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The effectiveness of combined vaginal progesterone and cervical cerclage in preventing preterm birth: a systematic review and meta-analysis protocol

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Abstract

Background: Preterm birth (PTB) is the leading cause of death in children under five. Preventive therapies targeted towards women with risk factors such as a prior PTB or a short cervix reduce the rate of PTB. Cervical cerclage, vaginal progesterone, and a combination of the two have been used with no consensus as to whether combined treatment is more effective than any single treatment alone. The objective of this review is to determine the efficacy of combined treatment compared to cerclage alone, and combined treatment compared to progesterone alone. **Methods:** Studies will be sourced from six electronic databases and reference lists. Randomised control trials (RCTs), non-randomised control trials, and cohort studies assessing single therapy (either progesterone or cerclage) versus combined therapy in women with a singleton pregnancy will be included. Two independent reviewers will conduct study screening (at abstract and full text level), data extraction and risk of bias assessment with disagreements resolved by an experienced researcher. Random or fixed effects models will be used depending on data heterogeneity and data will be presented as Risk Ratio (RR) for dichotomous data or Mean Difference (MD) for continuous data with a Confidence Interval (CI) of 95% used for all outcomes. **Discussion:** This review will provide clarity regarding the evidence on singular and combined treatment and will assist clinicians and health services in delivering best practice antenatal care. **Registration:** PROSPERO on 8th of October, 2020 with registration number CRD42020195975 **Key words:** Cervical, Stitch, Cerclage, Progesterone, Preterm Birth.

Strengths and limitations:

- The systematic review will follow the rigorous methods outlined in this protocol which have been written as per Cochrane guidelines.
- This will be the first systematic review to answer this question.
- Data will be screened and extracted by two reviewers.
- Lack of reviewer and moderator blinding at inclusion/exclusion level.
- Lack of blinding of reviewers and moderators for papers at quality assessment Robins 1, Rob 2, and GRADE.

Introduction

Preterm birth (PTB), defined as birth before 37 weeks(1), occurs in 5-13% of all pregnancies(2). It is associated with neonatal mortality and is the leading cause of death in children less than five years(3), as well as significant neonatal morbidity such as infant respiratory distress syndrome, intraventricular haemorrhage, necrotising enterocolitis, and retinopathy of prematurity(4).

The majority of PTB occurs either spontaneously or following preterm premature rupture of membranes (PPROM)(5). It is well established that a cervical length of less than 25mm, measured between 18 and 25 weeks, is a good predictor of spontaneous PTB (sPTB) with rates of 31.2% to 41.3%(6, 7). Vaginal progesterone(8) and cervical cerclage(6, 9) are effective single treatments for the prevention of sPTB in these women, as well as those with a prior history of PTB.

Cervical cerclage is a treatment proven to prevent PTB and reduce neonatal morbidity and mortality(10, 11, 12) by mechanically maintaining a long and closed cervix. In contrast, progesterone has an inhibitory action on uterine contractility by inhibiting the production of

stimulatory prostaglandins and expression of contraction associated protein genes in the myometrium(13, 14). It has been shown to play an important role in maintaining a pregnancy until term(15). Vaginal progesterone when used in women with a short cervix, even in the absence of other risk factors, has been shown to reduce PTB before 34 weeks by 35%(8). Progesterone therapy can effectively manage cervical shortening in women with cervical length (CL) of <25 mm, but appears less effective in those with a CL <10 mm(8). With regard to PTB rates, at 37 weeks cervical cerclage has a 20% success rate in preventing PTB (16), while vaginal progesterone has a 10% success rate at the same number of weeks gestation (8).

More recently, studies have assessed the combination of the cervical cerclage and vaginal progesterone to improve PTB prevention (10, 11). To our knowledge, only one systematic review published in 2013 has addressed progesterone as an adjunctive therapy to cerclage; however, the included studies were not randomised and assessed synthetic progestin 17-hydroxyprogesterone caproate (17-OHPC), which found no difference in the outcome of PTB (16). More recently, adjuvant vaginal progesterone therapy for women who underwent cervical cerclage indicated by ultrasound(11) or physical(10) examination was found to be associated with decreased rates of PTB and admission to the neonatal intensive care unit (NICU). Given these recent promising findings and the lack of guidance on this topic, we sought to determine the effect of combining both cerclage and progesterone on PTB by conducting a systematic review and meta-analysis. This paper describes the proposed protocol for this meta-analysis.

