Ultrasound characteristics, serum biochemistry and outcome of ectopic pregnancies presenting during COVID-19 pandemic

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CONTRIBUTION

What are the novel findings of this work?
Gestational age at the first transvaginal sonography scan and at diagnosis, location, size, morphology and complication rate of ectopic pregnancies were similar in the year before (2019) and during (2020) the coronavirus disease 2019 (COVID-19) pandemic. Although the proportions of patients according to final management strategy were similar in 2019 vs 2020, we observed higher serum human chorionic gonadotropin levels and reduced success of initial conservative treatments in those managed during the COVID-19 pandemic.

What are the clinical implications of this work?
During the COVID-19 pandemic, women continued to access appropriate care for ectopic pregnancy, with no evidence of diagnostic delay, poorer outcome or increased complication rate. This is reassuring and suggests that changes in guidance designed to rationalize the management of early-pregnancy patients have not led to poorer outcome in women with ectopic pregnancy in our population.

ABSTRACT

Objective To describe and compare the characteristics of ectopic pregnancies (EPs) in the year prior to vs during the coronavirus disease 2019 (COVID-19) pandemic.

Methods This was a retrospective analysis of women diagnosed with an EP on transvaginal sonography conducted at a center in London, UK, providing early-pregnancy assessment, between 1 January 2019 and 31 December 2020. Women were identified via the Astraia ultrasound reporting system using coded and non-coded outcomes of EP or pregnancy outside the uterine cavity. Data related to predefined outcomes were collected using Astraia and Cerner electronic reporting systems. Main outcome measures included clinical, ultrasound and biochemical features of EP, in addition to reported complications and management.

Results There were 22,683 consultations over the 2-year period. Following consultation, a similar number and proportion of EPs were diagnosed in 2019 (141/12,657 (1%)) and 2020 (134/10,026 (1%)). Both cohorts were comparable in age, ethnicity, weight and method of conception. Gestational age at the first transvaginal sonography scan and at diagnosis were similar, and no difference in location, size or morphology of EP was found between the two cohorts. Serum human chorionic gonadotropin (hCG) levels at the time of EP diagnosis were higher in 2020 than in 2019 (1005 IU/L vs 665 IU/L; P = 0.03). The proportions of women according to type of final EP management were similar, but the rate of failed first-line management was higher during vs before the pandemic (16% vs 6%; P = 0.01). The rates of blood detected in the pelvis (hemoperitoneum) on ultrasound (23% vs 26%; P = 0.58) and of ruptured EP confirmed surgically (9% vs 3%; P = 0.07) were similar in 2019 vs 2020.

Conclusions No difference was observed in the location, size, morphology or gestational age at the first ultrasound examination or at diagnosis of EP between women diagnosed before vs during the COVID-19 pandemic. Complication rates and final management strategy were

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also unchanged. However, hCG levels and the failure rate of first-line conservative management measures were higher during the pandemic. Our findings suggest that women continued to access appropriate care for EP during the COVID-19 pandemic, with no evidence of diagnostic delay or an increase in adverse outcome in our population. © 2021 International Society of Ultrasound in Obstetrics and Gynecology.

INTRODUCTION

The World Health Organization (WHO) declared the coronavirus disease 2019 (COVID-19) a global pandemic in March 2020, having both direct and indirect impacts on UK healthcare provision. Emergency department attendance was reduced by 25% in the first week following government-imposed lockdown1,2. The British Medical Association estimated that there were 1.32–1.50 million fewer elective hospital admissions in April, May and June 2020, with planned services in May 2020 operating at 31% of the preceding 2018–2019 average3,4.

Both the Royal College of Obstetricians and Gynaecologists (RCOG) and the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) developed guidelines that aimed to rationalize early pregnancy and gynecological ultrasound service provision during the COVID-19 pandemic. Both advised that a scan should be carried out within 24 h for women with risk factors or symptoms associated with ectopic pregnancy (EP)4–6. In the event of an EP diagnosis, conservative management strategies were encouraged to minimize exposure to hospitals4. Surgery was recommended when no other management option was feasible5,7. For all patients, a policy of telephone triage was introduced in the UK before women were able to access a hospital for the assessment of early-pregnancy problems.

