Interventions to prevent spontaneous preterm birth in women with singleton pregnancy who are at high risk: systematic review and network meta-analysis

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ABSTRACT

OBJECTIVES

To compare the efficacy of bed rest, cervical cerclage (McDonald, Shirodkar, or unspecified type of cerclage), cervical pessary, fish oils or omega fatty acids, nutritional supplements (zinc), progesterone (intramuscular, oral, or vaginal), prophylactic antibiotics, prophylactic tocolytics, combinations of interventions, placebo or no treatment (control) to prevent spontaneous preterm birth in women with a singleton pregnancy and a history of spontaneous preterm birth or short cervical length.

DESIGN

Systematic review with bayesian network meta-analysis.

DATA SOURCES

The Cochrane Pregnancy and Childbirth Group's Database of Trials, the Cochrane Central Register of Controlled Trials, Medline, Embase, CINAHL, relevant journals, conference proceedings, and registries of ongoing trials.

ELIGIBILITY CRITERIA FOR SELECTING STUDIES

Randomised controlled trials of pregnant women who are at high risk of spontaneous preterm birth because of a history of spontaneous preterm birth or short cervical length. No language or date restrictions were applied.

OUTCOMES

Seven maternal outcomes and 11 fetal outcomes were analysed in line with published core outcomes for preterm birth research. Relative treatment effects (odds ratios and 95% credible intervals) and certainty of evidence are presented for outcomes of preterm birth <34 weeks and perinatal death.

RESULTS

Sixty one trials (17 273 pregnant women) contributed data for the analysis of at least one outcome. For preterm birth <34 weeks (40 trials, 13 310 pregnant women) and with placebo or no treatment as the comparator, vaginal progesterone was associated with fewer women with preterm birth <34 weeks (odds ratio 0.50, 95% credible interval 0.34 to 0.70, high certainty of evidence). Shirodkar cerclage showed the largest effect size (0.06, 0.00 to 0.84), but the certainty of evidence was low. 17OHPC (17α-hydroxyprogesterone caproate; 0.68, 0.43 to 1.02, moderate certainty), vaginal pessary (0.65, 0.39 to 1.08, moderate certainty), and fish oil or omega 3 (0.30, 0.06 to 1.23, moderate certainty) might also reduce preterm birth <34 weeks compared with placebo or no treatment. For the fetal outcome of perinatal death (30 trials, 12 119 pregnant women) and with placebo or no treatment as the comparator, vaginal progesterone was the only treatment that showed clear evidence of benefit for this outcome (0.66, 0.44 to 0.97, moderate certainty). 17OHPC (0.78, 0.50 to 1.21, moderate certainty), McDonald cerclage (0.59, 0.33 to 1.03, moderate certainty), and unspecified cerclage (0.77, 0.53 to 1.11, moderate certainty) might reduce perinatal death rates, but credible intervals could not exclude the possibility of harm. Only progesterone treatments are associated with reduction in neonatal respiratory distress syndrome, neonatal sepsis, necrotising enterocolitis, and admission to neonatal intensive care unit compared with controls.

CONCLUSION

Vaginal progesterone should be considered the preventative treatment of choice for women with singleton pregnancy identified to be at risk of spontaneous preterm birth because of a history of spontaneous preterm birth or short cervical length. Future randomised controlled trials should use vaginal progesterone as a comparator to identify better treatments or combination treatments.

SYSTEMATIC REVIEW REGISTRATION

PROSPERO CRD42020169006

WHAT IS ALREADY KNOWN ON THIS TOPIC

NICE (National Institute for Health and Care Excellence) guidelines currently recommend vaginal progesterone or cervical cerclage for women with short cervix and a history of spontaneous preterm birth

Large randomised controlled trials of vaginal progesterone recently caused doubt about the effectiveness of this treatment

A recent survey of preterm birth prevention clinics in the UK found that a wide variety of treatment regimens and treatment combinations are offered

WHAT THIS STUDY ADDS

Vaginal progesterone seems to be the best preterm birth prevention treatment for women with a singleton pregnancy who are at high risk and are asymptomatic

Future randomised controlled trials should use vaginal progesterone as a comparator to identify better treatments or treatment combinations for preterm birth prevention in women with singleton pregnancy who are at high risk

Introduction

Complications of preterm birth are the leading cause of neonatal mortality and were responsible for 35% of the world's 2.5 million deaths in 2018.[1] Many survivors might have long term disability, including cerebral palsy, visual or hearing impairment, delayed social development, increased behavioural problems, and increased risk of chronic disease in adulthood.[2-4]

Preterm birth is most commonly defined as any birth before 37 weeks' gestation[5]; two thirds of all preterm births are spontaneous,[6] while the remainder are started by healthcare providers for maternal or fetal indications.

Advances have been made to identify women at risk of spontaneous preterm birth in two distinct populations of pregnant women: those who are asymptomatic during their antenatal care, and those who are symptomatic and might present with acute pain or bleeding. The incidence of preterm birth and the management strategies used in each population are different. This review has focused on the interventions offered to women with singleton pregnancies who are asymptomatic. The best predictors of spontaneous preterm birth in this population are short cervical length (<25 mm)[7] and a history of spontaneous preterm birth.[8]

The National Institute for Health and Care Excellence (NICE) preterm birth guidelines currently recommend offering a choice between vaginal progesterone and cervical cerclage for women with short cervix and a history of spontaneous preterm birth.[9] NICE also recommends considering vaginal progesterone in women with a short cervical length <25 mm or a history of spontaneous preterm birth.[9] Recent large negative randomised controlled trials of vaginal progesterone[10 11] caused doubt about the effectiveness of this treatment. A survey of UK preterm birth prevention clinic practice found that a wide variety of treatment regimens and treatment combinations are offered[12]: only 19% of English preterm birth clinics currently use vaginal progesterone as first line treatment and 16% routinely give vaginal progesterone to women with a history of spontaneous preterm birth.[13]

Because randomised controlled trials and direct comparisons of all available treatment options would not be feasible,[14] we performed a network meta-analysis. By evaluating all available evidence, direct and indirect, within a network linked by comparisons made through randomised controlled trial data, the network meta-analysis produces estimates of the relative effects for each treatment compared with all others in the network. The probability of one treatment being the best for a specific outcome can then be calculated; different treatment options for each outcome can then be ranked from best to worst. We present a network meta-analysis comparing the effectiveness of current preventative treatments for spontaneous preterm birth in high risk populations.

Methods

This systematic review and network meta-analysis is reported in accordance with PRISMA (preferred reporting items for systematic reviews and meta-analyses) network meta-analysis guidelines (supplementary file 1), as part of a larger project. Details of our preplanned analyses have been published in the Cochrane Library.[15]

Search strategy and selection criteria

To identify eligible trials, we searched the Cochrane Pregnancy and Childbirth's Trial Register, containing over 25 000 reports of controlled trials in the field of pregnancy and childbirth. We performed regular searches of the Cochrane Central Register of Controlled Trials, Medline, Embase, CINAHL, relevant journals, conference proceedings, and registries of ongoing trials. Abstracts were excluded unless we could obtain full study data from the authors or database publications. The last search was completed on 8 August 2021; no language or date restrictions were made (supplementary file 2 gives search strategy). Two reviewers independently screened search results and retrieved the full text of potentially relevant reports. Disagreements were resolved by discussion (involving additional reviewers if appropriate).

