

Review

To Fight or to Flee? A Systematic Review of Ectopic Pregnancy Management and Complications During the Covid-19 Pandemic

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Abstract. *Background/Aim:* During the COVID-19 pandemic, concerns regarding theoretical risks of surgery contributed to changes in clinical management to prevent contamination. We looked at the effect the pandemic had on the management of ectopic pregnancy. Our review compares published data on pre-COVID to COVID management of ectopic pregnancies and evaluates the differences where Early Pregnancy Unit (EPU) structures exist. *Materials and Methods:* We performed a systematic review of the published evidence using a keyword strategy. The “Population Intervention Comparison and Outcome” (PICO) criteria were used to select studies. Three independent reviewers agreed on the data extracted after screening of the literature. The total population analysed included 3122 women. A meta-analysis of the included studies was completed using a random or fixed effect model depending on the heterogeneity (I^2). Our outcomes were the following: type of management of ectopic pregnancy (EP), incidence of ruptured EP and rate of complications. We compared units with and without EPU infrastructure. *Results:* We included every study which recruited women diagnosed with ectopic pregnancy and compared the type of management during and prior the COVID-19 peak. Our literature search yielded 34 papers. 12 were included using the PRISMA guidelines. We observed 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 overall but a reduction of surgical management in EPU structures. There was no difference in the ectopic rupture rate within the EPU branch [$OR=0.66$ (0.33-1.31), $p=0.24$, $I^2=37\%$]. In contrast, in non-EPU (NPEU) structures there was a clear increased risk of ruptured ectopic pregnancy [$OR=2.86$ (1.84-4.46), $p<0.01$, $I^2=13\%$] and complications [$OR=1.69$ (1.23-2.31), $p=0.001$, $I^2=45\%$]. *Conclusion:* The risk of ruptured ectopic and complications was significantly higher in the absence of EPU structures. This worldwide trend was not reflected in the UK, where EPU systems are widespread, suggesting that EPU structures contributed to prompt diagnosis and safe management. In the post-COVID era, healthcare systems have come to realise that pandemics might become the norm and thus the onus is to identify services that have worked seamlessly.

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 delays in diagnoses (2-7). Despite improvements in the management of EP, it still 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 management. 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 the use of pneumoperitoneum and electrosurgery during laparoscopy

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Key Words: Ectopic pregnancy, Covid-19, pandemic, early pregnancy units, ectopic pregnancy rupture, review.



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(10, 11), also contributed to significant changes in clinical management to prevent contamination of healthcare professionals (12-14). Within a few months, advice from academic 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 the impact, cope with the effects, resist the adverse outcomes and recover from the negative impacts. To ensure that the above four vulnerability parameters are addressed effectively it is necessary to identify and evolve effective and safe methods of healthcare delivery. It is imperative to identify protocols and services in place which would work effectively and in alignment with the restrictions and alternative methods of working 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 by the UK system. All NHS Trusts offer a structured emergency gynaecology service (early pregnancy unit or EPU), as a standard of care, 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 varies, and the results are conflicting. This rapid review aims to compare the management of ectopic pregnancies during COVID-19 peak waves *versus* prior standard practice. In addition, this review intends to assess the impact of the pandemic on the risk of ectopic pregnancy rupture at presentation as well as the overall reported complication rates. Finally, we plan to specifically compare those outcomes across units with or without early pregnancy assessment infrastructure (EPU).

Materials and Methods

Systematic review registration. A systematic review was performed following a prospective protocol according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. 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 ultrasound scan or clinically with ectopic pregnancy (Population) and compared the type of management surgical *versus* non-surgical (Intervention) during and/or prior to the 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, screening of the literature and data extraction. 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 October 13th, 2021. The search terms “ectopic pregnancy”, “covid”, “coronavirus” and “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. 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, 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.

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 the I^2 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 the editor, four reviews, one statement and 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).

