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Protocol of a systematic review and network meta-analysis for the prevention and treatment of perinatal depression

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ABSTRACT
Introduction Perinatal depression is common and can often lead to adverse health outcomes for mother and child. Multiple pharmacological and non-pharmacological treatments have been evaluated against usual care or placebo controls in meta-analyses for preventing and treating perinatal depression compared. It is not yet established which of these candidate treatments might be the optimal approach for prevention or treatment.

Methods and analysis A systematic review and Bayesian network meta-analyses will be conducted. Eight electronic databases will be searched for randomised controlled trials that have evaluated the effectiveness of treatments for prevention and/or treatment of perinatal depression. Screening of articles will be conducted by two reviewers independently. One network meta-analysis will evaluate the effectiveness of interventions in preventing depression during the perinatal period. A second network meta-analysis will compare the effectiveness of treatments for depression symptoms in women with perinatal depression. Bayesian 95% credible intervals will be used to estimate the pooled mean effect size of each treatment, and surface under cumulative ranking area will be used to rank the treatments’ effectiveness.

Ethics and dissemination We shall report our findings so that healthcare providers can make informed decisions on what might be the optimal approach for addressing perinatal depression to prevent cases and improve outcomes in those suffering from depression through knowledge exchange workshops, international conference presentations and journal article publications.

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INTRODUCTION
Background Depression is the leading cause of disability worldwide, it is a major contributor to the global burden of disease, affecting a variety of populations.1 Depression experienced during pregnancy and after birth, also known as perinatal depression, is common and can affect up to 20% of mothers.2 Previous systematic reviews have shown that the prevalence of perinatal depression is generally higher in low-to-middle-income countries than high-income countries in both the antenatal and postnatal stages.3 4 With perinatal mental disorders, including depression, being more prevalent in mothers who are the most socio-economically disadvantaged.5 Cultural factors also have been indicated to be sources of inequality for perinatal mental illness, these include cultural gender-bias, gender-biased violence; both physically and mentally.6 Perinatal depression can cause a range of adverse health outcomes for women and the development of their children. Depression during pregnancy can lead to multiple problems, including premature delivery, gastrointestinal pain, poorer self-report health and functioning, it can also lead to an increased risk of smoking or alcohol abuse.5 6 Longer-term depression beyond 1-year post partum, can lead to later problems during
parenting, including lower interaction and sensitivity between mother and infant. Long lasting depression has been shown to lead to further difficulties in later years for the offspring, including emotional and behavioural difficulties. 

Successful prevention of postnatal depression occurring can be achieved. Identifying those with depression early; either during the antenatal period (during pregnancy) or in the postnatal period (up to 1-year post partum) provides a critical opportunity for earlier treatments and prevents poorer outcomes from occurring. 

Despite its significant burden on maternal and child health, less than half of pregnant women suffering from depression are identified within healthcare. Attitudes towards identifying cases of perinatal depression among clinicians are positive. Still, there is a need for support strategies that can identify and treat those at risk of perinatal depression within routine practice. A systematic review suggested that the Wholey questions, a set of two-item yes/no answered questions were a valid and feasible approach for identifying possible positive cases of perinatal depression.

Once identified, healthcare services can provide interventions for preventing those at risk of depression occurring in the future or offering treatments for those with depression. There is a wide variety of interventions that are shown to be effective in treating depression symptoms in perinatal women compared with non-active controls: psychological interventions, pharmacological interventions or combinations of both; psychoeducation or parenting education; psychosocial interventions for treatment and prevention; systemically oriented psychotherapies; mindfulness; family therapy; physical activity; and yoga-based interventions. In later stage postnatal women, meta-analyses have suggested cognitive behavioural therapy, interpersonal therapy, counselling and other psychological interventions are effective in treating depression symptoms when compared with usual care. Another meta-analysis on antidepressants for postnatal depression in a small number of studies show that selective serotonin reuptake inhibitors are effective for depression compared with placebo.

Clinical guidelines recommend screening and treatment for perinatal depression, these guidelines do not provide recommendations on which treatments are most effective. Treatment options for depression during pregnancy may vary depending on different severities of depression. Many treatments previously evaluated were identified as effective on depression symptoms compared with usual care or placebo, but the relative comparability of these treatments has not previously been investigated. Relative comparisons of different treatments would allow healthcare providers to make informed decisions on how different active treatments can be compared. The relative comparison of treatments could also provide evidence for the optimal approach to treating perinatal depression based on all available evidence.