We included randomised controlled trials of pregnant women at high risk of spontaneous preterm birth because of individual risk factors, including previous spontaneous preterm birth, midtrimester loss, or cervical insufficiency due to cervical surgery or any known uterine anomalies and short cervical length on ultrasound. Trials were included when they compared two or more of the following interventions or compared an active agent with a placebo or no treatment (control): bed rest, cervical cerclage (McDonald, Shirodkar, or unspecified type of cerclage), cervical pessary, fish oils or omega fatty acids, nutritional supplements (zinc), progesterone (intramuscular, oral, or vaginal), prophylactic antibiotics, prophylactic tocolytics, combinations of interventions, and placebo or no treatment (control).

Outcome measures

We analysed several outcomes for pregnant women and offspring identified from the core outcome set for preterm birth[16]: women—preterm birth <37 weeks' gestation, preterm birth <34 weeks' gestation, spontaneous preterm birth <34 weeks' gestation, preterm birth <28 weeks' gestation, maternal death, preterm prelabour rupture of membranes, and maternal infection; offspring—perinatal death, neonatal death, gestational age at birth in weeks, low birthweight <2500 g, neonatal respiratory distress syndrome, neonatal pulmonary disease, intraventricular haemorrhage, periventricular leukomalacia, necrotising enterocolitis, proven neonatal sepsis, and admission to neonatal intensive care unit.

Data extraction and assessment of risk of bias

One reviewer extracted data from the trial reports; these were independently checked by a second reviewer with differences resolved by discussion. Two reviewers independently assessed risk of bias for each trial using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions[17]; differences were discussed.

We extracted continuous data for gestational age at birth and converted all data to the same unit of measurement (weeks). For all other outcomes, we

extracted dichotomous data (or calculated these numbers from other reported statistics). Key trial and participant characteristics (supplementary table 1) were compared to assess whether effect modifiers were similarly distributed across trials, and to identify potential sources of clinical heterogeneity and inconsistency.

Data synthesis and statistical analysis

We conducted a pairwise meta-analysis when direct evidence was available and a network meta-analysis to simultaneously compare all relevant interventions and placebo or no treatment for each outcome. Separate nodes in the network represented differences in the type or route of interventions (eg, different types of cerclage, pessary, progesterone, antibiotics, or tocolytics). Placebo and no treatment were combined into a single control node. Different doses were not represented within the nodes.

The key assumptions of a network meta-analysis are homogeneity and consistency. For each outcome, clinical heterogeneity was assessed by comparing key trial and participant characteristics of studies within treatment comparisons. If clinical heterogeneity was judged to be present between the studies contributing to an outcome, then results of random effects models were presented. We assessed and compared the model fit and complexity of fixed effect and random effect network meta-analysis models by using the deviance information criterion, posterior mean residual deviance, and effective number of parameters.[18]

A further assumption of network meta-analysis is consistency of the direct and indirect evidence for each treatment effect. The consistency assumption is likely to hold when each patient is equally likely to have been allocated any of the interventions. Inconsistency might be present if differences in treatment effect modifying characteristics exist across treatment comparisons. To assess consistency, we examined characteristics of studies across treatment comparisons (all trials) and applied inconsistency models (unrelated mean effects models).[19 20] We also planned to carry out meta-regression to assess homogeneity and consistency assumptions, but data were too limited.

Dichotomous data were analysed as odds ratios, presented as posterior median odds ratios with 95% credible intervals. Continuous data were analysed as mean differences, also presented as posterior median mean differences with 95% credible intervals.

Drawing conclusions

We used a partially contextualised framework published by GRADE (grading of recommendations assessment, development, and evaluation) as guidance to report our findings from the network meta-analysis.[21 22] This framework allows classification of interventions into different groups by considering magnitude of effect and certainty of the evidence to draw appropriate conclusions. Summary of findings tables were produced for two outcomes critical for clinical decision making: preterm birth <34 weeks and perinatal death. Preterm birth <34 weeks was chosen as a more important outcome for clinical decision making than preterm birth <37 weeks. This choice was based on the inverse proportion of infant morbidity and mortality by gestational age, with mortality rates beyond 34 weeks approximating those for early term births[23] and clinical maternal interventions such as corticosteroids used for fetal lung maturation mandated until 34 weeks' gestation.[9] The clinical importance of this 34 week cut-off point is also reflected in the fact that preterm birth <34 weeks remains the main clinical indication for referral to specialist clinics in the UK.[12]

We assigned graphical icons to present the direction of effect estimates and confidence in the available data. The graphical icons indicate mutually exclusive assessment categories: clear evidence of benefit, clear evidence of harm, clear evidence of no effect or equivalence, possible benefit, possible harm, or unknown benefit or harm.[24]

Patient and public involvement

Patients were involved in both the development of the research question and the implemented core outcome sets in preterm birth. This was through the Harris Wellbeing PTB PPI group during the RECAP study and as part of the Crown initiative,[16] respectively.

Results

Results of the search and included studies

The search identified 1770 potentially eligible records and 1011 records were excluded after title and abstract screening. A total of 395 studies were screened and 334 studies were excluded (fig 1). Sixty one trials (17 273 pregnant women) contributed data for at least one outcome and were included in quantitative synthesis (network meta-analysis; table 1, table 2, supplementary table 3). Supplementary table 2 gives risk of bias assessment for the included trials and supplementary file 4 provides references of the included studies.

Supplementary file 3 presents network diagrams for each outcome and supplementary file 5 gives a summary of results for trials disconnected from the network for each outcome. Supplementary table 5 provides model fit statistics and the resulting network meta-analysis model used for each outcome.

Network meta-analysis results for women and offspring

Figure 2 presents network meta-analysis results for the outcomes preterm birth <34 weeks' gestation and perinatal death. Supplementary files 6 and 7 present network meta-analysis results for other outcomes. Vaginal progesterone was associated with fewer women with preterm birth <34 weeks' gestation compared with control treatment (odds ratio 0.50, 95% credible interval 0.34 to 0.70, high certainty of evidence). Shirodkar cerclage showed the largest effect size (0.06, 0.00 to 0.84, low certainty; fig 2, fig 3). However, the only evidence we found from a randomised controlled trial about the effectiveness of Shirodkar

