

# To fight or to flee? – a systematic review of ectopic pregnancy management during Covid-19.

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## Abstract

**Background:** Concerns about virus spread during surgery contributed to changes in the clinical management of ectopic pregnancies (EP) during the COVID19 pandemic. **Objective:** To compare published data on EP management prior versus during the COVID-19 pandemic and evaluate any difference in the management, rupture rate and complications where Early Pregnancy Unit (EPU) structures exist. **Search strategy:** We performed a systematic review of the literature using a keyword strategy based on our PICO criteria. **Selection criteria:** We included studies which recruited women diagnosed with ectopic pregnancy and compared the management during and prior the COVID-19 pandemic peak. **Data collection and Analysis:** Three independent reviewers screened the literature and extracted the data. Meta-analysis of the data was performed on Revman. **Main Results:** Our search yielded 34 studies; 12 were included in our meta-analysis (3122 women). We found no difference in the type of management of EP between the pre-Covid and Covid cohorts [2714 women, OR 0.99(0.63-1.55), p=0.96, I2=77%]. We observed a non-statistically significant reduction of surgical management within the EPU branch ([OR 0.47(0.19-1.13), p=0.09, I2=81%]). There was no difference in the ectopic rupture rate in units with EPU [OR= 0.66 (0.33-1.31), p=0.24, I2=37%]. In contrast, in non-EPU (NPEU) the risk of ruptured EP [OR=2.86(1.84-4.46), p<0.01 I2=13%] and complications [OR=1.69(1.23-2.31), p=0.001, I2=45%] were increased. **Conclusions:** The worldwide trend was not reflected in the UK suggesting that EPU may have contributed to prompt diagnosis and safe management of EP. **Funding:** No funding was received. **Keywords:** ectopic pregnancy, COVID 19, meta-analysis, early pregnancy unit

## Introduction

The risk of ectopic pregnancy (EP) is reported as 1 to 2% of all pregnancies (1). During the COVID-19 Pandemic, in an attempt to prevent overwhelming of healthcare systems and reduce community transmission of the virus, governments advised patients to attend hospital only when absolutely necessary. As a result, some studies reported a significant reduction in presentation to emergency gynaecological services, potentially leading to significant delay in diagnosis (2-7). EP remains associated with significant morbidity and a maternal mortality rate of 0.2 per 1000 in the UK (8). Current management options include expectant, medical and surgical treatment. Laparoscopic surgery is increasingly becoming the gold standard for surgical management (9). Concerns regarding the theoretical risks of surgery during the COVID-19 pandemic – including the use of aerosol generating procedures such as general anaesthetics and use of pneumoperitoneum and electrosurgery during laparoscopy (10, 11)- contributed to significant changes in clinical management to prevent contamination of healthcare professionals (12-14). Within a few months, advice from learned societies to change protocols for presentation in early pregnancy assessment units (15) and recommendations around the safe use of laparoscopy for emergency treatment during the pandemic were released (16-18).

The economic stability of all nations during the pandemic has been tested based upon their ability to anticipate and cope with the effects, resist the adverse outcomes and recover from the negative impacts. To address the above four vulnerability parameters effectively it is necessary to identify effective and safe methods of healthcare delivery. It is imperative to identify protocols and services that work effectively and in alignment with the restrictions brought about by the pandemic. Keeping these essential national policies in mind, we have looked at the effect the pandemic has had on the management of one of the most common acute life-threatening disease conditions in Gynaecology: ectopic pregnancy (EP).

Ideal pathways for the management of EP are through early pregnancy assessment units as exemplified in the UK. All NHS Trusts offer a structured emergency gynaecology service (early pregnancy unit or EPU), where women can self-refer with early pregnancy symptoms such as pain or vaginal bleeding. This helps to avoid prolonged waiting time and improves patient safety (19). Previous reviews focusing on pregnancy outcomes during the COVID-19 pandemic have suggested an increase in surgical management of EP (20). However, the quality of published evidence is varied and the results are conflicting. This rapid review compares the management of ectopic pregnancies during COVID-19 peak waves versus prior standard practice. Additionally, it assesses the impact of the pandemic on the risk of ectopic pregnancy rupture and the reported complication rates. Finally, we specifically compare those outcomes across units with or without early pregnancy assessment infrastructure (EPU).

## Method

A systematic review was performed following a prospective protocol according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

### *Registration:*

The protocol was registered prospectively into PROSPERO (registration number: CRD42021257133).