Rationale

Using a Bayesian network meta-analysis facilitates all interventions to be compared equally with one-another by using the direct evidence (within study comparisons of treatments) and indirect evidence (comparing treatments across different studies), which previous systematic review studies and clinical guidelines in perinatal depression have not yet explored. This approach can provide evidence for the relative comparative effectiveness of each treatment and potentially identify the optimal approach for preventing cases and treating symptoms of perinatal depression.

We will conduct a comprehensive systematic review of available peer-reviewed published trial studies for all pharmacological and non-pharmacological interventions, addressing perinatal depression by conducting a network meta-analysis. Based on this we will be able to compare each treatments’ effectiveness with one-another and recommend types of interventions that may optimally address the prevention and treatment of perinatal depression. An example of this could be making relative comparisons on the effectiveness of interventions that require fewer resources for health providers to implement that is scalable against more resource intensive interventions that require trained specialists or equipment to implement and the level of trade-off in clinical effectiveness between those interventions. Another advantage of Bayesian network meta-analysis is statistical certainty can be estimated, this allows for identifying potentially promising interventions with low levels of statistical certainty that may require further investigation to establish effectiveness.

Objectives

This study will assess the clinical benefits of different interventions for addressing the prevention and treatment of perinatal depression. Two objectives have been developed for this study.

1. To identify the optimal approach for preventing perinatal depression in women.
2. To identify the optimal approach for the treatment of perinatal depression in women.

METHODS

The protocol of this study has been developed following the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols guidelines (online supplemental appendix 1) and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension statement on the reporting of systematic reviews that incorporate network meta-analysis of healthcare interventions.

Eligibility criteria

Study selection and eligibility criteria were based on the Population, Intervention, Comparison, Outcome, Study design (PICOS)-related to objectives 1 and 2 (table 1). Briefly, studies on participants who are perinatal women.
between 20 weeks gestation to 1 year after birth will be included. We selected 1 year after birth to reflect the time period in which there is a risk of postpartum depression occurring between day 1 to 1-year post partum.\(^{32}\) We did not specify any limitations on interventions as this review aims to identify and evaluate all intervention types that address depression within the target population. Given the advantages of the network meta-analysis approach, no limitations will be placed on the comparison group for studies. Outcomes for objective 1 will be: confirmed cases of depression and for objective 2: measurements of depression severity or symptoms. Study design will only include randomised controlled trials to minimise the risk of bias when comparing effectiveness of interventions. Eligibility is displayed in table 2. Studies that include participants with substance abuse, psychotic or developmental disorders or medical conditions, long-term care, residential facilities or those in institutions (psychiatric inpatients) were excluded as the treatment needs of these populations’ depression symptoms differ compared with those with depression alone.\(^{34}\) Included articles were limited to those written in English, there was no limitation of publication year for included articles.

### Sources of information

Databases searched electronically will be MEDLINE, British Nursing Index (BNI), EMBASE, Cumulative Index to Nursing and Allied Health (CINAHL Plus), PsycINFO, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews and Web of Science (WoS). We selected MEDLINE, EMBASE and WoS databases based on recommendations for Cochrane Handbook covering major health sciences topics. We also selected specialist subject databases BNI, CINAHL Plus and PsycINFO based on their relevance to the study objectives. WHO's trials portal and clinicaltrials.gov will be searched to identify unpublished studies or studies still ongoing.

We shall conduct searches of reference lists and forward citation of identified and included studies using the Web of Science database for additional papers. We shall exclude studies that are published systematic review or literature review identified during our electronic searches but shall examine the reference lists for additional candidate studies.

### Search strategy

Searches of online databases will commence in August 2021. The search strategy has been developed based on the two sets of PICOS with one for each review question. We identified all search terms, related to the two sets of PICOS, from previously published meta-analyses on the prevention or treatment of perinatal depression\(^{15-25}\) to maximise sensitivity of our search strategy in identifying

