

# Impact of severe acute respiratory syndrome coronavirus 2 on ectopic pregnancy management in the United Kingdom: a multicentre observational study

S Platts,<sup>a</sup>  J Ranawaka,<sup>a</sup> R Oliver,<sup>a</sup> S Patra-Das,<sup>b</sup> P Kotabagi,<sup>c</sup> C Neophytou,<sup>d</sup> N Shah,<sup>e</sup>  M Toal,<sup>b</sup> P Bassett,<sup>f</sup> A Davison,<sup>b</sup> M Gbegbaje,<sup>d</sup> K Rao,<sup>e</sup> S Rouabhi,<sup>c</sup> S Watson,<sup>b</sup> F Odejinmi<sup>a</sup>

<sup>a</sup> Department of Obstetrics and Gynaecology, Whipps Cross University Hospital, Barts Health Trust, London, UK <sup>b</sup> Department of Obstetrics and Gynaecology, Homerton University Hospital, London, UK <sup>c</sup> Department of Obstetrics and Gynaecology, North Middlesex University Hospital, London, UK <sup>d</sup> Department of Obstetrics and Gynaecology, Royal London Hospital, Barts Health NHS Trust, London, UK <sup>e</sup> Department of Obstetrics and Gynaecology, Newham Hospital, Barts Health NHS Trust, London, UK <sup>f</sup> Statsconsultancy Ltd, Amersham, Buckinghamshire, UK

Correspondence: Dr S Platts, Whipps Cross University Hospital, London, E11 1NR, UK. Email: sophie.platts@nhs.net

Accepted 3 May 2021. Published Online 14 June 2021.

**Objective** To describe the impact of coronavirus disease 2019 (COVID-19) on the management of women with ectopic pregnancy.

**Design** A multicentre observational study comparing outcomes from a prospective cohort during the pandemic [COVID-19-ectopic pregnancy registry (CEPR)] compared with a historical pre-pandemic cohort [non-COVID-19-ectopic pregnancy registry (NCEPR)].

**Setting** Five London university hospitals.

**Population and methods** Consecutive patients diagnosed clinically and/or radiologically with ectopic pregnancy (March 2020–August 2020) were entered into the CEPR and results were compared with the NCEPR cohort (January 2019–June 2019). An adjusted analysis was performed for potentially confounding variables.

**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** Three hundred and forty-one women met the inclusion criteria: 162 CEPR and 179 NCEPR. A significantly lower percentage of women underwent surgical management versus

non-surgical management in the CEPR versus NCEPR (58.6%; 95/162 versus 72.6%; 130/179;  $P = 0.007$ ). Among patients managed with expectant management, the CEPR had a significantly lower mean number of hospital visits compared with NCEPR (3.0, interquartile range [IQR] [3, 5] versus 9.0, [5, 14];  $P < 0.001$ ). Among patients managed with medical management, the CEPR had a significantly lower median number of hospital visits versus NCEPR (6.0, [5, 8] versus 9, [6, 10];  $P = 0.003$ ). There was no observed difference in complication rates between cohorts.

**Conclusion** Women were found to undergo significantly higher rates of non-surgical management during the COVID-19 first wave compared with a pre-pandemic cohort. Women managed non-surgically in the CEPR cohort were also managed with fewer hospital attendances. This did not lead to an increase in observed complication rates.

**Keywords** coronavirus disease 2019, fallopian tubes, methotrexate/therapeutic use, pregnancy, ectopic.

**Tweetable abstract** A higher rate of non-surgical management of ectopic pregnancy during the COVID-19 pandemic did not increase complication rates.

Please cite this paper as: Platts S, Ranawaka J, Oliver R, Patra-Das S, Kotabagi P, Neophytou C, Shah N, Toal M, Bassett P, Davison A, Gbegbaje M, Rao K, Rouabhi S, Watson S, Odejinmi F. Impact of severe acute respiratory syndrome coronavirus 2 on ectopic pregnancy management in the United Kingdom: a multicentre observational study. BJOG 2021;128:1625–1634.

## Introduction

The reported worldwide rate of ectopic pregnancy is 1.5–2% and patients can be managed expectantly, medically or

surgically.<sup>1</sup> Ectopic pregnancy may be associated with severe morbidity, and disease outcome is heavily influenced by timing of presentation, time to diagnosis, patient's socio-economic status and individualisation of care.<sup>2,3</sup> Severe

acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the  $\beta$  coronavirus responsible for coronavirus disease 2019 (COVID-19), which was declared a pandemic by the World Health Organization in March 2020.<sup>4</sup> Evolving evidence suggests that COVID-19 has had a significant impact on women's health care globally, evidenced by two recent studies that demonstrated an increase in the number of stillbirths during the pandemic compared with a pre-pandemic cohort.<sup>5,6</sup>

In the UK, non-urgent and non-cancer elective care was postponed in response to COVID-19. There was concern that people may not seek care from the National Health Service (NHS) during the pandemic out of fear of contracting COVID-19 or wishing not to burden NHS services by attending hospital.<sup>7</sup> Emergency department attendances in the month of May 2020, 2 months following declaration of the pandemic, dropped by 41.9% compared with 2019.<sup>8</sup>

The provision of emergency gynaecological care was altered in response to specific theoretical concerns surrounding virus transmission. These included concern regarding the spread of COVID-19 from aerosol-generating procedures, in particular laparoscopic surgery.<sup>9–11</sup> Compounding this, there was a nationwide lack of personal protective equipment (PPE) at the start of the pandemic.<sup>12</sup> When patients needed to have surgery, there was a reported high mortality rate in COVID-19 patients.<sup>13</sup>

