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# Risk of thromboembolism in patients with COVID-19 who are using hormonal contraception: a Cochrane systematic review

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Received 5 January 2023
Accepted 25 January 2023
Published Online First 7 March 2023



**To cite:** Hansen K, Cohen MA, Ramanadhan S, *et al*. *BMJ Sex Reprod Health* 2023;**49**:201–209.

## ABSTRACT

**Background** The coronavirus disease COVID-19 is associated with an increased risk of thrombotic events. Individuals with COVID-19 using hormonal contraception could be at additional risk for thromboembolism, but evidence is sparse.

**Methods** We conducted a systematic review on the risk of thromboembolism with hormonal contraception use in women aged 15–51 years with COVID-19. We searched multiple databases through March 2022, including all studies comparing outcomes of patients with COVID-19 using or not using hormonal contraception. We applied standard risk of bias tools to evaluate studies and GRADE methodology to assess certainty of evidence. Our primary outcomes were venous and arterial thromboembolism. Secondary outcomes included hospitalisation, acute respiratory distress syndrome, intubation, and mortality.

**Results** Of 2119 studies screened, three comparative non-randomised studies of interventions (NRSIs) and two case series met the inclusion criteria. All studies had serious to critical risk of bias and low study quality. Overall, there may be little to no effect of combined hormonal contraception (CHC) use on odds of mortality for COVID-19-positive patients (OR 1.0, 95% CI 0.41 to 2.4). The odds of hospitalisation for COVID-19-positive CHC users may be slightly decreased compared with non-users for patients with body mass index <35 kg/m$^2$ (OR 0.79, 95% CI 0.64 to 0.97). Use of any type of hormonal contraception may have little to no effect on hospitalisation rates for COVID-19-positive individuals (OR 0.99, 95% CI 0.68 to 1.44).

**Conclusions** Not enough evidence exists to draw conclusions regarding risk of thromboembolism in patients with COVID-19 using hormonal contraception. Evidence suggests there may be little to no or slightly decreased odds of hospitalisation, and little to no effect on odds of mortality for hormonal contraception users versus non-users with COVID-19.

### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Individuals with COVID-19 have an elevated risk of thrombotic events. However, it is unknown whether or not concurrent use of hormonal contraception further increases this risk.

### WHAT THIS STUDY ADDS

⇒ Not enough evidence exists to draw conclusions regarding the risk of thromboembolism or other surrogates for severe disease in reproductive-aged patients with COVID-19 using hormonal contraception.

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This review identifies a large gap in the literature, though it is a topic of paramount importance. More robust evidence related to hormonal contraception, COVID-19, and thromboembolism risk could inform international guidelines regarding the appropriate use of hormonal contraceptive in COVID-19-positive women.

## INTRODUCTION

The coronavirus disease COVID-19—caused by infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)—has affected millions worldwide and led to significant mortality and morbidity, including a high incidence of related thrombotic events.[1] The prothrombotic effects of COVID-19 may be related to increased inflammatory cytokine release, platelet activation, endothelial dysfunction, upregulation of

the renin–angiotensin–aldosterone system, and blood flow abnormalities.[1–3] It is not yet completely understood how disease pathogenicity may be modulated by various individual-level characteristics, including the influence of endogenous or exogenous sex hormones.

Oestrogen and progesterone may play a protective role in the pathogenicity of COVID-19. There are well-documented sex differences in COVID-19 outcomes, with increased mortality seen in males[4] and a protective effect from death in post-menopausal women treated with oestrogen.[5] Among a cohort of hospitalised COVID-19-positive people in China, the proportion of non-menopausal women with severe COVID-19 disease was significantly lower than the proportion with severe COVID-19 disease among age-matched men.[6] Estradiol levels have been shown to be negatively correlated with disease severity as well as interleukin (IL) IL-6 and IL-8 levels.[6] In both humans and mouse models, estradiol suppresses production of pro-inflammatory cytokines while stimulating the anti-inflammatory cytokine response.[7] Additionally, estradiol may decrease gene expression of angiotensin-converting enzyme 2 (ACE2) receptors in bronchial epithelial cells,[8] which are the means of cell entry for SARS-CoV-2.

It is unclear whether hormonal contraception use increases or attenuates the known risk of thromboembolism in those with COVID-19. Use of combined hormonal contraception (CHC)—which includes combined oestrogen and progestin-containing methods such as pills, patches, and rings—confers a two- to threefold increased risk of venous thromboembolism (VTE) compared with non-use.[9] Ethinyl estradiol (EE) in CHCs leads to increased levels of coagulation factors II, VII, VIII, X and fibrinogen, and decreased plasma levels of anticoagulant factors, including antithrombin and tissue factor pathway inhibitor.[10] This effect is dose dependent, with higher levels of EE affording increased risks of thromboembolism. Progestin-only contraception (POC)—which includes systemic progestin-only methods such as pills, injectables, implants, and intrauterine devices—do not appear to increase risk of VTE in most populations, though some studies have shown increased risk of VTE with depot medroxyprogesterone acetate use.[11]

