



Contents lists available at ScienceDirect

The Lancet Regional Health - Europe

journal homepage: www.elsevier.com/lanepe

Research paper

Effects of the COVID-19 pandemic on timely care for extrauterine pregnancies: A retrospective analysis

Matan Anteby, Liel Van Mil, Nadav Michaan, Ido Laskov, Dan Grisaru*

Gynecologic Oncology Department, Tel Aviv Sourasky Medical Center, Sackler Faculty of Medicine, Tel Aviv University, 6 Weizmann Street, Tel Aviv 64239, Israel

ARTICLE INFO

Article History:

Received 9 November 2020

Revised 17 December 2020

Accepted 4 January 2021

Available online 13 January 2021

ABSTRACT

Background: The COVID-19 pandemic may have taken a toll upon the rate of extrauterine pregnancy (EUP)-related admissions and emergent surgeries.

Methods: This retrospective study compared current and past visits to the emergency services of a large metropolitan university-affiliated medical center in Tel-Aviv, Israel. Data on EUP-related and regular early pregnancy care-related presentations to the emergency department (ED) during the COVID-19 pandemic were collected and compared to a historical control group admitted during 2018-2019. The primary outcome was the rate of ruptured EUP. Secondary outcomes included the rate of EUPs requiring surgery, symptoms, blood products, blood loss, embryonic heart rate, β -HCG levels, and intensive care unit transfer.

Findings: During the COVID-19 pandemic there was a 28.3% reduction in women seeking early pregnancy and emergent gynecological medical care. ED visits due to suspected EUP were similar: the study group comprised of 100 women and the combined control group from previous years included 208 women with confirmed EUP. Baseline maternal characteristics were similar between the groups. The rate of ruptured EUP's was significantly more common during the COVID-19 pandemic than in previous years [odds ratio (OR) 2•403 (1•272–4•539), $p = 0•006$]. Moreover, during the pandemic patients admitted due to EUP were significantly more symptomatic [OR 1•815 (1•072–3•074), $p = 0•017$] and had more blood loss demonstrated as substantial hemoglobin decline [OR 2•441 (1•07–5•565), $p = 0•028$] as well as hemoperitoneum during surgery [OR 2•672 (1•095–6•52), $p = 0•035$]. The number of women receiving blood products was higher in the study group yet not reaching statistical significance [7% vs 3•4%, OR 2•161 (0•737–6•339), $p = 0•128$]. The overall rate of surgically treated EUP was similar between the groups [OR 1•070 (0•660–1•734), $p = 0•439$] and there was no significant difference in non-surgical management.

Interpretation: The COVID-19 pandemic has a toll on early pregnancy emergent care due to EUP with a significantly higher risk of tubal rupture and morbidity. Physicians should expect delayed presentation of symptomatic EUP and act accordingly.

Funding: This research received no funding.

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1. Introduction

Since the novel coronavirus disease (COVID-19) outbreak in China and the declaration of a pandemic by the World Health Organization on March 11, 2020 [1], the lives of billions worldwide have been affected. As of October 2020, COVID-19 has taken the lives of more than one million people. Israel has one of the highest fatality rates in the world, with over 183 deaths per million people as to October 2020 [2]. Two major two-week lockdown periods were decided upon by the Israeli government in April and September 2020. During these lockdowns no major restrictions regarding seeking emergent and

pregnancy related medical care were issued. Social distancing in combination with basic hygiene habits are commonly being applied to avoid COVID-19 infection. In fear of contacting the disease, some have been distancing themselves to the extent of avoiding medical care. This has taken a toll on emergent non-COVID-19-related visits to the emergency department (ED) and, as such, on non-COVID-19-related deaths [3].

Extrauterine pregnancy (EUP) is a life-threatening condition, which occurs in approximately 1–2% of all pregnancies [4,5] and accounts for 2•7% of pregnancy-related mortality [6]. Deaths usually result from rupture of the fallopian tube leading to internal bleeding. Risk factors for EUP have been studied in depth in the medical literature [7–10], and they include a previous EUP, in vitro fertilization (IVF), mechanical obstruction of the fallopian tubes due to previous

* Corresponding author.

E-mail address: grisaru@tauex.tau.ac.il (D. Grisaru).