Initial guidance on ectopic pregnancy management during the pandemic was provided by the Royal College of Obstetricians & Gynaecologists (RCOG)<sup>14</sup> and International Society of Ultrasound in Obstetrics and Gynaecology.<sup>15</sup> Decision-making regarding management was advised to be by a senior gynaecologist and patients were offered conservative therapy or medical management if they met criteria.<sup>14</sup> 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.<sup>14</sup> Several perioperative guidelines were issued within a short time, including the joint British Society for Gynaecological Endoscopy (BSGE) and RCOG guideline, issued on 26 March 2020, supporting the use of laparoscopy, but with necessary caution. This guidance stated 'Non-surgical methods of treatment should be actively recommended to reduce the risk of COVID-19 transmission to healthcare 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)' (Appendix S2).<sup>16</sup>

## Objectives

The primary aim of this multicentre study was to describe the impact of the COVID-19 pandemic on the management of women with ectopic pregnancy, compared with a historical pre-pandemic cohort. Secondarily, we aimed to

explore the effect of management on clinical burden, hospital attendances, surgical outcomes and patient safety.

## Methods

### Study design

This was an observational, multicentre study of women diagnosed either clinically and/or by ultrasound with ectopic pregnancy in a secondary-care hospital setting. Prospective data were collected from the date of the UK Government COVID-19 lockdown on 23 March 2020, until 23 August 2020. Data were entered into a prospective COVID-19-ectopic pregnancy registry (CEPR) from five London university teaching hospitals (Whipps Cross Hospital, Royal London Hospital, Newham Hospital, North Middlesex Hospital and Homerton Hospital). Patient demographics and outcomes – including risk factors for ectopic pregnancy (previous ectopic pregnancy, previous tubal surgery, previous pelvic surgery, previous pelvic infection, intrauterine contraceptive device in situ at time of conception, use of assisted reproductive technology such as in vitro fertilisation), SARS-CoV-2 polymerase chain reaction status, management (expectant, medical and surgical), management within/outside standard pre-pandemic ectopic pregnancy protocol,<sup>17,18</sup> length of treatment (non-surgical management), length of stay (surgical management) and 30-day complications and volume of haemoperitoneum at surgery – were collected. An exploratory analysis for hypothesis discussion was performed comparing results with a non-COVID-19 ectopic pregnancy registry (NCEPR) of patients from January 2019 to June 2019 from all five hospitals. The NCEPR cohort data were collected retrospectively at each site using the developed standardised data collection tool, which included the same variables but with the obvious omissions of COVID-19-specific variables (e.g. PPE usage). Appendix S1 illustrates the data collection tools used. Patients were not involved in the development of the research. A core outcome set was not used because a relevant core outcome set does not exist.

### Ethics

This study was registered with the research and audit department of each participating UK centre. As we were using routinely collected, anonymised data, formal research ethics approval was not required and patient-specific consent for this study was not deemed necessary. We used the online National Research Ethics Service decision tool (<http://www.hra-decisiontools.org.uk>) to confirm this.

### Statistical analysis

Descriptive statistics were used to summarise patient demographics and clinical characteristics. Continuous variables were described by the mean and standard deviation if

found to be normally distributed, or the median and interquartile range (IQR) if not. Continuous variables were compared using the unpaired *t* test for variables found to follow a normal distribution, and the Mann–Whitney *U* test otherwise. Categorical variables were compared between groups using the chi-square test.

Subsequent analyses examined the difference in outcomes between the CEPR and NCEPR groups. All analyses were performed using regression methods; binary outcomes were analysed using logistic regression and continuous outcomes were analysed using linear regression. These continuous outcomes were all found to have positively skewed distributions, and so were analysed on the log scale.

For each outcome, three different analyses were performed:

- *Analysis 1*: Unadjusted for any other factors – all patients included
- *Analysis 2*: Unadjusted for any other factors – including only patients with full data for those variables included in Analysis 3
- *Analysis 3*: Adjusted for factors found to show some evidence of a difference between groups from the first stage in the analysis

The adjusted analysis (Analysis 3) included adjustments for all those variables showing even slight evidence of a difference between groups ( $P < 0.2$ ) from the initial analyses. Difference in outcome between groups is expressed as an odds ratio, with corresponding confidence interval. All statistical analyses were performed using STATA (version 15.1; StataCorp, College Station, TX, USA).

## Results

A total of 341 women were included in the study across five hospitals. One hundred and sixty-two were included in the CEPR cohort and 179 were included in the paired NCEPR cohort.

### Patient demographics and risk factors

Patient demographics are presented in Table 1. When the CEPR cohort was compared with the NCEPR cohort there was no difference in the mean age (31.4 years [SD 5.7] versus 31.6 years [SD 5.9];  $P = 0.78$ ), median parity (1.0 [IQR 0, 1] versus 0 [IQR 0, 1];  $P = 0.22$ ) or median human chorionic gonadotrophin (hCG) (1607 IU/l [IQR 647, 3792] versus 1777 IU/l [IQR 877, 5221];  $P = 0.12$ ). There was a statistically significant difference in the median gestational age of the CEPR cohort versus NCEPR cohort (6.7 weeks [SD 1.7] versus 6.0 weeks [SD 1.6];  $P = 0.002$ ). There was a difference in ethnicity of patients between the groups, with a higher proportion of Asian women and lower proportion of black women in the CEPR group versus NCEPR group. Women in the NCEPR cohort were significantly more likely to have risk factors for ectopic

pregnancy ( $P = 0.02$ ) and a history of previous ectopic pregnancy ( $P = 0.004$ ).