There is currently no international consensus regarding the influence of hormonal contraceptive use on thrombosis risk among COVID-19-positive women. At present, the WHO supports the use of all forms of contraception during the COVID-19 pandemic.[12] The Society of Family Planning recommends that CHCs be discontinued for all hospitalised women infected with COVID-19 given the theoretical increased risk of thromboembolism, but progestin-only and non-hormonal methods may be continued.[13] Specific recommendations for CHC use in COVID-19-positive women vary across the globe, with some guidelines recommending cessation of CHCs or transition to POCs depending on disease severity. Synthesising the evidence related to CHCs, COVID-19 and thromboembolism risk could bring clarity to this space and affect international guidelines.

This review aims to determine whether hormonal contraception increases the risk of venous and arterial thrombosis as well as other markers of COVID-19 severity among COVID-19-positive women, and if this risk differs by type of hormonal contraception or other individual characteristics. It is likely that the conclusions of this review will change as new evidence is generated.

## METHODS

We conducted this systematic review according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.[14] We searched for all published, unpublished, and ongoing studies, without restrictions on language or publication status. We searched the following databases from their inception to March 2022: Cochrane Central Register of Controlled Trials via EBM Reviews (Ovid), MEDLINE ALL (Ovid), Embase.com, CINAHL (EBSCOhost), LILACs, Global Health (Ovid), and Scopus. For greater detail, please see the full Cochrane Review publication.[15]

Studies employing the following designs were included: randomised trials (clustered or individually randomised); quasi-experimental designs, such as non-randomised studies of interventions (NRSIs); and cohort studies with a control group. As these data are emerging, we also included non-comparative studies and case series if they had at least five cases. While randomised controlled trials represent the most rigorous type of study for addressing questions of efficacy and safety, we included other types of studies for this topic because we did not expect to find adequate trial evidence to address our review objectives. It is extremely unlikely that a hormonal contraception method would be randomised in this clinical situation. Additionally, the efficacy and safety outcomes of interest are very rare and the number of participants willing to be randomised to hormonal contraceptive methods would likely be limited. This reduces the feasibility and likelihood of adequately powered randomised trials. NRSIs are likely to provide the best available data for observing differences in outcomes associated with different hormonal contraceptive methods among women with COVID-19.

We included studies of women of reproductive age (ages 15–51 years) who were COVID-19-positive (or presumed positive). We excluded women who were pregnant or less than 3 weeks postpartum given the elevated risk of VTE during this time-period.[16]

We sought studies comparing COVID-19-positive women using CHC with similar non-pregnant women using either no contraception, non-hormonal contraception, or POC. We planned the following

intervention comparisons for this review: CHC versus no contraception; CHC versus non-hormonal contraception; CHC versus POC; POC versus no contraception; and POC versus non-hormonal contraception. Our primary outcome was diagnosis of VTE or arterial thromboembolism during the study period. Our secondary outcomes were mortality, critical illness requiring hospitalisation, diagnosis of acute respiratory distress syndrome (ARDS), and intubation.

Titles and abstracts were screened independently by two authors. We retrieved the full-text study reports and two authors independently screened the full-text and identified studies for inclusion. We resolved any disagreement through discussion or, when required, we consulted a third review author. The study characteristics and outcome data from included studies were extracted, and information was entered into a standard data collection form.

We assessed the risk of bias for key outcomes from NRSIs using the Risk of Bias in Non-randomised Studies of Interventions (ROBINS-I) instrument.[17] We considered the following factors to be possible confounding factors for this topic: age, personal history of VTE, recent pregnancy, obesity, severity of COVID-19, ethinyl estradiol dose, and progestogen type.

We used Cochrane GRADE methods and GRADEpro[18 19] to assess the certainty of evidence and to prepare 'Summary of findings' tables (table 1 and table 2). Given that we used the ROBINS-I tool to assess risk of bias for included NRSIs, we designated the evidence for each NRSI to start at 'high certainty' and we then downgraded the certainty of the evidence as appropriate. Two review authors worked independently to assess evidence certainty (eg, high, moderate, low or very low) and resolved inconsistencies through discussion or through a third author.

Had we obtained multiple, comparable studies, we would have calculated intervention effectiveness in a meta-analysis, to produce pooled OR, RR, or mean difference effect estimates with 95% CI. Narrative synthesis was conducted for outcomes lacking adequate data to combine studies.