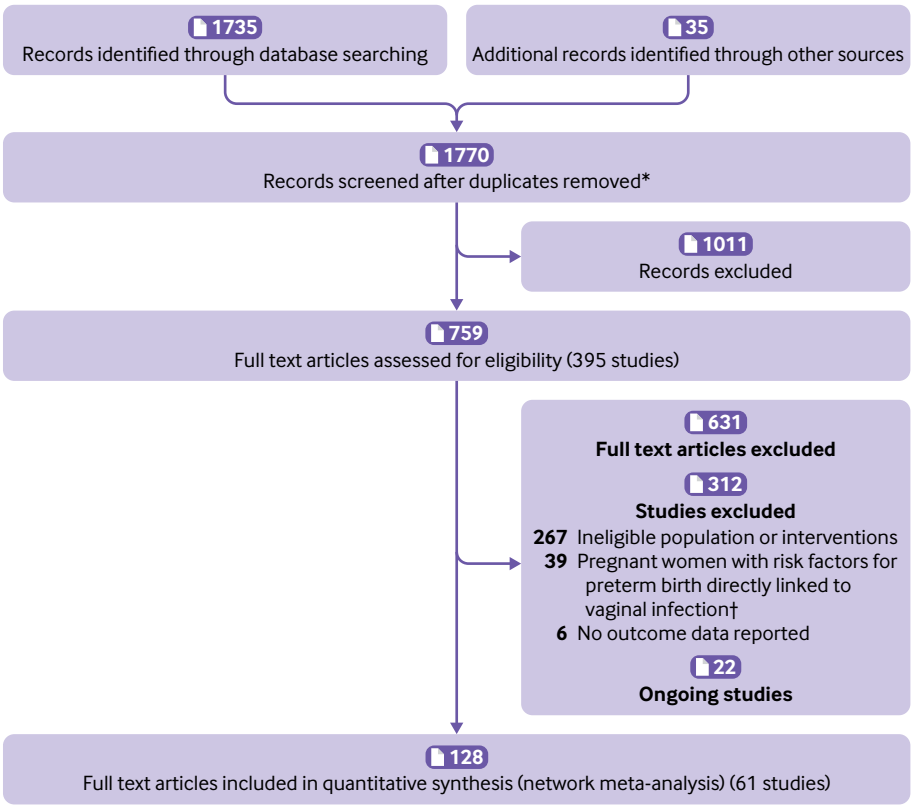

Fig 1 | PRISMA (preferred reporting items for systematic reviews and meta-analyses) study flow diagram. *No duplicates because only Cochrane Pregnancy and Childbirth's Trial Register (containing over 25 000 reports of controlled trials in the field of pregnancy and childbirth, and identified from regular searches of Cochrane Central Register of Controlled Trials, Medline, Embase, CINAHL, relevant journals, conference proceedings, and registries of ongoing trials) was searched. †Thirty nine studies of pregnant women with risk factors for preterm birth linked directly to vaginal infection will be included in a separate network meta-analysis as part of a larger project examining a series of network meta-analyses within different populations of pregnant women[14]

cerclage comes from a single small trial[25] comparing Shirodkar cerclage (n=34), McDonald cerclage (n=34), and bed rest (n=30). Only a single event of spontaneous preterm birth <34 weeks was reported for Shirodkar cerclage, resulting in the extreme odds ratio estimate, but low certainty of evidence. 17OHPC (17α-hydroxyprogesterone caproate; 0.68, 0.43 to 1.02, moderate certainty), vaginal pessary (0.65, 0.39 to 1.08, moderate certainty), and fish oil or omega 3 (0.30, 0.06 to 1.23, moderate certainty) could also be associated with fewer women with preterm birth <34 weeks, but credible intervals could not exclude the possibility of harm (fig 3).

Vaginal progesterone was associated with fewer perinatal deaths compared with control treatment (0.66, 0.44 to 0.97, moderate certainty). Additionally, 17OHPC (0.78, 0.50 to 1.21, moderate certainty), McDonald cerclage (0.59, 0.33 to 1.03, moderate certainty), and unspecified cerclage (0.77, 0.53 to 1.11, moderate certainty) might reduce perinatal death rates, but credible intervals could not exclude the possibility of harm (fig 4).

Supplementary tables 6-9 provide probabilities of each treatment being the best and rankings of treatments for each outcome. Rankings of treatments varied by outcome and were influenced by imprecise effect estimates due to low numbers of events, making these less reliable for clinical interpretation.

In current clinical practice, women identified as high risk for preterm birth would be expected to receive some form of preventative treatment. Compared with placebo or no treatment, vaginal progesterone showed the best comparative effectiveness. To establish if a treatment is superior or equivalent to vaginal progesterone, we performed a network meta-analysis with vaginal progesterone as a comparator, which failed to identify a superior alternative (fig 5, fig 6, supplementary files 6 and 7).

Direct evidence

Supplementary table 10 provides direct evidence from pairwise meta-analysis when available, and equivalent network meta-analysis results for each comparison for each outcome.

Certainty of evidence

Figure 3 and figure 4 present the certainty of evidence for the outcome of preterm birth <34 weeks and perinatal death, respectively. Wide 95% credible intervals were estimated for some pairwise comparisons because of low numbers of trials, often a single trial, and low numbers of events for some

Table 1 | Included studies and treatments

Study	Treatment 1	No of women randomised	Treatment 2	No of women randomised	Treatment 3	No of women randomised	Total
Ahuja 2015	Placebo	40	Vaginal progesterone	40	NA	NA	80
Akbari 2009	Placebo	75	Vaginal progesterone	75	NA	NA	150
Althuisius 2001	Bed rest+amoxicillin+metronidazole	16	Cerclage (McDonald)+bed rest+amoxicillin+metronidazole	20	NA	NA	36
Ashoush 2017	Placebo	106	Oral progesterone	106	NA	NA	212
Azargoon 2016	Placebo	52	Vaginal progesterone	51	NA	NA	103
Bafghi 2015	17OHPC	39	Vaginal progesterone	39	NA	NA	78
Berghella 2004	Bed rest	30	Cerclage (McDonald)+bed rest	31	NA	NA	61
Blackwell 2018	Placebo	578	17OHPC	1130	NA	NA	1708
Breart 1979	Oral progesterone	106	17OHPC	105	NA	NA	211
Cabrera-Garcia 2015	Vaginal progesterone	126	Pessary	128	NA	NA	254
Care 2019	Pessary	6	Cerclage (unspecified)	7	Vaginal progesterone	5	18
Cetingoz 2011	Placebo	70	Vaginal progesterone	80	NA	NA	150
Chandiramani 2010	Vaginal progesterone	17	Cerclage (unspecified)	20	NA	NA	37
Choi 2020	Vaginal progesterone	131	17OHPC	135	NA	NA	266
Crowther 2017	Placebo	389	Vaginal progesterone	398	NA	NA	787
da Fonseca 2003	Placebo	75	Vaginal progesterone	81	NA	NA	156
Danesh 2010	Placebo	55	Nutritional supplements: zinc	55	NA	NA	110
Danti 2014	Placebo	43	Tocolytics: nifedipine	44	NA	NA	87
Dugoff 2018	No treatment	61	Pessary	61	NA	NA	122
El-Gharib 2013	Vaginal progesterone	80	17OHPC	80	NA	NA	160
Elimian 2016	Vaginal progesterone	92	17OHPC	82	NA	NA	174
Ezechi 2004	No treatment	43	Cerclage (McDonald)	38	NA	NA	81
Fonseca 2007	Placebo	138	Vaginal progesterone	136	NA	NA	274
Glover 2011	Placebo	14	Oral progesterone	19	NA	NA	33
Goya 2012	No treatment	193	Pessary	192	NA	NA	385
Grobman 2012	Placebo	330	17OHPC	327	NA	NA	657
Harper 2010	17OHPC	418	Omega 3+17OHPC	434	NA	NA	852
Hassan 2011	Placebo	229	Vaginal progesterone	236	NA	NA	465
Hui 2013	No treatment	55	Pessary	53	NA	NA	108
Ibrahim 2010	Placebo	25	17OHPC	25	NA	NA	50
Ionescu 2011	Vaginal progesterone	46	Cerclage (unspecified)	46	NA	NA	92
Jabeen 2012	Placebo	30	17OHPC	30	NA	NA	60
Jafarpour 2020	No treatment	50	17OHPC	50	NA	NA	100
Johnson 1975	Placebo	25	17OHPC	25	NA	NA	50

17OHPC=17α-hydroxyprogesterone caproate; NA=not applicable.

treatments, such as nutritional supplements, bed rest, and combination treatments. Extreme results (odds ratios >100) were estimated for some treatment comparisons when no events occurred, such as maternal infection, intraventricular haemorrhage, necrotising enterocolitis, and neonatal sepsis (supplementary files 6 and 7).