### Anatomical location of ectopic pregnancies

When the CEPR cohort was compared with the NCEPR cohort, there was no difference in the proportion of tubal ectopics versus non-tubal ectopics (including scar, interstitial/cornual, cervical, abdominal and ovarian) ( $P = 0.28$ ). All ectopic pregnancies identified were included in the analysis, including scar or cervical ectopics managed by evacuation, as we believe that the management of all ectopic pregnancies should be explored to be representative of clinical practice.

### Subsequent analyses

The second stage of the analysis considered a comparison of the outcomes between the CEPR and NCEPR cohorts. As outlined in the Methods section, factors showing even slight differences between groups ( $P < 0.2$ ) were included in the adjusted analysis. There were missing data for 71 of the 341 patients for the baseline/demographic factors included in the adjusted analysis (NCEPR  $n = 35$ , CEPR  $n = 36$ ). The factors included in this adjusted analysis were gestational age, hCG (log scale), ethnicity, risk factors for ectopic and previous ectopic.

### Management of ectopic pregnancies

There was no difference between the CEPR and NCEPR cohorts in the proportion of women scanned within 24 hours (140/156 [89.7%] versus 142/153 [92.8%];  $P = 0.30$ ), nor in the number of women treated with the standard management protocol for ectopic pregnancy management (7/162 [4.3%] versus 9/179 [5.0%];  $P = 0.803$ ). This was the case for both unadjusted and adjusted analyses (Table 2). Figure 1 illustrates the management of patients in the CEPR and NCEPR cohorts (unadjusted analysis). Overall, a significantly lower percentage of women underwent surgical management of ectopic pregnancy in the CEPR cohort versus NCEPR (58.6% [95/162] versus 72.6% [130/179];  $P = 0.007$ ). This was the case for both unadjusted and adjusted analyses; the odds of a patient receiving surgical management in the CEPR cohort were only around half of the odds for a patient in the NCEPR cohort (unadjusted OR 0.53 [95% CI 0.34–0.84], adjusted OR 0.51 [95% CI 0.32–2.81]) (Table 2). There was no difference in the number of patients who were converted from one initial management option to another in the CEPR versus NCEPR cohort (10/162 [6.2%] versus 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 in

**Table 1.** Comparison of demographic and baseline characteristics

Variable	Category	CEPR		NCEPR		P value
		n		n		
Age (years)	–	162	31.4 ± 5.7	179	31.6 ± 5.9	0.78
Parity	–	161	1 [0, 1]	176	0 [0, 1]	0.22
Gestational age (weeks)	–	140	6.7 ± 1.7	156	6.0 ± 1.6	0.002
hCG (IU/l)	–	153	1607 [647, 3792]	174	1777 [877, 5221]	0.12
Ethnicity	White	153	66 (43.1%)	137	70 (41.9%)	0.01
	Black		20 (13.1%)		39 (23.4%)	
	Asian		45 (29.4%)		28 (16.8%)	
	Mixed		2 (1.3%)		7 (4.2%)	
	Other		20 (13.1%)		23 (13.8%)	
Risk factor for ectopic pregnancy	No	161	106 (65.8%)	179	96 (53.6%)	0.02
	Yes		55 (34.2%)		83 (46.4%)	
Previous ectopic pregnancy	No	161	148 (91.9%)	179	145 (81.0%)	0.004
	Yes		13 (8.1%)		34 (19.0%)	
Ectopic location	Tubal	162	142 (88.8%)	178	165 (92.7%)	0.28
	Other		18 (11.2%)		13 (7.3%)	
	Scar		5		2	
	Interstitial/cornual		11		6	
	Abdominal		2		2	
	Cervical		0		2	
	Ovarian		0		1	

Summary statistics: mean ± standard deviation, median [interquartile range], or number (percentage).

the CEPR cohort compared with the NCEPR cohort (73.1% [49/67] versus 57.1% [28/49];  $P = 0.0778$ ). However, when adjusted for possible confounding factors (including hCG), this was found to be statistically significant ( $P = 0.01$ ), with the odds of medical management (in the non-surgical cohort) being over three times higher in the CEPR cohort than the NCEPR cohort (OR 3.46 [95% CI 1.29–9.24]) (Table 2). Separate sub-group analysis of hCG levels for all patients revealed a non-significant trend towards lower median hCG in the expectant CEPR cohort versus expectant NCEPR cohort (337 IU/l [175, 912] versus 494 IU/l [341, 945];  $P = 0.135$ ). Among those patients managed with expectant management, the CEPR cohort had a significantly lower median number of hospital visits compared with the the NCEPR cohort (3.0 [3, 5] versus 9.0 [5, 14],  $P = <0.001$ ). Similarly, among patients managed with medical management, the CEPR cohort had a significantly lower median number of hospital visits than the NCEPR cohort (6.0 [5, 8] versus 9.0 [6, 10],  $P = 0.003$ ). Median numbers of hospital visits for expectant and medically managed patients were also found to be statistically significantly different once adjusted for potentially confounding variables (Table 2).