## RESULTS

### Study characteristics

Our study search yielded 8220 studies, of which 2119 remained for title and abstract screening after

**Table 1** Summary of findings on the risk of mortality, hospitalisation, venous thromboembolism, and intubation among COVID-19 patients in tertiary care settings using combined hormonal contraception compared with those using no form of hormonal contraception

| Outcomes* | Anticipated absolute effects† (95% CI) | | Relative effect (95% CI) | Number of participants (studies) | Certainty of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Risk with no hormonal contraception | Risk with combined hormonal contraception | | | | |
| Mortality | 5 per 1000 | **5 per 1000** (2 to 11) | **OR 1.00** (0.41 to 2.40) | 18 892 (1 observational study) | ⊕⊖⊖⊖ Very low‡§¶ | |
| Hospitalisation | 7 per 1000[d] | **5 per 1000** (4 to 6)** | **OR 0.79** (0.64 to 0.97) | 295 689 (1 observational study) | ⊕⊖⊖⊖ Very low¶††‡‡ | CHC use may reduce hospitalisation slightly. COVID-19 positivity not confirmed through testing; women were using a mobile phone application to track COVID-19 symptoms. Restricted to patients with BMI <35 kg/m$^2$ |
| Venous thromboembolism | 1 of 6 paediatric COVID-19 patients with pulmonary embolism had reportedly been using combined hormonal contraception. 1 of 7 reproductive-aged female COVID-19 patients with cerebral venous thromboembolism was using 'oral contraceptive pills'. This patient also had positive anti-phospholipid antibodies | | | 13 (2 observational studies) | ⊕⊖⊖⊖ Very low§§¶¶ | 2 case series were included with 13 total patients, describing VTE in COVID-19 patients. Neither case study ascertained active use of hormonal contraception at time of the outcome[i] |
| Intubation | 1 of 6 people who were not using hormonal contraception required intubation compared with 1 of 1 person reportedly using oral contraceptive pills | | | 7 (1 observational study) | ⊕⊖⊖⊖ Very low§§*** | Case series of 7 reproductive-aged women, all of whom were COVID-19-positive and developed cerebral VTE |

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.
*The outcomes of arterial thromboembolism and ARDS were not measured and are not included in this table.
†The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
‡Downgraded for serious risk of bias given no ascertainment of combined hormonal contraception exposure and no information on variables used for propensity score matching, increasing risk of residual confounding.
§Downgraded for indirectness given no ascertainment of combined hormonal contraception use during time of outcome.
¶Downgraded for imprecision given results reported in only 1 study.
**Overall 1889 of 295 689 total patients were hospitalised for an absolute risk of 6.4 per 1000 total. Hospitalisations were not reported separately for those using combined hormonal contraception (n=64 253) vs those not using contraception (n=231 436). Anticipated absolute effects were estimated by applying the adjusted relative effect estimate to determine the expected number of intervention and control patients who were hospitalised.
††Downgraded for serious risk of bias due to risk of selection bias and all data are self-reported by users.
‡‡Downgraded for indirectness as users of the application were not confirmed to be COVID-19-positive, but were tracking symptoms given concern for possible COVID-19 positivity.
§§Downgraded 2 levels for risk of bias as case series are likely to be subject to significant bias.
¶¶Downgraded for imprecision for small sample sizes.
***Downgraded 2 levels for imprecision given small sample size and results reported in only 1 study.
ARDS, acute respiratory distress syndrome; BMI, body mass index; CHC, combined hormonal contraception; VTE, venous thromboembolism.

**Table 2** Summary of findings on the risk of hospitalisation and intubation among COVID-19 patients in tertiary care settings using any type of hormonal contraception compared with those using no form or hormonal contraception

| Outcomes* | Anticipated absolute effects† (95% CI) | | Relative effect (95% CI) | Number of participants (studies) | Certainty of the evidence (GRADE) |
|---|---|---|---|---|---|
| | Risk with no contraception | Risk with any type of hormonal contraception (oestrogen plus progestin or progestin-only) | | | |
| Hospitalisation | 38 per 1000 | **38 per 1000** (26 to 54) | **OR 0.99** (0.68 to 1.44) | 123 (1 observational study) | ⨁⊖⊖⊖ Very low‡§¶ |
| Intubation | 0 of 79 patients who did not use hormonal contraception required intubation compared with 0 of 44 patients who used hormonal contraception. | | | 123 (1 observational study) | ⨁⊖⊖⊖ Very low‡§¶ |

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.
*The outcomes of mortality, VTE, arterial thromboembolism, and ARDS were not measured and are not included in this table.
†The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
‡Downgraded for serious risk of bias given no ascertainment of hormonal contraception exposure and no information on variables used for adjustment, increasing risk of residual confounding.
§Downgraded for indirectness as the study was not performed in patients confirmed to be using contraception at time of outcome.
¶Downgraded 2 levels for imprecision due to small sample size with wide CI with results reported in only 1 study.
ARDS, acute respiratory distress syndrome; VTE, venous thromboembolism.

removal of duplicates. Of these, 31 full-text articles were reviewed, and five studies met inclusion criteria. The study selection process was recorded in a PRISMA flow diagram[14] (figure 1).

