Cochrane Library

Cochrane Database of Systematic Reviews

Risk of thromboembolism in patients with COVID-19 who are using hormonal contraception (Protocol)

Cohen MA, Stewart F, Paynter R, Edelman A, Henderson J

Cohen MA, Stewart F, Paynter R, Edelman A, Henderson J.
Risk of thromboembolism in patients with COVID-19 who are using hormonal contraception (Protocol).
Cochrane Database of Systematic Reviews 2021, Issue 3. Art. No.: CD014908.
DOI: 10.1002/14651858.CD014908.

www.cochranelibrary.com

TABLE OF CONTENTS

[Intervention Protocol]

Risk of thromboembolism in patients with COVID-19 who are using hormonal contraception

Megan A Cohen[1], Fiona Stewart[2], Robin Paynter[1], Alison Edelman[1], Jillian Henderson[1,3]

[1]Department of Obstetrics and Gynecology, Oregon Health and Science University, Portland, Oregon, USA. [2]c/o Cochrane Incontinence, Population Health Sciences Institute, Newcastle University, Newcastle upon Tyne, UK. [3]Evidence-based Practice Center, Kaiser Permanente, Portland, Oregon, USA

Contact address: Megan A Cohen, coheme@ohsu.edu, megan.a.cohen@gmail.com.

Editorial group: Cochrane Fertility Regulation Group.
Publication status and date: New, published in Issue 3, 2021.

Citation: Cohen MA, Stewart F, Paynter R, Edelman A, Henderson J. Risk of thromboembolism in patients with COVID-19 who are using hormonal contraception (Protocol). *Cochrane Database of Systematic Reviews* 2021, Issue 3. Art. No.: CD014908. DOI: 10.1002/14651858.CD014908.

ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To determine if use of hormonal contraception increases risk of venous and arterial thromboembolism in women with COVID-19.

A secondary objective is to maintain the currency of the evidence, using a living systematic review approach.

BACKGROUND

Description of the condition

The novel coronavirus disease (COVID-19), caused by infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread rapidly worldwide. COVID-19 has affected millions and led to significant mortality and morbidity, including a high incidence of related thrombotic events (Ahmed 2020). The prothrombotic effects of COVID-19 are thought to be related to increased inflammatory cytokine release, platelet activation, endothelial dysfunction, upregulation of the renin-angiotensin-aldosterone system, and blood flow abnormalities (Ahmed 2020; Bikdeli 2020). Data regarding the pathogenicity of COVID-19 continue to emerge, but it is not yet entirely certain how this may be modulated by various individual-level characteristics and medications, including the influence of sex hormones.

Description of the intervention

Hormonal contraception includes: combined estrogen and progestin pills, patches, and rings; systemic progestin-only methods, including pills, injectables, and rings; and progestin-releasing intrauterine devices. Hormonal contraception is a common medication used by over 250 million people worldwide (UN 2019). It is unclear if hormonal contraception use among COVID-19 positive women increases or attenuates risk of thromboembolism.

How the intervention might work

Combined hormonal contraception (CHC), which contains estrogen, may exacerbate thrombotic risk in individuals infected with COVID-19. Use of combined hormonal contraceptive methods confers a two-to-three-fold increased risk of venous thromboembolism (VTE) compared to non-use (de Bastos 2014). 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, as shown in human studies (Abou-Ismail 2020). This effect is dose dependent, with higher levels of EE affording increased risks of thromboembolism. Coagulation factor levels may not return to normal until several weeks after CHC cessation (Robinson 1991). The use of CHCs containing third-generation and fourth-generation progestins, such as drospirenone, desogestrel, or gestodene, is also associated with one and a half to two times the odds of increased risk of VTE compared to use of levonorgestrel-containing contraceptives; however, that association is more controversial given the data limitations and biases (Dragoman 2018). Progestin-only contraceptive (POC) methods 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 (Tepper 2016).

Estrogen 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 (Jin 2020). Among a cohort of hospitalized COVID-19 positive people in China, the proportion of nonmenopausal women with severe COVID-19 disease was significantly lower than the proportion with severe COVID-19 disease among age-matched men (Ding 2020). Estradiol levels were shown to be negatively correlated with disease severity as well as interleukin (IL) IL-6 and IL-8 levels (Ding 2020). In humans and mouse models, estradiol is seen to suppress production of pro-inflammatory cytokines while stimulating the anti-inflammatory cytokine response (Mauvais-Jarvis 2020). Additionally, estradiol may decrease gene expression of angiotensin-converting enzyme 2 (ACE2) receptors in bronchial epithelial cells (Stelzig 2020), which are the means of cell-entry for SARS-CoV-2. SARS-CoV-2 has also been shown to activate platelets by binding ACE2 receptors, leading to increased risk of thrombosis in mouse models (Zhang 2020).