Research in context

Evidence before this study

As of October, 2020, our search of PubMed using keywords "COVID-19" OR "SARS-CoV-2" AND "ectopic pregnancy" OR "extrauterine pregnancy" yielded 5 articles in English. Only one addressed the difference in extrauterine pregnancy (EUP) during the COVID-19 pandemic- a report from Italy on the first months of the Italian lockdown. Described were only 16 cases with EUP, of which 11 underwent urgent laparoscopy. There was no difference in the rate of this procedure between the study group and a control group.

PubMed was then searched for "COVID-19" AND "surgery" which yielded more than 8000 articles, most were irrelevant to our study. The toll the COVID-19 pandemic has on non-COVID-19-related morbidity and mortality was addressed in medical journal editorials and studied mainly in the field of cardiology and general surgery. Although a previous multicenter report showed a reduction in acute appendicitis during the pandemic, two larger studies reported a significant increase in perforated and gangrenous appendicitis due to delay of care.

Added value of this study

The largest to address the collateral effect of COVID-19 on the rate and severity of ectopic pregnancies.

All Emergency department visits due to suspected EUP during the current COVID-19 pandemic were identified and collected. Data were gathered from case files during the COVID-19 pandemic starting with the first Israeli to be infected on February 27, 2020 until September 27, 2020. All suspected EUP visits to the ED during the pandemic were analyzed (after exclusion, $n = 100$) and compared to a historical control group that included 206 patients treated for suspected EUP at our department in the same seven-month period during 2018 and 2019.

Our primary outcome, the rate of ruptured EUPs diagnosed in the operating room was significantly higher during the COVID-19 pandemic. Secondary outcomes reaching statistical significance were higher likelihood of symptoms upon arrival as well as a more substantial blood hemoglobin decline and hemoperitoneum.

Implications of all the available evidence

Findings from this article show that the COVID-19 pandemic has taken a toll on early pregnancy emergent care of women with EUP. It is crucial that obstetricians and gynecologists become proactive when it comes to early pregnancy diagnosis and anticipate delayed presentation of women with symptomatic EUP.

Our working hypothesis was that the COVID-19 pandemic may compromise non-COVID-19-related admissions to the hospital and especially impact early pregnancy care. The importance of diagnosing the exact location of the pregnancy, especially in these troublesome times, was highlighted by the latest International Society of Ultrasound in Obstetrics & Gynecology consensus statement[13]. To the best of our knowledge, only one report on the effect of the COVID-19 pandemic on the rate of emergent surgeries due to EUP has been published thus far [14]. That single-center Italian study showed a 20% reduction in EUP-related hospital admission, but it assessed only 16 women in a four-month timeframe. Our objective in this report was to assess the toll this pandemic has taken upon the rates of EUP-related ED admissions and emergent surgeries in comparison to the pre-pandemic era. We aimed to investigate differences in specific parameters related to EUP pregnancies between the two time periods.

2. Methods

This study was conducted at a university-affiliated, tertiary medical center in Tel Aviv, Israel, which averages approximately 12 thousand births per year. It was approved by our local institutional review board (IRB #0840-20-TLV) which waived informed consent for the retrospective analysis.

All ED visits due to suspected EUP during the current COVID-19 pandemic were identified and collected. Data were gathered from case files during the COVID-19 pandemic starting with the first Israeli to be infected on February 27, 2020 until September 27, 2020. All suspected EUP visits to the ED during the pandemic were analyzed and compared to a historical control group that included patients treated for suspected EUP at our department in the same seven-month period during 2018 and 2019. Medical files were reviewed for patient characteristics and demographics. We focused upon the modality of treatment during hospitalization and the outcomes of any surgery that had been performed.

Inclusion criteria were women aged 18–50 years who were admitted to our medical center and assessed for tubal EUP. Diagnosis was made after serial US examinations as well as abnormal serum β -HCG increment. Treatment during the study and control periods was given according to our department algorithm (previously reported upon by Levin et al.[11]) with either expectant management, MTX, or surgery according to patient's medical history, physical examination, hemodynamic stability, beta unit of human chorionic gonadotropin (β -HCG) levels, and US findings. Women were followed from admission, through the course of treatment, and up to resolution of the pregnancy. After their discharge, they attended the outpatient clinic where their β -HCG levels were measured and additional necessary US examinations were carried out until final pregnancy resolution. We excluded patients with a suspected EUP but who were later diagnosed as having an intrauterine pregnancy. Also excluded were surgical scar and cervical EUPs due to the difficult diagnosis and their lack of a uniform modality of treatment decision tree.