Three studies—Seeland *et al*,[20] Mujumdar *et al*,[21] and Costeira *et al*[22]—were comparative NRSIs with 314 704 participants in total (table 3). Seeland *et al*[20] and Costeira *et al*[22] stratified outcomes for premenopausal and postmenopausal patients, and we included only information from the premenopausal women. Seeland *et al*[20] and Mujumdar *et al*[21] ascertained current use of contraceptives as well as COVID-19 positivity using diagnostic codes within medical records.

Of note, Costeira *et al*[22] determined contraceptive use as well as presumed COVID-19 positivity based on self-reported data from reproductive-aged women in the UK who used the COVID-19 Symptom Study Smartphone Application from 7 May to 15 June 2020. Users were not required to be COVID-19 positive, so this may represent a different population than outlined in our protocol. However, we anticipate that users of the application who were tracking symptoms were doing so due to concern for having COVID-19. The study also represented some of the best data available to date. Therefore, we included the study for analysis.

One study, Mujumdar *et al*,[21] included all users of any type of hormonal contraception as their exposure group while the others compared CHC users to people without any hormonal therapy. No comparative studies directly assessed venous or arterial thromboembolism as an outcome. Seeland *et al*[20] measured our secondary outcomes of mortality, while Mujumdar *et al*[21] and Costeira *et al*[22] measured hospitalisation rates and intubation. No studies reported data on our secondary outcome of ARDS.

We included two case series that reported COVID-19-positive patients who experienced VTE, Chima *et al*[23] and Hameed *et al*.[24] Chima *et al* reported on adolescent patients with pulmonary embolism (PE), and Hameed *et al* reported on patients with cerebral venous thromboembolism (CVT).

### Risk of bias

We used the ROBINS-I tool to assess risk of bias in the three included NRSIs. We judged all three NRSIs to be at serious or critical risk of bias. We judged the two case series to be at high risk of bias given the nature of the study design. There was also no information presented in the case series regarding the temporality of contraceptive use in relation to the thromboembolic outcomes.

We noted serious risk of bias due to confounding for all three NRSIs. We judged Seeland *et al*[20] to be at serious risk of bias from confounding as they did not identify which covariates were used for propensity score matching. Similarly, Mujumdar *et al*[21] did not report on variables used for confounding assessment. Costeira *et al*[22] did adjust for body mass index (BMI) and age, but did not include all prespecified confounders, and we judged there to be additional risk that variables were not validly measured as they were self-reported. No study included personal history of thromboembolism, estradiol dose, or progestogen type as confounding variables, which we pre-specified as likely confounders.

