



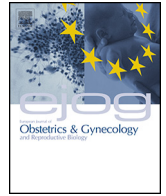
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Increase rate of ruptured tubal ectopic pregnancy during the COVID-19 pandemic



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ABSTRACT

Objective: During the 2020 COVID-19 pandemic there was a decrease in emergency room arrivals. There is limited evidence about the effect of this change in behavior on women's health. We aimed to evaluate the impact of the COVID-19 pandemic on the diagnosis, treatment and complications of women presenting with a tubal Ectopic Pregnancy (EP).

Study design: This is a single centre retrospective cohort study. We compared the clinical presentation, treatment modalities and complications of all women presenting in our institution with a tubal EP during the COVID-19 pandemic between 15 March and 15 June 2020, with women who were treated in our institution with the same diagnosis in the corresponding period for the years 2018–2019.

Results: The study group included 19 cases of EP (N = 19) that were treated between the 15 March 2020 and 15 June 2020. The control group included 30 cases of EP (N = 30) that were admitted to in the corresponding period during 2018 and 2019. Maternal age, parity, gravity and mode of conception (natural vs. assisted) were similar between the two groups. There was no difference in the mean gestational age (GA) according to the last menstrual period. In the study group more women presented with sonographic evaluation of high fluid volume in the abdomen than in the control group (53 % vs 17 %, P value 0.01). This finding is correlated with a more advanced disease status. In the study group there was a highly statistically significant 3-fold increase in rupture among cases ($P < 0.005$) and a 4-fold larger volume of blood in the entrance to the abdomen ($P < 0.002$). We found that there were no cases of ruptured EP in the group of women who were pregnant after assisted reproduction.

Conclusion: We found a higher rate of ruptured ectopic pregnancies in our institution during the COVID-19 pandemic. Health care providers should be alerted to this collateral damage in the non-infected population during the COVID-19 pandemic.

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Introduction

In an ectopic pregnancy (EP) there is implantation outside the uterus; in about 95 % of cases this occurs in the Fallopian tubes [1]. The incidence of ectopic pregnancy is about 1% in women aged 24–44, and in Western countries 85 % of cases are detected before they present with a rupture [2]. If not diagnosed at an early stage, it can lead to a gynecological emergency with substantial bleeding into the abdomen, hypovolemic shock and maternal death [3,4].

Due to this being a life-threatening condition, treatment was traditionally surgical [5]. In the late 1980s, early diagnosis of tubal pregnancy, with the aid of serum human chorionic gonadotropin (β -hCG), high-resolution ultrasound, and the more liberal use of laparoscopy, has dramatically reduced both maternal mortality and the need for radical surgery. Furthermore, the diagnosis of the condition before the onset of severe symptoms allows for a conservative approach of medical treatment, especially with methotrexate administration or expected management. The benefits of drug treatment and surgical avoidance are many and clear [5–7].

Medical treatment is most efficient in the early stages of pregnancy. The longer the ectopic pregnancy continues, the greater the risk of complications such as massive bleeding, complicated surgery, the need for blood transfusion and occasionally maternal death [8,9].

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At the end of 2019, the COVID-19 pandemic evolved in China and subsequently spread worldwide [9]. In Israel, the first COVID-19 case was diagnosed on 21 February 2020 and accordingly the Israeli Ministry of Health published restrictions on individuals entering the country from abroad. From the beginning of March onwards strict restrictions on movement and gathering were introduced and on 23 March full lockdown was imposed. Between 15 March and 15 June, 19,315 people were infected and 302 died of COVID-19. In order to stop the spread of the virus, the public was instructed to stay at home and go out only for essential needs.

Whilst obtaining medical services was defined as an essential need, nonetheless, there was a decrease in ambulatory procedures and hospitals reported a decrease in emergency room arrivals.

We therefore carried out a study to assess whether this change in behavior caused a delay in the diagnosis and treatment of ruptured EP and increased the likelihood of ruptured ectopic pregnancy.

Methods

All women diagnosed with a tubal EP at Shamir Medical Center between 15 March and 15 June 2020 (cases) were identified from a computerized database. For comparison, those diagnosed in the same three-month period in 2018 and 2019 were also identified (controls). All diagnoses were made in our center, on the basis of ultrasound findings and maternal blood β -hCG level and all cases of ruptured ectopic pregnancy were confirmed by surgery.

For each EP, information was collected from clinic records on: obstetric background - maternal age, parity, gravidity, assisted reproduction, EP risk factors and gestational age (GA) based on menstrual dates; findings at presentation to the emergency room (ER) - clinical, laboratory and sonographic; and treatment - modality, operational findings, estimated blood loss, administration of blood products, post-operative care, complications and number of hospitalization days. Intraoperative findings were extracted from the operation report written immediately after surgery. Risk factors for EP are previous EP, past pelvic inflammatory disease (PID) or intra-uterine device (IUD) in situ.