### *Selection criteria:*

Predefined “Population intervention Comparison Outcomes – PICO” criteria were used to select studies for inclusion. We included any study which recruited women who were diagnosed on US scan or clinically with ectopic pregnancy (Population), and compared the type of management surgical versus non-surgical (Intervention) during and/or prior Covid-19 peak waves. The primary outcome of the study was the type of management of EP, the secondary outcomes were the incidence of ruptured EP at presentation and the rate of complications. We compared these outcomes prior to and during the COVID-19 peak waves. These outcomes were then also compared across units with (EPU) or without EPU (NEPU) organised infrastructure.

### *Search Strategy:*

A systematic bibliographic search of peer reviewed journals of eight computerised databases was undertaken (PubMed, NHS evidence, CINAHL, EMBASE, EMCARE, MEDLINE, LitCovid and Cochrane library), with no language restriction. The last search was conducted on 13<sup>th</sup> October 2021. The search terms “ectopic pregnancy” and “covid” or “coronavirus” or “Sars-cov” were used in all possible combinations. The search was augmented by identifying additional studies from references cited in primary sources and review manuscripts.

### *Screening of the literature and data extraction:*

Three independent reviewers screened the literature (AM, MS and SP). A data extraction spreadsheet was developed and agreed between authors. The selected studies were comprehensively examined and relevant data were extracted from each paper and inputted by the first author (AM) and crosschecked by the authors MS and SP. Any disagreement was resolved by the senior author FO. TP contacted all corresponding authors or hospitals to enquire about the existence of EPU structure or any specific guideline for management of ectopic pregnancy during the pandemic peak wave.

### *Quality assessment:*

A modified set of questions was used to assess the internal and external validity of the studies. Internal validity was assessed based on study design (prospective/ retrospective/ randomised), recruitment of population (consecutive/randomised/other) and ascertainment of reported outcomes (USS diagnosis or clinical, Surgical Confirmation). External validity was assessed by reviewing the representativeness of the population. All items were classified as being of high or low risk for bias. A study found to be of high risk for bias in more than two categories for internal validity was classified as "high risk" for internal validity. The single item (population representativeness) classifies each study as being of high or low risk for external validity.

#### *Patient involvement:*

Patient were not involved in the design and conduct of this research. Data were extracted from relevant published studies to perform a systematic review.

#### *Data synthesis:*

Analysis of pooled rates of outcomes using random or fixed effects model and computed 95% CI were performed. Selection of model of meta-analysis was based on the calculated heterogeneity which was assessed using I<sup>2</sup> statistic. All analyses were performed on RevMan (version 5.0).

## **Results**

The initial literature search yielded 34 titles and abstracts. Following primary screening two conference abstracts were excluded. 17 articles were removed as they did not meet inclusion criteria: five case reports, four letters to editor, four reviews, one statement, one survey. Five studies were excluded due to the lack of clarity in the data presented which did not allow for numerical extraction. 12 studies were included in this meta-analysis.

#### *Figure 1*

#### *Included study characteristics*

12 studies, involving a total of 3122 women, were eligible for data extraction (Table 1). Five studies were from Europe (UK and Italy) (3) (21) (22) (23, 24), four from America (USA and Canada) Gomez (4) (6) (7) (25) and three from the Middle East (Israel) (2, 26),(27) . Nine studies were single centre retrospective studies (2, 3, 6)(10)(22, 23, 25-27), one was a multicentred prospective study (21) and two multicentred retrospective studies (4),(24). All studies compared a cohort of women diagnosed with an ectopic pregnancy during the first Covid wave in early 2020, with a similar cohort managed pre-Covid: 2018-2019. The Covid timeframes are strictly matched with the national lockdown in four studies (3) (6) (23) (26). The other studies used a timeframe incorporating the lockdown period but extending beyond when restrictions were lifted. The pre-Covid timeframes were based on a similar period the year before, 2019, or from 2 previous years (2018 and 2019) or during the months preceding the first Covid wave. The total population of the analysis includes 3122 women; 1828 women in the pre-Covid population versus 1294 women in the Covid population. The two cohorts were matched for demographics in each individual study. EPU system are implemented nationally in the UK only. Studies conducted in Italy, Israel, US and Canada do not have such structures in the hospitals involved.

#### *Table 1*

#### *Quality assessment:*

67% (N=8) of the included studies were classified as low risk for external validity. Only 18% (N=2) of the studies were low risk for internal validity, mostly due to the predominance of retrospective studies. All studies included consecutive recruitment over a time frame.

#### *Figure 2*

#### *Outcomes:*

Surgical versus non-surgical management

10 studies involving 2714 women, reported on the method of management of ectopic pregnancies during Covid compared to a pre-Covid cohort (2,3,6)(21-27). A total of 719 women underwent surgical management in the pre-Covid cohort versus 551 in the Covid cohort. In the pre-Covid cohort, 761 patients with ectopic pregnancy were managed non-surgically compared with 669 women in the Covid cohort. Details of women managed medically with methotrexate and conservatively can be found in Appendix S1.