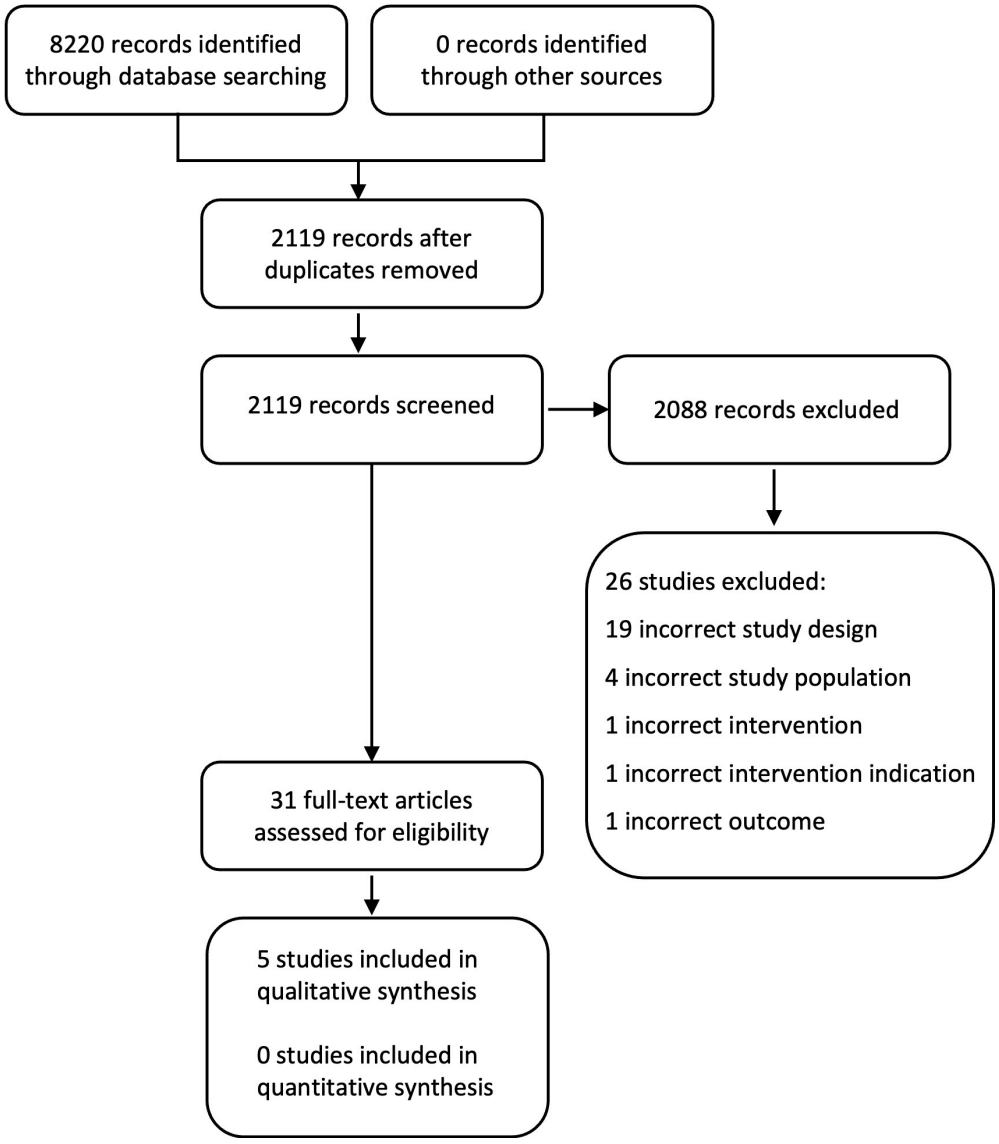


**Figure 1** PRISMA literature search flow diagram for the systematic review of risk of thromboembolism in patients with COVID-19 using hormonal contraception.

Seeland *et al*[20] and Mujumdar *et al*[21] derived their data from electronic health records, but they were retrospective cohorts, so we rated them as moderate risk of bias due to selection of participants. As Costeira *et al*[22] relied on patient use of their mobile electronic tracking application, we judged there to be serious risk of selection bias as individuals using contraception may be more conscious of potential health risks and more likely to use a health and symptom mobile tracking application.

We judged Seeland *et al*[20] and Mujumdar *et al*[21] to be at critical risk of bias due to deviations from intended intervention, as they did not ascertain whether patients were actively using the forms of contraception documented in the medical record at the time of the outcome. We judged Costeira *et al*[22] to be at moderate risk of bias for deviations from intended intervention as they utilised patient self-report for determining active use of contraception.

Both Mujumdar *et al*[21] and Costeira *et al*[22] performed analyses on a smaller subsample due to missing data. We deemed Mujumdar *et al*[21] to have serious risk of bias due to its small sample size, which was further reduced due to missing data for the outcome variable (hospitalisation). Seeland *et al*[20] reported no information on missing data or how they were handled.

Hospitalisation (Mujumdar *et al*[21]) and mortality (Seeland *et al*[20]) are definite outcomes unlikely to be measured incorrectly in electronic health record data. We thus judged these to have low risk of bias. The outcome of hospitalisation for Costeira *et al*,[22] however, was derived from self-reported data, so we judged this to be at moderate risk of bias as conceivably some people could have misclassified the outcome; for example, if a patient only had an emergency department visit but reported this as a hospitalisation.

**Table 3** Characteristics of included studies

| Study | Study design | Country/ setting | Intervention(s) description | Inclusion criteria | Confounders (variables, how measured) | Analysis method | Outcomes of interest | Total participants (n) |
|---|---|---|---|---|---|---|---|---|
| Seeland *et al*, 2020[20] | Retrospective database cohort | Derived from electronic health records of multiple healthcare organisations across 17 countries | Hormone use: estradiol and CHC. Hormone use was identified via RxNorm codes 4083 (estradiol), 4124 (ethinyl estradiol), progestins VA:HS800, and systemic contraceptives VA:HS200 | Pre-menopausal women aged 15–49 who were COVID-19-positive in the last 7 months | TriNetX analytics tools were used to assess baseline characteristics including 'demographics, diagnoses, procedures, and medication'. No information on exactly which variables were collected or how they were measured | A logistic regression analysis was performed for the combined outcome variable 'death' incorporating the propensity score matching | Mortality | n=18892 |
| Mujumdar *et al*, 2020[21] | Retrospective database cohort | Tertiary medical centre in the USA | Hormonal contraception including levonorgestrel-intrauterine device, progestin-only pills, CHC, and injectable progestin reported in medical chart | Reproductive age women ages 12–49 who tested COVID-19-positive | Uncertain | Logistic regression | Hospitalisation. Intubation | n=123 COVID-19-positive patients |
| Costeira *et al*, 2021[22] | Prospective cohort study | Users of the application in the UK | Combined hormonal oral contraceptive use (self-report) | Female app users aged 20–45 with BMI between 18–35 $kg/m^2$ | Age, BMI, smoking status (self-reported) | Binomial generalised mixed models with a log-odds/ logit link function used for association Age: continuous fixed effect. BMI: continuous fixed effect. Smoker: categorical fixed effect – never, former, and current. Sensitivity analyses performed to match the mean and median age of cases and controls for the exposure variables in subsets of users in 5-year age bins | Hospitalisation | n=295689 |
| Chima *et al*, 2021[23] | Case series | 41 healthcare organisations participating in TriNetX - data for 8 patients in the USA | CHC Case definition: pulmonary embolism: defined using any ICD-10 root diagnostic code; medications 30 days before and after acute PE diagnosis and COVID-19 diagnosis | Paediatric patients <18 years old with PE and COVID-19-positive. PE diagnosed concurrently or within 30 days of COVID-19 diagnosis | Age, BMI, race, ethnicity, lab results, medications | Descriptive | Pulmonary embolism | n=6 girls |
| Hameed *et al*, 2021[24] | Case series | Multicentre multinational study – 10 tertiary care centres in Pakistan, Egypt, Singapore, and the USA | 'Oral contraception' CVT case definition: 'Diagnosis of CVT was confirmed by at least one of the following imaging studies according to the established criteria: MR imaging, MR venography, CT, CT venography, or cerebral venography | Patients aged 18 or older with 'recent COVID-19 infection, confirmed either by reverse transcriptase-polymerase chain reaction assay of a nasopharyngeal swab or serum antibody testing for COVID-19' | 'Risk factors, clinical features, laboratory findings, imaging findings, COVID-19-related information' | Descriptive: frequencies and correlations | Cerebral venous thrombosis | n=7 women with CVT |