There are concerns that a fear of attending hospital due to the risk of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection may have led women to delay accessing care for early pregnancy and acute gynecological problems. Findings from Italy and Israel suggest higher rates of surgery, ruptured EP and blood loss in women with EP during vs before the COVID-19 pandemic8–10. In New York, USA, 83% of women with EP presenting to an emergency department during the first wave of the pandemic were hemodynamically unstable, requiring urgent surgical intervention, compared with 23.5% in the previous year11. From an obstetric perspective, delayed presentation to the emergency department and subsequent increase in the number of emergency interventions secondary to the pandemic have been described12.

We aimed to describe and compare the characteristics of EPs presenting to an early-pregnancy assessment center in Inner London, UK, during vs before the COVID-19 pandemic.

METHODS

Design and settings

This retrospective observational cohort study was performed at a dual center providing early-pregnancy and acute gynecological services in Northwest London, UK. All cases of EP for this study were identified on transvaginal sonography (TVS).

Relevant case records were identified via a search of the Astraia™ (Astraia Software GmbH, Ismaning, Germany) database over a 2-year period from 1 January 2019 to 31 December 2020, encompassing the time period prior to and during the COVID-19 pandemic, when the structure of our service was adapted according to national and international recommendations4–6. Search terms included a coded or non-coded diagnosis of EP or pregnancy outside the uterine cavity. Heterotopic pregnancies were included. Pregnancies were dated according to the last menstrual period or embryo transfer date.

Electronic case records were reviewed, and information related to predefined outcome measures was recorded as part of this retrospective analysis. The manuscript was written in accordance with the STROBE cohort study statement. The evaluated time period prior to the COVID-19 pandemic was between January 2019 and December 2019, and the time period during the COVID-19 pandemic was between January 2020 and December 2020.

In addition to delaying non-essential appointments, reducing follow-up appointments and reducing surgical management of miscarriage and EP, telephone triage was performed to rationalize service provision, in accordance with RCOG and ISUOG COVID-19 guidelines4–6. Measures were in place from January 2020 onwards, with the most stringent implementation between April 2020 and September 2020.

Outcome measures

Month of diagnosis, age, ethnicity, weight, mode of conception, gestational age at first TVS scan and at diagnosis, obstetric history, morphological and biochemical features of EP, admission and management were recorded.

Statistical analysis

Continuous data were assessed for normality using the D’Agostino–Pearson normality test. If data were distributed normally, a two-tailed t-test was performed, assuming both populations had similar SD. Normally distributed data are presented as mean with 95% CI. If data were not distributed normally, a two-tailed Mann–Whitney U-test was performed to compare ranks. Data with non-normal distribution are presented as median and interquartile range (IQR). Given the nature of the dataset and the study question, data were not paired.

Categorical data were analyzed using Fisher’s exact test when comparing one or two variables and using

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RESULTS

There were 21% fewer early-pregnancy and acute gynecological consultations during the COVID-19 pandemic compared to the previous year, with 12,657 consultations in 2019 compared to 10,026 in 2020 (Table 1). All consultations were face-to-face. The ratio of new (52%) to follow-up (48%) consultations was the same in both years (P = 0.88), with a lower proportion of blood tests performed in 2019 (2222 (18%)) vs 2020 (2184 (22%)) (P < 0.0001). There was no difference between 2019 and 2020 in the rates of miscarriage (18% vs 20%), pregnancy of unknown location (PUL) (7% vs 7%) or EP (1% vs 1%) observed in the unit (P = 0.38).

A total of 275 EPs were diagnosed in the 2-year period, including 141 (51%) cases in 2019 and 134 (49%) cases in 2020 (Table S1). Thirteen (9%) EP patients did not complete follow-up in 2019, and nine (7%) did not complete follow-up in 2020 (Table 1).

Women with EP diagnosed prior to and during the pandemic were comparable in age (mean (95% CI), 32.2 (31.2–33.3) vs 33.0 (32.1–33.9) years; P = 0.25), ethnicity (P = 0.74) and weight (median (IQR), 68.0 (59.0–76.0) vs 67.0 (59.0–76.8) kg; P = 0.74) (Table 2).