Why it is important to do this review

Synthesizing the evidence regarding the influence of hormonal contraceptive use on thrombosis risk among COVID-19 positive women will affect national guidelines for contraceptive use, for which there is no current global consensus. At present, the World Health Organization supports the use of all forms of contraception during the COVID-19 pandemic (WHO 2020). The Society of Family Planning currently recommends that CHCs be discontinued for all hospitalized women with COVID-19, but progestin-only and non-hormonal methods may be continued. CHC use may be continued for non-hospitalized or asymptomatic women with COVID-19, but it is recommended to discuss the theoretical increased risk of thromboembolism (Benson 2020). The Board of the Italian Society of Contraception states that CHC can be continued for asymptomatic COVID-19 positive women or women with mild symptoms, but should be stopped for severe symptoms (including severe pneumonia), immobilization, and in cases of increased thromboembolic risk (Fruzzetti 2020). The Italian guidance states that CHC can be restarted immediately after recovery, but makes no mention of initiating prophylactic anticoagulation (Fruzzetti 2020). The French guideline suggests continuing CHC, given the delay in return to baseline coagulation risk, but recommends adding weight-based prophylactic low-molecular weight heparin (LMWH) if the woman has symptomatic COVID-19 or additional risk factors (CNGOF 2020). The Faculty of Sexual and Reproductive Healthcare (FSRH) of the Royal College of Obstetricians and Gynaecologists states that, in the absence of clear evidence regarding thromboembolism risk with COVID-19, it can make no recommendation to deviate from existing guidance regarding assessment of VTE risk for prescribing CHC (FSRH 2020). However, the FRSH recognizes that CHC will likely be stopped for hospitalized women, and recommends considering providing alternative progestin-only or other effective contraception prior to discharge. For non-hospitalized women with COVID-19, the FSRH recommends considering on a case-by-case basis whether women should switch to progestin-only contraception, taking into account whether the woman will be adherent and able to receive supplies. Current recommendations in Spain for perimenopausal women using CHC as contraception suggest discontinuing CHC and starting prophylactic LMWH for women hospitalized with COVID-19 (especially for those requiring intensive care), and discontinuing CHC use for non-hospitalized women with COVID-19 during the acute illness phase associated with immobilization (Ramírez 2020). For women recovering from COVID-19 pneumonia with persistent symptoms requiring only outpatient monitoring, the Spanish guidelines recommend discontinuing CHC use and initiating LMWH use (Ramírez 2020). If hormonal therapy is required, Spanish recommendations suggest considering switching to POC use, unless women have mild symptoms and only suspected, not confirmed, COVID-19 (Ramírez 2020).

This review will help to determine which types of hormonal contraception increase risk of venous and arterial thrombosis among COVID-19 positive women, and if this differs by subgroups of COVID-19 severity or other individual characteristics. Evidence and recommendations are rapidly evolving as this is a novel coronavirus; therefore, we intend to perform a living systematic review. It is likely that the conclusions of this review, including estimates of effect, will change as new evidence is generated.

OBJECTIVES

To determine if use of hormonal contraception increases risk of venous and arterial thromboembolism in women with COVID-19.

A secondary objective is to maintain the currency of the evidence, using a living systematic review approach.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomized controlled trials (RCTs) and non-randomized studies of interventions (NRSIs). We will include parallel RCTs including those randomized at the individual or cluster level, but will not include cross-over trials because this is not feasible for studies of the intervention evaluated in this review. While RCTs represent the most rigorous type of study for addressing questions of efficacy and safety, we will include NRSIs for this topic because we do not expect to find adequate trial evidence to address the review objectives. It is extremely unlikely for the hormonal contraception method to be randomized in this clinical situation. Additionally, the efficacy and safety outcomes of interest are very rare and the number of participants willing to be randomized to hormonal contraceptive methods would likely be limited. This reduces the feasibility and likelihood of adequately powered randomized 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 will include studies irrespective of their publication status and language of publication.

We will include cohort studies that compare individuals or clusters exposed to the intervention to a comparable group of unexposed individuals or clusters over the same time period (e.g. comparative cohort, case-control studies nested in a prospective cohort).

We will include cohort studies that compare individuals or clusters exposed to the intervention over one time period to a comparable group of unexposed individuals or clusters from another time period (e.g. before-after study designs, interrupted time series), or from different geographic sites. As these data are emerging, we will also include case series and non-comparative studies of CHC users with COVID-19.

Types of participants

We will include studies of women of reproductive age (ages 15 to 51) who are COVID-19 positive. We will exclude women who are pregnant or less than three weeks postpartum. According to the Centers for Disease Control Medical Eligibility Criteria for Contraceptive Use, women without underlying risk for venous thromboembolism who are not breastfeeding should wait until three weeks postpartum to initiate CHCs, given the elevated risk of venous thromboembolism in the immediate postpartum time period (Curtis 2016). We will include studies of women using hormonal contraception for contraceptive purposes and exclude women using hormonal methods for medical treatment of abnormal uterine bleeding or other conditions; however, we will not exclude studies if fewer than 10% of women were using hormonal methods for non-contraceptive purposes.

Types of interventions

We will include studies comparing COVID-19 positive women using combined hormonal contraception with similar nonpregnant individuals not using contraception or using non-hormonal contraception. We will also include studies comparing COVID-19 positive women using combined hormonal contraception with those using progestin-only methods of hormonal contraception.

The comparisons for this review will be:

- Combined hormonal contraception versus no contraceptive method
- Combined hormonal contraception versus non-hormonal contraception
- Combined hormonal contraception versus progestin-only contraception
- Progestin-only contraception versus no contraceptive method
- Progestin-only contraception versus non-hormonal contraception

Types of outcome measures

Primary outcomes

1. Venous thromboembolism during the study period
2. Arterial thromboembolism during the study period

Secondary outcomes

1. Mortality
2. Critical illness requiring intensive care unit hospitalization
3. Acute respiratory distress syndrome
4. Intubation

Search methods for identification of studies

The Fertility Regulation Group Information Specialist will conduct a search for all published, unpublished, and ongoing studies, without restrictions on language or publication status. The search strategies for each database will be modeled on the search strategy designed for MEDLINE Ovid (Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily), available in Appendix 1.