BMI, body mass index; CHC, combined hormonal contraception; CVT, cerebral venous thromboembolism; ICD-10, International Classification of Diseases, 10th revision; PE, pulmonary embolism.

### Effects of interventions

Four studies reported on outcomes for use of CHC compared with no use of contraception in COVID-19 patients (Chima *et al*,[23] Hameed *et al*,[24] Seeland *et al*[20]) or patients who were at risk of having COVID-19 (Costeira *et al*[22]) (table 1). Only one study (Mujumdar *et al*[21]) reported on outcomes for use of any type of hormonal contraception compared with no use of contraception in COVID-19 patients (table 2). The included studies reported outcomes on mortality, hospitalisation rates, intubation, and thromboembolism. No studies reported data on ARDS.

#### Mortality

Seeland *et al*[20] measured mortality of COVID-19-positive patients who were users of CHC versus contraception non-users with data derived from electronic health records from healthcare organisations in 17 countries. Given the limitations of the database, the authors could not ascertain current contraceptive use at the time of the outcome. Based on results from this NRSI, there may be little to no effect of combined hormonal contraception use on odds of mortality for COVID-19-positive patients (adjusted OR 1.0, 95% CI 0.41 to 2.4), but the evidence is very uncertain.

#### Hospitalisation rates

Costeira *et al*[22] found that CHC users may have a slight decrease in their odds of hospitalisation compared with non-users, after adjusting for BMI, age, and smoking status (adjusted OR 0.79, 95% CI 0.64 to 0.97). This study evaluated hospitalisation for COVID-19 in individuals self-reporting use or non-use of CHC, where COVID-19 disease status was not confirmed through testing but via symptom reporting through a mobile tracking application; thus we deemed this evidence to be of low certainty, downgraded for serious risk of bias and for indirectness. Mujumdar *et al*[21] found little to no effect on risk of hospitalisation for COVID-19-positive patients based on exposure to any hormonal contraception (adjusted OR 0.99, 95% CI 0.68 to 1.44). They obtained their data from electronic health records from one tertiary care organisation, but could not ascertain current contraceptive use at the time of the outcome. The evidence from this study is very uncertain.

#### Intubation

Mujumdar *et al*[21] found that no COVID-19 patients in their study required intubation, regardless of whether or not they were exposed to hormonal contraception. In one case series of seven COVID-19 patients, two required intubation. Of these, one patient was on CHC, while the other was not.[24] Thus, there may be little to no effect of combined hormonal contraception use on odds of requiring intubation in patients with COVID-19, but the evidence is very uncertain.

#### Venous or arterial thromboembolism

The two case series together reported on 13 patients with a VTE concurrent with COVID-19 infection. Of these 13 patients, two were reportedly using CHC. One of the six female paediatric patients (<18 years in age) with COVID-19 who developed a PE was taking hormonal contraception.[23] One of seven reproductive-aged women with COVID-19 and CVT was taking oral contraceptive pills.[24] Notably, this individual was also diagnosed with antiphospholipid antibody syndrome, a thrombophilia. Of note, no comparative studies reported on arterial or venous thromboembolic outcomes. The evidence for any effect of CHC on the risk of developing VTE is very uncertain. There was no evidence assessing the risk of arterial embolism.

## DISCUSSION

There is an increased risk of thromboembolism in patients with COVID-19.[1 21 2] While CHC use is an independent risk factor for thrombosis, evidence describing risks of hormonal contraception use during the COVID-19 pandemic is sparse.[9] Our primary objective was to assess the risk of venous or arterial thromboembolism in patients with COVID-19 disease using CHC. Our secondary objectives were to investigate other markers of COVID-19 severity such as ARDS, intubation, hospitalisation, and mortality for those using CHC or other forms of hormonal contraception. We identified only five studies addressing these objectives.[20–24]

We found no comparative studies assessing thromboembolism risk among COVID-19-positive individuals using hormonal contraception compared with non-users. Two case series[23 24] reported on a total of 13 individuals with VTE who were COVID-19 positive, of whom only two individuals were taking combined contraception or oral contraceptive pills. The evidence for any effect of CHC use on the risk of developing VTE is very uncertain, and we found no evidence assessing risk of arterial embolism.

