Vaginal Progesterone for Prevention of Preterm Birth in Asymptomatic High-Risk Women with a Normal Cervical Length: A Systematic Review and Meta-Analysis Protocol

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Protocol

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Abstract

Background: Preterm birth (PTB) is estimated to affect 14.9 million babies globally every year. Global rates of PTB continue to increase from 9.8% to 10.6% over a 15-year period from 2000 to 2014. Vaginal progesterone is commonly used by clinicians as a prevention strategy, with recent evidence affirming the benefit of vaginal (micronized) progesterone to prevent PTB in women with a shortened cervix (<25mm). Given the low incidence of a short cervix at mid-gestation in high-risk populations further evidence is required. The objective of this review is to determine if vaginal progesterone reduces spontaneous preterm birth (sPTB) before 37 weeks in asymptomatic high-risk women with a singleton pregnancy with a normal mid-gestation cervical length.

Methods: Studies will be sourced from MEDLINE and Embase databases with the search terms “progesterone” and “preterm birth”. Studies will be screened and included if they assess vaginal progesterone compared to placebo in women with a normal cervical length. The primary outcome will be sPTB <37 weeks, with secondary outcomes of sPTB <34 weeks.

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. The Mantel-Haenszel statistical method and random effects analysis model will be used to produce treatment effect odds ratios and corresponding 95% confidence intervals.

Discussion: This review will assess the current body of evidence and provide clarity regarding the potential benefits and best practice of use of vaginal progesterone in asymptomatic women with high risk singleton pregnancies and normal cervical length.

Trial registration: This study has been registered on PROSPERO with the registration number CRD42020152051

Background

Preterm birth (PTB) is estimated to affect 14.9 million babies worldwide every year(1), with a higher burden in low and middle income countries(2). This has generated a geographic divide with several European countries such as Finland and Sweden having the lowest PTB rates < 6%, whilst low income countries such as Malawi in Africa, have the highest PTB rate of 18.1%(3). Similarly, estimated global PTB rates have increased from 9.8% in 2000 to 10.6% in 2014(2). Despite approximately 80% of these preterm births occurring in disadvantaged countries in sub-Saharan Africa and Asia, data suggests that rates of PTB are also steadily increasing in high income countries(2). This is a worrying trend as PTB remains the leading cause of death for children under the age of five(4). Furthermore, it increases the risk of short term complications including infant respiratory distress syndrome and intraventricular haemorrhage, as well as life-long impacts including increased risk of neurodevelopmental delay and adult non-communicable diseases(5).

A number of interventions have been shown to significantly decrease the rate of spontaneous preterm birth (sPTB) including: specialist antenatal clinics for women at high risk of PTB(6); cervical cerclage for women with a previous sPTB and/or a short cervix (< 25 mm)(7, 8) and vaginal progesterone for women with cervical length < 25 mm (11–15). Progesterone decreases uterine contractility through inhibition of production of prostaglandins in the myometrium(9) and has been shown to be important in maintaining a pregnancy until term(10). A recent individual patient data (IPD) meta-analysis affirmed the benefit of vaginal progesterone in prevention of sPTB in women with a short cervix (< 25 mm) with a 20% reduction in sPTB before 36 weeks, and a greater reduction of 35% before 34 weeks(8). This IPD suggested that vaginal progesterone is still beneficial even in nulliparous women with only a short cervix as a risk factor(8). As only 5.8–7.3% of high risk women(11, 12), and 0.45–1.68% in unselected populations(13–15) have a short cervix at mid gestation, the number of women who benefit from progesterone is relatively low. It is currently unclear whether vaginal progesterone would be of benefit to the other high-risk women with a normal mid-gestation cervical length (> 25 mm).

There are an increasing number of centres that offer mid-gestation cervical length screening as routine care, therefore we sought to determine whether use of vaginal progesterone in high risk women with a normal mid-gestation cervical length is effective in prevention of sPTB.

Aim

This proposed systematic review will answer the question does vaginal progesterone reduce spontaneous preterm birth before 37weeks in asymptomatic high-risk women with a singleton pregnancy with a normal mid-gestation cervical length?

Methods

Registration:

This study was registered prospectively with the PROSPERO database of systematic reviews (registration no. CRD42020152051) and will be completed in accordance with the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol (PRISMA-P). Information regarding registration can be accessed from http://www.crd.york.ac.uk/PROSPERO.

Search Strategy:

The search strategy will be developed focusing on identifying the relevant intervention with no population related keywords. EMBASE and MEDLINE electronic databases will be searched for eligible, peer-reviewed literature with the following search terms: preterm birth OR premature birth AND progesterone. We will place no restriction on the length of study follow-up time, or on country, year, or language of publication. However, the search will be limited to studies on humans. Medical subject headings (MeSH) will be used when relevant.

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:

This review will consider all studies that include asymptomatic pregnant women being treated with vaginal progesterone. We will exclude studies that include women with a short cervix or who were symptomatic. Studies that exclusively studied women with multi-gestation were will be excluded.