Our primary outcome was the rate of ruptured EUPs diagnosed in the operating room. Secondary outcomes included the rate of EUPs requiring surgical intervention, symptomatic patients at arrival (bleeding or abdominal pain), need for blood product transfusions, substantial blood loss (defined as a >3 gr/dl decline in hemoglobin levels from arrival until discharge), hemoperitoneum (at least 1000 ml of blood assessed by the surgeon), ectopic embryonic heart rate identified by US, intensive care unit (ICU) transfers, as well as the β -HCG levels upon admission and peak levels. .

2.1. Statistical analysis

Demographic, medical, and obstetrical characteristics of the women in the study and control groups were compiled and

abdominal surgeries or pelvic inflammatory disease, cigarette smoking, and older age. The management of suspected EUP in a hemodynamically stable patient may include watchful waiting or treatment with methotrexate (MTX). Recent reports[11,12] showed that up to one-half of EUPs may be managed expectantly with watchful waiting. MTX treatment has a high success rate, estimated at 87%[12]. At present, surgery is not the first line of treatment in the stable, asymptomatic patient, but rather indicated in cases of failed MTX treatment, EUP with visible embryonic heart rate on ultrasound (US), and recurrent EUP in the same fallopian tube. A ruptured tubal pregnancy with hemoperitoneum is a potentially life-threatening medical emergency and should be treated as soon as possible in the operating room, usually with a salpingectomy.

compared. Normally distributed variables were analyzed utilizing student *T*-test. Non-parametric variables were analyzed with the Mann–Whitney *U* test for continuous data and Fisher’s exact test for non-continuous data, in which effects were expressed as odds ratios and 95% confidence intervals. The effect of continuous variables was expressed as differences in means or medians. Separate univariate analyses were conducted for each potential predictor of EUP outcome. Significance was set at the conventional 5% level. The statistical analysis was conducted with IBM SPSS Statistics for Windows, version 22 (IBM Corp., Armonk, N.Y., USA).

2.2. Role of the funding source

No funding was received for this work.

