Impact of SARS-Cov-2 on ectopic pregnancies management in the United Kingdom: a multicentre paired observational study

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Abstract

Objective: to describe the impact of COVID-19 on the management of patients with ectopic pregnancy. **Design**: a multicentre study comparing outcomes from a prospective cohort during the pandemic [Covid-ectopic pregnancy registry (CEPR)] compared to an historical pre-pandemic cohort [non-Covid ectopic pregnancy registry (NCEPR)]. **Setting**: five London university hospitals. **Population and Methods:** consecutive patients diagnosed clinically and/or radiologically with ectopic pregnancy (March/2020-Aug/2020) were entered into the CEPR and an exploratory matched analysis was performed comparing results to NCEPR patients (January/2019-June/2019). **Main outcome measures:** patient demographics, management (expectant, medical and surgical), length of treatment, number of hospital visits (non-surgical management), length of stay (surgical management) and 30-day complications. **Results:** 341 patients met inclusion: 162 CEPR and 179 NCEPR. A significantly higher percentage of women underwent non-surgical management versus surgical management in the CEPR versus NCEPR (58.6% [95/162] vs 72.6% [130/179]; p= 0.0084]. Amongst patients managed with expectant management the CEPR had a significantly lower mean number of hospital visits compared to NCEPR [3.6 [SD 1.4] vs 13.7 [SD 13.4], p= 0.0053]. Amongst patients managed with medical management, the CEPR had a significantly lower mean number of hospital visits [NCEPR 6.4 [SD 2.3] vs 8.8 [SD 3.9], p= 0.0014]. There was no observed difference in complication rates between cohorts. **Conclusion:** women were found to undergo significantly higher rates of non-surgical management during COVID-19 first wave vs NCEPR cohort. Women managed non-surgically in CPER cohort were also managed with fewer hospital attendances. This did not lead to an increase in observed complications rates.

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Tweetable abstract: higher rates of non-surgical management of ectopic pregnancy during COVID-19 pandemic does not increase complication rates

INTRODUCTION

The reported worldwide rated of ectopic pregnancy is 1.5% to 2% and patients can be managed expectantly, medically or surgically. Ectopic pregnancy may be associated with severe morbidity and disease outcome is heavily influenced by timing of presentation, timely diagnosis by healthcare professionals, patient's socioeconomic status and individualisation of care (1,2). SARS-CoV-19 is the β corona virus responsible for COVID-19 which was declared a pandemic by the WHO in March 2020. In order that National Health Service (NHS) did not become overwhelmed, governments around the world, including the United Kingdom (UK), postponed non-urgent and non-cancer elective care. There was concern that people may not seek care during the pandemic from the NHS because of fear of contracting COVID-19 or wishing not to burden NHS services by attending hospital(3). Emergency department attendances in the month of May dropped by 41.9% and emergency admissions dropped by 27.2% in 2019 compared to 2020(4).

The provision of emergency gynaecological care was altered due to specific theoretical concerns surrounding its transmission. This included concern regarding the spread of COVID-19 infection during aerosol generating procedures (AGPs) such as surgery, and particularly, laparoscopic surgery(5-7). Compounding this, there was a nationwide lack of personal protective equipment (PPE) for surgeons at the start of the pandemic(8). Where patients needed to have surgery, there was a reported high mortality rate in COVID-19 positive patients(9). The role of methotrexate in medical management and the theoretical risk of immunosuppression was also to be considered, in turn with potential increased vulnerability to viral illness with its use.

Initial guidance on ectopic pregnancy management was provided by the Royal College of Obstetricians & Gynaecologists (RCOG)(10) and International Society of Ultrasound in Obstetrics and Gynaecology (IUSOG)(11). This included guidance to offer ultrasound scan to women within 24 hours if they had a positive pregnancy test and abdominal pain or bleeding particularly in women who had risk factors for ectopic pregnancy. Decision making was advised to be by a senior gynaecologist and patients offered conservative therapy or medical management if they met criteria(10). RCOG guidance stated 'it is likely the detrimental effects of methotrexate in COVID-19 are minimal in well women' and patients were not advised to home shield following administration(10). Several perioperative guidelines were issued within a short time, including the joint BSGE and RCOG guideline, issued on March 26th 2020, supporting the use of laparoscopy, but with necessary caution. This guidance included the statement 'Non-surgical methods of treatment should be actively

recommended to reduce the risk of COVID-19 transmission to health care workers, and reduce the need for hospital admission, provided they are a safe alternative (for example but not limited to methotrexate for unruptured ectopic pregnancy)'(12).