Electronic searches

We will search the following databases from their inception.

- Cochrane Central Register of Controlled Trials via EBM Reviews (Ovid)
- MEDLINE (Ovid) (Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily)
- Embase.com
- CINAHL (Cumulative Index to Nursing and Allied Health Literature)

- LILACS (Latin American and Caribbean Health Science Information database; lilacs.bvsalud.org/en/)
- Global Health (Ovid)
- Scopus

We will search the following trials registries.

- The World Health Organization International Clinical Trials Registry Platform www.who.int/trialsearch
- ClinicalTrials.gov www.clinicaltrials.gov

We will search the following grey literature sites.

- China National Center for Bioinformation 2019 Novel Coronavirus Resource bigd.big.ac.cn/ncov/publication/
- Centers for Disease Control and Prevention Coronavirus Disease 2019 (COVID-19) www.cdc.gov/coronavirus/2019-ncov/cases-updates/
- The European COVID-19 Data Platform www.covid19dataportal.org/the-european-covid-19-data-platform
- The World Health Organization COVID-19 Global literature on coronavirus disease search.bvsalud.org/global-literature-on-novel-coronavirus-2019-ncov/
- National Library of Medicine LitCOVID www.ncbi.nlm.nih.gov/research/coronavirus/
- Open ICPSR COVID-19 Data Repository www.openicpsr.org/openicpsr/covid19
- COVID-Evidence covid-evidence.org/

Living systematic review considerations

As this is a living systematic review, we will update the majority of searches monthly. For the electronic databases and other electronic sources (including clinical trials registries), we will set up auto-alerts (where possible) to deliver a monthly search yield by email. We will review the search methods and strategies every six months to ensure they reflect any terminology changes in the topic area, or in the databases. We anticipate that we will maintain the living systematic review for two years.

Searching other resources

We will check the bibliographies of included studies and any relevant systematic reviews identified for further references to relevant studies. We will contact experts/organizations in the field to obtain additional information on relevant studies. If necessary, we will contact authors of included studies for data clarification and further information.

Living systematic review considerations

In developing this living systematic review, we will note when key conferences are to be held and will search conference proceedings when published. We will contact corresponding authors of ongoing studies as we identify them and will ask them to advise when study results are available, or to share early or unpublished data. We will contact the corresponding authors of any newly included studies for advice regarding other relevant studies. We will manually search the reference lists of all newly included studies.

Data collection and analysis

Selection of studies

We will download all titles and abstracts retrieved by electronic searching to a reference management database and remove duplicates. Two reviewers (MAC, AE) will independently screen titles and abstracts for inclusion. We will retrieve the full-text study reports/publications and two reviewers (MAC, AE) will independently screen the full-text, identify studies for inclusion, and identify and record reasons for exclusion of the ineligible studies. We will resolve any disagreement through discussion or, if required, we will consult a third review author (FS). We will list studies that initially appeared to meet the inclusion criteria but that we later excluded in the 'Characteristics of excluded studies' table. We will collate multiple reports of the same study so that each study rather than each report is the unit of interest in the review. We will also provide any information we can obtain about ongoing studies. We will record the selection process in sufficient detail to complete a PRISMA flow diagram (Liberati 2009).

Living systematic review considerations

We will immediately screen any new citations retrieved by the monthly searches. We expect initial search yields to be fairly small, so we intend to screen all records manually; however, we may employ automated techniques over time if the volume of retrieved citations increases substantially.

Data extraction and management

We will use a standard data collection form for study characteristics and outcome data; we will pilot the form on at least one study in the review. Two reviewers (MAC, AE) will independently extract the following study characteristics from the included studies.

- Methods: study design, number of study centers and location, study setting, withdrawals, date of study, follow-up.
- Participants: number, mean age, age range, severity of condition, diagnostic criteria, inclusion criteria, exclusion criteria, other relevant characteristics.
- Interventions: type of hormonal contraception, comparison, length of hormonal contraception use, timing of hormonal contraception initiation, medication adherence.
- Outcomes: main and other outcomes specified and collected, time points reported.
- Notes: funding for trial, notable conflicts of interest of trial authors, ethical approval.

Two reviewers (MAC, AE) will independently extract outcome data from included studies. We will note in the 'Characteristics of included studies' table if a trial reported outcome data in an unusable way. We will resolve disagreements by consensus or by involving a third review author (FS).

Assessment of risk of bias in included studies

Two review authors (MAC, AE) will independently assess risk of bias for each study. We will resolve any disagreements by discussion or by involving another author (FS).

We will assess the risk of bias in randomized trials using version two of the Cochrane 'Risk of bias' tool (ROB2) (Sterne 2019). Our effect of interest will be the effect of assignment, also known as the intention-to-treat effect. We will assess all of the outcomes

defined in this protocol for risk of bias. We will answer the signaling questions to assess the following domains.

- Bias arising from the randomization process
- Bias due to deviations from intended interventions
- Bias due to missing outcome data
- Bias in measurement of the outcome
- Bias in selection of the reported result

An additional domain is included for cluster-randomized trials.