Overall there was no difference in the type of management (surgical versus non-surgical) [OR 0.99(0.63-1.55),  $p=0.96$ ,  $I^2=77\%$ ] in the pre-Covid vs Covid cohorts. A similar trend was reported in the NEPU group [OR=1.40(0.89-2.20),  $p=0.15$ ,  $I^2=58\%$ ]. In the EPU group there was an increased trend of non-surgical management, however, overall this was not statistically significant [OR 0.47(0.19-1.13),  $p=0.09$ ,  $I^2=81\%$ ].

### Figure 3

#### Ruptured ectopic rate

9 studies including 1531 women compared the number of ruptured ectopic pregnancies during Covid to a matched pre-Covid cohort (2,6,21-27). Data collected from these studies were analysed to compare the rate of rupture between the two cohorts. During the Covid pandemic 99/564 cases of ruptured ectopic were reported versus 179/967 in the pre-Covid cohort. (Appendix S2)

Random effects meta-analysis revealed that during Covid there was an increased pooled risk of rupture rate [OR 1.91 (1.01-3.61),  $p=0.01$ ,  $I^2=60\%$ ]. However, sensitivity analysis focused on EPU structures revealed no difference in the pooled risk of rupture rate during the Covid pandemic [OR= 0.66 (0.33-1.31),  $p=0.24$ ,  $I^2=37\%$ ]. In contrast, in NEPU structures there was a clear increase pooled risk of ruptured ectopic pregnancy at presentation [OR=2.86(1.84-4.46),  $p<0.01$ ,  $I^2=13\%$ ].

### Figure 4

#### Complication rates

Five studies including 2435 women commented specifically on complication rates (2,4,21,25,26) ( Appendix S3). However, there was considerable variation in the reporting of complications. Blood transfusion or iron infusion, hemoperitoneum of more than a litre, admission to ICU, significant operative procedure, prolonged hospitalisation and repeat procedure were reported as complications. The most common complication reported in the five studies included was the use of blood products.

### Figure 5

During the pandemic, there was an overall increased pooled risk for complications secondary to the management of ectopic pregnancy [OR=1.45(1.09-1.93),  $p=0.01$ ,  $I^2=57\%$ ]. Focusing on NEPU structures this trend was even higher [OR=1.69(1.23-2.31),  $p=0.001$ ,  $I^2=45\%$ ]. However, in the single EPU structure included the analysis there was no difference in the reported complications during the pandemic [OR=0.78 (0.38-1.60),  $p=0.50$ ].

### Discussion

This rapid systematic review of 12 studies compares the management of ectopic pregnancy during the peak of covid-19 with a similar cohort pre-Covid. Despite the initial perceived risks of viral transmission associated with surgery and general anaesthetics (10), there was no significant difference in the rate of surgical management between the covid-19 and pre-Covid cohorts overall. This trend is confirmed in studies conducted where EPU structures have not been implemented.

Werner *et al* reported an increased rate of undiagnosed EP during the height of Covid-19 resulting in a higher rate of haemodynamically unstable patients and need for surgical management (28). Similar findings of increased surgical management, mostly secondary to higher rate of rupture, were expressed in a meta-analysis of three studies by Chmielewska *et al* (20) . However, in hospitals where EPU structures exist, there is a clear trend towards non-surgical management. Conservative or medical management was advised for the appropriately selected patients (11). This finding is particularly supported by 2 multicentred studies by Platts

and Kyriacou (21,24). This trend could be explained by the advice from national bodies recommending the use of conservative and medical management for EP during the pandemic (15). This guidance was motivated by safety concerns with the aim to limit hospital foot fall and unnecessary exposure to potential aerosol generating procedures for both patients and staff. When surgery was required, in the UK, minimal access surgery was recommended over open surgery with use of additional precautions (smoke extractor, full PPE, minimal use of electrosurgery) as the lack of evidence of coronavirus transmission did not mean infection is not possible (18, 29) .