Ectopic pregnancy management during Covid 19

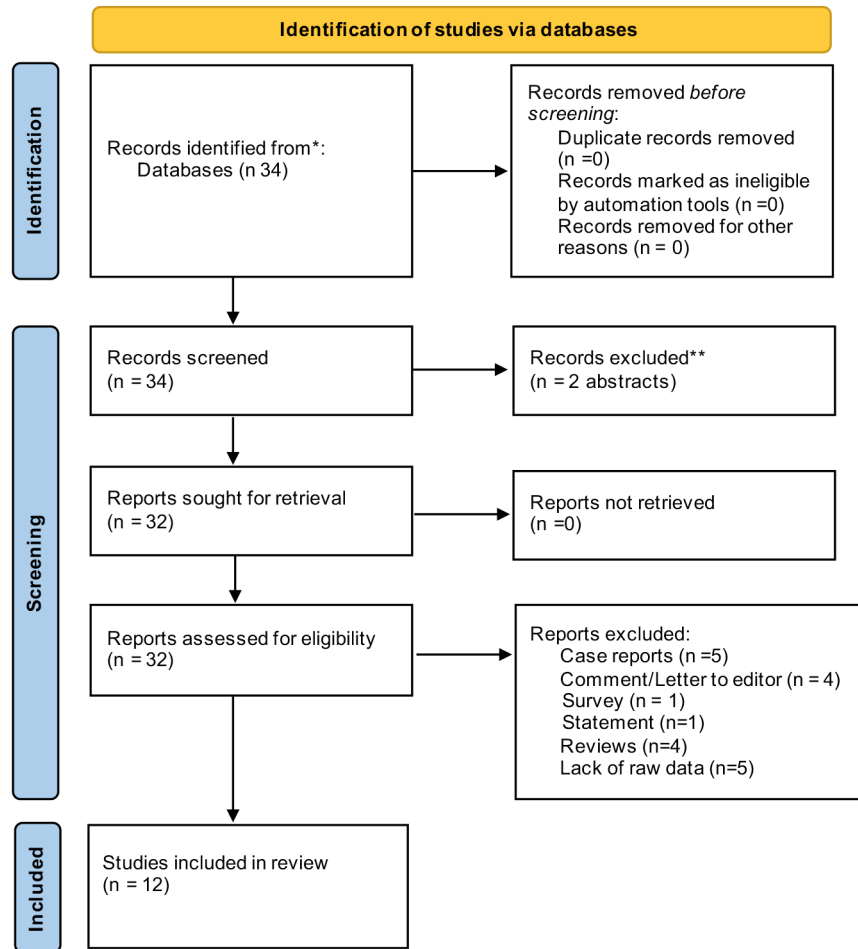


Figure 1. PRISMA flowsheet. Pathway of identification, screening, and selection of studies to be reviewed.

Included study characteristics. 12 studies, involving a total of 3122 women, were eligible for data extraction (Table I). Five studies were from Europe (UK and Italy) (3, 21-24) 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 3,122 women; 1,828 women in the pre-Covid population *versus* 1,294 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.

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. Ten studies involving 2,714 women, reported on the method of

Table I. Characteristics of the included studies.

Study (ref)	Year	Country	Study design	Type	Pre Covid-19 timeframe	Covid timeframe	Lockdown period	Population size Pre COVID	Population size COVID	Total population size
Platts (21)	2021	UK	Prospective cohort	Multi-centre	January 2019 – June 2019	March 2020 – August 2020	Mixed	162	179	341
Gomez (4)	2021	Canada	Cross sectional study	Multi-centre	12 th March 2019 – 1 st July 2019	11 th March 2020 – 30 th June 2020	Mixed	815	701	1,516
Anteby (2)	2021	Israel	Retrospective study	Single centre	February 2018 – September 2018 and February 2019 – September 2019	February 2020 – September 2020	Mixed	208	100	308
Casadio (23)	2021	Italy	Retrospective study	Single centre	January 2014 – February 2020	1 st March 2020 – 30 th April 2020	Yes	201	9	210
Dell'Utri (3)	2020	Italy	Retrospective study	Single centre	23 th February 2019 – 24 th June 2019	23 th February 2020 – 23 th June 2020	Yes	34	23	57
Mehri (6)	2021	US	Retrospective study	Single centre	25 th March 2019 – 27 th May 2019	23 th March 2020 – 25 th May 2020	Yes	19	10	29
Toma (25)	2021	US	Retrospective study	Single centre	March 2019 – February 2020	March 2020 – June 2020	Mixed	136	62	198
Deniz (22)	2021	UK	Retrospective study	Single centre	January 2019 – July 2019	January 2020 – July 2020	Mixed	27	22	49
Barg (26)	2020	Israel	Retrospective study	Single centre	10 th March 2019 – 12 th May 2019	10 th March 2020 – 12 th May 2020	Yes	43	29	72
Spurlin (7)	2020	US	Retrospective study	Single centre	1 st February 2020 – 15 th March 2020	16 th March 2020 – 15 th April 2020	Mixed	12	6	18
Dvash (27)	2021	Israel	Retrospective study	Single centre	15 th March 2018 – 15 th June 2019	15 th March 2020 – 15 th June 2020	Mixed	30	19	49
								1,687	1,160	2,847