- Bias arising from identification or recruitment of individual participants within clusters

We will use the variant of ROB2 for cluster RCTs if we identify eligible trials with this study design.

For each outcome, we will use the signaling questions to categorize each domain as either 'low risk of bias', 'some concerns', or 'high risk of bias'. We will record our answers to the signaling questions on the ROB2 Excel tool and make this available in an online repository. We will summarize the 'Risk of bias' judgments across different studies for each of the domains for each prespecified outcome. For each study, we will derive an overall judgment from the tool, as follows.

- Low risk of bias: the study is considered to show a low risk of bias.
- Some concerns: a few concerns are expected to be associated with the study in at least one domain but it does not warrant categorization as a study with a high risk of bias with regard to any domain.
- High risk of bias: the study is considered to be at high risk of bias in at least one domain; or a few concerns with regard to multiple domains are observed in the study such that these concerns significantly lower confidence in the study results.

We will assess the risk of bias for key outcomes from NRSI using the Risk Of Bias In Non-randomised Studies - of Interventions (ROBINS-I) instrument (Sterne 2020). We consider 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, progestogen type. Using the ROBINS-I tool, which includes signaling questions for assessing different potential sources of bias, we will evaluate the following domains.

- Pre-intervention
  - Bias due to confounding
  - Bias in selection of participants into the study (selection bias)
- At intervention
  - Bias in classification of interventions (information bias)
- Post-intervention
  - Bias due to deviations from intended interventions (confounding)
  - Bias due to missing data (selection bias)
  - Bias in measurement of outcomes (information bias)
  - Bias in selection of the reported result (reporting bias)

Where information on risk of bias relates to unpublished data or correspondence with a trialist, we will note this in the 'Risk of bias' table. We will not exclude studies on the grounds of their risk of bias, but will clearly report the risk of bias when presenting the results of the studies. When considering treatment effects, we will take into account the risks of bias for the studies that contribute to that outcome.

Applying 'Risk of bias' assessments in this review

We will take into account the risk of bias for the studies that are used to estimate intervention effects. We will provide figures to illustrate the risk of bias. We will conduct sensitivity analyses (see Sensitivity analysis section below) to assess whether estimated effects differ when high risk of bias studies are excluded from analyses. The 'Risk of bias' assessment will inform the GRADE ratings and 'Summary of Findings' tables.

Measures of treatment effect

We will analyze dichotomous data as odds ratios with 95% confidence intervals and any relevant continuous data as mean difference (MD), or standardized mean difference (SMD), with 95% confidence intervals. We will ensure that we enter data into the analysis with a consistent direction of effect (i.e. reversing the numeric coding of scales if needed). Where studies report count data, that is, the number of events rather than the number of people who experienced at least one event, we will use the number of events and number of person-years to calculate rate ratios, as described in chapter 6.7 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2020).

We will use SMDs when studies use different scales to measure the same outcome, necessitating the standardization of studies' results to a uniform scale before they can be combined. The SMD expresses the size of the intervention effect in each study relative to the variability observed in that study, thus studies for which the difference in means is the same proportion of the standard deviation will have the same SMD, regardless of the actual scales used to make the measurements. To interpret the SMD, we will use the Cohen's effect size rubric, where 0.2 represents a small effect, 0.5 a moderate effect and 0.8 a large effect (Cohen 1988). If possible, we will express the study SMDs using a recognizable and standard metric used by some of the included studies, or will employ other strategies to aid interpretability, as outlined in chapter 15.5 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2020b).

For studies reporting results that are not in a format that can be directly entered into meta-analysis, we will use guidance provided in chapter 6 of the *Cochrane Handbook for Systematic Reviews of Interventions* to convert the data to the necessary format (Higgins 2020).

Unit of analysis issues

We will perform the primary analysis per individual randomized. We will abstract information on the study design and unit of analysis for each study, indicating whether clustering of observations is present due to allocation to the intervention at the group level or clustering of individually randomized observations (e.g. patients within clinics). Available statistical information needed to account for the implications of clustering on the estimation of outcome variances will be abstracted, such as design effects or intra-cluster correlations, and whether the study adjusted results for the correlations in the data. In cases where the study does not account for clustering, we will ensure that appropriate adjustments are made to the effective sample size following Cochrane guidance (Higgins 2020). Where possible, we will derive the intra-cluster

correlation (ICC) for these adjustments from the trial itself, or from a similar trial. If an appropriate ICC is unavailable, we will conduct sensitivity analyses to investigate the potential effect of clustering by imputing a range of values of ICC.

If any trials have multiple arms that are compared against the same control condition and we need to include them in the same meta-analysis, we will divide the control group numerators and denominators by the number of interventions to be included in the meta-analysis, to avoid double counting observations.

Dealing with missing data

We will contact investigators or study sponsors in order to verify key study characteristics and obtain missing numerical outcome data for those studies identified as abstract only.

We will calculate missing standard deviations or other necessary data using other data from the trial, such as confidence intervals, based on methods outlined in chapter 6 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2020).

We will report the number of studies that have results missing for the synthesis of each outcome.

We will show all responses and data provided in the 'Characteristics of included studies' table. Where we make any assumptions about missing data, we will report the potential impact in the 'Discussion' section of the review.

Assessment of heterogeneity

We will describe the clinical diversity and methodological variability of the evidence in the review text and will use tables to describe study characteristics, including design features, population characteristics, and intervention details.