The treatment modality was selected on the basis on our department's policy and by patient preference when immediate surgery was not indicated. All women who were hemodynamically unstable, had sonographic findings demonstrating increased free fluid in the abdomen, empty uterus and findings on either side of the pelvis consistent with a ruptured ectopic pregnancy, those with a fetal heartbeat at presentation or β -hCG level above 5000 iu/mL had laparoscopic surgery. All others were a choice between expectant management, methotrexate IM and laparoscopic salpingectomy.

Statistical analysis was performed using SPSS software (SPSS Inc., Chicago, IL, USA, version 25, Chicago, IL, USA). The descriptive statistics for continuous variables were the mean and standard deviation; and the Wilcoxon Rank Sum Test was used for comparisons between cases and controls. Frequencies were compared using the Chi-square test and Fisher's exact test. A P-value < 0.05 was considered statistically significant.

The study was approved by the local institutional review board (registration number 0146-20-ASF)

Results

The study group included 19 cases of ectopic pregnancy that were treated in our department between the 15 March 2020 and 15 June 2020. The control group included 30 cases of EP that were admitted to our department in the corresponding period during 2018 and 2019: 13 cases in 2019 and 17 cases in 2018.

Table 1
Obstetric background of cases and controls.

	Cases N = 19	Controls N = 30	P-value
Maternal age (years)	32.4±6.02	32.3±4.97	0.76
Gravidity	2.47 ± 1.61	3.13±1.81	0.20
Parity	1.32 ± 1.52	1.13 ± 1.13	0.89
Assisted conception	3 (16 %)	5 (17 %)	0.91
EP risk factors	5 (28 %)	2 (7%)	0.04
Gestation age* (weeks)	6.5 ± 1.54	6.3±1.15	0.70
Pregnancy confirmed (weeks)	5.06 ± 5.75	6.86 ± 6.55	0.26
Prior ultrasound	2 (10 %)	16 (53 %)	0.01

* Based on menstrual dates.

Table 1 compares the obstetric background in cases and controls. Maternal age, parity, gravidity and mode of conception (natural vs. assisted) were similar between the two groups. There was no difference in the mean GA according to last menstrual period reported by the patient. We also did not find a difference in the mean GA at which the patient first discovered that she was pregnant (according to her report on arrival). In the study group there was a higher rate of women with at least one EP risk factor (28 % vs. 7%, $P < 0.04$) and fewer had an ultrasound examination prior to hospitalization (10 % vs. 53 %, $P = 0.01$).

The clinical and laboratory findings upon arrival to the ER were similar between the two groups (Table 2). In both groups most women presented with at least one symptom - vaginal bleeding or abdominal pain. Unfortunately, we do not have data regarding how long women experienced symptoms before seeking medical help, but we found that in the study group more women presented with sonographic evaluation of high amounts of free fluid in the abdomen than in the control group (53 % vs 17 %, $P < 0.01$). This finding is correlated with more advanced disease status.

In the cases group, there was a larger proportion of cases which had laparoscopic surgery and none was treated with expectant management, although this difference did not reach statistical significance. There was a significant 3-fold increase in tubal rupture among cases ($P < 0.005$) and a 4-fold larger volume of blood in the entrance to the abdomen ($P < 0.002$). Nonetheless the mean number of hospitalization days was similar in both groups (Table 3, Fig. 1).

Table 4 shows the details of 8 women who conceived after assisted reproduction (in vitro fertilization or ovulation induction) - 3 in the study group and 5 in the control group. None of the women who conceived after assistant reproduction presented to the ER with rupture EP. Only one patient had a β -hCG levels above 5000 iu/mL, which by our department protocol is an indication for laparoscopy rather than pharmacologic therapy. All other patients

Table 2
Clinical, laboratory and ultrasound findings at presentation among cases and controls.

	Cases N = 19	Controls N = 30	P value
Clinical			
Abdominal pain	12 (63 %)	13 (43 %)	0.18
Vaginal bleeding	10 (53 %)	19 (63 %)	0.33
Heart rate	92.89 ± 19.85	85.07 ± 11.86	0.204
Blood pressure systolic	102 ± 12	112 ± 12	0.46
Blood pressure diastolic	64.83 ± 11.49	68.63 ± 11.88	0.04
Laboratory			
β -hCG level (iu/mL)	8141 ± 4998	4032 ± 2390	0.12
HB (units)	12.66 ± 1.34	12.3 ± 1.93	0.88
Ultrasound			
Complex mass	16 (84 %)	22 (73 %)	0.63
Heartbeat	2 (11 %)	1 (3.7 %)	0.55
Increased abdominal fluid*	10 (53 %)	5 (17 %)	0.01

* Estimated by the physician during the ultrasound examination.