Two observational studies[20 22] and one case series[24] assessed markers of COVID-19 severity for users of CHC versus non-users. We found little to no effect of combined hormonal contraceptive use on odds of mortality among COVID-19 patients, but the evidence is very uncertain.[20] Combined hormonal contraception use may slightly decrease the odds of hospitalisation for individuals with a BMI <35 kg/m$^2$; however, the study population was not confirmed to be COVID-19-positive and the evidence is very uncertain.[22] Use of CHC among COVID-19-positive patients appears to have little to no effect on the odds of intubation, but again this evidence is very uncertain.[24]

One observational study[21] assessed markers of COVID-19 severity among users of hormonal contraception (including both CHC and POC) versus non-users of contraception. There may be no effect of any hormonal contraception use on odds of hospitalisation

for COVID-19-positive patients, but the evidence is very uncertain. We could not measure the relative effect of hormonal contraceptive use on intubation as no intubations occurred in either group. The quality of evidence for risk of thrombosis for CHC users versus non-users who are COVID-19-positive is extremely low.

This review has identified a large gap in the literature, though it is a topic of paramount importance. Future studies would benefit from collecting pertinent information on confounders. These include: patient age; BMI; history of prior thromboembolism; medical comorbidities associated with increased risk of VTE; reason for hormonal contraception use (contraception versus treatment of medical condition); recent pregnancy or other thrombophilia; contraception formulation including type of oestrogen and dose of oestrogen for combined hormonal contraception; and duration of contraception use. No studies reported indication for hormonal contraceptive use, which is important because individuals who use hormonal management for medical conditions such as heavy menstrual bleeding may have different risk profiles compared with individuals using hormones for contraceptive purposes. Additionally, several studies included were downgraded due to failure to ascertain actual contraceptive use and adherence at the time of the outcome. Certainty of the evidence would improve if current use or recent use of contraception were regularly ascertained for individuals at time of the outcome of interest. As COVID-19 continues to evolve and new variants emerge, reporting of variants as well as therapeutics used for treatment may also be important for analysis, but were not reported in any studies. Additionally, there were no data for populations of differing COVID-19 severity, that is, ambulatory versus hospitalised patients, which is needed before evidence-based recommendations can be provided to hormonal contraceptive users who contract COVID-19.

## CONCLUSION

Although the evidence is of very low certainty and there is heterogeneity among studies in exposures, populations and outcomes, the current available evidence suggests there may be little to no or slightly decreased odds of hospitalisation and little to no effect on odds of mortality for hormonal contraception users versus non-users who are COVID-19-positive. There is not enough evidence to draw conclusions regarding risk of venous or arterial thromboembolism in patients with COVID-19 who are using hormonal contraception.

**Acknowledgements** We would like to acknowledge and thank the Cochrane Fertility Regulation Group for their support in adapting the original Cochrane Review on which this publication is based and the authorship team of the primary publication.

**Contributors** Conceiving and designing the review: Megan A Cohen (MAC), Alison Edelman (AE), Jillian Henderson (JH). Guarantor: JH. Co-ordinating the review: MAC. Designing search strategies: Robin Paynter (RP), MAC, AE. Searching and selecting studies for inclusion in the review: Katie Hansen (KH), Shaalini Ramanadhan (SR), MAC, AE, JH. Collecting data for the review: MAC, AE. Assessing the risk of bias in the included studies: MAC, AE, JH. Analysing the data: MAC, AE, JH. Assessing the certainty in the body of evidence: MAC, AE, JH. Interpreting the data: MAC, AE, JH. Writing the review: KH, SR, MAC, AE, JH.

**Funding** The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

**Competing interests** KH, MC, SR have declared that they have no conflict of interest. AE: reports PI of an implant study for Merck, paid to institution; PI of an oral contraceptive study for HRA Pharma, paid to institution; reports royalties or licenses from Up to Date, personal payment. These are not COVID-19 related, but are hormonal contraception related. JH and RP have declared that they have no conflict of interest.

**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Not applicable.

**Ethics approval** Not applicable.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** Data sharing not applicable as no datasets generated and/or analysed for this study. No data are available.

**Author note** This review article is based on a Cochrane Review published in the Cochrane Database of Systemic Reviews (CDSR) 2023, Issue 1, DOI: https://doi.org/10.1002/14651858.CD014908.pub2 (see www.cochranelibrary.com for more information). As Cochrane Reviews are regularly updated as new evidence emerges, the CDSR should be consulted for the most recent version of this review.