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 are not included.

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 result 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. Nine studies including 1,531 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 out of 564 cases

of ruptured EP were reported *versus* 179 out of 967 in the pre-Covid cohort.

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). 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

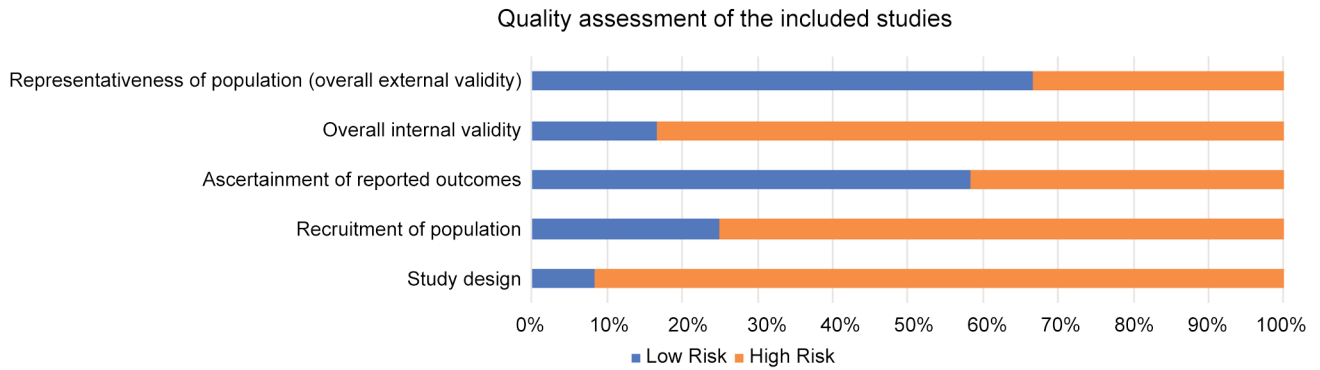


Figure 2. Quality assessment of the 12 studies included. Evaluation of internal and external validity of each study from which data was used for the systematic review. Criteria used are detailed in the Materials and Methods section.