Discussion

Principal findings

This network meta-analysis showed that vaginal progesterone should be the clinical treatment of choice for women with singleton pregnancies at high risk of spontaneous preterm birth. 17OHPC and cervical cerclage have shown potential to reduce the risk of preterm birth <34 weeks and neonatal deaths; however, compared with vaginal progesterone, they are not superior.

Strengths and limitations

A strength of this network meta-analysis is the systematic inclusion of relevant randomised controlled trials. Sixty one trials that included 17 273 pregnant women contributed data for at least one outcome. The risk of bias in the studies was considered low overall. High risk of performance bias was present in studies when blinding could not be achieved, such as insertion of a suture, but this would not be expected to have major influence on key outcomes of interest.

There has been controversy over the use of progestogens in women at high risk for the prevention of spontaneous preterm birth after publication of several large negative randomised controlled trials.[10 11 26] This specific topic has been addressed in the recently completely individual participant level data meta-analysis EPPPIC (Evaluating Progestogen for the Prevention of Preterm Birth International Collaborative), with results that are consistent with our findings.[27]

We have evaluated a specific group of pregnant women at high risk with singleton pregnancy where there remains clinical equipoise about current preventative treatments. Most trials included women with a short cervix, a history of spontaneous preterm birth, or both, as these groups overlap in clinical practice. From clinical trial data, approximately one third of women with a short cervix will have a history of preterm birth, and conversely, a third of women with a history of preterm birth will develop a short cervix. It is possible that women with a short cervix and no history

Table 2 | Included studies and treatments (continued from table 1)

Study	Treatment 1	No of women randomised	Treatment 2	No of women randomised	Treatment 3	No of women randomised	Total
Karbasian 2016	Vaginal progesterone	73	Pessary+vaginal progesterone	73	NA	NA	146
Keeler 2009	Clindamycin+17OHPC	37	Cerclage (McDonald)	42	NA	NA	79
Maher 2013	17OHPC	256	Vaginal progesterone	262	NA	NA	518
Majhi 2009	No treatment	50	Vaginal progesterone	50	NA	NA	100
Meis 2003a	Placebo	153	17OHPC	310	NA	NA	463
MRC/RCOG 1993	No treatment	645	Cerclage (unspecified)	647	NA	NA	1292
Nicolaides 2016	No treatment	469	Pessary	466	NA	NA	935
Norman 2016	Placebo	610	17-OHPC	618	NA	NA	1228
O'Brien 2007	Placebo	327	Vaginal progesterone	332	NA	NA	659
Olsen 2000	Placebo	122	Fish oil	110	NA	NA	232
Otsuki 2016	Bed rest	35	Cerclage (McDonald)	35	Cerclage (Shirodkar)	36	106
Owen 2009	No treatment	153	Cerclage (McDonald)	149	NA	NA	302
Pirjani 2017	17OHPC	152	Vaginal progesterone	152	NA	NA	304
Rai 2009	Placebo	75	Oral progesterone	75	NA	NA	150
Rush 1984	No treatment	98	Cerclage (McDonald)	96	NA	NA	194
Rust 2001	Antibiotics: clindamycin	58	Cerclage (McDonald)	55	NA	NA	113
Saccone 2017	No treatment	150	Pessary	150	NA	NA	300
Saghafi 2011	No treatment	50	17OHPC	50	NA	NA	100
Shadab 2018	Placebo	66	17OHPC	66	NA	NA	132
Shahgheibi 2016	Placebo	50	17OHPC	50	NA	NA	100
Shambhavi 2018	17-OHPC	50	Vaginal progesterone	50	NA	NA	100
To 2004	No treatment	127	Cerclage (Shirodkar)+erythromycin	126	NA	NA	253
van Os 2015	Placebo	39	Vaginal progesterone	41	NA	NA	80
Vanda 2020	Vaginal progesterone	83	17OHPC	83	NA	NA	166
Vermuelen 1999	Placebo	85	Antibiotics: clindamycin	83	NA	NA	168
Wajid 2016	17OHPC	400	Vaginal progesterone	400	NA	NA	800
Winer 2015	No treatment	54	17OHPC	51	NA	NA	105

17OHPC=17α-hydroxyprogesterone caproate; NA=not applicable.

of spontaneous preterm birth might respond differently from those with a history of spontaneous preterm birth and long cervix in ongoing pregnancy; it is for future research to tease out any possible differences in the size and direction of treatment effects for specific subgroups of women at high risk. It should be emphasised that all women included in these randomised controlled trials had singleton pregnancies and were at high risk for spontaneous preterm birth, and therefore could have been randomised to any of these preventative interventions.

We felt that it is important to analyse different progestogens as separate interventions, but acknowledge that we did not consider various dosing regimens. Additionally, the results from this network meta-analysis cannot be applied to other high risk groups of women at risk for spontaneous preterm birth, for example women with multiple pregnancy.

Spontaneous preterm birth is a heterogeneous disease. It would be unwise to assume that a single treatment could reduce the risk of spontaneous preterm birth for every woman presenting with risk factors. Individual treatment of women at risk in specialist settings using alternative treatments is not precluded by the findings of this network meta-analysis. We need to continue to identify better predictors, and importantly target how and why treatments work for individual women.

Conclusions and implications for practice

Vaginal progesterone is currently the best preterm birth prevention treatment for women with a singleton pregnancy who are asymptomatic but at high risk of preterm birth. No other treatment can be regarded as superior, but promising results have been observed for alternative routes of administration (oral, intramuscular), and treatments such as cerclage and pessary.

It will be increasingly difficult to offer no treatment or placebo to women with singleton pregnancy who have been identified at risk of preterm birth. We suggest that vaginal progesterone should become the new gold standard comparator. For future randomised controlled trials, the goal should be for any alternative treatment, or combination, to show superiority in cost effectiveness and, at the very least, non-inferiority in terms of safety. Our findings have important implications for national and international guidelines for the prevention of preterm birth and future research in this field.