To assess statistical heterogeneity, we will visually inspect forest plots and describe the direction and magnitude of effects, and the degree of overlap between confidence intervals. We will also consider the statistics generated in forest plots that measure statistical heterogeneity. We will use the I^2 statistic to quantify inconsistency among the trials in each analysis. We will also consider the P value from the Chi^2 test to assess whether this heterogeneity is significant ($P < 0.1$). If we identify substantial heterogeneity, we will report the finding and explore possible explanatory factors using prespecified subgroup analysis.

We will use a rough guideline to interpret the I^2 value rather than a simple threshold, and our interpretation will take into account an understanding that measures of heterogeneity (I^2 and Tau^2) will be estimated with high uncertainty when the number of studies is small (Deeks 2020).

- 0% to 40%: heterogeneity might not be important
- 30% to 60%: may represent moderate heterogeneity*
- 50% to 90%: may represent substantial heterogeneity*
- 75% to 100%: considerable heterogeneity*

*The importance of the observed value of I^2 depends on (1) the magnitude and direction of effects, and (2) the strength of evidence for heterogeneity (e.g. P value from the Chi^2 test, or a confidence interval for I^2).

Assessment of reporting biases

If we have enough studies available for meta-analysis to support a funnel plot (at least 10), we will create and visually inspect the funnel plot and run a formal statistical test for asymmetry, as proposed by Egger 1997. We plan to provide a funnel plot for risk of deep venous thromboembolism, risk of pulmonary embolism, and risk of arterial thromboembolism, data permitting. Where there are fewer than 10 studies available for inclusion in a meta-analysis, we will note the difficulty of excluding publication bias. In the event that we observe funnel plot asymmetry, we will discuss the potential for this to be attributed to small study effects and not just non-reporting bias.

Data synthesis

We will assess the intervention effect separately for RCTs and NRSIs with similar designs. We will undertake meta-analyses to estimate pooled effects when the studies report adequate comparable data that can support statistical pooling. When we suspect that data are skewed, based on the reporting of median and interquartile ranges, we will note the skewness and discuss the implication, but will not pool medians with means.

For outcomes with data that cannot be statistically pooled, we will present descriptive forest plots showing the individual study results to illustrate the range of effects reported.

If data are adequate to support meta-analysis, the analytic approach we take will be based on an evaluation of the clinical and methodological diversity of the included studies, as well as the statistical heterogeneity. For rare outcomes and the zero-count events that are likely to be present in the evidence for this review, we will use the Peto odds ratio method for the main analyses. For more common outcomes, we will generate the pooled effect using the DerSimonian and Laird random-effects estimation technique. We will consider calculating a fixed-effect estimate using the Mantel-Haenszel approach if we can assume that the included studies are estimating the same intervention effect, if the intervention effects are relatively consistent in direction and magnitude, and heterogeneity is low. We will also consider the Mantel-Haenszel approach if there is evidence of potential variation in outcome effects by study size (i.e. small-study effects). We will discuss the implications and assumptions of the choice of meta-analysis model if results differ, but the default approach for this topic will be the random-effects model. We will illustrate each meta-analysis using a forest plot to display effect estimates and 95% confidence intervals for both individual studies' effects and the pooled effect.

If we cannot summarize the study data quantitatively, we will follow guidance available for synthesis without meta-analysis outlined in Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (McKenzie 2020).

Subgroup analysis and investigation of heterogeneity

We will interpret tests for subgroup differences in effects with caution, given the potential for confounding with other study characteristics and the observational nature of the comparisons, as recommended in chapter 10.11.2 in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2020). When adequate data are available to conduct meaningful subgroup analyses, we will evaluate factors that could explain observed statistical

heterogeneity. We will conduct a statistical test for interactions with either a simple significance test to investigate differences between two or more subgroups (Borenstein 2013), or use meta-regression to evaluate potential subgroups differences in outcomes according to the factors described below (Borenstein 2013). We will only use meta-regression if there are more than 10 studies available for meta-analysis.

Given the potential differences in the intervention effect related to dose and hormone type discussed in the background section, we will conduct subgroup comparisons to see if the intervention has a dose-response effect with increasing ethinyl estradiol dose or progestin component.

We plan to carry out the following subgroup analyses of factors that may contribute to heterogeneity in the effects of the intervention.

- Studies using ethinyl estradiol dosage < 30 mcg versus studies ≥30 mcg
- Types of progestin contraception (i.e. oral progestin-only contraception, injectable, progestin-releasing intrauterine device)
- Studies investigating hospitalized women versus women treated as outpatients
- Studies from areas with large outbreaks of COVID-19 versus studies from areas without large outbreaks
- Type of anticoagulation (i.e. prophylactic anticoagulation, intermediate-dose anticoagulation, therapeutic anticoagulation)

We will use the following outcomes in subgroup analyses if there are enough studies reporting the outcome to support valid subgroup comparisons.

- Venous thromboembolism
- Arterial thromboembolism
- Mortality
- Ambulatory versus non-ICU hospitalized versus ICU hospitalized women with COVID-19

Sensitivity analysis

We will perform sensitivity analyses defined a priori to assess the robustness of our conclusions and explore the impact of the factors specified below on effect sizes.