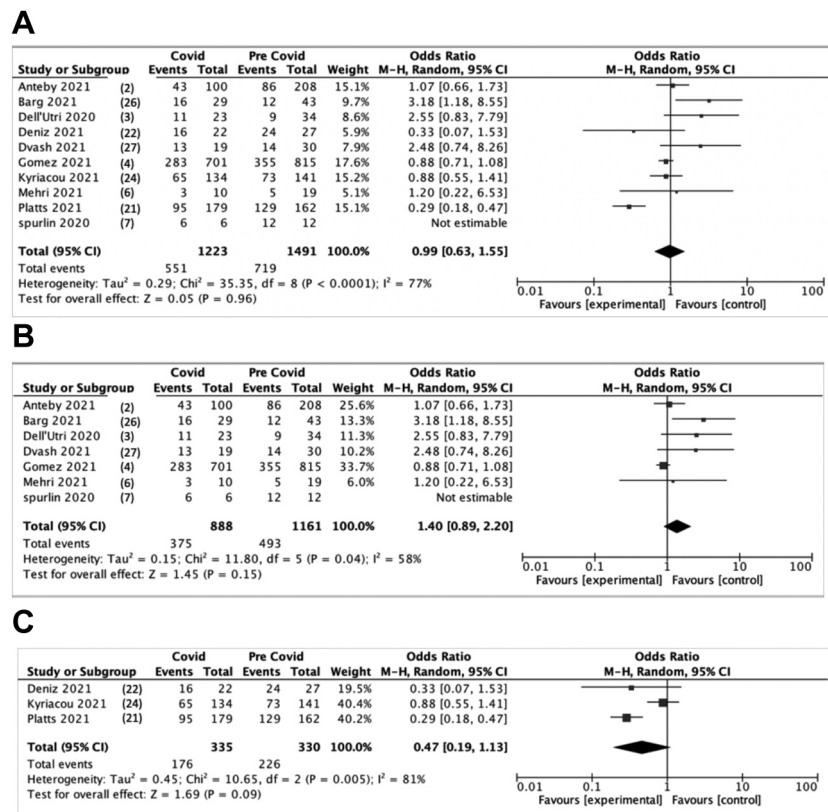


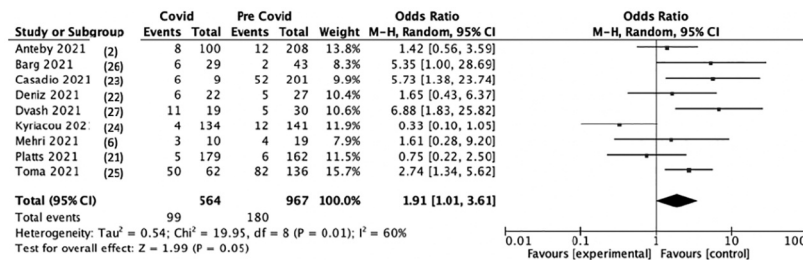
Figure 3. Forest plots comparing surgical vs. non-surgical management of ectopic pregnancy during Covid vs. pre-Covid 19. (A) Overall comparison of surgical vs. non-surgical management of ectopic pregnancy. (B) Without EPU (NEPU) surgical vs. non-surgical management. (C) EPU surgical vs. non-surgical 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), $p=0.50$].

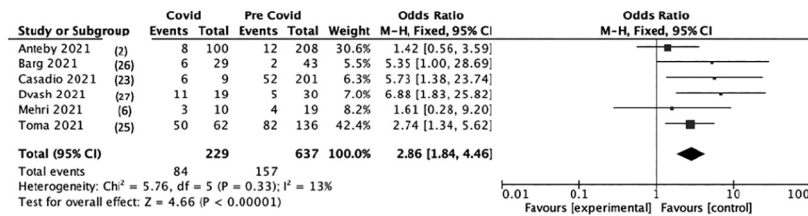
Discussion

This rapid systematic review based on 12 studies compares management of ectopic pregnancies during the peak of covid-19 with a similar cohort pre-Covid. Despite the initial perceived risks of viral transmission associated with surgery

A



B



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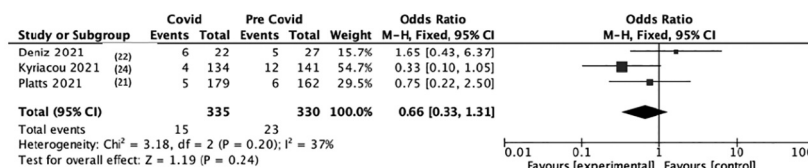


Figure 4. Comparison of rupture ectopic rate during Covid and pre-Covid 19. (A) Overall rate of ectopic rupture. (B) Without EPU (NEPU) rate of ectopic rupture. (C) EPU rate of ectopic rupture.

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 the 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 (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 (24). 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 corona virus 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 as much as possible for fear of infection by Covid-19. In these circumstances, women were found to be more symptomatic at presentation (2, 26). Such a delay in presentation offers an explanation to the increased rates of ruptured ectopic pregnancies, 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