Contributors: ZA and NM conceived the original study. SJN, NM, SD, LG, LH, CTS, and ZA designed the review protocol. NM, LG, and LH developed the search strategy and selected studies. NM and LG extracted data. SD, SJN, AC, and ZA analysed the data. AC and SJN drafted the manuscript and ZA, LG, CTS, and SD revised the manuscript critically for important intellectual content. All authors approved the final version of the article. AC, SJN, and ZA are guarantors. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/disclosure-of-interest/ and declare: support from Wellbeing of Women charity for the submitted work; no financial relationships with any organisations that might have an

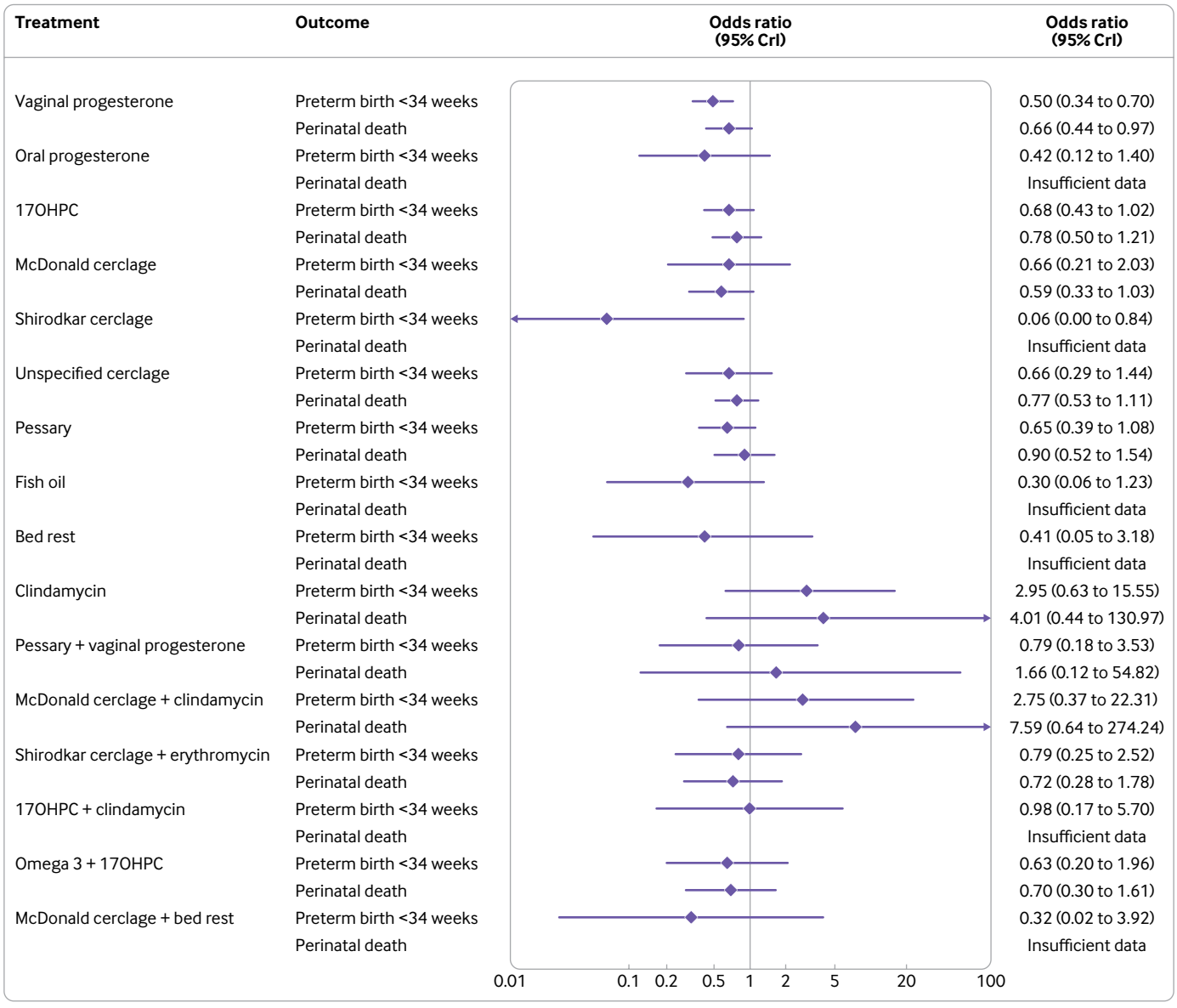

Fig 2 | Network meta-analysis results for preterm birth ‹34 weeks and perinatal death. 17OHPC=17α-hydroxyprogesterone caproate. CrI=credible interval

interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: Not required.

Data sharing: No additional data are available. All data are available in the supplementary material provided by the authors or within the original manuscripts of the included studies.

Dissemination to participants and related patient and public communities: We will disseminate our findings to patient organisations and media outlets, including social media and relevant websites.

The lead authors (the manuscript's guarantors) affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Provenance and peer review: Not commissioned; externally peer reviewed.

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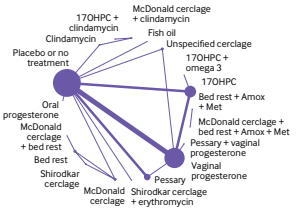
Patient or population: pregnant women at high risk of spontaneous preterm birth

Interventions: bed rest, cervical cerclage (McDonald, Shirodkar, or unspecified), cervical pessary, fish oils or omega fatty acids, nutritional supplements (zinc), progesterone (intramuscular, oral, vaginal), prophylactic antibiotics (clindamycin), prophylactic tocolytics (nifedipine), combination of interventions

Comparator (reference): placebo or no treatment

Outcome: prevention of preterm birth <34 weeks

Setting: antenatal outpatient



Total studies: 40 RCTs Total participants: 13 310	Relative effect (95% CrI)	Anticipated absolute effect (95% CrI)			Certainty of evidence	Interpretation of findings
		Without intervention	With intervention	Difference		
Vaginal progesterone (9 RCTs; 3023 participants)	0.50 (0.34 to 0.70) Network estimate	191 per 1000*	96 per 1000	95 fewer per 1000 (126 fewer to 57 fewer)	High	✓
Oral progesterone (1 RCT; 148 participants)	0.42 (0.12 to 1.40) Network estimate	191 per 1000*	80 per 1000	111 fewer per 1000 (168 fewer to 76 more)	Low due to imprecision†	?
17OHPC (5 RCTs; 2987 participants)	0.68 (0.43 to 1.02) Network estimate	191 per 1000*	130 per 1000	61 fewer per 1000 (109 fewer to 4 more)	Moderate due to imprecision‡	⊕
McDonald cerclage (1 RCT; 302 participants)	0.66 (0.21 to 2.03) Network estimate	191 per 1000*	126 per 1000	65 fewer per 1000 (151 fewer to 197 more)	Low due to imprecision†	?
Shirodkar cerclage (no direct evidence, indirect only)	0.06 (0.00 to 0.84) Network estimate	191 per 1000*	11 per 1000	180 fewer per 1000 (191 fewer to 31 fewer)	Low due to imprecision¶ but large effect size	⊕
Unspecified cerclage (1 RCT; 1264 participants)	0.66 (0.29 to 1.44) Network estimate	191 per 1000*	126 per 1000	65 fewer per 1000 (136 fewer to 84 more)	Low due to imprecision†	?
Pessary (5 RCTs; 1830 participants)	0.65 (0.39 to 1.08) Network estimate	191 per 1000*	124 per 1000	67 fewer per 1000 (117 fewer to 15 more)	Moderate due to imprecision‡	⊕
Fish oil or omega 3 (1 RCT; 228 participants)	0.30 (0.06 to 1.23) Network estimate	191 per 1000*	57 per 1000	134 fewer per 1000 (180 fewer to 44 more)	Moderate due to imprecision‡	⊕
Bed rest (no direct evidence, indirect evidence only)	0.41 (0.05 to 3.18) Network estimate	191 per 1000*	78 per 1000	113 fewer per 1000 (181 fewer to 416 more)	Low due to imprecision†	?
Clindamycin (1 RCT; 168 participants)	2.95 (0.63 to 15.55) Network estimate	191 per 1000*	563 per 1000	372 more per 1000 (70 fewer to 2970 more)	Very low due to imprecision§**	?
Combination (pessary + vaginal progesterone; no direct evidence, indirect evidence only)	0.79 (0.18 to 3.53) Network estimate	191 per 1000*	151 per 1000	40 fewer per 1000 (157 fewer to 483 more)	Low due to imprecision§	?
Combination (McDonald + clindamycin; no direct evidence, indirect evidence only)	2.75 (0.37 to 22.31) Network estimate	191 per 1000*	525 per 1000	334 more per 1000 (120 fewer to 4070 more)	Very low due to imprecision§**	?
Combination (Shirodkar cerclage + erythromycin; 1 RCT; 253 participants)	0.79 (0.25 to 2.52) Network estimate	191 per 1000*	151 per 1000	40 fewer per 1000 (143 fewer to 290 more)	Low due to imprecision†	?
Combination (17OHPC + clindamycin; no direct evidence, indirect evidence only)	0.98 (0.17 to 5.70) Network estimate	191 per 1000*	187 per 1000	4 fewer per 1000 (159 fewer to 898 more)	Very low due to imprecision¶**	?
Combination (omega 3 + 17OHPC; no direct evidence, indirect evidence only)	0.63 (0.20 to 1.96) Network estimate	191 per 1000*	120 per 1000	71 fewer per 1000 (153 fewer to 183 more)	Low due to imprecision§	?
Combination (McDonald cerclage + bed rest; no direct evidence, indirect evidence only)	0.32 (0.02 to 3.92) Network estimate	191 per 1000*	61 per 1000	130 fewer per 1000 (187 fewer to 558 more)	Very low due to imprecision†¶	?
Placebo or no treatment	Reference comparator	Not estimable	Not estimable	Not estimable	Reference comparator	Reference comparator