Aim

This systematic review has two aims: 1) to compare the use of cerclage alone to cerclage and vaginal progesterone combined, and 2) to compare progesterone alone to the combined use of

cerclage and vaginal progesterone in order to determine which of these is associated better maternal and neonatal outcomes in relation to PTB. Our proposed review will answer the questions *in women requiring prophylactic treatment for short cervix is combined treatment favourable to cerclage alone?* And *in women requiring prophylactic treatment for short cervix is combined treatment favourable to vaginal progesterone alone?*

Methods

Registration:

This systematic review protocol was submitted to the International Prospective Register of Systematic Reviews (PROSPERO) on the 8th of October 2020 and was last updated on this date (registration number CRD42020195975). This review and meta-analysis will be completed in accordance using the recommendations of both Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol (PRISMA-P)(17) and the Cochrane Handbook for Systematic Reviews of Interventions(18).

Information regarding registration can be accessed from http://www.crd.york.ac.uk/PROSPERO.

Eligibility Criteria:

The eligibility of studies included will be based on inclusion and exclusion criteria applied to the domains of participant, exposure, comparator, study type, and outcome.

Participants:

The review will consider all studies which include women who are undergoing ultrasound or history indicated cerclage, vaginal progesterone, or both for the prevention of PTB. Only singleton pregnancies will be assessed.

Intervention:

Studies comparing combined cerclage and vaginal progesterone treatment with vaginal progesterone alone or cerclage alone.

Cerclage

There are two commonly performed vaginal cerclage procedures which were first described by Shirodkar and McDonald. In the McDonald approach a suture is placed around the cervix in purse-string fashion and securely tied anteriorly. The McDonald approach requires no dissection into para-cervical tissues (19, 20). The Shirodkar technique involves a transverse anterior colpotomy, dissection of the bladder up to the internal cervical os and a posterior colpotomy with dissection of peritoneum upwards to the internal os. The suture is placed subcutaneously and the knot tied in the posterior defect and buried under the vaginal epithelium(19, 21, 22) or tied exterior to the epithelium in the modified approach. Both Shirodkar techniques will be considered.

Vaginal Progesterone

Vaginal progesterone is available as a gel, suppository, or pessary(14). It is the most bioavailable form of progesterone for uterine and cervical effects with the fewest side effects. Its micronized form decreases particle size and increases surface area resulting in improved absorption with less metabolic and vascular side effects(23). The vaginal route also allows rapid absorption and avoids first pass hepatic metabolism, resulting in high bioavailability in the uterus(24).

Combined Treatment

Cervical cerclage (McDonald or Shirodkar technique) used in combination with vaginal progesterone.

Outcomes:

The primary outcome is PTB, defined as birth <37 weeks gestation. Secondary dichotomous outcomes will be PTB <34 weeks, <32 weeks, <28 weeks; PPROM; caesarean section; and neonatal complications: NICU admission, intubation, and neonatal mortality. The continuous secondary outcomes will be gestational age at delivery; birthweight; and number of days between intervention and delivery.

Types of studies:

The review will include randomised and pseudo-randomised control trials, non-randomised experimental control trials, and cohort studies. All included papers must compare cerclage to combined treatment and/or vaginal progesterone to combined treatment. Those studies which also presented a control group will be included.

Search strategy:

Electronic bibliographic databases will be searched for eligible, peer-reviewed literature including: Medline (Ovid), EMBASE (Ovid), PsycINFO (Ovid), Scopus, CINAHL (EBSCOhost) and Cochrane Library (Wiley). Reference lists of included studies will also be screened for eligible papers. Studies recommended by experts, the references of textbooks, and grey literature will also be reviewed for this purpose. We will place no restriction on the length of study follow-up time or on country, year, or language of publication. All studies will be human trials.

The search strategy will be developed through discussion with experts and academics, pilot searches, and by assessing systematic reviews with similar questions. The search strategy will focus on identifying relevant interventions with no population or outcome related keywords used. The intervention search terms will be: cervical OR cervix OR rescue; stitch OR cerclage OR suture; progesterone OR progestin OR prometrium OR progest. Medical subject headings (MeSH) will be used when relevant and present databases.

Data collection and analysis

Study Selection

Identified titles and abstracts will be downloaded into Endnote(25) where duplicated studies will be removed. Remaining papers will then be uploaded to Covidence(26) and then screened against the eligibility criteria outlined above. Full texts of remaining studies will be sourced and screened before undergoing critical appraisal and data extraction. All screening will be performed by two independent reviewers and any disagreements will be addressed by a senior research moderator. No reviewers or moderators will be blinded to titles, authors, journals, or institutions.

Data management

The search will be uploaded to Covidence(26), an Internet-based software which allows collaboration between multiple reviewers during the study selection process, backup copies of all studies will also be kept in an Endnote library(25).

