-value |
|---------------------------------|----------------------|------------------|---------|
| Fallopian tube                  | 88 (89.8%)           | 84 (89.4%)       | 0.288c  |
| Ovarian                         | 1 (1%)               | 0 (0%)           |         |
| Abdominal                       | 3 (3.1%)             | 0 (0%)           |         |
| Intestinal                     | 2 (2.8%)             | 2 (2.1%)         |         |
| Rudimentary horn                | 0 (0%)               | 2 (2.1%)         |         |
| Ectopic of unknown location     | 4 (4.1%)             | 6 (6.4%)         |         |

EP- ectopic pregnancy, SD- standard deviation.

b Wilcoxon rank-sum test

c Fisher's test.

d Chi-square Exact test.

**Table 2**

The presentation of ectopic pregnancy in the pandemic (March 2020 to August 2021) and in an earlier period (March 2018 to August 2019).

| Symptom                                | Pandemic period      | Earlier period | P-value |
|----------------------------------------|----------------------|----------------|---------|
| Abdominal pain as a presenting symptom | 42 (42.9%)           | 26 (27.7%)     | 0.035a  |
| Asymptomatic (sonographic presentation or inappropriate beta-HCG rise) | 35 (35.7%)           | 54 (57.4%)     | 0.004b  |
| Hemoglobin at presentation (g/dL)      | 12.1 ±1.24           | 12.27±1.38     | 0.439a  |
| Beta-HCG at presentation (IU/L)        | 1421.5 (14–70,628)   | 903.5 (27–45,797) | 0.391b  |
| Peak beta-HCG value (IU/L)             | 1502.5 (51–81,490)   | 1265.5 (27–45,797) | 0.594c  |
| EP size at presentation (cm)           | 2 (0.8–6.4)          | 1.95 (0.69–6)  | 0.614d  |
| Embryonic cardiac motion in EP (%)    | 14 (14.3%)           | 7 (7.4%)       | 0.166e  |

EP- ectopic pregnancy, SD- standard deviation.

a Chi-square Exact test.

b Wilcoxon rank-sum test.

c independent samples t-test.

d Fisher's test.

e Chi-square Exact test.
the diagnosis of EP. However, similarities were found between the periods in the rate of EP, the proportion of women with EP who required blood products, the proportion with an embryonic cardiac motion on TVS, and the ratio between surgical, MTX, and expectant management. Moreover, we found no differences in EP presentation and treatment trends before and after introduction of vaccination against COVID-19.

The impact of this pandemic on several medical conditions has been described, mainly in the fields of emergent surgery [13,21-23] and cardiology [12]. A multicenter analysis demonstrated a significant reduction in the volume of ST-elevation myocardial infarction-related catheterization due to the late presentation of patients in the emergency room during the COVID-19 outbreak [12]. Other study reported increased perforated and gangrenous appendicitis due to delayed care [13].

In gynecology, we described a higher rate of molar pregnancy in the pandemic due to delays in diagnosis [8]. The present report corroborates reports of a higher rate of symptomatic presentation of EP and more surgical interventions for EP [9,24]. A possible explanation for this trend is delays in seeking timely medical care due to the pandemic and to fears of exposure to the virus.

This study’s novelty is that women with EP during the pandemic were more likely to undergo urgent laparoscopy and to present at advanced gestational age at the first medical encounter. Notably, the median gestational age at presentation was only three days greater during the pandemic period. Nonetheless, this delay in presentation likely explains the higher rates of symptomatic patients and urgent surgery, and the greater blood loss in the pandemic compared to the earlier period. This is because even a slight delay in presentation can affect morbidity and management of EP.

We presume that the diagnostic delay did not result from government prohibitions, as the staffing of pregnancy clinics did not change during the pandemic. We suspect that the delay in presentation is related to the reluctance to seek medical care due to fear of exposure to COVID-19. Surprisingly, the concern continued in the post-vaccination period. This is evident from the lack of differences in presentation, rates of urgent surgery, and morbidity between the pre- and post-vaccination periods. Further, no differences were observed in the presentation week, symptoms, or beta-HCG levels between women who underwent urgent surgery in the pandemic and the earlier period.

A higher proportion of women in the pandemic compared to the earlier period had post-surgical anemia, this finding supports the appropriateness of more frequent decisions to perform urgent surgery for EP treatment during the pandemic, and suggests that these decisions did not stem from collateral effects of the pandemic. The likelihood of conservative or medical treatment of EP decreases with increased gestational week and symptoms.