Method of conception was similar in 2019 vs 2020, with 126 (89%) vs 118 (88%) women conceiving naturally and 15 (11%) vs 16 (12%) women having assisted conception (P = 0.85). The majority of EP cases in both 2019 (89 (63%)) and 2020 (78 (58%)) were diagnosed on the first TVS examination, with the remainder having been classified initially as PUL in both groups (52 (37%) vs 56 (42%); P = 0.46).

History, sonographic and biochemical features

Thirteen (9%) patients in 2019 had a history of EP compared with 14 (10%) cases in 2020 (P = 0.84), with the majority having undergone surgical management (Table 3). The median (IQR) gestational age at the first TVS scan (41.0 (27.5–48.0) vs 38.0 (29.0–44.3) days; P = 0.13) and at diagnosis on TVS (42.0 (30.5–50.5) vs 41.0 (32.5–48.3) days; P = 0.34) were similar before and during the COVID-19 pandemic (Table 3 and Figure 1a,b). Both in 2019 and in 2020, most women had tubal EP (90% vs 93%; P = 0.67) (Table 3), with non-tubal cases including cornual, interstitial, myometrial, ovarian, cervical and Cesarean scar pregnancies.

EP size was documented by measuring the mean and largest diameters on TVS. There was no difference in the mean EP diameter (median (IQR), 15.3 (11.0–22.3) vs 14.7 (11.5–18.3) mm; P = 0.25) or largest EP diameter (median (IQR), 18.0 (13.0–24.1) vs 16.0 (13.0–22.0) mm; P = 0.22) in the period prior to vs during the pandemic (Table 3 and Figure 1c,d). In 2019 vs 2020, similar proportions of women had an inhomogeneous mass

| Characteristic | 2019 (n = 12,657) | 2020 (n = 10,026) | P |
|----------------|------------------|------------------|---|
| Face-to-face consultation | 12,657 (100) | 10,026 (100) | > 0.99* |
| New consultation | 6576 (52) | 5219 (52) | 0.88* |
| Follow-up consultation | 6081 (48) | 4807 (48) | 1.1:1 |
| Ratio of new to follow-up consultations | 1.1:1 | 1.1:1 | 0.38† |
| Blood test | 2222 (18) | 2184 (22) | < 0.0001* |
| Ratio of total consultations to blood tests | 5.7:1 | 4.6:1 | 15 (11%) |
| Natural | 126 (89) | 118 (88) | 0.46‡ |
| Assisted | 15 (11) | 16 (12) | 0.74‡ |
| PUL prior to EP diagnosis | 52 (37) | 56 (42) | 0.74‡ |
| EP diagnosis at first scan | 89 (63) | 78 (58) | 0.85¶ |

Data are given as mean [95% CI], n (%) or median (IQR), unless indicated otherwise. P-values were calculated using: *Fisher’s exact test; †chi-square test; ‡Mann–Whitney U-test; ¶Fisher’s exact test. PUL, pregnancy of unknown location.
(58% vs 60%), an empty gestational sac (26% vs 22%), a gestational sac containing only a yolk sac (9% vs 11%) and a gestational sac containing an embryo with cardiac activity (6% vs 6%) detected on ultrasound ($P = 0.62$). Hemoperitoneum was seen on TVS in 23% of cases in 2019 and in 26% of cases in 2020 ($P = 0.58$), with similar median (IQR) deepest pool measurements (41.8 (31.1–51.4) vs 40.1 (28.5–54.5) mm; $P = 0.81$) (Table 3).

For all cases with EP, median (IQR) serum human chorionic gonadotropin (hCG) levels were lower in 2019 compared to 2020 (665 (224–2330) vs 1005 (412–2938) IU/L; $P = 0.03$) (Table 3 and Figure 2). This difference in median (IQR) serum hCG levels between 2019 and 2020 was also observed when comparing only cases with tubal EP (603 (182–2216) vs 952 (411–2544) IU/L; $P = 0.03$) (Table 3).