Data collection

Two reviewers will extract data through Covidence(26) using a standardised electronic form consistent with data collection items recommended by the Cochrane Handbook for Systematic

Reviews of Interventions(18). This process will be piloted prior to use and any discrepancies will be moderated by a third senior research moderator. Once extracted, upon reviewer agreement, data will be transferred from Covidence(26) into Review Manager data-analysis software(27).

The following data will be extracted:

- Study characteristics: authors; publication date; study design; country of study; sample size; confounding factors of participants; publication status; trial size; funding; and risk of bias information.
- Intervention characteristics: type of intervention used; reason for intervention; patient characteristics (maternal age, gravity, parity), and any co-interventions received.
- Outcomes: maternal, fetal and neonatal outcome data and definitions of each of the outcomes as described below.

Outcomes and prioritisation:

Primary outcome

PTB defined as live or stillbirth with a gestational age between 20 and 37 weeks. Primary outcome is birth <37wks gestation with sub-analysis at <34wks, <32wks, and <28wks.

For outcomes which report this data as *"greater than" X weeks gestation*, data extractors will manually invert the figure to less than.

Secondary outcomes

Dichotomous

1. PPROM

2. Caesarean section
3. NICU admission
4. Intubation
5. Neonatal mortality

Continuous

6. Gestational age at delivery
7. Birthweight
8. Number of days between intervention and delivery

Assessment of risk of bias

Each paper will be assessed for risk of bias using the Cochrane Collaboration tool for assessing risk of bias (ROBINS I and RoB-2)(28, 29). Each study will be reviewed independently by two assessors and disagreements will be resolved through mediation with a third reviewer. High quality studies are those which achieve a score of seven or eight, average are scored four to six, and below four will be considered low quality. We will not be excluding any study based on these scores, however risk of bias will be taken into account when outcomes are assessed in regard to impact as per the Grade of Recommendation, Assessment, Development and Evaluations (GRADE)(30).

The Risk of Bias in Non-Randomised Studies of Interventions (ROBINS-I) tool(28) will be used to assess the risk of bias in included observational studies. The risk of bias will be rated as no information, low risk, moderate risk, serious risk, or critical risk across seven domains. The seven domains of this tool are (1) confounding; (2) selection of participants; (3) classification of intervention; (4) deviation from interventions; (5) missing outcome data; (6) measurement of outcomes; and (7) selection of reported results overall.

Randomised trials will be assessed with the Risk of Bias in Randomised Studies of Interventions (RoB2)(28). This tool assesses five domains which are (1) the randomisation process; (2) deviations from intended interventions; (3) missing outcome data; (4) measurement of the outcome, and (5) selection of the reported results. Studies which score a high risk of bias in one or more domains or which have concerns for several domains will be judged as at serious risk of bias.

Cochrane GRADE Assessment

The GRADE tool will be used to assess quality of evidence for the primary outcome(30). The outcome will be assessed in terms of bias risk, consistency, directness, precision, and publication bias. The primary outcome's quality will be judged to be (i) high quality - we are very confident the true effect is close to that of the estimated effect; (ii) moderate - it is possible that there is a substantial difference but we are moderately confident the true effect is close to that of the estimated effect; (iii) low - we are limited in our confidence that the estimated effect and true effect reflect each other; and (iv) very low - we have very little confidence that the true and estimated effect align, the true effect is likely to be substantially different to our estimate. GRADE will be conducted by two independent reviewers and discrepancies will be resolved through discussion, disagreements which cannot be resolved will be mediated by a third reviewer.

Graphic representations of potential bias within and across the studies will be calculated using RevMan 5.3 (Review Manager 5.3)(27). All items in the risk of bias assessment will be considered independently without an attempt to collate and assign an overarching score.

Data synthesis

Meta-analysis will be constructed by pooling studies using Covidence(26) and RevMan 5.3 software(27). Forest plots and I^2 values will be used to explore the heterogeneity of data. Heterogeneity of data will be examined using forest plots and quantified throughout using the calculation of the I^2 value. An I^2 of greater than or equal to 50% will be used to indicate substantial heterogeneity and a random-effects model will be used. For all I^2 less than 50%, a fixed effects model will be used. Outcomes with less than five studies will be analysed using a fixed effects models(31). For reporting consistency between outcomes, the monotherapy (cerclage or progesterone respectively) intervention was made the reference set for all analyses, standardising the direction of effect across all primary and secondary outcomes.