Intervention:

Studies comparing vaginal progesterone either compared to placebo or no treatment will be included. Studies that involved other methods of progesterone administration such as intramuscular injection will be excluded.

Vaginal Progesterone

Vaginal progesterone is available as a gel, suppository, or pessary(9). It is the most bioavailable form of progesterone for uterine and cervical effects with the fewest side effects. Its micronization decreases particle size and increases surface area. This results in improved absorption with less metabolic and vascular side effects(16). The vaginal route also allows rapid absorption and avoids first pass hepatic metabolism, resulting in high bioavailability in the uterus(17).

Outcomes:

The primary outcome is sPTB before < 37 weeks. The secondary outcome will be sPTB before < 34 weeks.

Types of studies:

The review will include randomised controlled trials. All included papers must vaginal progesterone to either placebo or no treatment. Those studies which also present a control group will be included.

Data collection and analysis

Study Selection

Titles and abstracts identified through all sources will be downloaded to Endnote(18) and duplicates will be removed. Studies will then be screened using the specified eligibility criteria above and studies that do not meet the criteria will be excluded. Full texts of remaining studies will be screened before undergoing critical appraisal and data extraction. All levels of screening will be conducted by two independent reviewers and any disputes between reviewers will be resolved by an independent moderator. None of these reviewers will be blinded to titles, authors, journals or institutions.

Data management

The search will be uploaded to an Endnote(18) library, which allows collaboration between multiple reviewers during the study selection process.

Data collection

Two reviewers will extract data through Endnote(18) using a standardised electronic data extraction sheet. Any discrepancies will be moderated by a third senior research reviewer. Once extracted, upon reviewer agreement, data will be transferred into Review Manager version 5.3 data-analysis software(19).

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, cervical length), 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

The primary outcome is sPTB before < 37 weeks gestation.

Preterm birth will be defined as live or stillbirth with a gestational age between 20 and 37 weeks.

Secondary outcome

The secondary outcome is sPTB before < 34 weeks gestation.

Assessment of risk of bias

Risk of bias for each paper will be assessed using the Joanna Briggs Institute critical appraisal method for randomised control trials(20). Studies which are deemed to have not addressed the possibility of bias in the design, conduct or analysis will then be excluded.

Study quality will be assessed using the Cochrane GRADE tool(21). Evidence will be assessed in terms of risk of bias, consistency, directness, precision and publication bias. With regard to GRADE, quality will be assessed as being one of 4 grades: (i) high - we are very confident that the true effect is close to that of the estimate of the effect; (ii) moderate - we are moderately confident in the effect estimate, and the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different; (iii) low - our confidence in the effect estimate is limited, and the true effect may be substantially different from the estimate of the effect, and (iv) very low-we have very little confidence in

the effect estimate, and the true effect is likely to be substantially different from the estimate of effect. Two independent reviewers will conduct the assessment, with discrepancies resolved through discussion and consensus between the two reviewers, or consultation with a third reviewer.

Review Manager version 5.3(19) will be used to compute graphic representations of potential bias within and across studies.

Data synthesis

Extracted data will be manually entered into Review Manager version 5.3(19). 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 using the calculation of the I^2 value. Sensitivity analyses will be performed if there is significant heterogeneity between included studies which will be defined as I^2 of greater than or equal to 50%. The meta-analysis will be performed using the Mantel-Haenszel statistical method and random effects analysis model to produce treatment effect ratios and corresponding 95% confidence intervals.

Missing data

For studies which present 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.

Meta-bias(es)

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

Sensitivity analysis

Sensitivity analysis will be conducted on the primary outcome for sPTB < 37weeks gestation for vaginal progesterone versus either placebo or no treatment. This will be done by removing studies which are judged to have an overall high risk of bias, allowing us to examine their impact on the effect estimate of the primary outcome.

Discussion

This systematic review and meta-analysis aims to determine the effectiveness of vaginal progesterone for prevention of PTB in asymptomatic high-risk women with a normal cervical length. It is hoped this paper will synthesise multiple recent large scale trials to provide valuable therapeutic information to specialists in their clinical decisions for women at risk of PTB. It is hoped women at high risk of obstetric complications, their families, and the wider community will benefit from these findings. The results of this paper will help to inform guidelines and reduce the short and long term negative health outcomes of preterm birth.

List Of Abbreviations

CI Confidence interval

CINAHL Cumulative Index of Nursing and Allied Health Literature.

GRADE Grading of Recommendations, Assessment, Development and Evaluations

IPD Individual Patient Data

MD Mean difference

MeSH Medical subject headings

P value Probability value

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

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

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Competing interests

J.P. is supported by the Hunter New England Health Local Health District Clinical and Health Service Research Fellowship Scheme. The authors declare they have no other competing interests.

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Authors contributions

K.P.W. and L.M. led the writing of this manuscript with input from R.D., A.I. and A-M.A..

J.P. and C.E.P. conceived and designed the paper. C.W. provided guidance on the statistical plan, and J.P. and C.E.P. provided expertise relating to obstetric care. All authors read and approved the final manuscript.

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