### Surgical management

Sub-group analysis of hCG in patients managed surgically illustrated that there was no evidence of a significant

difference between the cohorts (CEPR median hCG 2733 IU/l [1314, 7477] versus NCEPR median hCG 2508 IU/l [1171, 7864];  $P = 0.890$ ). Further analysis of women managed surgically revealed no difference in the proportion of surgical procedures performed by registrar versus consultant grade (52/72 [72.2%]) in the CEPR cohort when compared with the NCEPR cohort (77/100 [77%];  $P = 0.48$ ) (Table 2). There was no difference found in the median length of hospital stay (hours) for surgical cases in the CEPR cohort (24.0 hours [24, 48]) versus the NCEPR cohort (24.0 hours; [24, 45];  $P = 0.43$ ). There was no difference in the median volume of haemoperitoneum at surgery (CEPR 200 ml [10, 500] versus NCEPR 150 ml [50, 400],  $P = 0.95$ ) and no difference in the number of surgical cases with haemoperitoneum greater than or equal to 500 ml (CEPR 27/82 [32.9%] versus NCEPR 26/109 [23.9%];  $P = 0.17$ ). There were similar proportions of cases in each cohort documented as ruptured ectopic pregnancy and haemodynamically unstable (CEPR 5/162 [3.1%] versus NCEPR 6/179 [3.4%],  $P = 1.000$ ).

### COVID-19 in CEPR cohort

In the CEPR cohort, 7.4% (15/162) of patients 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 SARS-CoV-2

**Table 2.** Management of ectopic pregnancies

	Analysis	NCEPR		CEPR		Odds ratio <sup>a</sup> (95% CI)	P value
		n	n (%)	n	n (%)		
Outcome for all ectopic pregnancies							
Complication	Unadjusted 1 <sup>b</sup>	179	15 (8.4%)	162	12 (7.4%)	0.87 (0.40–1.93)	0.74
	Unadjusted 2 <sup>c</sup>	144	12 (8.3%)	126	6 (4.8%)	0.55 (0.20–1.51)	0.25
	Adjusted <sup>d</sup>	144	–	126	–	0.60 (0.20–1.78)	0.36
Scanned within 24 hours	Unadjusted 1 <sup>b</sup>	153	142 (92.8%)	156	140 (89.7%)	0.68 (0.30–1.51)	0.34
	Unadjusted 2 <sup>c</sup>	124	117 (94.4%)	123	112 (91.1%)	0.61 (0.23–1.63)	0.32
	Adjusted <sup>d</sup>	124	–	123	–	0.67 (0.23–1.95)	0.47
Management within protocol	Unadjusted 1 <sup>b</sup>	177	168 (94.9%)	160	154 (96.3%)	1.38 (0.48–3.95)	0.55
	Unadjusted 2 <sup>c</sup>	142	134 (94.4%)	125	120 (96.0%)	1.43 (0.46–4.50)	0.54
	Adjusted <sup>d</sup>	142	–	125	–	1.24 (0.35–4.32)	0.74
Surgical management	Unadjusted 1 <sup>b</sup>	179	130 (72.6%)	162	95 (58.6%)	0.53 (0.34–0.84)	0.007
	Unadjusted 2 <sup>c</sup>	144	107 (74.3%)	126	68 (54.0%)	0.41 (0.24–0.68)	0.001
	Adjusted <sup>d</sup>	144	–	126	–	0.51 (0.32–2.81)	0.03
Non-surgical management: medical/expectant management							
Medical management (versus expectant)	Unadjusted 1 <sup>b</sup>	49	28 (57.1%)	67	49 (73.1%)	2.04 (0.93–4.46)	0.07
	Unadjusted 2 <sup>c</sup>	37	18 (48.7%)	58	42 (72.4%)	2.77 (1.17–6.58)	0.02
	Adjusted <sup>d</sup>	37	–	58	–	3.46 (1.29–9.24)	0.01

	Analysis	NCEPR		CEPR		Odd ratio <sup>a</sup> (95% CI)	P-value
		n	Median [IQR]	n	Median [IQR]		
Expectant management							
Median no. of visits	Unadjusted 1 <sup>b</sup>	21	9 [5, 14]	16	3 [3, 5]	0.37 (0.23–0.60)	<0.001
	Unadjusted 2 <sup>c</sup>	19	9 [5, 14]	14	3 [3, 5]	0.38 (0.23–0.64)	0.001
	Adjusted <sup>d</sup>	19	–	14	–	0.34 (0.19–0.62)	0.001
Median length of treatment (days)	Unadjusted 1 <sup>b</sup>	21	10 [6, 20]	18	10 [8, 14]	1.02 (0.65–1.59)	0.94
	Unadjusted 2 <sup>c</sup>	19	10 [6, 20]	16	10 [8, 17]	1.06 (0.66–1.70)	0.81
	Adjusted <sup>d</sup>	19	–	16	–	1.21 (0.72–2.02)	0.46
Medical management							
Median no. of visits	Unadjusted 1 <sup>b</sup>	26	9 [6, 10]	48	6 [5, 8]	0.75 (0.62–0.91)	0.003
	Unadjusted 2 <sup>c</sup>	16	8 [5, 11]	41	6 [5, 7]	0.72 (0.57–0.90)	0.004
	Adjusted <sup>d</sup>	16	–	41	–	0.76 (0.60–0.96)	0.02
Median length of treatment (days)	Unadjusted 1 <sup>b</sup>	26	29 [21, 46]	49	24 [17, 35]	0.83 (0.61–1.13)	0.23
	Unadjusted 2 <sup>c</sup>	16	26 [18, 35]	42	23 [17, 31]	0.93 (0.64–1.35)	0.69
	Adjusted <sup>d</sup>	16	–	42	–	0.95 (0.65–1.37)	0.77