Objectives

The primary aim of this multicentre study was to describe the impact of the COVID-19 pandemic on the management of patients with ectopic pregnancy, compared to a historical pre-pandemic cohort. Secondarily, we aim to explore the effect of management on clinical burden, hospital attendances, surgical outcomes and patient safety.

METHOD

Study Design

A prospective multicentre study on patients diagnosed either clinically and/or by ultrasound with ectopic pregnancy in a secondary care hospital setting. Data was collected from the date of the UK Government COVID-19 lockdown on 23rd March 2020 until the 23rd August 2020. Data was entered into a prospective Covid-ectopic pregnancy registry (CEPR) from five London university teaching hospitals (Whipps Cross Hospital, Royal London Hospital, Newham Hospital, North Middlesex Hospital, Homerton Hospital). Patient demographics, Covid-PCR-status, management (expectant, medical and surgical), management within/outside of standard pre-pandemic ectopic pregnancy protocol(13,14), length of treatment (non-surgical management), length of stay (surgical management), and 30-day complications and volume of haemoperitoneum at surgery were collected. Appendix S1 illustrates data collection tool used. An exploratory matched analysis for hypothesis discussion was performed comparing results to a non-Covid ectopic pregnancy registry (NCEPR) of patients from January 2019 to June 2019 from all five hospitals. The study was registered by the local principal investigator at each site as a clinical audit. Routine, anonymised data was collected which did not influence clinical care.

Ethics

This study was reviewed and prospectively approved by the local service evaluation board (Barts Health NHS Trust Quality Improvement; United Kingdom; Reference Number: 11199), and subsequently by investigators at the participating sites. Patient specific consent for this study was not deemed necessary.

Statistical analysis

Descriptive statistics were used to summarise patient demographics and clinical characteristics. All statistical analyses were performed using GraphPad®. The normally

distributed data were expressed as mean ± standard deviation. Comparative analysis between cohorts was performed with a Fisher's exact test. A p value < 0.05 was considered statistically significant.

RESULTS

A total of 341 patients were included in the study across five hospitals. 162 patients were included in the CEPR cohort and 179 patients were included in the paired NCEPR cohort.

Patient demographics and risk factors

Patient demographics are presented in **Table 1**. When CEPR cohort was compared to NCEPR cohort there was no difference observed in the mean age (31.4 [SD 5.8] vs 31.6 [SD 5.9]; p= p= 0.7743), mean parity (0.9 [SD 1.1} vs 0.8 [SD 1.1]; p= 0.3596) or mean HCG (5866 [SD 14866] vs 5911 [SD 9858]; p=0.7565). There was a statistically significant difference in the mean gestation of the CEPR cohort vs NCEPR cohort (6.6 [SD 1.6] vs 6.0 weeks [SD 1.6]; p=0.0023). Women in NCEPR cohort were significantly more likely to have risk factors for ectopic pregnancy (p=0.0280) and a history of previous ectopic pregnancy (p=0.0043).

Anatomical location of ectopic pregnancies

When CEPR cohort was compared to NCEPR cohort, there was a difference in the proportion of tubal ectopics versus non-tubal ectopics (including scar, interstitial/cornual, cervical, abdominal and ovarian) (p= 0.0449).

Management of ectopic pregnancies

There was no difference between the CEPR and NCEPR cohorts in the proportion of women scanned within 24 hours (140/162 [86.4%] vs 141/179 [78.8%]; p=0.3072), nor the number of women treated out-with the standard management protocol for ectopic pregnancy management (7/162 [4.3%] vs (9/179) [5.0%]; p= 0.8030) (**Table 2**). **Figure 1** illustrates the management of patients in CEPR and NCEPR cohorts. Overall, a significantly higher percentage of women underwent non-surgical management of ectopic pregnancy versus surgical management, in the CEPR cohort versus NCEPR (58.6% [95/162] vs 72.6% [130/179]; p= 0.0084] (**Table 2**). There was no difference in the number of patients who were converted from one initial management option to another in the CEPR vs NCEPR cohort (10/162 [6.2%] vs 9/179 [5.0%]; p=0.8139) (**Figure 1**).