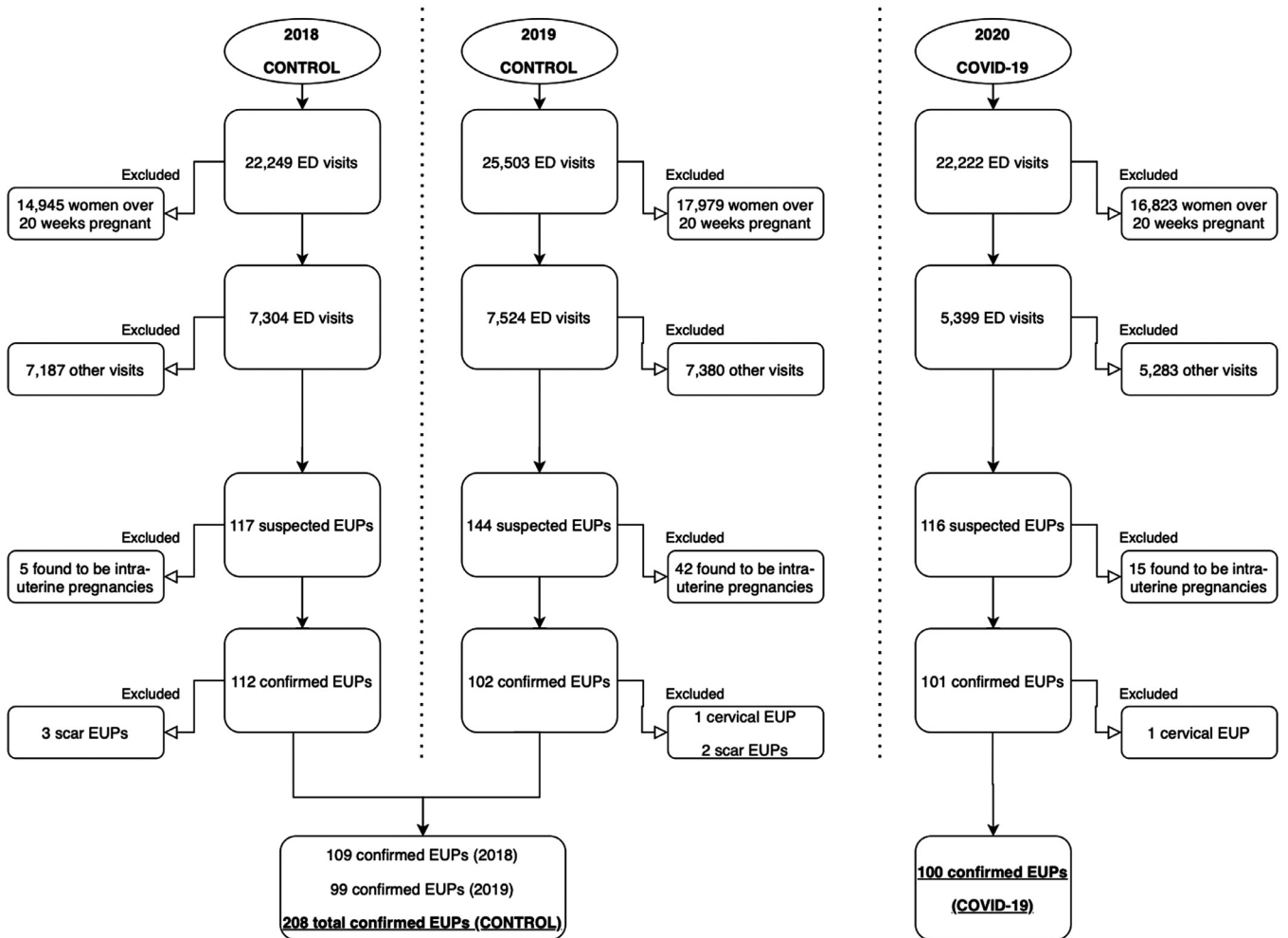
3. Results

During the seven-month study period (February 27, 2020 to September 27, 2020), a total of 22,222 women sought treatment in our obstetrics and gynecology hospital’s ED compared to 22,249 women in the same time frame during 2018 and 25,503 in 2019. The number of live births in our institution at this specific time frame was 6,794, 7,390, and 5677 during 2018, 2019, and 2020, respectively. After excluding women with over 20 weeks’ gestation, we observed a 28.3% reduction in women seeking early pregnancy and other

gynecological emergent medical care in our ED in the 2020 study period (*n* = 5399) compared to 2019 (*n* = 7524), and a 26•1% reduction compared to 2018 (*n* = 7304). However, admission rates due to suspected EUP were similar: there were 116 cases during the COVID-19 period vs 117 cases in the 2018 group and 144 cases in the 2019 group. After excluding cases eventually diagnosed as having an intra-uterine pregnancy or those with a non-tubal EUP, the final study (pandemic) group was comprised of 100 women and the combined control group (from 2018 and 2019) included 208 women with confirmed EUP, 13•8 mean cases per 30 days versus 14•3, respectively (Fig. 1).

The baseline maternal characteristics were similar between the study and the control groups (Table 1). The mean age of women at admission in both groups was 33 years. Approximately one-half of the women in each group were nulliparous (49% in the study group and 44•2% in the control group). Roughly one in every four EUP admissions was an IVF pregnancy (25% study, 21•6% control). A little over one in every ten women had sustained a previous EUP (10•6% study, 13% control), 11 of whom had more than one previous EUP (five study, six control).

Outcomes are described in Table 2. The primary outcome, rate of ruptured EUPs was significantly more common during the COVID-19 pandemic than in previous years [OR 2•403 (1•272–4•539), *p* = 0•006]. Nonetheless, the overall rate of surgically treated EUPs (laparoscopic salpingectomy) was similar between the groups



COVID-19- novel corona virus disease 19; ED- emergency department; EUP-extrauterine pregnancy; scar- cesarean section uterine scar

Fig. 1. Flowchart of visits the obstetrics and gynecology emergency department.

Table 1
Baseline characteristics of women with an extrauterine pregnancy.

	COVID-19 period (n = 100)	2018-2019 (n = 208)	p value
Age (years)	33•26 ± 5•25	33•5 ± 4•69	0•645
Nulliparous	49 (49%)	92 (44•2%)	0•253
IVF	25 (25%)	45 (21•6%)	0•301
Previous EUP	13 (13%)	22 (10•6%)	0•327
Previous PID	6 (6%)	7 (3•4%)	0•216
IUD	2 (2%)	13 (6•3%)	0•085

Group data are n with available data (%) or mean ± standard deviation.
COVID-19= novel coronavirus disease 19; IVF= in vitro fertilization; EUP= extrauterine pregnancy; PID= pelvic inflammatory disease; IUD= intrauterine device

[OR 1•070 (0•660–1•734), $p = 0•439$]. There was no significant difference in the rate of EUPs that resolved spontaneously with expectant management [OR 1•222 (0•721–2•073), $p = 0•27$]. No significant change was noted in the number of women treated with MTX [OR 0•654 (0•391–1•093), $p = 0•066$] with an approximate 90% success rate in both groups.