Measures of treatment effect

Dichotomous outcomes will be assessed and reported using risk ratios (RR) while continuous data will be reported on using mean difference (MD) or standardised mean difference (SMD), 95% confidence intervals (CI) will be used for all data sets. A SMD will be used when studies report a comparable but not identical measure for the same outcome. To avoid discarding important data from papers that do not report the mean and SD of continuous data we will attempt to calculate means and SDs using known parameters. For papers which reported median and range, the Hozo's approach will be used(32). For papers which reported median and interquartile range, the Wan's approach will be employed(33). Data that are too positivity or negatively skewed renders the mean and standard deviated unsuitable for these approaches, particularly when the standard deviation is large(34). For this reason, data which are not suitable to be estimated with mean and standard deviation will be excluded as per the Cochrane Handbook(34). Where meta-analysis is not possible alternative synthesis methods, including summarising effect estimates and combining p-values, will be used as recommended by the Cochrane Handbook for Systematic Reviews of Interventions(18).

Missing data

For studies which presented missing data we will attempt to contact authors. However, if this is not possible, we will conduct sensitivity analysis which will exclude trials with >30% missing data (18).

Meta-bias(es)

To determine reporting bias, we will attempt to investigate to see if protocols for included studies were published prior to those studies being started.

Sensitivity analysis

Sensitivity analysis will be conducted on the primary outcome for birth <37 weeks gestation for dual interventions (cerclage vs combined and progesterone vs combined). This will be done by removing studies which are judged to have an overall critical risk of bias, allowing us to examine their impact on the effect estimate of the primary outcome.

Additional sensitivity analysis will be conducted excluding studies which assessed combined therapy in a sequential manner. For this sensitivity analysis we will define 'stepwise' as cerclage that is placed >14 days following the failure of progesterone to prevent further cervical shortening, or as progesterone that is initiated >14 days following the failure of cerclage wherein the initial intervention has been ineffective in preventing cervical shortening.

Discussion

This systematic review and meta-analysis will determine the differences in effectiveness of cerclage alone versus combined treatment, as well as the differences in effectiveness between

progesterone alone versus combined treatment. These results will provide valuable synthesis of information to specialists in their clinical decisions for women at risk of PTB. It is hoped that women at high risk of sPTB and its complications benefit from these findings. The results of this paper could potentially bring updates to clinical management guidelines and reduce the short and long-term negative health outcomes of preterm birth for women and their children.

Patient and public involvement

There was no patient or public involvement in this paper nor will there be in the systematic review it describes.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Competing interests

JP is supported by the Hunter New England Health Clinical and Health Research Fellowship.
The authors declare they have no other competing interests.

Author's contributions

R.D., A.I., K. P. W., L.M., A-M.A., and J.E.M. led the development of this manuscript. C.W. and J.E.M. provided guidance on the statistical plan, J.P. and C.E.P. provided expertise relating to obstetric care. All authors read and approved the final manuscript.

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List of abbreviations

CI Confidence interval

CINAHL Cumulative Index of Nursing and Allied Health Literature.

GRADE Grading of Recommendations, Assessment, Development and Evaluations

MD Mean difference

MeSH Medical subject headings

NICU Neonatal intensive care unit

PTB Preterm birth

P value Probability value

PRISMA-P Preferred Reporting Items or Systematic Reviews and Meta-Analyses Protocol

PROM Premature rupture of membranes

PPROM Preterm premature rupture of membranes

PROSPERO International Prospective Register of Systematic Reviews

RCT Randomised control trial

RDS Respiratory distress syndrome

RevMan Review Manager 5.3

ROBINS I Risk of Bias in Non-Randomised Studies of Interventions

ROBINS II Risk of Bias in Randomised Studies of Interventions

RR Risk ratio

SPTB Spontaneous preterm birth

SMD Standardised mean difference

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3-4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4-5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5-6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5-7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	9-10
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	10-11
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	11-12
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	13

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	10-11,13
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	13
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	NA
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	NA
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	NA
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	NA
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	NA
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	13-14
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	13-14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13-14
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	14

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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The effectiveness of combined vaginal progesterone and cervical cerclage in preventing preterm birth: a systematic review and meta-analysis protocol

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The effectiveness of combined vaginal progesterone and cervical cerclage in preventing preterm birth: a systematic review and meta-analysis protocol