Non-surgical management

Sub-group analysis of women managed non-surgically revealed a non-significant trend of more women managed by medical management versus expectant management (49/67; 73.1%) in the CEPR cohort when compared to NCEPR (28/49; 57.1%; *p*= 0.0778) (**Table 2**). Amongst those patients managed with expectant management, the CEPR cohort had a significantly lower mean number of hospital visits compared NCEPR (3.6 [SD 1.4] vs 13.7 [SD 13.4], p= 0.0053). Similarly, amongst patients managed with medical management, the CEPR cohort had a significantly lower mean number of hospital visits NCEPR [6.4 [SD 2.3] vs 8.8 [SD 3.9], *p*= 0.0014] (**Table 2**).

Surgical management

Sub-group analysis of women managed surgically revealed no difference in the number of surgical procedures performed by consultant versus registrar grade (23/95 [24.2%]) in the CEPR cohort when compared to NCEPR cohort (24/130 [18.5%]; *p*=0.3977) (**Table 2**). There was no difference found in the mean length of hospital stay for surgical cases in the CEPR cohort (36.0 hours [SD 21.8]) vs the NCEPR cohort (32.9 hours; [SD 14.27]; *p*= 0.2292). There was no difference in the mean volume of haemoperitoneum (ml) at surgery (CEPR 489 [SD 663] vs NCEPR 323 [SD 519], p=0.0587), nor the number of surgical cases with haemoperitoneum greater than or equal to 500mls (CEPR 27/95 [28.4%] vs NCEPR 28/130 [21.5%]; p=0.2725). There were similar number of cases in each cohort documented as ruptured ectopic pregnancy and haemodynamically unstable (CEPR 5/162 [3.1%] vs NCEPR 6/179 [3.4%], p=1.000).

COVID-19 investigations in CEPR cohort

In 7.4% (15/162) of patients in the CEPR cohort reported delay in their presentation to hospital due to the COVID-19 pandemic. 47% (77/162) of patients in the CEPR cohort were asked about symptoms of coronavirus and 49.4% (80/162) of patients were investigated with a COVID-19 PCR swab. Of those 80 patients tested with a COVID-19 PCR swab, none (0/80) were positive for COVID-19.

Surgical management of ectopic pregnancies in CEPR cohort

Laparoscopic guidance was reported to be followed for all but two cases [2/88 (2.3%)] in the CEPR cohort. 81.0% (64/95) of CEPR surgical cases were undertaken with surgeons wearing full PPE.

30-day Complications

Complications were reported in 7.4% (12/162) of cases in the CEPR cohort versus 8.4% (15/179) of cases in the NCEPR cohort, p=0.8417. **Table 3** illustrates complications

(including post-operative reported 30-day complications) for CEPR and NCEPR cohorts. 3/162 (1.9%). 3/162 (1.9%) patients in the CEPR cohort experienced ruptured ectopic following initial non-surgical management versus 4/179 (2.2%) patients in the NCEPR cohort (p= 1.00). The majority of patients who experienced complications were patients initially managed with non-surgical management (in both CEPR 8/12 and 9/15 NCEPR cohorts).

DISCUSSION

Main Findings

This study is the first prospective comparative study, to the authors knowledge, to report on the impact of the COVID-19 pandemic on the management of patients with ectopic pregnancy across multiple centres, compared to a matched historical pre-pandemic cohort within the UK.

We hypothesised that women with ectopic pregnancy would present later during the pandemic, and that as a result, more women would present with haemodynamic instability. This hypothesis was rejected as only a minority of women delayed their presentation due to COVID-19 and there was no increase in patients presenting with haemodynamic instability. We hypothesised that there would be a decrease in the proportion of tubal compared to non-tubal ectopic pregnancies as some ectopic pregnancies will naturally resorb if women wait longer to present. This study did demonstrate an increase in the proportion of non-tubal ectopic pregnancies compared to tubal pregnancies.

Similar to a recent study by Bhambhvani and colleagues there was no decrease in the number of women presenting with ectopic pregnancy during the peak of the pandemic(15). Our present results illustrate the mean gestation of pregnancy in patient's presenting in the CEPR cohort was higher than the NCEPR cohort (6.6 [SD 1.6] vs 6.0 weeks [SD 1.6]; *p*=0.0023). However, this does not represent a clinically significant difference.