	Analysis	NCEPR [N = 130]		CEPR [N = 95]		Odd ratio <sup>a</sup> (95% CI)	P-value
		n	n (%)	n	n (%)		
Surgical management							
Laparotomy <sup>e</sup>	Unadjusted 1 <sup>b</sup>	126	3 (2.4%)	88	2 (2.3%)	0.95 (0.16–5.83)	0.96
	Unadjusted 2 <sup>c</sup>	104	3 (2.9%)	64	0 (0.0%)	–	–
	Adjusted <sup>d</sup>	104	–	64	–	–	–
First operator registrar	Unadjusted 1 <sup>b</sup>	100	77 (77.0%)	72	52 (72.2%)	0.78 (0.39–1.56)	0.48
	Unadjusted 2 <sup>c</sup>	83	66 (79.5%)	51	34 (66.7%)	0.52 (0.23–1.13)	0.10
	Adjusted <sup>d</sup>	83	–	51	–	0.55 (0.23–1.32)	0.18
Haemoperitoneum ≥500 ml	Unadjusted 1 <sup>b</sup>	109	26 (23.9%)	82	27 (32.9%)	1.57 (0.83–2.96)	0.17
	Unadjusted 2 <sup>c</sup>	88	20 (22.7%)	60	15 (25.0%)	1.13 (0.53–2.44)	0.75
	Adjusted <sup>d</sup>	88	–	60	–	1.17 (0.50–2.76)	0.72
Median length of stay (hours)	Unadjusted 1 <sup>b</sup>	124	24 [24, 45]	71	24 [24, 48]	1.05 (0.93–1.19)	0.43

**Table 2.** (Continued)

	Analysis	NCEPR [N = 130]		CEPR [N = 95]		Odd ratio <sup>a</sup> (95% CI)	P-value
		n	n (%)	n	n (%)		
Median haemoperitoneum (ml)	Unadjusted 2 <sup>c</sup>	101	24 [24, 48]	50	24 [24, 48]	1.03 (0.90–1.18)	0.64
	Adjusted <sup>d</sup>	101	–	50	–	1.01 (0.88–1.17)	0.84
	Unadjusted 1 <sup>b</sup>	109	150 [50, 400]	82	200 [10, 500]	1.02 (0.49–2.12)	0.95
	Unadjusted 2 <sup>c</sup>	88	100 [50, 300]	60	100 [0, 450]	0.60 (0.26–1.40)	0.24
	Adjusted <sup>d</sup>	88	–	60	–	0.64 (0.25–1.60)	0.34

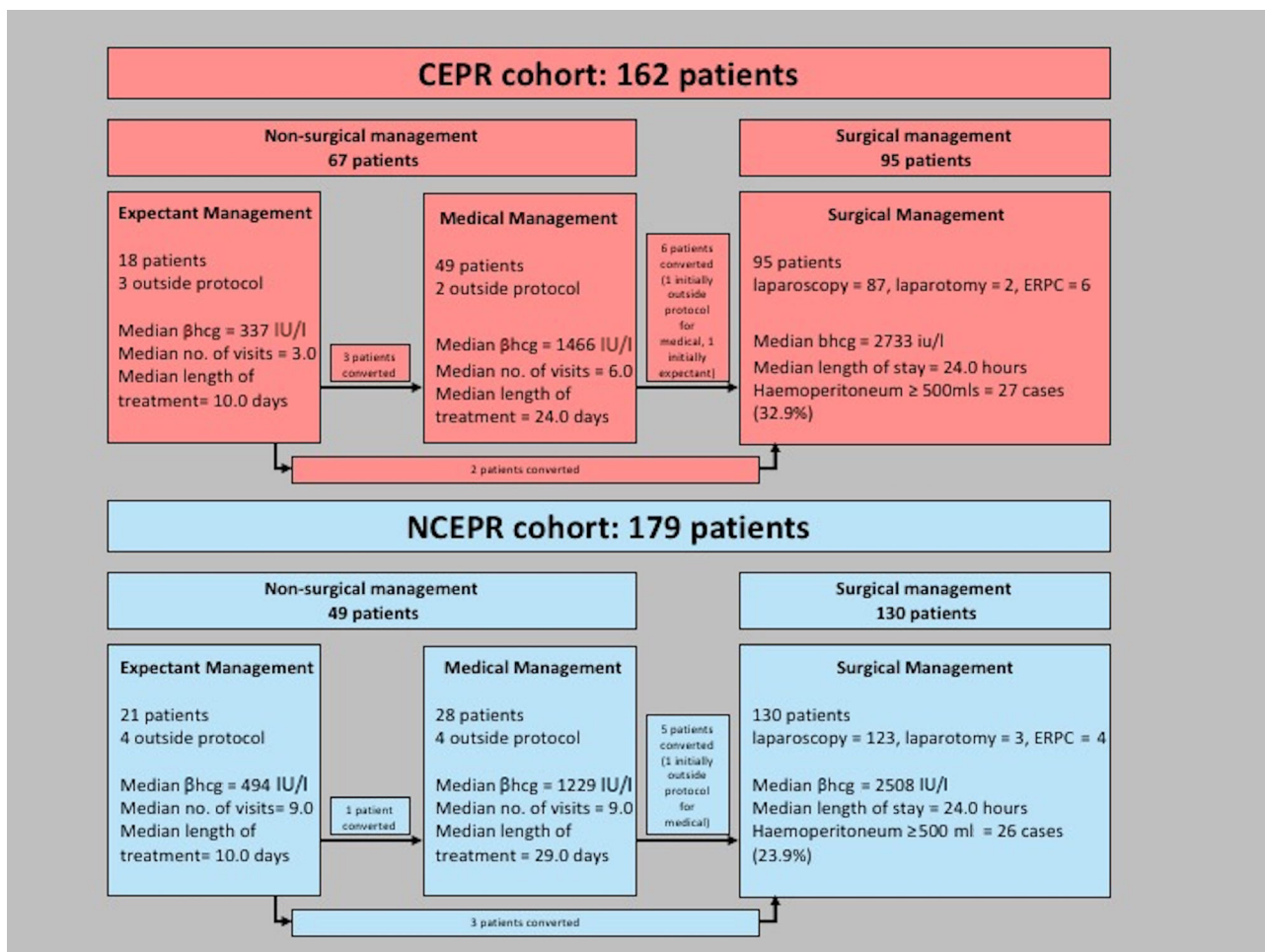
<sup>a</sup>Odds ratios reported as odds for CEPR group relative to odds for NCEPR group.