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Abstract

Introduction: Preterm birth (PTB) is the leading cause of death in children under five. Preventive therapies targeted towards women with risk factors such as a prior PTB or a short cervix reduce the rate of PTB. Cervical cerclage, vaginal progesterone, and a combination of the two have been used with no consensus as to whether combined treatment is more effective than any single treatment alone. The objective of this review is to determine the efficacy of combined treatment compared to cerclage alone, and combined treatment compared to progesterone alone. **Methods and analysis:** Studies will be sourced from the electronic databases Medline (Ovid), EMBASE (Ovid), PsycINFO (Ovid), Scopus, CINAHL (EBSCOhost) and Cochrane Library (Wiley) and reference lists. We will not exclude any papers due to publication date. Randomised control trials (RCTs), non-randomised control trials, and cohort studies assessing single therapy (either progesterone or cerclage) versus combined therapy in women with a singleton pregnancy will be included. Two independent reviewers will conduct study screening (at abstract and full text level), data extraction and risk of bias assessment with disagreements resolved by an experienced researcher. Random or fixed effects models will be used depending on data heterogeneity and data will be presented as Risk Ratio (RR) for dichotomous data or Mean Difference (MD) for continuous data with a Confidence Interval (CI) of 95% used for all outcomes.. **Ethics and dissemination:** not applicable due to nature of the study type. **Registration:** PROSPERO on 8th of October, 2020 with registration number CRD42020195975 **Key words:** Cervical, Stitch, Cerclage, Progesterone, Preterm Birth.

Strengths and limitations:

- The systematic review will follow the rigorous methods outlined in this protocol which have been written as per Cochrane guidelines.
- This will be the first systematic review to answer this question.
- Data will be screened and extracted by two reviewers.
- Lack of reviewer and moderator blinding at inclusion/exclusion level.
- Lack of blinding of reviewers and moderators for papers at quality assessment Robins 1, Rob 2, and GRADE.

Introduction

Preterm birth (PTB), defined as birth before 37 weeks(1), occurs in 5-13% of all pregnancies(2). It is associated with neonatal mortality and is the leading cause of death in children less than five years(3), as well as significant neonatal morbidity such as infant respiratory distress syndrome, intraventricular haemorrhage, necrotising enterocolitis, and retinopathy of prematurity(4).

The majority of PTB occurs either spontaneously or following preterm premature rupture of membranes (PPROM)(5). It is well established that a cervical length of less than 25mm, measured between 18 and 25 weeks, is a good predictor of spontaneous PTB (sPTB) with rates of 31.2% to 41.3%(6, 7). Vaginal progesterone(8) and cervical cerclage(6, 9) are effective single treatments for the prevention of sPTB in these women, as well as those with a prior history of PTB.

Cervical cerclage is a treatment proven to prevent PTB and reduce neonatal morbidity and mortality(10, 11, 12) by mechanically maintaining a long and closed cervix. In contrast,

progesterone has an inhibitory action on uterine contractility by inhibiting the production of stimulatory prostaglandins and expression of contraction associated protein genes in the myometrium(13, 14). It has been shown to play an important role in maintaining a pregnancy until term(15).

More recently, studies have assessed the combination of the cervical cerclage and vaginal progesterone to improve PTB prevention (10, 11). To our knowledge, only one systematic review published in 2013 has addressed progesterone as an adjunctive therapy to cerclage; however, the included studies were not randomised and assessed synthetic progestin 17-hydroxyprogesterone caproate (17-OHPC), which found no difference in the outcome of PTB (13). To our knowledge, there has not been any systematic review addressing combined treatment of progesterone and cerclage versus singular treatment since 2017 (16); with no review specifically assessing vaginal progesterone in combined treatment. More recently, adjuvant vaginal progesterone therapy for women who underwent cervical cerclage indicated by ultrasound(11) or physical(10) examination was found to be associated with decreased rates of PTB and admission to the neonatal intensive care unit (NICU). Given these recent promising findings and the lack of guidance on this topic, we sought to determine the effect of combining both cerclage and progesterone on PTB by conducting a systematic review and meta-analysis. This paper describes the proposed protocol for this meta-analysis.

Aim

This systematic review has two aims: 1) to compare the use of cerclage alone to cerclage and vaginal progesterone combined, and 2) to compare progesterone alone to the combined use of cerclage and vaginal progesterone in order to determine which of these is associated better maternal and neonatal outcomes in relation to PTB. Our proposed review will

answer the questions *in women requiring prophylactic treatment for short cervix is combined treatment favourable to cerclage alone?* And *in women requiring prophylactic treatment for short cervix is combined treatment favourable to vaginal progesterone alone?*

Methods

Registration:

This systematic review protocol was submitted to the International Prospective Register of Systematic Reviews (PROSPERO) on the 8th of October 2020 and was last updated on this date (registration number CRD42020195975). This review and meta-analysis will be completed in accordance using the recommendations of both Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol (PRISMA-P)(17) and the Cochrane Handbook for Systematic Reviews of Interventions(18).

Information regarding registration can be accessed from http://www.crd.york.ac.uk/PROSPERO.