Table 3
Treatment and outcome in cases and controls.

	Cases N = 19	Controls N = 30	P value
Management			
Expectant	0	6 (20 %)	0.11
Methotrexate	6 (33 %)	10 (33 %)	
Laparoscopic surgery	13 (68 %)	14 (47 %)	
Rupture	11 (58 %)	5 (17 %)	0.005
Blood in abdomen (ml) *	248±297	1129±922	0.001
Hospitalization (days)	2.26±1.15	2.9±1.03	0.049

* Estimated by surgeon during the operation.

could choose between surgical and pharmacologic therapy according to their personal preference. The patient who refused surgery was hospitalized for further supervision and evaluation, and she was operated on without complication after rupture occurred during hospitalization.

Discussion

We found a higher rate of ruptured tubal EP in our department during the COVID-19 pandemic than in the past (58 % vs. 17 %, $P < 0.005$). Only 2 (10 %) women in the study group, as oppose to 16 (53 %) women in the control group reported that they had an ultrasound examination prior to the day of hospitalization (some had an ultrasound examination earlier that day after which they

were referred to the ER). Most women in both groups experienced symptoms of vaginal bleeding or abdominal pain before hospitalization, which emphasizes the fact that most diagnoses of EP are made after the patient is symptomatic rather than on routine examination of asymptomatic patients. Although we do not have data regarding how long patients experienced the symptoms before hospitalization in our institute, we believe that women during the COVID-19 pandemic tended to wait longer after the appearance of symptoms before seeking medical help. The fact that most women in the study group did not have any ultrasound examination prior to admission raises even more concern considering that the group included more women with at least one risk factor for EP (past EP, past PID or IUD in situ).

There were no cases of ruptured EP among those with assisted reproduction; moreover, all but one of them were suitable for medical therapy (stable, low β -hCG levels and no fetal heartbeat) and could choose which treatment modality they preferred. We believe that the absence of rupture in such patients is explained by frequent medical observation and high patient awareness, which led to earlier detection and more simple treatment. This emphasizes the importance of patient and doctor alertness, combined with available medical treatment, in preventing rupture EP.

The Royal College of Obstetricians & Gynecologists published guidelines for antenatal screening in pregnancy during the evolving COVID-19 pandemic. Those guidelines instructed the physicians to give medical care on-line or by phone whenever possible [10].

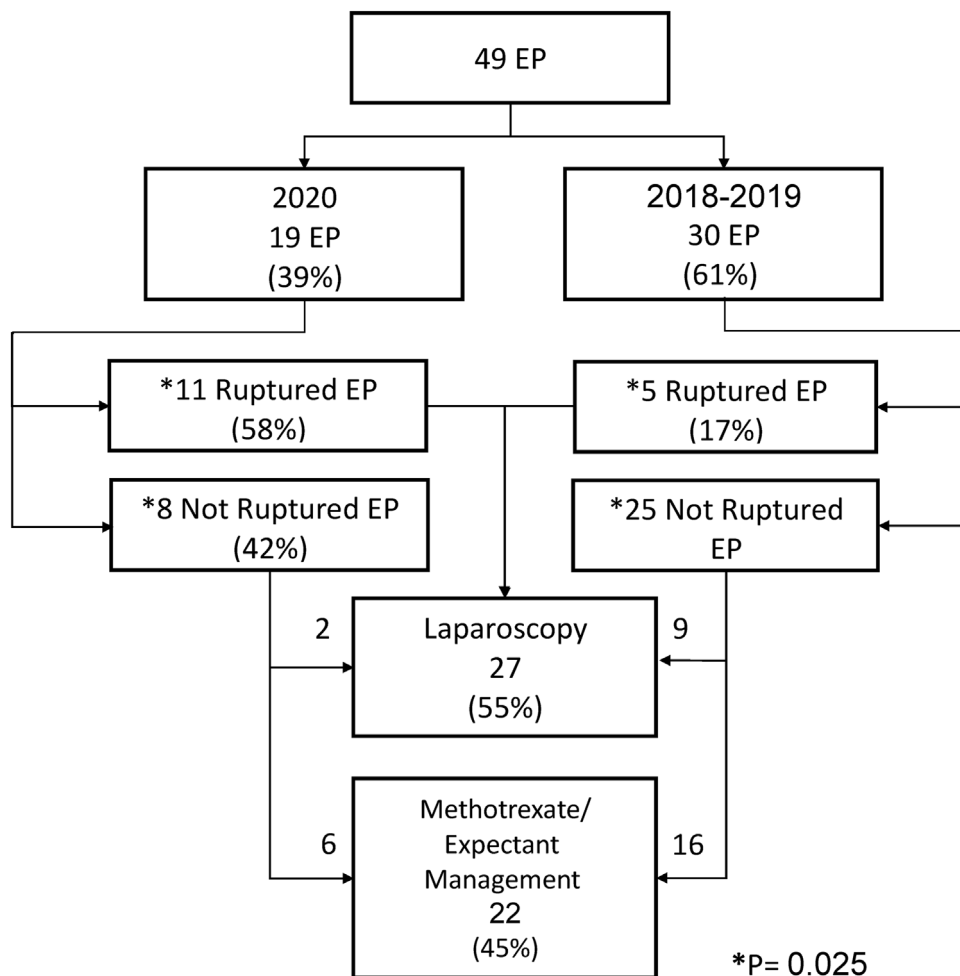


Fig. 1. Distribution of patients by year, presentation and treatment modality.