<sup>b</sup>Using all patients in the analysis.

<sup>c</sup>Using the same patients as in the adjusted analysis

<sup>d</sup>Adjusted for: gestational age, hCG (log scale), ethnicity, risk factors for ectopic and previous ectopic pregnancy.

<sup>e</sup>Only patients undergoing laparoscopy or laparotomy included in analysis. Excluding ERPC patients. Insufficient numbers of patients with a laparotomy for Analyses 2 and 3 to be performed.



**Figure 1.** Management of ectopic pregnancies in CEPR and NCEPR.

**Table 3.** Complications

Complication type (30 days)	CEPR N = 162	NCEPR N = 179	Clavien–Dindo grade (post-operative)
No complication	150 (92.6%)	164 (91.6%)	n/a
Ruptured ectopic pregnancy following initial expectant/medical management	3 (1.9%)	4 (2.2%)	n/a
Conversion from laparoscopy to laparotomy	1 (0.6%)	3 (1.7%)	n/a
Significant additional intra-operative procedure <sup>a</sup>	0	2 (1.1%)	n/a
Anaphylaxis to muscle relaxant requiring ITU admission <sup>b</sup>	1 (0.6%)	0	n/a
Methotrexate toxicity	1 (0.6%)	0	n/a
Transfusion pre-operatively	0	1 (0.6%)	n/a
Transfusion pre-methotrexate	1 (0.6%)	0	n/a
Concurrent LRTI	0	1 (0.6%)	1
Transfusion post-operatively	0	2 (1.1%)	2
Post-operative pyrexia	1 (0.6%)	0	1
Re-presentation with post-operative pain/bleeding	3 (1.9%)	1 (0.6%)	1
Re-presentation with post-operative infection (PID) <sup>b</sup>	1 (0.6%)	0	1
Re-presentation post-operative pain and rising hCG <sup>c</sup>	1 (0.6%)	0	2
Repeat laparoscopy <sup>d</sup>	0	1 (0.6%)	3b

ITU, intensive treatment unit; LRTI, lower respiratory tract infection; PID, pelvic inflammatory disease.

<sup>a</sup>One patient required adhesiolysis, salpingectomy + bilateral ovarian cystectomy and one patient required salpingectomy + small bowel resection.

<sup>b</sup>Same patient.

<sup>c</sup>Required further management with methotrexate.

<sup>d</sup>First laparoscopy for evacuation of blood and second laparoscopy for oophorectomy after ongoing rising hCG.

polymerase chain reaction swab. Of those 80 patients tested with a polymerase chain reaction swab, none (0/80) were positive for SARS-CoV-2.

### Surgical management of ectopic pregnancies in CEPR cohort

COVID-19 pandemic 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,  $P = 0.74$ . The odds ratio for complication in the CEPR cohort versus NCEPR cohort were 0.87 (CI 0.40, 1.93) and 0.60 (CI 0.20, 1.78) in the adjusted analysis (Table 2). Table 3 illustrates complications (including post-operative reported 30-day complications) for CEPR and NCEPR cohorts (Appendix S3). 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 ( $P = 1.000$ ). 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 within the UK. The five hospitals included in this study continued to provide early pregnancy services in line with BSGE/RCOG guidance by having a senior clinician in theatre for all surgical cases and by each hospital endeavouring to maintain senior clinician decision-making in the early pregnancy unit. However, the particulars of re-organisation of hospitals during the COVID-19 pandemic will vary among hospitals. This in itself is a strength of this study, as it helps to reduce bias by including data from a number of hospitals.

We hypothesised that women with ectopic pregnancy would present later during the pandemic and, as a result, more women would present with haemodynamic instability. This hypothesis was rejected because only a minority of women delayed their presentation because of COVID-19 and there was no increase in patients presenting with haemodynamic instability. This is in contrast to the study by Casadio et al., which reported that the proportion of ruptured ectopic pregnancies was significantly higher during the lockdown in comparison with the pre-lockdown

period (6/9 [66.7%] versus 52/201 [25.9%];  $P = 0.02$ ).<sup>19</sup> However, the small sample size ( $n = 9$ ) in their COVID-19 cohort significantly limits any definitive conclusions that can be drawn from their findings.