As to the secondary outcomes: Women who had been admitted due to a confirmed EUP during the COVID-19 pandemic were significantly more symptomatic at arrival [OR 1•815 (1•072–3•074), $p = 0•017$] and had more substantial blood loss demonstrated by >3 gr/dl decline in hemoglobin [OR 2•441 (1•07–5•565), $p = 0•028$] and more patients presenting with hemoperitoneum (>1000 ml) during surgery [OR 2•672 (1•095–6•52), $p = 0•035$]. The number of women receiving blood products was higher in the study group, albeit not statistically significant [7% vs 3•4 %, OR 2•161 (0•737–6•339) $p = 0•128$].

β -HCG levels, both at arrival and at their peak level during hospitalization, were not significantly different between the groups. Upon arrival, 12% of the women in the study group had an apparent embryonic pulse in the ectopic site. This finding was also more frequent than in previous years (7•2%) although not found to be significant [OR 1•755 (0•788–3•904) $p = 0•121$]. All but two of the EUPs with a visible heart rate were symptom-free and treated with uneventful surgery. Only one woman, from the control group, was admitted to the ICU.

4. Discussion

In the present study we have shown that women with EUP who arrived at the ED during the pandemic were significantly more

symptomatic, and had a higher risk of a ruptured ectopic pregnancy as well as a more substantial blood hemoglobin decline and hemoperitoneum. We could not demonstrate a difference before and during the pandemic, in the number of women with EUP who required blood products, those with a visible ectopic embryonic heart rate on US, or the ratio between surgical treatment, MTX treatment, or expectant management.

The toll this pandemic has on non-COVID-19-related morbidity and mortality has been addressed in medical journal editorials[15] and studied mainly in the field of cardiology[16] and general surgery [17–19]. In their large multicenter analysis, Garcia et al.[16] demonstrated a significant reduction in ST-elevation myocardial infarction-related catheterization since the COVID-19 outbreak, which may possibly be due to patients' reluctance to seek timely medical care while risking exposure to the virus. Although a previous multicenter report showed a reduction in acute appendicitis during the pandemic[19], two larger studies reported a significant increase in perforated and gangrenous appendicitis due to delay of care[17,18]. We suspect that our results support the same trend of greater morbidity due to delayed medical care. This delay was not due to any government regulations or prohibitions. While fertility clinics withheld most treatments during April-June 2020, early pregnancy clinics, both public and private, worked as before during the pandemic and the reluctance to seek medical care is presumed to stem from patients' fear of socializing. It is noteworthy that the reduction in ED arrivals in our maternity hospital during the pandemic became apparent only after excluding women seeking medical assistance after 20 weeks of gestation. Despite the 28•3% reduction seen in our non-EUP cases, ED presentations due to EUP remained unchanged. Therefore, we can

Table 2
Extrauterine pregnancy outcomes.

	COVID-19 period (n = 100)	2018-2019 (n = 208)	Odds Ratio (95% CI)	p value
Ruptured EUP	23 (23%)	23 (11•1%)	2•403 (1•272–4•539)	0•006**
Symptomatic at admission	74 (74%)	127 (61•1%)	1•815 (1•072–3•074)	0•017*
β -HCG (U/l) at arrival median (IQR)	1233 (2019) (n = 88)	847 (1546) (n = 190)	••	0•14
β -HCG (U/l) peak level median (IQR)	1296 (2470) (n = 88)	1071 (2140) (n = 190)	••	0•55
EUP with visible heart rate	12 (12%)	15 (7•2%)	1•755 (0•788–3•904)	0•121
Spontaneous resolution	30 (30%)	54 (26%)	1•222 (0•721–2•073)	0•270
MTX	29 (29%)	80 (38•5%)	0•654 (0•391–1•093)	0•066
Surgery	43 (43%)	86 (41•3%)	1•070 (0•660–1•734)	0•439
Hemoglobin decline >3 gr/dl	13 (13%)	12 (5•8%)	2•441 (1•070–5•565)	0•028*
Hemoperitoneum during surgery (≥ 1000 MI)	13/43 (30%)	12/86 (14%)	2•672 (1•095–6•52)	0•035*
Need for blood products	7 (7%)	7 (3•4%)	2•161 (0•737–6•339)	0•128
ICU transfer	0 (0%)	1 (0•48%)	••	••

Group data are n with available data (%), median (IQR). Effects are presented as odds ratios (95% confidence interval).