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## REFERENCES

1 Ahmed S, Zimba O, Gasparyan AY. Thrombosis in coronavirus disease 2019 (COVID-19) through the prism of Virchow's triad. *Clin Rheumatol* 2020;39:2529–43.
2 Bikdeli B, Madhavan MV, Jimenez D, *et al*. COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up: JACC state-of-the-art review. *J Am Coll Cardiol* 2020;75:2950–73.
3 Zhang S, Liu Y, Wang X, *et al*. SARS-cov-2 binds platelet ACE2 to enhance thrombosis in COVID-19. *J Hematol Oncol* 2020;13:120.
4 Jin J-M, Bai P, He W, *et al*. Gender differences in patients with COVID-19: focus on severity and mortality. *Front Public Health* 2020;8:152:152.:.
5 Sund M, Fonseca-Rodríguez O, Josefsson A, *et al*. Association between pharmaceutical modulation of oestrogen in

postmenopausal women in Sweden and death due to COVID-19: a cohort study. *BMJ Open* 2022;12:e053032.
6 Ding T, Zhang J, Wang T, *et al*. Potential influence of menstrual status and sex hormones on female severe acute respiratory syndrome coronavirus 2 infection: a cross-sectional multicenter study in Wuhan, China. *Clin Infect Dis* 2021;72:ciaa1022:e240–8.:.
7 Mauvais-Jarvis F, Klein SL, Levin ER. Estradiol, progesterone, immunomodulation, and COVID-19 outcomes. *Endocrinology* 2020;161:bqaa127.
8 Stelzig KE, Canepa-Escaro F, Schiliro M, *et al*. Estrogen regulates the expression of SARS-cov-2 receptor ACE2 in differentiated airway epithelial cells. *Am J Physiol Lung Cell Mol Physiol* 2020;318:L1280–1.
9 de Bastos M, Stegeman BH, Rosendaal FR, *et al*. Combined oral contraceptives: venous thrombosis. *Cochrane Database Syst Rev* 2014:CD010813.
10 Abou-Ismail MY, Citla Sridhar D, Nayak L. Estrogen and thrombosis: a bench to bedside review. *Thromb Res* 2020;192:40–51.
11 Tepper NK, Whiteman MK, Marchbanks PA, *et al*. Progestin-only contraception and thromboembolism: a systematic review. *Contraception* 2016;94:678–700.
12 World Health Organization. Coronavirus disease (COVID-19): contraception and family planning. 2020. Available: https://www.who.int/news-room/questions-and-answers/item/coronavirus-disease-covid-19-contraception-and-family-planning
13 Stifani BM, Madden T, Micks E, *et al*. Society of family planning clinical recommendations: contraceptive care in the context of pandemic response. *Contraception* 2022;113:1–12.
14 Liberati A, Altman DG, Tetzlaff J, *et al*. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* 2009;339:b2700.
15 Cohen MA, Edelman A, Paynter R, *et al*. Risk of thromboembolism in patients with COVID-19 who are using hormonal contraception. *Cochrane Database Syst Rev* 2023;1:CD014908.
16 Curtis KM, Tepper NK, Jatlaoui TC, *et al*. U.S. medical eligibility criteria for contraceptive use, 2016. *MMWR Recomm Rep* 2016;65:1–103.
17 Schünemann HJ, Cuello C, Akl EA, *et al*. GRADE guidelines: 18. How ROBINS-I and other tools to assess risk of bias in nonrandomized studies should be used to rate the certainty of a body of evidence. *J Clin Epidemiol* 2019;111:105–14.
18 Schünemann HJ, Higgins JP, Vist GE, *et al*. Chapter 14: completing 'summary of findings' tables and grading the certainty of the evidence. In: *Cochrane Handbook for Systematic Reviews of Interventions Version 6 [Internet]. Cochrane*. 2020. Available: www.training.cochrane.org/handbook
19 *GRADEpro GDT*. Hamilton (ON): McMaster University (developed by Evidence Prime), Available: gradepro.org
20 Seeland U, Coluzzi F, Simmaco M, *et al*. Evidence for treatment with estradiol for women with SARS-cov-2 infection. *BMC Med* 2020;18:369.
21 Mujumdar V, Levy AT, Madding R, *et al*. Effect of hormonal contraception on illness severity in women with positive sars-cov2 tests. *Fertility and Sterility* 2020;114:e540–1.
22 Costeira R, Lee KA, Murray B, *et al*. Estrogen and COVID-19 symptoms: associations in women from the COVID symptom study. *PLoS One* 2021;16:e0257051.
23 Chima M, Williams D, Thomas NJ, *et al*. COVID-19-associated pulmonary embolism in pediatric patients. *Hosp Pediatr* 2021;11:e90–4.
24 Hameed S, Wasay M, Soomro BA, *et al*. Cerebral venous thrombosis associated with COVID-19 infection: an observational, multicenter study. *Cerebrovasc Dis Extra* 2021;11:55–60.