This will involve the following:

- Restricting the analysis to published studies that have been peer-reviewed.
- Restricting the analysis to studies with a low risk of bias, as specified in the section 'Assessment of risk of bias in included studies'.
- Restricting the analysis to studies performed in high/very high Human Development Index (HDI) settings versus medium/low HDI settings as defined by the United Nations Development Programme (UNDP 2020).

Given that there is no formal statistical test that can be used for sensitivity analysis, we will provide informal comparisons between the different ways of estimating the effect under different assumptions (Higgins 2020).

Summary of findings and assessment of the certainty of the evidence

We will evaluate the evidence according to the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the certainty of the body of evidence as it relates to our prespecified outcomes.

We will follow the methods and recommendations described in Chapter 14 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2020a), and will use GRADEpro GDT software.

We will provide separate 'Summary of findings' tables for the following comparisons.

- Combined hormonal contraception versus no contraceptive method
- Combined hormonal contraception versus non-hormonal contraception
- Combined hormonal contraception versus progestin-only contraception
- Progestin-only contraception versus no contraceptive method
- Progestin-only contraceptive versus non-hormonal contraception

We will summarize evidence for a given outcome from RCTs and NRSIs in separate rows.

We will use footnotes to give justifications for our decisions to downgrade the certainty of evidence and provide comments to aid readers' understanding of the review where necessary.

Two review authors (MAC, AE) will make independent judgments about the certainty of the evidence, with disagreements resolved by discussion or involving a third author (JH). We will justify the judgments, document them and incorporate them into reporting of results for each outcome.

Deciding when to incorporate new evidence

Living systematic review consideration

Whenever we identify new evidence relevant to the review (meaning studies, data or other information), we will extract the data and assess risk of bias, as appropriate. We will immediately incorporate any new evidence into the next anticipated review update. We will publish updates every four months while the review is in living mode, as appropriate.

ACKNOWLEDGEMENTS

We acknowledge the help and support of Cochrane Fertility Regulation Review group and copy-editors.

REFERENCES

Additional references

Abou-Ismail 2020

Abou-Ismail MY, Sridhar DC, Nayak L. Estrogen and thrombosis: a bench to bedside review. *Thrombosis Research* 2020;**192**:40-51.

Ahmed 2020

Ahmed S, Zimba O, Gasparyan AY. Thrombosis in Coronavirus disease 2019 (COVID-19) through the prism of Virchow's triad. *Clinical Rheumatology* 2020;**39**:2529-43.

Benson 2020

Benson L, Madden T, Tarleton J, Micks E. Society of Family Planning interim clinical recommendations: contraceptive provision when healthcare access is restricted due to pandemic response. www.wisconsincan.info/uploads/2/0/5/4/20541726/society_for_family_planning_interim_clinical_recommendations_for_contraceptive_provision_042420.pdf 2020.

Bikdeli 2020

Bikdeli B, Madhavan MV, Jimenez D, Chuich T, Dreyfus I, Driggin E, et al, Global COVID-19 Thrombosis Collaborative Group, endorsed by the ISTH NATF ESVM and the IUA, supported by the ESC Working Group on Pulmonary Circulation and Right Ventricular Function. COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up: JACC state-of-the-art review. *Journals of the American College of Cardiology* 2020;**75**(23):2950-73.

Borenstein 2013

Borenstein M, Higgins JP. Meta-analysis and subgroups. *Prevention Science* 2013;**14**:134–43.

CNGOF 2020

Prévention du risque thromboembolique veineux chez les femmes COVID + non hospitalisées utilisant un traitement hormonal (Contraception, Traitement hormonal de ménopause, Tamoxifène). http://www.cngof.fr/coronavirus-go-cngof/apercu?path=HEMOSTASE%2B-%2BRISQUE%2BDE%2BMTE%252FHemostase-PreventionMVTECOVIDHormones.pdf&i=36239 2020.

Cohen 1988

Cohen J. Statistical Power Analysis in the Behavioral Sciences. 2nd edition. Hillsdale (NJ): Lawrence Erlbaum Associates, Inc., 1988.

Curtis 2016

Curtis KM, Tepper NK, Jatlaoui TC, Berry-Bibee E, Horton LG, Zapata LB, et al. U.S. medical eligibility criteria for contraceptive use, 2016. *MMWR Recommendations and Reports* 2016;**65**(3):1-103.

de Bastos 2014

de Bastos M, Stegeman BH, Rosendaal FR, Vlieg AV, Helmerhorst FM, Stijnen T, et al. Combined oral contraceptives: venous thrombosis. *Cochrane Database of Systematic Reviews* 2014, Issue 3. Art. No: CD010813. [DOI: 10.1002/14651858.CD010813.pub2] [PMID: 24590565]

Deeks 2020

Deeks JJ, Higgins JP, Altman DG, editor(s). Chapter 10: Analysing data and undertaking meta-analyses. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.1 (updated September 2020). Cochrane, 2020. Available from www.training.cochrane.org/handbook.

Ding 2020

Ding T, Zhang J, Wang T, Cui P, Chen Z, Jiang J, 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. *Clinical Infectious Diseases* 2020;**1022**:Online ahead of print. [DOI: 10.1093/cid/ciaa1022]

Dragoman 2018

Dragoman MV, Tepper NK, Fu R, Curtis KM, Chou R, Gaffield ME. A systematic review and meta-analysis of venous thrombosis risk among users of combined oral contraception. *International Journal of Gynaecology and Obstetrics* 2018;**141**(3):287-94.