ICU transfer- due to only one patient no analysis was performed

* $p < 0•05$

** $p < 0•01$

COVID-19= novel coronavirus disease 19; β -HCG= beta unit of human chorionic gonadotropin; EUP= extrauterine pregnancy; MTX= methotrexate; ICU= intensive care unit; CI= confidence interval.

speculate that women with an early pregnancy, do seek medical care regarding the viability and location of their pregnancies, but with a considerable delay.

Although the rate of ruptured EUPs in this study increased during the COVID-19 pandemic period, it is interesting to note that the overall rate of EUP-related surgery did not rise respectively. A plausible explanation for this finding could lie in a shift towards watchful waiting and MTX treatment instead of surgery during the pandemic, however, our results showed that this was not the case as the number of spontaneous EUP resolution and MTX treatment was similar between the groups. β -HCG levels upon arrival to the ED were available for most of the women in both groups. All of the cases without recorded β -HCG levels had been treated with surgery, and most of them were diagnosed with a ruptured EUP and substantial hemoglobin decline (8/12 in the study group vs 11/18 in the control group). This may serve to explain the similar β -HCG levels for available cases upon admission and at their peak level during hospitalization.

Dell'Utri et al.[15] recently analyzed emergent gynecological and obstetrical admissions in Milan, Italy during a four-month period. They described 16 cases of EUPs, of which 11 underwent urgent laparoscopy. There was no difference in the rate of this procedure between the study group and a control group.

To the best of our knowledge, our current study is the largest to address the collateral effect of COVID-19 on the rate and severity of ectopic pregnancies. It is also the only one that demonstrated an indirect negative effect of the pandemic on this population. Case files were not only sought through ICD coding, but also manually inspected. The historical control group was comprised of women who were treated during the same time period of two previous consecutive years. By doing this, we avoided changes in rate due to seasonal or holiday effects on the rates of ED visits due to EUP. The lack of difference in patient characteristics (Table 1) supports this assumption.

This study's main limitation is its retrospective design. Although it is assumed that COVID-19 did not have a direct effect on the pathogenesis of EUP, this has not been tested in prospective studies or clinical trials. We were unable to provide information about the number of women who were positive for COVID-19 during their stay at the hospital since mandatory testing prior to admission to our facility was introduced only by mid-September 2020 (until then, assessment of COVID-19 was done only for patients with suspected exposure or relevant symptoms). Nevertheless, as far as we know, none of the study patients contacted the virus during their admission or during follow-up. In addition, the choice of a historical control group may harbor uncontrollable variables, such as the change in EUP care throughout the years, although there had not been any significant changes in our departmental medical care during the relevant three-year period. Regardless, contemporaneous controls would not have been relevant for our specific study goals. We are aware that we may have missed cases of women who continued care in other medical centers and therefore were lost to follow-up. Hopefully, our out-patient clinic from which we also gathered medical information, made this limitation impertinent.

In conclusion, the COVID-19 pandemic has taken a toll on early pregnancy emergent care of women with EUP. This effect may persist and even intensify as authorities continue to recommend the avoidance of unnecessary human contact and to issue lockdowns and various prohibitions. Therefore, it is crucial that obstetricians and gynecologists become proactive when it comes to early pregnancy diagnosis and anticipate delayed presentation of women with symptomatic EUP.

Data sharing

Participant data collected during the trial as well as statistical analysis is available and can be shared by contacting the corresponding author following publication.

Contributors

M.A and D.G conceived of the presented idea and study design. M. A and L.V.M collected the data and analyzed it. D.G, I.L and N.M oversaw data collection and statistical analysis. M.A wrote the manuscript with input from D.G, I.L and N.M.

Declaration of Competing Interest

M.A, L.V.M, I.L, N.M and D.G have nothing to disclose.

Acknowledgment

Dr. Roi Anteby and Mrs. Ofra Reuven for statistical analysis
Mrs. Esther Eshkol for assistance with manuscript editing
This research received no funding.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.lanepe.2021.100026.

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