Eligibility Criteria:

The eligibility of studies included will be based on inclusion and exclusion criteria applied to the domains of participant, exposure, comparator, study type, and outcome.

Participants:

The review will consider all studies which include women who are undergoing ultrasound or history indicated cerclage, vaginal progesterone, or both for the prevention of PTB. Only singleton pregnancies will be assessed.

Intervention:

Studies comparing combined cerclage and vaginal progesterone treatment with vaginal progesterone alone or cerclage alone.

Cerclage

There are two commonly performed vaginal cerclage procedures which were first described by Shirodkar and McDonald. In the McDonald approach a suture is placed around the cervix in purse-string fashion and securely tied anteriorly. The McDonald approach requires no dissection into para-cervical tissues (19, 20). The Shirodkar technique involves a transverse anterior colpotomy, dissection of the bladder up to the internal cervical os and a posterior colpotomy with dissection of peritoneum upwards to the internal os. The suture is placed subcutaneously and the knot tied in the posterior defect and buried under the vaginal epithelium(19, 21, 22) or tied exterior to the epithelium in the modified approach. Both Shirodkar techniques will be considered.

Vaginal Progesterone

Vaginal progesterone is available as a gel, suppository, or pessary(14). It is the most bioavailable form of progesterone for uterine and cervical effects with the fewest side effects. Its micronized form decreases particle size and increases surface area resulting in improved absorption with less metabolic and vascular side effects(23). The vaginal route also allows rapid absorption and avoids first pass hepatic metabolism, resulting in high bioavailability in the uterus(24).

Combined Treatment

Cervical cerclage (McDonald or Shirodkar technique) used in combination with vaginal progesterone.

Outcomes:

The primary outcome is PTB, defined as birth <37 weeks gestation. Secondary dichotomous outcomes will be PTB <34 weeks, <32 weeks, <28 weeks; PPROM; caesarean section; and neonatal complications: NICU admission, intubation, and neonatal mortality. The continuous secondary outcomes will be gestational age at delivery; birthweight; and number of days between intervention and delivery.

Types of studies:

The review will include randomised and pseudo-randomised control trials, non-randomised experimental control trials, and cohort studies. All included papers must compare cerclage to combined treatment and/or vaginal progesterone to combined treatment. Those studies which also presented a control group will be included.

Search strategy:

Electronic bibliographic databases will be searched for eligible, peer-reviewed literature including: Medline (Ovid), EMBASE (Ovid), PsycINFO (Ovid), Scopus, CINAHL (EBSCOhost) and Cochrane Library (Wiley). Reference lists of included studies will also be screened for eligible papers. Studies recommended by experts, the references of textbooks, and grey literature will also be reviewed for this purpose. We will place no restriction on the length of study follow-up time or on country, year, or language of publication. All studies will be human trials. See appendix one.

The search strategy will be developed through discussion with experts and academics, pilot searches, and by assessing systematic reviews with similar questions. The search strategy will

focus on identifying relevant interventions with no population or outcome related keywords used. The intervention search terms will be: cervical OR cervix OR rescue; stitch OR cerclage OR suture; progesterone OR progestin OR prometrium OR progest. Medical subject headings (MeSH) will be used when relevant and present databases.

Data collection and analysis

Study Selection

Identified titles and abstracts will be downloaded into Endnote(25) where duplicated studies will be removed. Remaining papers will then be uploaded to Covidence(26) and then screened against the eligibility criteria outlined above. Full texts of remaining studies will be sourced and screened before undergoing critical appraisal and data extraction. All screening will be performed by two independent reviewers and any disagreements will be addressed by a senior research moderator. No reviewers or moderators will be blinded to titles, authors, journals, or institutions.

Data management

The search will be uploaded to Covidence(26), an Internet-based software which allows collaboration between multiple reviewers during the study selection process, backup copies of all studies will also be kept in an Endnote library(25).

Data collection

Two reviewers will extract data through Covidence(26) using a standardised electronic form consistent with data collection items recommended by the Cochrane Handbook for Systematic Reviews of Interventions(18). This process will be piloted prior to use and any discrepancies will be moderated by a third senior research moderator. Once extracted, upon reviewer

agreement, data will be transferred from Covidence(26) into Review Manager data-analysis software(27).

The following data will be extracted:

- Study characteristics: authors; publication date; study design; country of study; sample size; confounding factors of participants; publication status; trial size; funding; and risk of bias information.
- Intervention characteristics: type of intervention used; reason for intervention; patient characteristics (maternal age, gravity, parity), and any co-interventions received.
- Outcomes: maternal, fetal and neonatal outcome data and definitions of each of the outcomes as described below.