We highlight a significantly increased rate of ruptured ectopic pregnancies within the Covid-19 cohort in the NEPU branch of our study. Many studies reported a significant reduction in the number of women presenting with gynaecological problems to emergency departments during the covid-19 pandemic (2). It is speculated that women who had to attend main emergency departments would delay their visit for fear of infection by Covid-19. In these circumstances, women were found to be more symptomatic at presentation (2, 26). Such delay in presentation offers an explanation to the increased rate of ruptured ectopic, and subsequently, to the higher use of blood transfusion and higher complication rate. A case series from a tertiary referral centre in India revealed 28 cases of rupture out of 32 diagnosis of ectopic pregnancies during an 8-month period at the peak of Covid-19 (30). Our meta-analysis did not reveal any increase in the rate of ectopic rupture during Covid in healthcare system with EPU structures. Kyriacou *et al* report no difference in the ectopic rupture rate during Covid despite a slightly higher level of hHCG at diagnosis (24).

Our data analysis revealed no difference in the complication rate in the EPU cohort. In contrast, in the NEPU cohort, the rate of complication was significantly increased (RR 1.69) during Covid-19. *Anteby et al* commented that in their study, women with a confirmed diagnosis of EP were significantly more symptomatic on arrival (2). This may explain the higher requirements of blood transfusion and other complications for women in the NEPU Covid cohort.

The structured systems of EPU in the UK, where women are encouraged to self-refer, may have prevented the delay in presentation disclosed in studies without EPU structures. Also, A and E would be very busy during covid peaks with even longer waiting time for non-covid related presentations. This may be coupled with the fact that these units are often away from the Accident and Emergency department, hence reducing women fears of possible nosocomial contamination with coronavirus. During the Covid peak wave, women continued to self-refer to EPU with symptoms such as pain or bleeding in early pregnancy and be assessed within 24 hours with a transvaginal scan. Equally, if further visits were indicated for follow up of PUL or medical treatment with methotrexate, they could safely attend consecutive visits in the EPU with an appointment. We did not find evidence of a similarly structured Early Pregnancy Unit system in any of the countries where other studies were published: USA, Canada, Israel and Italy. The value of such units has been assessed in the USA (31), Canada (32),(33), and Australia (34) with good evidence of cost effectiveness. Despite EPU reported efficiency in reducing repetitive assessments and improving follow up of women with ectopic pregnancy, it has not yet been integrated into healthcare systems worldwide.

We have analysed the effect of the pandemic restrictions on the presentation, management and ensuing complications of ectopic pregnancies based on data from 12 studies published world-wide, involving various healthcare systems, all impacted by the Covid-19 pandemic. This was also a good opportunity to compare existing structures of early pregnancy and emergency gynaecology services. And importantly, we have sought to identify the safest and most efficient method of service provision for ectopic pregnancy as wide dissemination of the knowledge of such a service and its adoption by all health services would ensure a robust recovery programme and will enable the health service to resist future pandemics efficiently.

A retrospective study reported a high patient satisfaction level after surgical care -including some gynaecological cases- during Covid 19. Patients rated the hospital stay high and also reported very good emotional and mental health following surgery (35). We did not identify any published patient's satisfaction survey related to early pregnancy care during Covid-19 in either type of healthcare structures (EPU and/or NEPU). Evaluating the stakeholders' opinion and feedback in EPU versus NEPU in times of a pandemic crisis could contribute to understanding the difference in outcomes that we revealed in our analysis.

## Limitations

Most studies included in our analysis were retrospective, and therefore there was an absence of standard operative procedures. There was no standardised method to report findings amongst these studies. For example, reporting a “ruptured ectopic” is defined by the presence of hemoperitoneum. There was no standardised reporting of patients’ haemodynamic status nor of reported complications amongst studies. Some studies only focused on management methods or rupture rate and did not disclose data regarding complication rates (6,15,17,18,21,22,23). Although delays in attendance to emergency services were described in many studies, only three studies compared gestational age at diagnosis.

## Conclusion

In the evanescent and changing landscape of post-Covid healthcare, clinical findings and advice continue to evolve and change. Worldwide, health care systems have come to realise that pandemics might be the norm for the future and thus the onus is to identify the most efficient means of practice that worked seamlessly during the pandemic. As our review demonstrates, there is a significant difference in outcomes between the NEPU and EPU groups of women who presented with ectopic pregnancy during the COVID-19 pandemic. We believe that this reinforces the need for worldwide development of EPU systems to prevent morbidity during future pandemics. The fight to implement EPU systems should be a response to help flee from the collateral damages of the pandemics. Policy makers and health care leaders should make safe care of women a priority in future pandemics or emergency situations and incorporating proven efficient ways of working will go far towards achieving this goal.

## Authors contribution

AM, MS and JO contributed to the design of the study. AM, MS and SP conducted the literature screening and data extraction independently. TP investigated the healthcare structures and guidelines in the different countries where data was extracted from. AM and MS analysed the data. JO participated to discussion about the results. AM wrote the first draft. All authors contributed to editing the paper.

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