✓ Clear evidence of benefit; evidence graded moderate or high quality

⊕ Potential for benefit; low quality evidence with clear benefit; moderate or high quality evidence with wide credible intervals

? Unknown harm or benefit; low or very low quality evidence with wide credible intervals

Fig 3 | Impact on preterm birth <34 weeks of various preventative treatments for pregnant women at risk of spontaneous preterm birth using placebo or no treatment as comparator. Solid lines represent direct comparison. Network meta-analysis estimates reported as odds ratios and 95% credible intervals instead of confidence intervals because bayesian analysis was conducted (credible interval is interpreted as interval where there is 95% probability that values of odds ratio will lie). Anticipated absolute effect compares two risks by calculating difference between risk of intervention group with risk of control group. GRADE (grading of recommendations assessment, development, and evaluation) working group grades of evidence (or certainty of evidence): high quality—very confident true effect lies close to that of estimate of effect; moderate quality—moderately confident in effect estimate; true effect is likely to be close to estimate of effect, but there is a possibility that it is substantially different; low quality—confidence in effect estimate is limited; true effect may be substantially different from estimate of effect; very low quality: very little confidence in effect estimate; true effect is likely to be substantially different from estimate of effect. *Based on an assumed control risk of spontaneous preterm birth <34 weeks of 19.1% (corresponding to a pooled 19.1% rate of spontaneous preterm birth <34 weeks in women receiving placebo or no treatment in included trials). †Serious imprecision because odds ratio <1 (suggesting greater likelihood of benefit than harm) but wide 95% credible interval (relative risk >1.25), suggesting appreciable harm. ‡Imprecision because 95% credible interval crosses 1, suggesting uncertainty in estimate. §Serious imprecision because odds ratio >1 (suggesting greater likelihood of harm than benefit) but wide 95% credible interval (relative risk <0.75); unable to rule out reasonable chance of benefit. ¶Serious imprecision because wide 95% credible interval, suggesting uncertainty in estimate probably due to single trial and low numbers of events contributing to network meta-analysis (n=34 Shirodkar cerclage arm, 1 preterm birth <34 weeks). **Serious imprecision because extremely wide 95% credible interval crossing 1. 17OHPC=17α-hydroxyprogesterone caproate; Amox=amoxicillin; CrI=credible interval; Met=metronidazole; RCT=randomised controlled trial

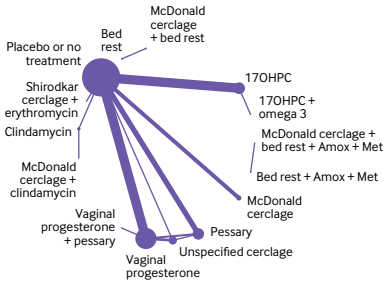
Patient or population: pregnant women at high risk of spontaneous preterm birth

Interventions: bed rest, cervical cerclage (McDonald, Shirodkar, or unspecified), cervical pessary, fish oils or omega fatty acids, nutritional supplements (zinc), progesterone (intramuscular, oral, vaginal), prophylactic antibiotics (clindamycin), prophylactic tocolytics (nifedipine), combination of interventions

Comparator (reference): placebo or no treatment

Outcome: perinatal death

Setting: antenatal outpatient



Total studies: 30 RCTs Total participants: 12 119	Relative effect (95% CrI)	Anticipated absolute effect (95% CrI)			Certainty of evidence	Interpretation of findings
		Without intervention	With intervention	Difference		
Vaginal progesterone (7 RCTs; 3499 participants)	0.66 (0.44 to 0.97) Network estimate	47 per 1000*	31 per 1000	16 fewer per 1000 (26 fewer to 1 fewer)	Moderate due to imprecision†	✓
17OHPC (6 RCTs; 3038 participants)	0.78 (0.50 to 1.21) Network estimate	47 per 1000*	37 per 1000	10 fewer per 1000 (24 fewer to 10 more)	Moderate due to imprecision‡	⊕
McDonald cerclage (3 RCTs; 575 participants)	0.59 (0.33 to 1.03) Network estimate	47 per 1000*	28 per 1000	19 fewer per 1000 (31 fewer to 1 more)	Moderate due to imprecision‡	⊕
Unspecified cerclage (no direct evidence, indirect evidence only)	0.77 (0.53 to 1.11) Network estimate	47 per 1000*	36 per 1000	11 fewer per 1000 (23 fewer to 5 more)	Moderate due to imprecision‡	⊕
Pessary (4 RCTs; 1730 participants)	0.90 (0.52 to 1.54) Network estimate	47 per 1000*	42 per 1000	5 fewer per 1000 (24 fewer to 26 more)	Low due to imprecision§	
Clindamycin (1 RCT; 168 participants)	4.01 (0.44 to 130.97) Network estimate	47 per 1000*	188 per 1000	141 more per 1000 (26 fewer to 6109 more)	Very low due to imprecision¶**	?
Combination (pessary + vaginal progesterone; 1 RCT; 144 participants)	1.66 (0.12 to 54.82) Network estimate	47 per 1000*	78 per 1000	31 more per 1000 (41 fewer to 2530 more)	Very low due to imprecision¶**	?
Combination (McDonald + clindamycin; 2 RCTs; 268 participants)	7.59 (0.64 to 274.24) Network estimate	47 per 1000*	357 per 1000	310 more per 1000 (17 fewer to 12 842 more)	Very low due to imprecision¶**	?
Combination (Shirodkar cerclage + erythromycin; 1 RCT; 253 participants)	0.72 (0.28 to 1.78) Network estimate	47 per 1000*	34 per 1000	13 fewer per 1000 (34 fewer to 37 more)	Low due to imprecision§	?
Combination (omega 3 + 17OHPC; 1 RCT; 852 participants)	0.70 (0.30 to 1.61) Network estimate	47 per 1000*	33 per 1000	14 fewer per 1000 (33 fewer to 29 more)	Low due to imprecision§	?
Placebo or no treatment	Reference comparator	Not estimable	Not estimable	Not estimable	Reference comparator	Reference comparator