Outcomes and prioritisation:

Primary outcome

PTB defined as live or stillbirth with a gestational age between 20 and 37 weeks. Primary outcome is birth <37wks gestation with sub-analysis at <34wks, <32wks, and <28wks.

For outcomes which report this data as *"greater than" X weeks gestation*, data extractors will manually invert the figure to less than.

Secondary outcomes

Dichotomous

1. PPROM
2. Caesarean section
3. NICU admission

4. Intubation
5. Neonatal mortality

Continuous

6. Gestational age at delivery
7. Birthweight
8. Number of days between intervention and delivery

Assessment of risk of bias

Each paper will be assessed for risk of bias using the Cochrane Collaboration tool for assessing risk of bias (ROBINS I and RoB-2)(28, 29). Each study will be reviewed independently by two assessors and disagreements will be resolved through mediation with a third reviewer. High quality studies are those which achieve a score of seven or eight, average are scored four to six, and below four will be considered low quality. We will not be excluding any study based on these scores, however risk of bias will be taken into account when outcomes are assessed in regard to impact as per the Grade of Recommendation, Assessment, Development and Evaluations (GRADE)(30).

The Risk of Bias in Non-Randomised Studies of Interventions (ROBINS-I) tool(28) will be used to assess the risk of bias in included observational studies. The risk of bias will be rated as no information, low risk, moderate risk, serious risk, or critical risk across seven domains. The seven domains of this tool are (1) confounding; (2) selection of participants; (3) classification of intervention; (4) deviation from interventions; (5) missing outcome data; (6) measurement of outcomes; and (7) selection of reported results overall.

Randomised trials will be assessed with the Risk of Bias in Randomised Studies of Interventions (RoB2)(28). This tool assesses five domains which are (1) the randomisation

process; (2) deviations from intended interventions; (3) missing outcome data; (4) measurement of the outcome, and (5) selection of the reported results. Studies which score a high risk of bias in one or more domains or which have concerns for several domains will be judged as at serious risk of bias.

Cochrane GRADE Assessment

The GRADE tool will be used to assess quality of evidence for the primary outcome(30). The outcome will be assessed in terms of bias risk, consistency, directness, precision, and publication bias. The primary outcome's quality will be judged to be (i) high quality - we are very confident the true effect is close to that of the estimated effect; (ii) moderate - it is possible that there is a substantial difference but we are moderately confident the true effect is close to that of the estimated effect; (iii) low - we are limited in our confidence that the estimated effect and true effect reflect each other; and (iv) very low - we have very little confidence that the true and estimated effect align, the true effect is likely to be substantially different to our estimate. GRADE will be conducted by two independent reviewers and discrepancies will be resolved through discussion, disagreements which cannot be resolved will be mediated by a third reviewer.

Graphic representations of potential bias within and across the studies will be calculated using RevMan 5.3 (Review Manager 5.3)(27). All items in the risk of bias assessment will be considered independently without an attempt to collate and assign an overarching score.

Data synthesis

Meta-analysis will be constructed by pooling studies using Covidence(26) and RevMan 5.3 software(27). Forest plots and I^2 values will be used to explore the heterogeneity of data. Heterogeneity of data will be examined using forest plots and quantified throughout using

the calculation of the I^2 value. A Random Effects Model will be used when a data set meets three of the following four criteria 1) there is an intention to use results beyond the included studies, 2) number of included studies greater than five, 3) there is statistical heterogeneity measured as an I^2 greater or equal to 50%, 4) it is reasonable to assume that included studies estimate a different underlaying true effect with normal distribution (31). If a data set does not meet three or more criteria a Fixed Effects Model will be used. All outcomes for which a Random Effects Model is used will undergo a second examination using the Hartung-Knapp-Sidik-Jonkman method for random effects to ensure considerable heterogeneity does not impact the data. For reporting consistency between outcomes, the monotherapy (cerclage or progesterone respectively) intervention was made the reference set for all analyses, standardising the direction of effect across all primary and secondary outcomes.

Measures of treatment effect

Dichotomous outcomes will be assessed and reported using risk ratios (RR) while continuous data will be reported on using mean difference (MD) or standardised mean difference (SMD), 95% confidence intervals (CI) will be used for all data sets. A SMD will be used when studies report a comparable but not identical measure for the same outcome. To avoid discarding important data from papers that do not report the mean and SD of continuous data we will attempt to calculate means and SDs using known parameters. For papers which reported median and range, the Hozo's approach will be used(32). For papers which reported median and interquartile range, the Wan's approach will be employed(33). Data that are too positivity or negatively skewed renders the mean and standard deviated unsuitable for these approaches, particularly when the standard deviation is large(34). For this reason, data which are not suitable to be estimated with mean and standard deviation will be excluded as per the Cochrane Handbook(34). Where meta-analysis is not possible alternative synthesis

methods, including summarising effect estimates and combining p-values, will be used as recommended by the Cochrane Handbook for Systematic Reviews of Interventions(18).