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<tr>
<th>Table 1</th>
<th>PICOS for search strategy and study selection criteria</th>
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<tr>
<td><strong>Objective 1</strong></td>
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<tr>
<td>Population</td>
<td>Perinatal mothers, or if not identified as perinatal within the study; females between 20th week of gestation to 1 year after birth, no limitation of setting, excluding those currently experiencing a depression episode</td>
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<tr>
<td>Intervention</td>
<td>Interventions that aimed to prevent perinatal depression including pharmacological and non-pharmacological interventions, interventions were not limited for setting</td>
</tr>
<tr>
<td>Comparison</td>
<td>Studies will not be limited for comparisons groups, and shall include other active interventions or non-active controls</td>
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<tr>
<td>Outcome</td>
<td>Depression diagnosis (determined through the clinical interview)</td>
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<tr>
<td>Study design</td>
<td>Randomised controlled trials only</td>
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<th>Table 2</th>
<th>Inclusion and exclusion criteria for study selection</th>
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<tr>
<td>Inclusion criteria</td>
<td>Exclusion criteria</td>
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<tr>
<td>► Research paper in a peer-reviewed journal</td>
<td>► Populations that include persons with substance abuse, psychotic or developmental disorders or medical conditions, in long-term care, residential facilities or those in institutions (psychiatric inpatients), studies that include subsets these populations were excluded if they exceeded 50% of the study sample</td>
</tr>
<tr>
<td>► Studies that met the PICOS criteria for either objectives 1 or 2</td>
<td>► Study designs other than randomised controlled trials</td>
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all definitions of perinatal depression and minimise risk to missing relevant studies. An example full list of search terms for the MEDLINE database can be found in online supplemental appendix 2.

Data management
Studies retrieved in our search strategy shall be downloaded and stored in EndNote (X9) where duplicates across different sources will be removed.

Study selection process
Screening of studies shall be conducted using the inclusion and exclusion criteria (table 2). Two reviewers (RDS, JG, SCH or HLI) shall conduct study selection, with both reviewers reviewing each retrieved study independently. Differences in assessment or any disagreements over the eligibility of studies were resolved by discussion, and in cases of disagreement, the third reviewer (KY-WL) would be consulted. Screening of studies shall be conducted in two different stages: (1) title and abstract, where studies will only be excluded if there is a clear disparity to eligibility criteria, if it is unclear, then articles or included articles will be further screened in the stage; (2) full article screening, where eligibility can be decided based on all reported article information, including supplementary materials. The rationale for the exclusion of studies will be recorded. Piloting of the data selection process shall take place prior to the full study selection, with 100 articles randomly selected from the search retrieved. Adjustments to the inclusion and exclusion criteria and study selection process may be made following piloting.

Data extraction
Data extraction shall be conducted by two of the reviewers (RDS, JG, SCH or HLI) independently using a standardised extraction form. Differences in assessment or any disagreements for data extraction of studies will be resolved by discussion, and in cases of disagreement, the third reviewer (KY-WL) will be consulted. The data extraction forms were taken from the Cochrane Consumers and Communication Review Group’s Data Extraction Template for Cochrane Reviews, and were modified to fit this systematic review. The extracted information will include study setting, study participant demographics and baseline characteristics, details of the intervention and control conditions, study methodology, recruitment and study completion rates, outcomes and times of measurement, indicators of acceptability to users, suggested mechanisms of intervention action and information for the assessment of the risk of bias. Missing data will be requested from study authors.

Risk of bias assessment
Risk of bias will be assessed using version 2 of the Cochrane Risk of Bias tool (RoB2). This tool includes five-domains based on the risk of biases within the randomisation process, deviation from intervention design, missing outcome data, measurement of outcome and reporting of results. The risk of bias assessment shall be completed following the guidance released with the RoB2. Possible risk of bias judgments shall include (1) low risk, (2) some concerns and (3) high risk of bias. Results of the risk of bias shall be presented within each domain of risk of bias, as well as an overall score for each study. Overall risk of bias shall be judged based on the suggested criteria of the RoB2 guidance document. Piloting and adaption of the wording in the risk of bias assessment, if necessary, shall be conducted prior to the full review. Risk of bias will be evaluated by two of the reviewers (RDS, JG, SCH or HLI) independently evaluate the risk of bias. Differences in assessment or any disagreements will be resolved by discussion, and in cases of disagreement, the third reviewer (KY-WL) will be consulted.