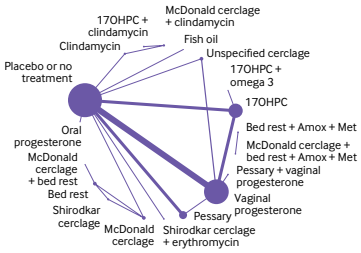
✓ Clear evidence of benefit; evidence graded moderate or high quality

⊕ Potential for benefit; low quality evidence with clear benefit; moderate or high quality evidence with wide credible intervals

? Unknown harm or benefit; low or very low quality evidence with wide credible intervals

Fig 4 | Impact on perinatal death of various preventative treatments for pregnant women at risk of spontaneous preterm birth using placebo or no treatment as comparator.Solid lines represent direct comparison. Network meta-analysis estimates reported as odds ratios and 95% credible intervals instead of confidence intervals because bayesian analysis was conducted (credible interval is interpreted as interval where there is 95% probability that values of odds ratio will lie). Anticipated absolute effect compares two risks by calculating difference between risk of intervention group with risk of control group. GRADE (grading of recommendations assessment, development, and evaluation) working group grades of evidence (or certainty of evidence): high quality—very confident true effect lies close to that of estimate of effect; moderate quality—moderately confident in effect estimate; true effect is likely to be close to estimate of effect, but there is a possibility that it is substantially different; low quality—confidence in effect estimate is limited; true effect may be substantially different from estimate of effect; very low quality: very little confidence in effect estimate; true effect is likely to be substantially different from estimate of effect. *Based on assumed control risk of perinatal death of 4.7% (corresponding to a pooled 4.7% rate of perinatal death in women receiving placebo or no treatment in included trials). †Imprecision because although 95% credible interval does not cross 1, total number of events is low. ‡Imprecision because 95% credible interval wide and crosses 1. §Serious imprecision because odds ratio ‹1 (suggesting greater likelihood of benefit than harm) but wide 95% credible interval (relative risk ›1.25), suggesting appreciable harm. ¶Serious imprecision because odds ratio ›1 (suggesting greater likelihood of harm than benefit) but wide 95% credible interval (relative risk ‹ 0.75); unable to rule out reasonable chance of benefit. **Serious imprecision because extremely wide 95% credible interval crossing 1. ††Very serious imprecision because 95% credible interval crosses unity with very wide 95% credible interval, suggesting uncertainty in estimate likely due to single trials or very low numbers of events (‹5) contributing to network meta-analysis. 17OHPC=17α-hydroxyprogesterone caproate; Amox=amoxicillin; CrI=credible interval; Met=metronidazole; RCT=randomised controlled trial

Patient or population: pregnant women at high risk of spontaneous preterm birth
Interventions: bed rest, cervical cerclage (McDonald, Shirodkar, or unspecified), cervical pessary, fish oils or omega fatty acids, nutritional supplements (zinc), progesterone (intramuscular, oral), prophylactic antibiotics (clindamycin), prophylactic tocolytics (nifedipine), combination of interventions
Comparator (reference): vaginal progesterone
Outcome: prevention of preterm birth <34 weeks
Setting: antenatal outpatient



Total studies: 40 RCTs Total participants: 13 310	Relative effect (95% CrI)	Anticipated absolute effect (95% CrI)			Certainty of evidence	Interpretation of findings
		Without intervention	With intervention	Difference		
Oral progesterone (no direct evidence, indirect evidence only)	0.83 (0.24 to 3.03) Network estimate	136 per 1000*	113 per 1000	23 fewer per 1000 (103 fewer to 276 more)	Low due to imprecision†	?
17OHPC (5 RCTs; 1142 participants)	1.34 (0.87 to 2.12) Network estimate	136 per 1000*	182 per 1000	46 more per 1000 (18 fewer to 152 more)	Low due to imprecision‡	?
McDonald cerclage (no direct evidence, indirect evidence only)	1.32 (0.42 to 4.40) Network estimate	136 per 1000*	180 per 1000	44 more per 1000 (79 fewer to 462 more)	Low due to imprecision‡	?
Shirodkar cerclage (no direct evidence, indirect only)	0.13 (0.00 to 1.76) Network estimate	136 per 1000*	18 per 1000	118 fewer per 1000 (136 fewer to 244 more)	Low due to imprecision§ and low event rate	?
Unspecified cerclage (2 RCTs; 103 participants)	1.32 (0.59 to 2.99) Network estimate	136 per 1000*	180 per 1000	44 more per 1000 (56 fewer to 271 more)	Low due to imprecision‡	?
Pessary (1 RCT; 254 participants)	1.29 (0.74 to 2.39) Network estimate	136 per 1000*	175 per 1000	39 more per 1000 (35 fewer to 189 more)	Low due to imprecision‡	?
Fish oil or omega 3 (no direct evidence, indirect only)	0.59 (0.12 to 2.63) Network estimate	136 per 1000*	80 per 1000	56 fewer per 1000 (120 fewer to 222 more)	Low due to imprecision§	?
Bed rest (no direct evidence, indirect evidence only)	0.82 (0.10 to 6.65) Network estimate	136 per 1000*	112 per 1000	24 fewer per 1000 (122 fewer to 768 more)	Low due to imprecision‡	?
Clindamycin (no direct evidence, indirect evidence only)	5.89 (1.22 to 32.75) Network estimate	136 per 1000*	801 per 1000	665 more per 1000 (30 more to 4318 more)	Very low due to imprecision¶**	?
Combination (pessary + vaginal progesterone; 2 RCTs; 244 participants)	1.58 (0.38 to 6.86) Network estimate	136 per 1000*	215 per 1000	79 more per 1000 (84 fewer to 797 more)	Low due to imprecision†	?
Combination (McDonald + clindamycin; no direct evidence, indirect evidence only)	5.48 (0.72 to 46.81) Network estimate	136 per 1000*	745 per 1000	609 more per 1000 (38 fewer to 6230 more)	Very low due to imprecision‡**	?
Combination (17OHPC + clindamycin; no direct evidence, indirect evidence only)	1.95 (0.33 to 12.05) Network estimate	136 per 1000*	265 per 1000	129 more per 1000 (91 fewer to 1503 more)	Very low due to imprecision‡**	?
Combination (omega 3 + 17OHPC; no direct evidence, indirect evidence only)	1.26 (0.40 to 4.08) Network estimate	136 per 1000*	171 per 1000	35 more per 1000 (82 fewer to 419 more)	Low due to imprecision†	?
Combination (McDonald cerclage + bed rest; no direct evidence, indirect evidence only)	0.64 (0.05 to 8.20) Network estimate	136 per 1000*	87 per 1000	49 fewer per 1000 (129 fewer to 979 more)	Very low due to imprecision‡**	?

