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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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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 $<35 \text{ kg/m}^2$ (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.



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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 males⁴ 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 effect† (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 ^l
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 of 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 diagram¹⁴ (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.

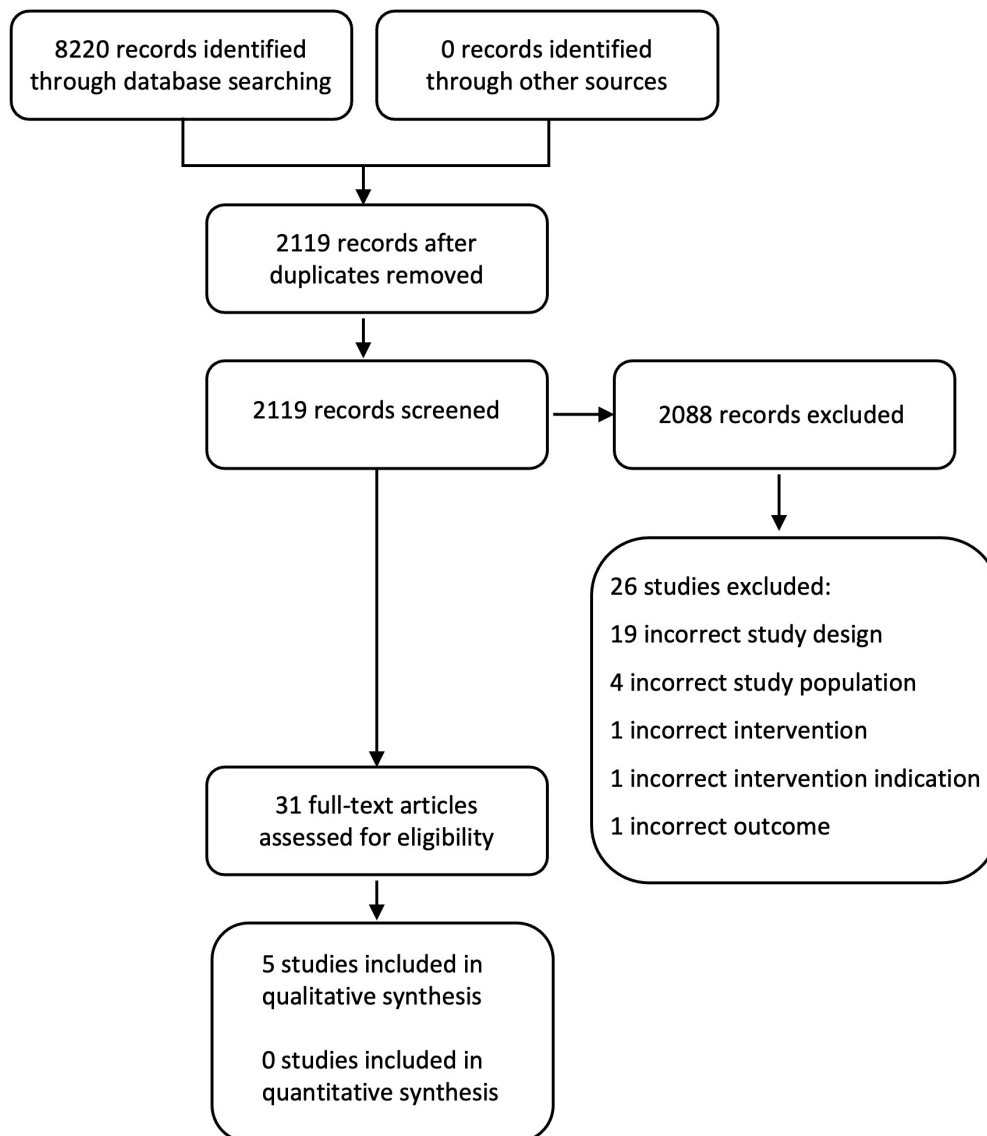


Figure 1 PRISMA literature search flow diagram for the systematic review of risk of thromboembolism in patients with COVID-19 using hormonal contraception.

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 <i>et al</i> , 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	TrinNet 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 <i>et al</i> , 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 <i>et al</i> , 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 <i>et al</i> , 2021 ²³	Case series	41 healthcare organisations participating in TrinNet - 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 <i>et al</i> , 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 22} 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 series²⁴ 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/m²; 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 study²¹ 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.

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