### Table 3

| Characteristic                      | 2019 (n = 141) | 2020 (n = 134) | $P$   |
|-------------------------------------|---------------|---------------|-------|
| History of EP                       | 13 (9)        | 14 (10)       | 0.84§ |
| Missing data                        | 0 (0)         | 2 (1)         |       |
| Two previous EPs                    | 5/13 (4)      | 2/14 (1)      |       |
| Previous EP management              |               |               |       |
| Expectant                           | 2             | 2             |       |
| Medical                             | 2             | 3             |       |
| Surgical                            | 12            | 11            |       |
| Missing data                        | 2             | 0             |       |
| GA at first TVS (days)*             | 41.0          | 38.0          | 0.13¶ |
| (27.5–48.0)                         | (29.0–44.3)   |               |       |
| GA at diagnostic TVS (days)*        | 42.0          | 41.0          | 0.34¶ |
| (30.5–50.5)                         | (32.5–48.3)   |               |       |
| Tubal EP                            | 127 (90)      | 124 (93)      | 0.67§ |
| Missing data                        | 1 (1)         | 0 (0)         |       |
| Mean EP diameter (mm)†              | 15.3          | 14.7          | 0.25¶ |
| (11.0–22.3)                         | (11.5–18.3)   |               |       |
| Largest EP diameter (mm)†           | 18.0          | 16.0          | 0.22¶ |
| (13.0–24.1)                         | (13.0–22.0)   |               |       |
| EP characteristics                  |               |               | 0.62**|
| Inhomogeneous mass                  | 82 (58)       | 81 (60)       |       |
| GS only                             | 36 (26)       | 30 (22)       |       |
| GS + YS                             | 13 (9)        | 15 (11)       |       |
| GS + YS + live fetal pole          | 9 (6)         | 8 (6)         |       |
| Missing data                        | 1 (1)         | 0 (0)         |       |
| Hemoperitoneum at diagnosis         | 33 (23)       | 35 (26)       | 0.58§ |
| Missing data                        | 0 (0)         | 2 (1)         |       |
| Deepest pool of hemoperitoneum (mm) | 41.8          | 40.1          | 0.81¶ |
|                                      | (31.1–51.4)   | (28.5–54.5)   |       |
| hCG at diagnosis of EP              | 665           | 1005          | 0.03¶ |
| (IU/L)†                             | (224–2330)    | (412–2938)    |       |
| hCG at diagnosis of tubal EP        | 603           | 952           | 0.03¶ |
| (IU/L)‡                             | (182–2216)    | (411–2544)    |       |

Data are given as $n$ (%), $n/N$ (%), $n$ or median (interquartile range). *Gestational age (GA) data at transvaginal sonography (TVS) were missing for 12 cases in 2019 and eight cases in 2020. †EP diameter data were missing in two cases in 2019 and five cases in 2020. ‡Human chorionic gonadotropin (hCG) level data were missing in two cases in 2019 and five cases in 2020. $P$-values were calculated using: §Fisher’s exact test; ¶Mann–Whitney U-test; or **chi-square test. GS, gestational sac; YS, yolk sac.

### Management and complications

Similar proportions of EPs were admitted for secondary care during vs before the COVID-19 pandemic (58% vs 63%; $P = 0.46$). There were significant differences between 2019 and 2020 when comparing the planned...
treatment strategy, with conservative management planned in 74 (52\%) vs 85 (63\%) cases and surgery planned in 66 (47\%) vs 46 (34\%) cases (P = 0.049) (Table 4).

However, the final type of EP management was similar prior to and during the pandemic, with the majority of patients undergoing surgical intervention (52\% in 2019 and 49\% in 2020; P = 0.49) (Table 4). Prior to the pandemic, 28\% of EPs were managed expectantly, whilst 20\% were managed medically with methotrexate. These rates were similar to those during the pandemic (P = 0.49), with 24\% of EPs managed expectantly and 25\% managed medically. Median hCG levels at the time of EP diagnosis in patients who were treated successfully using conservative measures were similar in 2019 and 2020 (expectant management: 219.0 vs 312.0 IU/L; P = 0.32, medical management: 815.5 vs 847.5 IU/L; P = 0.54) (Table 4).