Missing data

For studies which presented missing data we will attempt to contact authors. However, if this is not possible, we will conduct sensitivity analysis which will exclude trials with >30% missing data (18).

Meta-bias(es)

To determine reporting bias, we will attempt to investigate to see if protocols for included studies were published prior to those studies being started.

Sensitivity analysis

Sensitivity analysis will be conducted on the primary outcome for birth <37 weeks gestation for dual interventions (cerclage vs combined and progesterone vs combined). This will be done by removing studies which are judged to have an overall critical risk of bias, allowing us to examine their impact on the effect estimate of the primary outcome.

Additional sensitivity analysis will be conducted excluding studies which assessed combined therapy in a sequential manner. For this sensitivity analysis we will define 'stepwise' as cerclage that is placed >14 days following the failure of progesterone to prevent further cervical shortening, or as progesterone that is initiated >14 days following the failure of cerclage wherein the initial intervention has been ineffective in preventing cervical shortening.

Where individual patient data is available, neonatal outcomes and baseline maternal characteristics will be extracted from studies and sub-analysis will be conducted if there is found to be vast differences in these baseline characteristics.

Discussion

This systematic review and meta-analysis will determine the differences in effectiveness of cerclage alone versus combined treatment, as well as the differences in effectiveness between progesterone alone versus combined treatment. These results will provide valuable synthesis of information to specialists in their clinical decisions for women at risk of PTB. It is hoped that women at high risk of sPTB and its complications benefit from these findings. The results of this paper could potentially bring updates to clinical management guidelines and reduce the short and long-term negative health outcomes of preterm birth for women and their children.

Patient and public involvement

There was no patient or public involvement in this paper nor will there be in the systematic review it describes.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Data sharing

Not applicable.

Competing interests

JP is supported by the Hunter New England Health Clinical and Health Research Fellowship.

The authors declare they have no other competing interests.

Author's contributions

R.D., A.I., K. P. W., L.M., A-M.A., and J.E.M. led the development of this manuscript. C.W. and J.E.M. provided guidance on the statistical plan, J.P. and C.E.P. provided expertise relating to obstetric care. All authors read and approved the final manuscript.

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List of abbreviations

CI Confidence interval

CINAHL Cumulative Index of Nursing and Allied Health Literature.

GRADE Grading of Recommendations, Assessment, Development and Evaluations

MD Mean difference

MeSH Medical subject headings

NICU Neonatal intensive care unit

PTB Preterm birth

P value Probability value

PRISMA-P Preferred Reporting Items or Systematic Reviews and Meta-Analyses Protocol

PROM Premature rupture of membranes

PPROM Preterm premature rupture of membranes

PROSPERO International Prospective Register of Systematic Reviews

RCT Randomised control trial

RDS Respiratory distress syndrome

RevMan Review Manager 5.3

ROBINS I Risk of Bias in Non-Randomised Studies of Interventions

ROBINS II Risk of Bias in Randomised Studies of Interventions

RR Risk ratio

SPTB Spontaneous preterm birth

SMD Standardised mean difference

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Appendix 1 – Search Strategy

1. Cervical OR Cervix OR Rescue
2. Stitch* OR cerclage OR Suture
3. 1 AND 2
4. Progesterone OR progestin OR prometrium OR progest
5. 3 AND 4

For PubMed and Cochrane where MeSH headings are available the term "Cerclage, Cervical"[Mesh] will be added.

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: Recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review **Lines 1-2**
Update	1b	If the protocol is for an update of a previous systematic review, identify as such **NA**
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number **Line 48**
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author **Lines 13, 15-19, 22-23**
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review **NA**
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments **NA**
Support:		
Sources	5a	Indicate sources of financial or other support for the review **NA**
Sponsor	5b	Provide name for the review funder and/or sponsor **NA**
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol **NA**
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known **Lines 61-94**
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) **Lines 101-103**
METHODS		
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review **Lines 116-150**
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage **Lines 165-172**
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated **Lines 161-172, Appendix 1**
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review **Lines 181-202**

Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis) **Lines 182-189**
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators **Lines 288-302**
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications **Lines 204-212**
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale **Lines 214-231**
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis **Lines 233-270**
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised **Lines 272-302**
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ) **Lines 204- 286**
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) **Lines 313-323**
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned **NA**
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies) **Lines 309-311**
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE) **Lines 256-270**

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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