Data analysis
Effect measurements
Data from each study shall be extracted with effect size calculated. For studies addressing review question 1, follow-up data on the number of positive depressions cases in each arm shall be extracted allowing for relative risk (RR) to be calculated in each arms’ comparison, with RR of less than 1 representing reduced risk of depression. For review question 2, treatment effect shall be calculated using mean difference (MD) if possible, or standardised MD (SMD) for depression severity. To calculate SMD; difference in changes (from baseline to follow-up) for intervention arms shall be used, divided by the pooled SD of change. For studies with three or more arms, a reference group shall be taken to calculate the SMD. Studies with negative SMD effect sizes representing improvements in reducing depression severity. Score changes will be used to control for possible baseline differences between study arms. For studies with multiple follow-up time points, we shall use the longest duration, up to a maximum of 1 year from the end of the intervention. In studies using median and IQRs we shall impute these following the Cochrane Handbook. Studies that do not report the SD of change from baseline will be imputed following the Cochrane Handbook. A correlation coefficient for imputation of SD of change shall be estimated based on the mean correlation in studies that do report all relevant data. If no studies report baseline, follow-up and change values, we shall take the conservative value of r=0.5 to estimate SD of change. Where possible, we shall use the intention to treat sample for analyses. Interventions will be grouped for the network analysis using categories used by previous individual meta-analysis as a framework, new emerging interventions not previously evaluated in meta-analysis shall be organised and grouped by agreement with the reviewing team.

Network meta-analysis implementation
Two network meta-analyses shall be conducted for depression prevention, using RR and treatment of depression severity, using SMD. We shall estimate model consistency by comparing the RR or SMD of the direct (within study comparisons) and indirect comparisons (between study
comparisons), where direct comparisons are possible. The network meta-analysis will be conducted with a Bayesian Markov chain Monte Carlo (MCMC) method fitted using the Just Another Gibbs Samplers software within the R Statistical Software conducted within the BUGSnet package (R Core Team, 2020). We shall run four MCMC chains simultaneously in our model and construct two separate MCMC simulations to compare convergence. The Bayesian model shall run 5000 burn-in iterations and 100 000 simulation iterations. Convergence shall be assessed using the potential scale reduction factor, where we expect the model to reduce to below 1.05. Heterogeneity (direct evidence) and model consistency (direct vs indirect) will be assessed using the node split function of the BUGSnet package; sources of heterogeneity will be explored between studies. All results of each possible comparison of interventions shall be made using RR or SMD and 95% credible intervals, which can be considered Bayesian equivalent of CIs. Rank probabilities will represent the probability of the ranking performance of each intervention type. Surface under the cumulative ranking score will also be used to estimate the likelihood of the most effective intervention.36 37 A limitation of the network meta-analysis approach is that treatments that have not been previously combined in trials cannot be combined in the meta-analysis. This precludes an investigation of whether or not combining two or more treatments provides any extra benefits than one treatment only.

Treatments for women with depression during or after pregnancy can vary in different populations and across disease severity.38 To address this, network meta-regression and subgroup analysis shall be conducted to evaluate study characteristics that may influence the effect sizes of interventions within the network. Factors for exploring in the meta-regressions shall include the year of publication, the geographical region the study was conducted, study sample age, whether the study participants were at antenatal or early postnatal stage of motherhood, study sample’s baseline depression severity (if possible), risk of bias in all five domains and overall risk of bias. Publication bias shall be assessed using two funnel plots of all included studies for each objective; trim and fill analysis shall also be conducted.

Patient involvement
Patients and the public were not involved in the design of the protocol or analysis of this study.

Ethics and dissemination
Ethics is not required for this study, given that this is a protocol for a systematic review, which uses published data. The results of the review would be widely disseminated locally, nationally, and internationally. A paper would be submitted to a leading peer-review journal in this field, reporting of the study will adhere to the PRISMA extension statement on the reporting systematic reviews that incorporate network meta-analysis of healthcare interventions.39 When presenting our findings from this study, the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) scoring for evidence and strength of recommendations shall be made following the criteria in the GRADE handbook.38 The findings shall also be presented at a relevant international conference.

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Contributors RDS drafted the manuscript. KY-WL is the principal investigator of the study and is responsible for conducting the study overall. The study’s research question and design were conceived by RDS and KY-WL. Search terms for all databases were constructed and pilot tested by RDS, JG, HLI and SCH. Screening forms, data extraction forms and risk of bias forms were developed and piloted by RDS, KY-WL, JG, SCH and HLI. Assistance with preparation of the manuscript and clinical expertise into the design of the study’s PICOS and inclusion/exclusion criteria was given by CAW. Development and plan of analyses were prepared by RDS, DYTF and SA. All authors contributed to the preparation of this manuscript.

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