Similar to a recent study by Bhambhani et al.,<sup>20</sup> there was no decrease in the number of women presenting with ectopic pregnancy during the peak of the pandemic. Although the mean gestational age in patients presenting in the CEPR cohort was higher than in the NCEPR cohort (6.7 weeks [SD 1.7] versus 6.0 weeks [SD 1.6];  $P = 0.002$ ), this difference was not clinically significant.

In this study, fewer cases of ectopic pregnancy were managed surgically in the CEPR versus the NCEPR cohort. However, despite this change there was no evidence of a difference in the observed 30-day complication rate between cohorts. This supports the joint statement from RCOG/BSGE and subsequent RCOG guidance,<sup>14,16</sup> which recommended that non-surgical methods of treatment should be actively recommended to reduce the need for hospital admission.<sup>16</sup> However, it is important to explore the acceptability of this among patients, including the psychological impact of implications of methotrexate use, such as advice to avoid pregnancy for 3 months following treatment.

Furthermore, CEPR 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. Again, we must consider how fewer patient visits and avoidance of surgery may influence women's perceptions regarding the care they receive. Exploring these factors is important before implementation of longer-term changes in early pregnancy services.

Women in the 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 who 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 because of inherent differences within the demographics of the compared cohorts.

As part of our exploratory sub-group analysis, we observed a non-significant trend for a smaller proportion of women managed non-surgically to receive expectant management. This may have been clinician driven, as the providers were trying to guard against failed expectant management. This did not appear to result in a higher rate of reported complications. However, whether this will be integrated into 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 the first-line surgical approach in women with ectopic pregnancy.<sup>21</sup> There was no increase in the laparotomy rate for women who underwent surgical management (abdominal approach) in the CEPR cohort in this study (2.3% CEPR cohort versus 2.4% NCEPR cohort). Of the CEPR surgical cases, 81.0% (64/95) 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 COVID-19, 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 the proportion of surgical procedures performed by consultant versus registrar ( $P = 0.48$ ). Despite concern that the pandemic will have an impact on training opportunities in gynaecological surgery,<sup>22</sup> it is promising to consider that trainees will probably continue to operate during the pandemic in the context of emergency laparoscopy for the management of ectopic pregnancies.

The NHS in the UK has strived to continue to deliver emergency care, including early pregnancy services, evidenced by multiple statements in response to the changing delivery of care during the pandemic.<sup>14–16</sup> As previously stated, this includes clear guidance regarding early pregnancy scans.<sup>14</sup> This differs from Casadio et al.'s comments discussing potential explanations for increased numbers of ruptured ectopic pregnancies in their study, such as 'the reduction of early first-trimester scans, which are quite popular but elective in our region'.<sup>19</sup> It is important to consider how other countries have responded in their provision of both emergency and non-urgent healthcare services, including countries that do not offer free access to health care at the point of use. Despite encouraging findings from this study, data from studies worldwide raise concern regarding the potential deleterious consequences of an unstudied reduction of healthcare services. Robertson et al.<sup>23</sup> address this in a study quantifying the potential indirect effect of the COVID-19 pandemic, their analysis illustrating that widespread disruption to health systems in low- and middle-income countries will lead to substantial increases in maternal and child deaths.

### Strengths and weaknesses

We report on a multicentre study, but 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, although this study compared a pandemic cohort with a historical cohort in the same centres, patients were



not matched. Despite observed non-significant differences between cohorts, the subsequent exploratory comparative analysis should be viewed within this context. A specific weakness of this study is that the patient and clinician decision-making process regarding management of ectopic pregnancy was not specifically explored. In turn, further research is also required to ascertain whether higher rates of non-surgical management of ectopic pregnancy would be acceptable to women.

## Conclusion

This study explored the impact of advised management changes in women with ectopic pregnancy due to the COVID-19 pandemic, comparing their experience with that of a historical cohort pre-pandemic. Women were found to undergo significantly higher rates of non-surgical management during our first wave of COVID-19. Women managed non-surgically in the CPER cohort were also managed with fewer hospital attendances. There was no evidence of a statistical difference in the observed 30-day complication rate between cohorts. Further research is required to ascertain whether higher rates of non-surgical management could be routinely adopted in future practice, and whether this would be acceptable to women with ectopic pregnancy.

## Disclosure of interests

No conflicts to declare. Completed disclosure of interests form available to view online as supporting information.

## 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. SP and PB were responsible for statistical analysis. 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.

## Details of ethics approval

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 May 2020).

## Funding

None.

## Data availability statement

Data available on request from the authors.

## Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Appendix S1.** Template data collection forms.

**Appendix S2.** Comparison of recommendations from RCOG/BSGE, IUSOG and RCOG publications during COVID-19 pandemic 2020.