Table 3 Characteristics of women who underwent urgent laparoscopy for ectopic pregnancy (EP) in the pandemic (March 2020 to August 2021) and in an earlier period (March 2018 to August 2019).

| Characteristic                          | Pandemic period N = 42 | Earlier period N = 23 | P-value |
|----------------------------------------|------------------------|-----------------------|---------|
| Ruptured EP in urgent surgery (%)      | 20 (48%)               | 15 (65%)              | 0.173*  |
| Presence of intrabdominal bleeding (%) | 30 (71%)               | 20 (87%)              | 0.155*  |
| Intrabdominal bleeding>1000 ml (%)     | 4 (10%)                | 6 (26%)               | 0.076*  |
| Intrabdominal bleeding (ml), (median, range) | 200 (30–2800)          | 400 (0–3000)          | 0.268   |
| Hemoglobin:Hb after urgent surgery (median, range) | 10.5 (6.8–13.2)        | 10.85 (6–12.8)        | 0.568   |
| Anemia at discharge (Hb<9 gr/dL) (%)   | 9 (21%)                | 4 (17%)               | 0.697   |
| Delta Hb+2 gr/dl urgent surgery (%)    | 25 (60%)               | 7 (30%)               | 0.024*  |
| Blood products transfusion (%)         | 3 (7%)                 | 6 (26%)               | 0.086*  |
| Post-surgery Hospitalization (days), (median, range) | 1.54 (1–5)            | 2 (1–5)               | 0.036*  |

EP- ectopic pregnancy, HB- hemoglobin.
* Chi-square Exact test.
* Wilcoxon Rank-Sum test.
To the best of our knowledge, this study comprises one of the largest samples and the greatest time spans of the pandemic, of explorations of the collateral effect of this period on the presentation, severity and treatment of EP. An indirect negative effect of the pandemic throughout the entire period was demonstrated regardless of the lockdowns and the vaccine introduction. Notably, the earlier period comprised the same months as the pandemic period, during two previous consecutive years. This avoided changes in the rate of EP due to seasonal or holiday effects.

Certain limitations of our study should be acknowledged, foremost is its retrospective design. Moreover, since our medical center is a regional referral center, the patient population may not represent the entire population. This raises the possibility of referral bias. In addition, the reported rate is an approximation of EP incidence. Nonetheless, the ideal incidence of EP should be calculated as the proportion of pregnancies and not only deliveries.

We report a higher risk of urgent surgery for women with EP in the pandemic than an earlier period. This trend can be explained by the delay in presentation and diagnosis of EP during the Covid-19 pandemic period, even following the introduction of vaccination.

Our data suggest that the delay in diagnosis was caused by women’s worry of exposure to the disease at the time of the medical follow-up and not a pandemic collateral effect on the doctor’s decision. This concern did not change during the pandemic, subsequent to initiation of vaccination. Accordingly, obstetricians and gynecologists should encourage women to seek early medical evaluation in pregnancy, even during a pandemic, a war or other challenging situations. Evidence shows that social media has become an important vehicle for rapid information dissemination, particularly during the COVID-19 pandemic [25]. We suggest that during a pandemic, this platform for rapid information dissemination, particularly during the COVID-19 pandemic, can be used to increase public knowledge of EP and early pregnancy complications. Adopting a proactive approach to diagnosing EP early in pregnancy may facilitate anticipating women with symptomatic EP who present later than usual, with a high risk of urgent surgical intervention.

Authors’ contributions

A. Aiob- Planning, conduct, data analysis, design, manuscript writing and revision.
Raneen Abu shqara - Planning, conduct, data analysis, design and manuscript writing and revision.
Susana Mustafa Mikhail - Planning, conduct, data analysis and manuscript revision.
Avishalom Sharon- Planning, conduct, manuscript revision
Marwan Odeh- Planning, conduct, manuscript revision.
Lior Lowenstein- Planning, conduct, data analysis, design and manuscript revision.
All the authors interpreted the data, reviewed drafts and approved the final draft of the manuscript.

Details of ethics approval

This study was approved by the Institutional Review Board (Helsinki Committee) of Galilee Medical Center and the Israeli Ministry of Health before data collection (authorization number 0138–21-NHR, August 2021).

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Declaration of Competing Interest

The authors have no conflicts of interest related to this work.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jogoh.2022.102508.

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