More women required further treatment following failure of first-line management in 2020 compared with 2019 (16\% vs 6\%; P = 0.01). Median hCG levels at the time of EP diagnosis in women undergoing surgical intervention were lower in 2019 than in 2020 (1571.0 vs 2664.0 IU/L; P = 0.01). The rate of ruptured EP confirmed surgically was similar between 2019 and 2020 (9\% vs 3\%; P = 0.07) (Table 4).

SARS-CoV-2 positivity, self-isolation and delay in management

In 2020, 60\% of women admitted for secondary care underwent SARS-CoV-2 polymerase chain reaction testing and obtained a negative result, while 40\% were not tested (Table S2). Most women (88\%) were not self-isolating at the time of admission; the remainder were admitted elsewhere or had missing details regarding self-isolation. No cases that were managed as outpatients or admitted locally experienced management delay due to the pandemic.

DISCUSSION

We found no difference in the mode of conception, gestational age at the first TVS examination and at diagnosis, location, size and morphology on ultrasound of EPs diagnosed in the year before vs during the COVID-19 pandemic. The rates of pregnancy complications and secondary-care admissions and the proportion of patients managed conservatively and surgically were also similar between the two cohorts. Among patients who underwent surgical management, the levels of serum hCG at diagnosis were higher during the pandemic compared to the year before the pandemic. Although the proportions of patients undergoing each management strategy were similar between the two years, we observed a reduction in the success of conservative management strategies during the COVID-19 pandemic. No woman with EP managed as an outpatient or admitted locally experienced management delay due to the pandemic. Although there were fewer patient visits in 2020 than in 2019, the number of new and follow-up face-to-face consultations, loss to follow-up and rates of early-pregnancy complications were similar.

The main strength of this study is the relatively large number of women with EP included, allowing appropriate detailed comparison of multiple outcome measures. The inclusion of patients from an Inner London center ensured that the cohort studied was diverse and the findings were more likely to be generalizable to a wider population. The identification of cases by electronic notes. Another limitation is that this was a descriptive study. The key weakness of the study was its retrospective nature, as the true impact of the COVID-19 pandemic may not be captured completely in the electronic notes. Another limitation is that this was a descriptive study. We expected to find that women with EP presented later and with a higher rate of pregnancy complications, such as ruptured EP, during the pandemic. However, this hypothesis is not supported by the findings of this study. Our findings are also in contrast to those of the currently available literature on the impact of the COVID-19 pandemic on EP diagnosis and management,

Table 4 Secondary-care admission, management and biochemical characteristics and complications in 275 women diagnosed with ectopic pregnancy (EP), before (2019) and during (2020) the COVID-19 pandemic

| Characteristic | 2019 (n = 141) | 2020 (n = 134) | P |
|---------------|---------------|---------------|---|
| Admitted      | 89 (63)       | 78 (58)       | 0.46† |
| Failed first-line management | 8 (6) | 21 (16) | 0.01† |
| Missing data  | 1 (1)         | 3 (2)         |   |
| Planned management |          |               | 0.049† |
| Conservative  | 74 (52)       | 85 (63)       |   |
| Surgical      | 66 (47)       | 46 (34)       |   |
| Missing data  | 1 (1)         | 3 (2)         |   |
| Final management |          |               | 0.49‡ |
| Expectant     | 39 (28)       | 32 (24)       |   |
| Medical       | 28 (20)       | 34 (25)       |   |
| Surgical      | 73 (52)       | 65 (49)       |   |
| Missing data  | 1 (1)         | 3 (2)         |   |
| hCG at diagnosis (IU/L)* |          |               |   |
| Expectant management | 219.0 | 312.0 | 0.32§ |
| Medical management | (90.0–485.0) | (129.0–646.0) |   |
| Surgical management | (300.3–1582.0) | (465.8–1424.3) |   |
| Ruptured EP   | 12 (9)        | 4 (3)         | 0.07† |
| Missing data  | 0 (0)         | 3 (2)         |   |

Data are given as n (%) or median (interquartile range). *Human chorionic gonadotropin (hCG) level data were missing in four cases in 2019 and four cases in 2020. P-values were calculated using: †Fisher’s exact test; ‡chi-square test; §§Mann–Whitney U-test.
in which it has been suggested that hesitancy amongst patients in accessing healthcare resources led to an increase in the rates of surgery, ruptured EP, blood loss and hemodynamic instability6–13.