**Appendix S3.** Missing data for 30-day complications for CEPR and NCEPR cohorts. ■

## References

- 1 Panelli DM, Phillips CH, Brady PC. Incidence, diagnosis and management of tubal and nontubal ectopic pregnancies: a review. *Fertil Res Pract* 2015;1:1–20.
- 2 Odejinmi F, Huff KO, Oliver R. Individualisation of intervention for tubal ectopic pregnancy: historical perspectives and the modern evidence based management of ectopic pregnancy. *Eur J Obstet Gynecol Reprod Biol* 2017;210:69–75.
- 3 McGurk L, Oliver R, Odejinmi F. Severe morbidity with ectopic pregnancy is associated with late presentation. *J Obstet Gynaecol* 2019;39:670–4.
- 4 World Health Organisation. WHO Director-General's opening remarks at the media briefing on COVID-19 – 11 March 2020 [www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020]. Accessed 20 November 2020.
- 5 Kc A, Gurung R, Kinney MV, Sunny AK, Moinuddin MD, Basnet O, et al. Effect of the COVID-19 pandemic response on intrapartum care, stillbirth, and neonatal mortality outcomes in Nepal: a prospective observational study. *Lancet Glob Health* 2020;8:e1273–81.
- 6 Khalil A, Von Dadelszen P, Draycott T, Ugwumadu A, O'Brien P, Magee L. Change in the incidence of stillbirth and preterm delivery during the COVID-19 pandemic. *JAMA* 2020;324:705–6.
- 7 Appleby J. What is happening to non-covid deaths? *BMJ* 2020;369:m1607.
- 8 England N. A&E attendances and emergency admissions 2019–20 [www.england.nhs.uk/statistics/statistical-work-areas/ae-waiting-time-s-and-activity/ae-attendances-and-emergency-admissions-2019-20]. Accessed 20 November 2020.
- 9 Vigneswaran Y, Prachand VN, Posner MC, Matthews JB, Hussain M. What is the appropriate use of laparoscopy over open procedures in the current COVID-19 climate? *J Gastrointest Surg* 2020;24:1686–91.
- 10 Mallick R, Odejinmi F, Clark TJ. COVID-19 pandemic and gynaecological laparoscopic surgery: knowns and unknowns. *Facts Views Vis ObGyn* 2020;12:3–7.
- 11 De Simone B, Chouillard E, Di Saverio S, Pagani L, Sartelli M, Biffi WL, et al. Emergency surgery during the COVID-19 pandemic: what you need to know for practice. *Ann R Coll Surg Engl* 2020;102:323–32.
- 12 Royal College of Surgeons. Guidance for surgeons working during the COVID-19 pandemic. 2020. [https://www.rcseng.ac.uk/corona-virus/joint-guidance-for-surgeons-v1/]. Accessed 4 April 2020.
- 13 Nepogodiev D, Glasbey JC, Li E, Omar OM, Simoes JF, Abbott TE, et al. Mortality and pulmonary complications in patients undergoing surgery with perioperative SARS-CoV-2 infection: an international cohort study. *Lancet* 2020;396:27–38.

- 14 Royal College of Obstetricians and Gynaecologists (RCOG). Guidance for rationalising early pregnancy services in the evolving coronavirus (COVID-19) pandemic [www.rcog.org.uk/globalassets/documents/guidelines/2020-05-15-guidance-for-rationalising-early-pregnancy-services-in-the-evolving-coronavirus-covid-19-pandemic.pdf]. Accessed 25 May 2020.
- 15 ISUOG. IUSOG consensus statement on rationalization of early pregnancy care and provision of ultrasonography in context of SARS-CoV-2 [www.isuog.org/resource/isuog-consensus-statement-on-rationalization-of-early-pregnancy-care-and-provision-of-ultrasonography-in-context-of-sars-cov-2-pdf.html]. Accessed 25 April 2020.
- 16 Royal College of Obstetricians & Gynaecologists (RCOG), BSGE. Joint RCOG/BSGE statement on gynaecological laparoscopic procedures and COVID-19. Joint RCOG/BSGE statement on gynaecological laparoscopic procedures and COVID-19. 2020 [https://www.bsge.org.uk/news/joint-rcog-bsge-statement-on-gynaecological-laparoscopic-procedures-and-covid-19/]. Accessed 15 April 2020.
- 17 Elson CJ, Salim R, Potdar N, Chetty M, Ross JA, Kirk EJ, et al. Diagnosis and management of ectopic pregnancy: green-top guideline No. 21. *BJOG* 2016;123:15–55.
- 18 National Institute for Health and Care Excellence (NICE). Ectopic pregnancy and miscarriage: diagnosis and initial management NICE guideline [NG126] [https://www.nice.org.uk/guidance/ng126]. Accessed 25 April 2020.
- 19 Casadio P, Youssef A, Arena A, Gamal N, Pilu G, Seracchioli R. Increased rate of ruptured ectopic pregnancy in the COVID-19 pandemic: an analysis from the North of Italy. *Ultrasound Obstet Gynecol* 2020;56:289.
- 20 Bhambhani HP, Rodrigues AJ, Jonathan SY, Carr JB, Gephart MH. Hospital volumes of 5 medical emergencies in the COVID-19 pandemic in 2 US medical centers. *JAMA Intern Med* 2021;181:272–274.
- 21 Rimmer MP, Al Wattar BH, Barlow C, Black N, Carpenter C, Conti-Ramsden F, et al. Provision of obstetrics and gynaecology services during the COVID-19 pandemic: a survey of junior doctors in the UK National Health Service. *BJOG* 2020;127:1123–8.
- 22 Royal College of Obstetricians and Gynaecologists (RCOG). The impact of the redeployment of maternity staff during COVID-19 [www.rcog.org.uk/globalassets/documents/careers-and-training/workplace-and-workforce-issues/202006/2020-06-the-impact-of-the-redeployment-of-maternity-staff-during-covid-19.pdf]. Accessed 25 November 2020.
- 23 Robertson T, Carter ED, Chou VB, Stegmuller AR, Jackson BD, Tam Y, et al. Early estimates of the indirect effects of the COVID-19 pandemic on maternal and child mortality in low-income and middle-income countries: a modelling study. *Lancet Glob Health* 2020;8:e901–8.