? Unknown harm or benefit; low or very low quality evidence with wide credible intervals

Fig 5 | Impact on preterm birth <34 weeks of various preventative treatments for pregnant women at risk of spontaneous preterm birth using vaginal progesterone as comparator. Solid lines represent direct comparison. Network meta-analysis estimates reported as odds ratios and 95% credible intervals instead of confidence intervals because bayesian analysis was conducted (credible interval is interpreted as interval where there is 95% probability that values of odds ratio will lie). Anticipated absolute effect compares two risks by calculating difference between risk of intervention group with risk of control group. GRADE (grading of recommendations assessment, development, and evaluation) working group grades of evidence (or certainty of evidence): high quality—very confident true effect lies close to that of estimate of effect; moderate quality—moderately confident in effect estimate; true effect is likely to be close to estimate of effect, but there is a possibility that it is substantially different; low quality—confidence in effect estimate is limited; true effect may be substantially different from estimate of effect; very low quality: very little confidence in effect estimate; true effect is likely to be substantially different from estimate of effect. *Based on assumed control risk of spontaneous preterm birth <34 weeks of 13.6% (corresponding to a pooled 13.6% rate of preterm birth <34 weeks in women receiving vaginal progesterone in included trials). †Serious imprecision because odds ratio <1 (suggesting greater likelihood of benefit than harm) but wide 95% credible interval and includes appreciable harm (odds ratio >1.25). ‡Serious imprecision because odds ratio >1 (suggesting greater likelihood of harm than benefit) but wide 95% credible interval and includes appreciable benefit (odds ratio <0.75). §Serious imprecision because 95% credible interval extremely wide, but does not cross 1, suggesting greater likelihood of harm than benefit. ¶Imprecision because 95% credible interval crosses 1, suggesting uncertainty in estimate. **Extreme imprecision because 95% credible interval crosses 1 and extremely wide, suggesting gross uncertainty in estimate. 17OHPC=17α-hydroxyprogesterone caproate; Amox=amoxicillin; CrI=credible interval; Met=metronidazole; RCT=randomised controlled trial

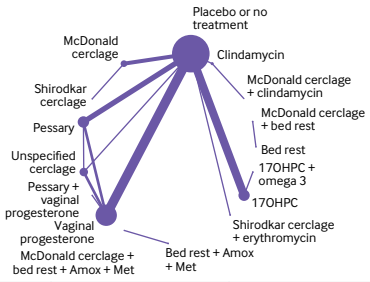
Patient or population: pregnant women at high risk of spontaneous preterm birth

Interventions: bed rest, cervical cerclage (McDonald, Shirodkar, or unspecified), cervical pessary, fish oils or omega fatty acids, nutritional supplements (zinc), progesterone (intramuscular, oral, vaginal), prophylactic antibiotics (clindamycin), prophylactic tocolytics (nifedipine), combination of interventions

Comparator (reference): vaginal progesterone

Outcome: perinatal death

Setting: antenatal outpatient



Total studies: 30 RCTs Total participants: 12 119	Relative effect (95% CrI)	Anticipated absolute effect (95% CrI)			Certainty of evidence	Interpretation of findings
		Without intervention	With intervention	Difference		
17OHPC (no direct evidence, indirect evidence only)	1.18 (0.65 to 2.15) Network estimate	23 per 1000*	27 per 1000	4 more per 1000 (8 fewer to 26 more)	Low due to imprecision†	
McDonald cerclage (no direct evidence, indirect evidence only)	0.89 (0.44 to 1.79) Network estimate	23 per 1000*	20 per 1000	3 more per 1000 (13 fewer to 18 more)	Low due to imprecision‡	?
Unspecified cerclage (3 RCTs; 146 participants)	1.17 (0.70 to 1.96) Network estimate	23 per 1000*	27 per 1000	4 more per 1000 (7 fewer to 22 more)	Low due to imprecision†	?
Pessary (2 RCTs; 261 participants)	1.37 (0.73 to 2.59) Network estimate	23 per 1000*	32 per 1000	9 fewer per 1000 (6 fewer to 37 more)	Low due to imprecision†	?
Clindamycin (no direct evidence, indirect evidence only)	6.12 (0.64 to 202.76) Network estimate	23 per 1000*	141 per 1000	118 more per 1000 (8 fewer to 4640 more)	Very low due to imprecision§	?
Combination (pessary + vaginal progesterone; 1 RCT; 144 participants)	2.14 (0.15 to 72.68) Network estimate	23 per 1000*	49 per 1000	26 more per 1000 (23 fewer to 1649 more)	Very low due to imprecision§	?
Combination (McDonald + clindamycin; no direct evidence, indirect evidence only)	11.60 (0.94 to 431.38) Network estimate	23 per 1000*	267 per 1000	244 fewer per 1000 (1 fewer to 9899 more)	Very low due to imprecision§	?
Combination (Shirodkar cerclage + erythromycin; no direct evidence, indirect evidence only)	0.93 (0.32 to 2.53) Network estimate	23 per 1000*	21 per 1000	2 fewer per 1000 (16 fewer to 35 more)	Low due to imprecision†	?
Combination (omega 3 + 17OHPC; no direct evidence, indirect evidence only)	0.91 (0.45 to 1.83) Network estimate	23 per 1000*	21 per 1000	2 more per 1000 (13 more to 19 more)	Low due to imprecision†	?
Vaginal progesterone	Reference comparator	Not estimable	Not estimable	Not estimable	Reference comparator	Reference comparator

? Unknown harm or benefit; low or very low quality evidence with wide credible intervals

Fig 6 | Impact on perinatal death of various preventative treatments for pregnant women at risk of spontaneous preterm birth using vaginal progesterone as a comparator. Solid lines represent direct comparison. Network meta-analysis estimates reported as odds ratios and 95% credible intervals instead of confidence intervals because bayesian analysis was conducted (credible interval is interpreted as interval where there is 95% probability that values of odds ratio will lie). Anticipated absolute effect compares two risks by calculating difference between risk of intervention group with risk of control group. GRADE (grading of recommendations assessment, development, and evaluation) working group grades of evidence (or certainty of evidence): high quality—very confident true effect lies close to that of estimate of effect; moderate quality—moderately confident in effect estimate; true effect is likely to be close to estimate of effect, but there is a possibility that it is substantially different; low quality—confidence in effect estimate is limited; true effect may be substantially different from estimate of effect; very low quality: very little confidence in effect estimate; true effect is likely to be substantially different from estimate of effect. *Based on assumed control risk of perinatal death of 2.3% (corresponding to a pooled 2.3% rate of perinatal death in women receiving vaginal progesterone in included trials). †Serious imprecision because odds ratio >1 (suggesting greater likelihood of harm than benefit) but wide 95% credible interval and includes appreciable benefit (odds ratio <0.75). ‡Serious imprecision because odds ratio <1 (suggesting greater likelihood of benefit than harm) but wide 95% credible interval and includes appreciable harm (odds ratio >1.25). §Very serious imprecision because 95% credible interval crosses 1 with wide credible intervals suggesting uncertainty in the estimate likely due to single trials and low numbers of events contributing to network meta-analysis, with additional high possibility of harm. 17OHPC=17α-hydroxyprogesterone caproate; Amox=amoxicillin; CrI=credible interval; Met=metronidazole; RCT=randomised controlled trial

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Web appendix: Supplementary materials