Egger 1997

Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;**315**:629-34.

Fruzzetti 2020

Fruzzetti F, Cagnacci A, Primiero F, Leo VD, Bastianelli C, Bruni V, et al. Contraception during Coronavirus-Covid 19 pandemia. Recommendations of the Board of the Italian Society of Contraception. *European Journal of Contraception & Reproductive Health Care* 2020;**25**(3):231-2.

FSRH 2020

FSRH Clinical Effectiveness Unit Statement: Use of combined hormonal contraception during the Covid-19 pandemic. https://www.fsrh.org/documents/fsrh-clinical-effectiveness-unit-statement-use-of-combined/ December 18, 2020.

GRADEpro GDT [Computer program]

McMaster University (developed by Evidence Prime) GRADEpro GDT. Hamilton (ON): McMaster University (developed by Evidence Prime), accessed 25 February 2021. Available at gradepro.org.

Higgins 2020

Higgins JP, Li T, Deeks JJ, editor(s). Chapter 6: Choosing effect measures and computing estimates of effect. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.1 (updated September 2020). In: Available from www.training.cochrane.org/handbook. Cochrane, 2020, 2020.

Jin 2020

Jin JM, Bai P, He W, Wu F, Liu XF, Han DM, et al. Gender differences in patients with COVID-19: focus on severity and mortality. *Front Public Health* 2020;**8**:152.

Liberati 2009

Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Medicine* 2009;**6**(7):e1000100.

Mauvais-Jarvis 2020

Mauvais-Jarvis F, Klein SL, Levin ER. Estradiol, progesterone, immunomodulation, and COVID-19 outcomes. *Endocrinology* 2020;**161**(9):Online ahead of print. [DOI: 10.1210/endocr/bqaa127]

McKenzie 2020

McKenzie JE, Brennan SE. Chapter 12: Synthesizing and presenting findings using other methods. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.1 (updated September 2020). Cochrane, 2020. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.1 (updated September 2020) 2020.

Ramírez 2020

Ramírez I, De la Viuda E, Baquedano L, Coronado P, Llaneza P, Mendoza N, et al. Managing thromboembolic risk with menopausal hormone therapy and hormonal contraception in the COVID-19 pandemic: recommendations from the Spanish Menopause Society, Sociedad Española de Ginecología y Obstetricia and Sociedad Española de Trombosis y Hemostasia. *Maturitas* 2020;**137**:57-62.

Robinson 1991

Robinson GE, Burren T, Mackie IJ, Bounds W, Walshe K, Faint R, et al. Changes in haemostasis after stopping the combined contraceptive pill: implications for major surgery. *BMJ* 1991;**302**(6771):269-71.

Schünemann 2020a

Schünemann HJ, Higgins JP, Vist GE, Glasziou P, Akl EA, Skoetz N, et al. Chapter 14: Completing 'Summary of findings' tables and grading the certainty of the evidence. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.1 (updated September 2020). Cochrane, 2020. Available from www.training.cochrane.org/handbook.

Schünemann 2020b

Schünemann HJ, Vist GE, Higgins JPT, Santesso N, Deeks JJ, Glasziou P, et al. Chapter 15: Interpreting results and drawing conclusions. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.1 (updated September 2020). Cochrane, 2020. Available from www.training.cochrane.org/handbook.

Stelzig 2020

Stelzig KE, Canepa-Escaro F, Schiliro M, Berdnikovs S, Prakash YS, Chiarella SE. Estrogen regulates the expression of SARS-CoV-2 receptor ACE2 in differentiated airway epithelial cells. *American Journal of Physiology-Lung Cellular and Molecular Physiology* 2020;**318**(6):L1280-1.

Sterne 2019

Sterne JA, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;**366**:l4898.

Sterne 2020

Sterne JA, Hernán MA, McAleenan A, Reeves BC, Higgins JP. Chapter 25: Assessing risk of bias in a non-randomized study. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.1 (updated September 2020). Cochrane, 2020. Available from www.training.cochrane.org/handbook.

Tepper 2016

Tepper NK, Whiteman MK, Marchbanks PA, James AH, Curtis KM. Progestin-only contraception and thromboembolism: a systematic review. *Contraception* 2016;**94**(6):678-700.

UN 2019

United Nations. Contraceptive use by method 2019: data booklet. United Nations, 2019. [DOI: 10.18356/1bd58a10-en]

UNDP 2020

Human Development Report 2020 | UNDP HDR. Human Development Report 2020 | UNDP HDR.

WHO 2020

World Health Organization. Coronavirus disease (COVID-19): Contraception and family planning. www.who.int/news-room/q-a-detail/coronavirus-disease-covid-19-contraception-and-family-planning 2020.