In this study fewer cases of ectopic pregnancy were managed surgically in the CEPR vs the NCPER cohort. However, despite this change there was no significant differences in the observed 30-day complication rate between cohorts. This supports the joint statement from RCOG/BSGE which recommended that non-surgical methods of treatment non-surgical methods of treatment should be actively recommended to reduce the need for hospital admission(12).

In this study no difference in proportion of patients with ruptured ectopic and haemodynamic instability were observed between cohorts. This is in contrast to Casadio and colleagues'

study, in which reported the proportion of ruptured ectopic pregnancies were significantly higher during the lockdown in comparison with the pre-lockdown period (6/9 [66.7%] vs. 52/201 [25.9%]; *p*=0.02)(16). However, this small sample size (*n* = 9) in the COVID-19 cohort significantly limits any definitive conclusions that can be drawn from their findings.

Furthermore, with regard to patients undergoing expectant or medical management, patients undergoing expectant or medical management had fewer hospital visits, again with no difference in reported complications. Fewer hospital visits clearly reduces the risk of inadvertent COVID-19 transmission to both healthcare workers and patients during the pandemic.

Women in NCEPR cohort were significantly more likely to have risk factors for ectopic pregnancy and a history of previous ectopic pregnancy. It could be theorised that women with a history of previous ectopic pregnancy, whom have been advised to attend for an early scan in subsequent pregnancies, were less likely to attend during the pandemic for fear of contracting COVID-19. However, this may also be a coincidental finding due to inherent differences within the demographics of the compared cohorts.

As part of our exploratory sub-group analysis, women managed non-surgically revealed a non-significant trend of fewer women managed by expectant management. This may have been clinician driven, as they were trying to guard against failed expectant management. This did not appear to result in higher reported complications. However, whether there this is integrated into routing post pandemic practice remains to be seen and requires further prospective evaluation.

Despite RCOG/BSGE guidance supporting the use of laparoscopy, a recent survey of junior doctors in the UK reported two-thirds of units adopting laparotomy as first-line surgical approach in women with ectopic pregnancy(17). There was no decrease in the laparoscopic approach for women who underwent surgical management (abdominal approach) in the CPER cohort in this study (97.8% CEPR cohort vs 97.6% NCEPR cohort). 81.0% (64/95) of CEPR surgical cases were undertaken with surgeons wearing full PPE, highlighting that not everyone adhered to PPE advice. As this pandemic progresses, the need to continue operating in emergency situations such as ectopic pregnancies on suspected, confirmed COVID-19 or unknown status patients will continue and the safety of healthcare staff is imperative.

It is encouraging to report that there was no difference in proportion of surgical procedures performed by consultant vs registrar (p=0.3977). Despite concern that the pandemic will have impact on training opportunities in Gynaecology(18), it is promising to consider that trainees will likely continue to operate during the pandemic in the context of emergency laparoscopy for surgical management of ectopic pregnancies.

Strengths and Weaknesses

Whilst we report on a prospective multi-centre study, this was not performed within the constraints of a prospective clinical trial. As such there was an absence of standard operative procedures, beyond the aforementioned national guidelines. However, this was pragmatic during a pandemic and reflects variation in real-world clinical practice. Furthermore, whilst this study was compared to a historical cohort in the same centres, patients were not matched on a per-patient level. Despite observed non-significant differences between cohorts, the subsequent exploratory comparative analysis should be viewed within this context.

CONCLUSION

This study explored the impact of advised management changes in women with ectopic pregnancy due to the COVID-19 pandemic, comparing their experience to a historical matched cohort pre-pandemic. Women were found to undergo significantly higher rates of non-surgical management during COVID-19 first wave. Women managed non-surgically in CPER cohort were also managed with fewer hospital attendances. This did not lead to an increase in observed complications rates. Further research is required to ascertain whether higher rates of non-surgical management could be routinely adopted in future practice.

Disclosure of interests

No conflicts to declare.

Contribution to Authorship

SP, JR and FO were responsible for the original manuscript design, drafting and revision for important intellectual content. SP, JR, SD, PK, CN, NS and MT were responsible for data collection, important intellectual input into the work and preparation and final approval of the manuscript. RO, AD, MG, KR, SR and SW were responsible for providing important intellectual input into the work and preparation and final approval of the manuscript.

Ethics

This study was reviewed and prospectively approved by the local service evaluation board (Barts Health NHS Trust Quality Improvement; United Kingdom; Reference Number: 11199 on 12/05/20).

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