For women attending early-pregnancy assessment, a recent report suggested a 2.5% increase in the proportion of those with a diagnosis of miscarriage during the COVID-19 pandemic. This may reflect effective triage, with priority being given to those with complications14. Although virtual clinics were not implemented, telephone triage rationalized service provision, reducing patient visits during the pandemic. As all women with heavy bleeding or abdominal or pelvic pain were invited for prompt review, similar proportions of miscarriage, PUL and EP were reported15. However, even with rationalization measures in place, women were keen to avoid hospital settings1–6 due to the risk of contracting SARS-CoV-2 infection.

In the UK, the average ratio of new to follow-up consultations in an early pregnancy unit has been reported15 to be 1.88:1. Our prepandemic ratio of 1.1:1 reflects the greater number of follow-up consultations associated with having several second-opinion referrals, conservative miscarriage and EP management and use of a two-visit mathematical model for PUL. Perhaps, most relevant is our unit policy of allowing relatively liberal access to follow-up for patients, as we believe this may help ameliorate some of the known psychological sequelae of early-pregnancy complications16–22.

During the pandemic, although we reduced the number of visits in 2020, a considerable number of low-risk women would have had follow-up under normal circumstances. As higher-risk patients continued to attend, our new-to-follow-up consultations ratio remained relatively unchanged compared to that before the pandemic.

The detection rates of EP on the first TVS scan in this study were lower than those reported in the literature23. This is likely due to variation in staffing, scanning protocols and sonographer expertise within our training unit. Reductions in staffing due to shielding during the pandemic is likely to explain why the initial detection rate was slightly lower in 2020.

Although we found no difference in the ultrasound features of EP in women diagnosed during the pandemic compared to those diagnosed in the preceding year, serum hCG levels were higher in the former group. Single measurements of serum hCG are generally unhelpful when evaluating PUL, but higher levels are associated with an increased risk of failure of conservative management strategies24. This is reflected by the higher failure rate of first-line management strategies during the pandemic observed in this study and may suggest that the current use of serum hCG levels as a marker of likely success of conservative management has some merit.

The rapid changes in guidance for the management of early pregnancy complications as a result of the COVID-19 pandemic encouraged our increased use of conservative management. However, adopting more liberal inclusion criteria appears to have been associated with an increase in the failure rate of first-line management4–6 in 2020. Although the proportions of patients according to the final management type were similar between those diagnosed before and during the pandemic, conservative management was recommended initially to more women in 2020 than in 2019. As conservative management failed in some of these women, a similar proportion underwent surgery as a final treatment in both years.

We found that the overall number and proportion of EPs diagnosed following assisted conception were similar in both years studied. However, when assessing the data more closely, there were no EP cases following fertility treatment in April, May or June 2020. This is consistent with the British Fertility Society guidance at that time25, which advised ceasing assisted conception services from mid-March to mid-May 2020. Similar overall numbers of EP cases following assisted conception in both years probably reflects fertility services increasing their capacity in order to deal with the backlog of cases once they reopened.

Our observations suggest that the guidance implemented to rationalize early-pregnancy care reduced attendances, with no evidence of women with EP being unable to access care in a timely and safe way. Although conservative management was encouraged, in our unit, this was associated with an increase in failure of this approach. Whilst our findings suggest that early-pregnancy care can be rationalized in the event of a healthcare emergency, such as the COVID-19 pandemic, this does not necessarily mean that the cancelled visits were unnecessary. Whilst rationing appointments was not associated with physical harm, it is important to acknowledge the psychological impact of early-pregnancy complications and the support and reassurance many women feel when attending consultation with what may appear to be relatively minor problems.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Table S1 Breakdown of ectopic pregnancy diagnosis by year and month, with associated statistical tests and missing data documentation

Table S2 SARS-CoV-2 testing, self-isolation at the time of admission and delays in ectopic pregnancy management during the COVID-19 pandemic

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