Table 4
Description of patients who conceived after assisted reproduction (ovulation induction/in vitro fertilization).

	Maternal age (years)	Obstetrical history	Conception	Gestational age*	β -hCG levels (iu/mL)	Rupture on admission (yes/no)	Treatment modality
Study (COVID-19 pandemic)							
1	27	Gravida 1, Para 0	Ovulation induction	6.6	789	NO	Methotrexate
2	33	Gravida 2, Para 1	In vitro fertilization	7.4	1931	NO	Methotrexate
3	40	Gravida 1, Para 0	In vitro fertilization	5.5	4138	NO	Laparoscopy
Control							
4	24	Gravida 3, Para 0	Ovulation induction	6	477	NO	Methotrexate
5	34	Gravida 1, Para 0	In vitro fertilization	5.1	3206	NO	Laparoscopy
6	37	Gravida 3, Para 0	In vitro fertilization	6.3	5030	NO	Laparoscopy- refused surgery on admission and developed ruptured EP during hospitalization
7	35	Gravida 4, Para 2	In vitro fertilization	5	1825	NO	Methotrexate
8	27	Gravida 1, Para 0	In vitro fertilization	6.1	1307	NO	Laparoscopy

* at embryo transfer based on last menstrual period.

We believe that some reduction in the availability of medical services and women's fear of possible exposure influenced them to reduce their medical care and checkups. Our study is in line with other reports showing reductions in emergency medical services during the COVID-19 epidemic in January-April 2020 [11,12].

In Italy, Lazzerini et al. described a substantial reduction in pediatric emergency department visits during March 2020 compared with previous years, which resulted in poor outcomes in many cases with delayed arrival to medical care. While pediatric emergency room visits may drop during a pandemic due to decreased contact between children, causing fewer infection transmission and less trauma, the obstetrical field should not be affected or expect less visits [13].

Several studies have addressed the impact of political and health crises on the quality of health care. Much of the failure to achieve the health goals set by the World Health Organization in third world countries is attributed to different kinds of crises. During a political or health crisis, women are less likely to seek health care [14,15]. In 2003 in Hong Kong following the SARS epidemic, 75 % of the population reported that they refrained from medical examination due to fear of infection [16].

Our study did not find a difference in the mean gestational age at which the diagnosis of ectopic pregnancy was made. This is not surprising mainly because ruptured ectopic pregnancy can occur at any GA [17,18]. During the COVID-19 pandemic, patients who knew they were pregnant avoided first trimester antenatal examinations, including a serum blood test and sonography evaluation, which accounts for a higher rate of ruptured ectopic pregnancy. It is usual for women with early pregnancy symptoms like vaginal bleeding or abdominal pain to seek medical counseling. We assume that because of COVID-19, there was a delay between the onset of symptoms and seeing a doctor, and this caused a higher rate of rupture independently of the GA at diagnosis [2].

The importance of the current study is being, to the best of our knowledge, the first to emphasize the influence of COVID-19 on an increased rate of rupture in ectopic pregnancy.

The strengths of our study lie in it being a single center study, with uniform data documentation, diagnostic criteria and management. All the cases of ruptured ectopic pregnancy were diagnosed during laparoscopy which minimizes the chance for selection bias.

Our study has some limitations. This is a retrospective study with limited data available for some parameters, such as duration and severity of symptoms before arriving to the ER and the availability of medical care according to local residence or doctor (for example- if their permanent doctor was unavailable because of quarantine). Another major limitation of our study is the small population size. Moreover, it is not impossible that some cases of ectopic pregnancies that occurred during the COVID-19 pandemic were not in fact included in our study because they presented only after the study period.

We believe that although the numbers are small the trend is obvious. The COVID-19 pandemic may last for a while and health care providers should encourage their patients to seek medical assistance when needed.

Conclusion

We found a higher rate of ruptured ectopic pregnancies in our institute during the COVID-19 pandemic.

This is usually an avoidable life-threatening early pregnancy complication. It should be carefully looked at by health care providers who should do their utmost to combat this collateral damage in the non-infected population during the COVID-19 pandemic.

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Declaration of Competing Interest

None.

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