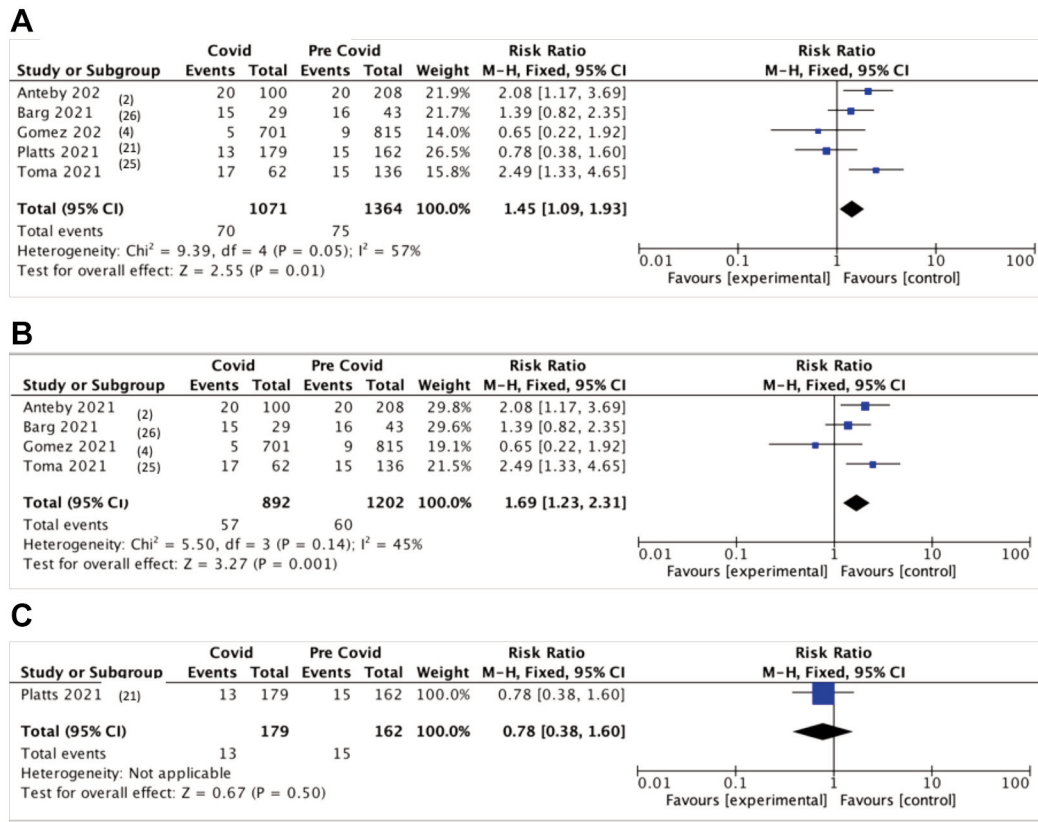


Figure 5. Forest plots representing complications of ectopic pregnancy during Covid vs. pre-Covid 19. (A) Overall complication rate. (B) Without EPU (NEPU) complication rate. (C) EPU complication rate.

meta-analysis did not reveal any increase in the rate of ectopic rupture during Covid in healthcare systems with EPU structures. Kyriacou *et al.* report no difference in the ectopic rupture rate during Covid despite a slightly higher level of bHCG 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, accident and emergency departments would be very busy during Covid peaks with even longer waiting times 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 the Covid-19 virus. 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, this system has not yet been integrated into healthcare systems worldwide.

Overall, 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 gynaecological services. 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 as 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.

This review allowed for data collection and analysis of the management of ectopic pregnancies diagnosed during the peak of Covid in comparison to similar pre-Covid timeframe. However, most studies included 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, 21-23). 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. We recommend, where such systems don't exist, a self-referral system whereby women are triaged according to their symptoms and risk factors and women at risk offered a scan appointment within 24 hours. Safe use of conservative and/or medical

management should be encouraged in the peak of a pandemic with timely follow-up. When surgery needs to be undertaken it should be done by safe minimal access with its known advantages including reduced hospital stay to reduce the risk of hospital acquired viral infection for both women and staff. 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.

Conflicts of Interest

The Authors have no conflicts of interest to disclose.

Authors' Contributions

Amelie Morin performed the literature search and is the principal author of the manuscript. Michail Sideris contributed to the systematic review protocol, data analysis and editing of the final draft. Sophie Platts and Tetyana Palamarchuk contributed to literature screening and data extraction. Funlayo Odejinmi conceived the methodology and research question and is the senior author of the study. All Authors have approved the final draft.

Acknowledgements

We are grateful to Miss Reeba Oliver and Miss Ora Jesner for reading and editing the final version of this manuscript. We warmly thank the staff of the Whipps Cross Hospital library for their assistance in conducting our literature search.

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Received April 18, 2022

Revised May 15, 2022

Accepted May 17, 2022