Zhang 2020

Zhang S, Liu YY, Wang XF, Yang L, Li H, Wang Y, et al. SARS-CoV-2 binds platelet ACE2 to enhance thrombosis in COVID-19. *Journal of Hematology & Oncology* 2020;**13**:161. [DOI: 10.1186/s13045-020-01003-z]

APPENDICES

Appendix 1. Model Search Strategy

Ovid MEDLINE(R) ALL 1946 to November 17, 2020
Date searched: 18 November 2020

1 exp Coronavirus/ (42432)
2 exp Coronavirus Infections/ (46184)
3 (coronavirus* or corona-virus* or OC43 or NL63 or 229E or HKU1 or HCoV* or ncov* or covid* or sars-cov* or sarscov* or Sars-coronavirus* or "Severe Acute Respiratory Syndrome").ti,ab,kw,kf. (88674)
4 or/1-3 (95624)
5 4 not (SARS or MERS or MERS-CoV or "Middle East respiratory syndrome" or camel* or dromedar* or equine or coronary or coronal or covidence* or covidien or "influenza virus" or HIV or bovine or calves or TGEV or feline or porcine or BCoV or PED or PEDV or PDCoV or FIPV or FCoV or SADS-CoV or canine or CCov or zoonotic or "avian influenza" or H1N1 or H5N1 or H5N6 or IBV or murine).ti,ab,kw,kf. (55485)
6 ((pneumonia or covid* or coronavirus* or corona virus* or ncov* or 2019-ncov or sars*).mp. or exp pneumonia/) and Wuhan.mp. (3628)
7 (2019-ncov or ncov19 or ncov-19 or 2019-novel CoV or sars-cov2 or sars-cov-2 or sarscov2 or sarscov-2 or Sars-coronavirus2 or Sars-coronavirus-2 or SARS-like coronavirus* or coronavirus-19 or covid19 or covid-19 or covid 2019 or ((novel or new or nouveau) adj2 (CoV or nCoV or covid or coronavirus* or corona virus or Pandemi*2)) or ((covid or covid19 or covid-19) and pandemic*2) or (coronavirus* and pneumonia)).ti,ab,kw,kf. (73718)
8 COVID-19.rx,px,ox. or severe acute respiratory syndrome coronavirus 2.os. (36298)
9 or/5-8 (83008)
10 Contraceptive Agents/ or Contraceptive Agents, Female/ or Contraceptives, Oral/ or exp Contraceptives, Oral, Hormonal/ or Contraceptives, Oral, Combined/ or Contraceptives, Oral, Sequential/ or Contraceptives, Oral, Synthetic/ or Hormonal Contraception/ or Contraceptive Agents, Hormonal/ or Intrauterine Devices, Medicated/ or "Long-Acting Reversible Contraception"/ (51730)
11 Cyproterone Acetate/ or Desogestrel/ or Estrogens/ or exp Ethinyl Estradiol/ or Ethinyl Estradiol-Norgestrel Combination/ or Ethynodiol Diacetate/ or Levonorgestrel/ or Lynestrenol/ or Medroxyprogesterone/ or Norethindrone/ or Norethindrone Acetate/ or Norgestrel/ or Progesterone/ or Progestins/ (130958)
12 (contraceptive or contraceptives or contraception or antifertility or anti-fertility or anticonception or anti-conception or birth-control).ti,ab,kw,oa,kf. (77731)
13 (CHC or CHCs or COC or COCs or COCP or COCPs or OCP or OCPs or POPs or ((monophasic or mono-phasic or biphasic or bi-phasic or triphasic or tri-phasic or quadriphasic or quadri-phasic or multiphasic or multi-phasic or normophasic or normo-phasic or minidose or mini-dose or morning-after or progestin-only) adj (pill or pills)) or ((first-generation or 1st-generation or second-generation or 2nd-generation or third-generation or 3rd-generation or fourth-generation or 4th-generation) adj2 (pill or pills or progest*))).ti. (1213)
14 (((progest* or levonorgestrel or LNG) adj2 (ball or balls or coil or coils or device or devices or IUD or IUDs or IUCD or IUCDs or IUS or IUSs or system or systems)) or (medicated adj2 (IUD or IUDs or IUCD or IUCDs or IUS or IUSs)) or LNGIUCD or LNGIUCDs or LNGIUD or LNGIUDs or LNGIUS or LNGIUSs).ti,ab,kw,oa,kf,nm. (2443)
15 ("cyproterone acetate" or desogestrel or drospirenone or dienogest or "estradiol valerate" or "oestradiol valerate" or estradiol or oestradiol or estrogen or oestrogen or EE or ethinylestradiol or ethinyloestradiol or ethinyl-estradiol or ethinyl-oestradiol or "ethynodiol diacetate" or ETN or etonogestrel or gestodene or LNG or levonorgestrel or lynestrenol or DMPA or "medroxyprogesterone acetate" or "nomegestrol acetate" or norelgestromin or norethindrone or norgestimate or norgestrel or progesterone or progestin* or progestogen or "segesterone acetate").ti,ab,kw,kf,nm,rn. (320324)
16 or/10-15 (398886)
17 and/9,16 (162)

HISTORY

Protocol first published: Issue 3, 2021

CONTRIBUTIONS OF AUTHORS

Conceiving the protocol: MC, AE, JH

Designing the protocol: MC, AE, JH

Co-ordinating the protocol: MC

Designing search strategies: RP, MC, AE

Writing the protocol: MC, AE, JH, FS, RP

Providing general advice on the protocol: AE, JH, FS

Securing funding for the protocol: Not applicable

Performing previous work that was the foundation of the current study: Not applicable

DECLARATIONS OF INTEREST

M Cohen: has declared that they have no conflict of interest.

A Edelman: 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 COVID19 related, but are homonal contraception related.

J Henderson: has declared that they have no conflict of interest.

F Stewart: has declared that they have no conflict of interest.

R Paynter: has declared that they have no conflict of interest.