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BMJ Open

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

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3 1 **The effectiveness of combined vaginal progesterone and cervical cerclage in preventing**
4
5 2 **preterm birth: a systematic review and meta-analysis protocol**
6
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1
2
3 26 Abstract: 224
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5 27 Main manuscript: 3475
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10 29 **Abstract**

11
12 30 **Background:** Preterm birth (PTB) is the leading cause of death in children under five.
13
14 31 Preventive therapies targeted towards women with risk factors such as a prior PTB or a short
15
16 32 cervix reduce the rate of PTB. Cervical cerclage, vaginal progesterone, and a combination of
17
18 33 the two have been used with no consensus as to whether combined treatment is more
19
20 34 effective than any single treatment alone. The objective of this review is to determine the
21
22 35 efficacy of combined treatment compared to cerclage alone, and combined treatment compared
23
24 36 to progesterone alone. **Methods:** Studies will be sourced from six electronic databases and
25
26 37 reference lists. Randomised control trials (RCTs), non-randomised control trials, and cohort
27
28 38 studies assessing single therapy (either progesterone or cerclage) versus combined therapy in
29
30 39 women with a singleton pregnancy will be included. Two independent reviewers will conduct
31
32 40 study screening (at abstract and full text level), data extraction and risk of bias assessment with
33
34 41 disagreements resolved by an experienced researcher. Random or fixed effects models will be
35
36 42 used depending on data heterogeneity and data will be presented as Risk Ratio (RR) for
37
38 43 dichotomous data or Mean Difference (MD) for continuous data with a Confidence Interval
39
40 44 (CI) of 95% used for all outcomes. **Discussion:** This review will provide clarity regarding the
41
42 45 evidence on singular and combined treatment and will assist clinicians and health services in
43
44 46 delivering best practice antenatal care. **Registration:** PROSPERO on 8th of October, 2020
45
46 47 with registration number CRD42020195975 **Key words:** Cervical, Stitch, Cerclage,
47
48 48 Progesterone, Preterm Birth.
49
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58 50 **Strengths and limitations:**

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2
3 51 • The systematic review will follow the rigorous methods outlined in this protocol which
4
5 52 have been written as per Cochrane guidelines.
6
7
8 53 • This will be the first systematic review to answer this question.
9
10 54 • Data will be screened and extracted by two reviewers.
11
12 55 • Lack of reviewer and moderator blinding at inclusion/exclusion level.
13
14
15 56 • Lack of blinding of reviewers and moderators for papers at quality assessment Robins
16
17 57 1, Rob 2, and GRADE.
18
19
20 58

59 **Introduction**

60 Preterm birth (PTB), defined as birth before 37 weeks(1), occurs in 5-13% of all
61 pregnancies(2). It is associated with neonatal mortality and is the leading cause of death in
62 children less than five years(3), as well as significant neonatal morbidity such as infant
63 respiratory distress syndrome, intraventricular haemorrhage, necrotising enterocolitis, and
64 retinopathy of prematurity(4).
65

66 The majority of PTB occurs either spontaneously or following preterm premature rupture of
67 membranes (PPROM)(5). It is well established that a cervical length of less than 25mm,
68 measured between 18 and 25 weeks, is a good predictor -of spontaneous PTB (sPTB) with rates
69 of 31.2% to 41.3%(6, 7). Vaginal progesterone(8) and cervical cerclage(6, 9) are effective
70 single treatments for the prevention of sPTB in these women, as well as those with a prior
71 history of PTB.
72

73 Cervical cerclage is a treatment proven to prevent PTB and reduce neonatal morbidity
74 and mortality(10, 11, 12) by mechanically maintaining a long and closed cervix. In contrast,
75 progesterone has an inhibitory action on uterine contractility by inhibiting the production of
60

1
2
3 76 stimulatory prostaglandins and expression of contraction associated protein genes in
4
5 77 the myometrium(13, 14). It has been shown to play an important role in maintaining a
6
7 78 pregnancy until term(15). Vaginal progesterone when used in women with a short cervix, even
8
9
10 79 in the absence of other risk factors, has been shown to reduce PTB before 34 weeks by 35%(8).
11
12 80 Progesterone therapy can effectively manage cervical shortening in women with cervical length
13
14 81 (CL) of <25 mm, but appears less effective in those with a CL <10 mm(8). With regard to PTB
15
16 82 rates, at 37 weeks cervical cerclage has a 20% success rate in preventing PTB (16), while
17
18 83 vaginal progesterone has a 10% success rate at the same number of weeks gestation (8).
19
20
21
22 84

23
24 85 More recently, studies have assessed the combination of the cervical cerclage and vaginal
25
26 86 progesterone to improve PTB prevention (10, 11). To our knowledge, only one systematic
27
28 87 review published in 2013 has addressed progesterone as an adjunctive therapy to
29
30 88 cerclage; however, the included studies were not randomised and assessed synthetic progestin
31
32 89 17-hydroxyprogesterone caproate (17-OHPC), which found no difference in the outcome of
33
34 90 PTB (16). More recently, adjuvant vaginal progesterone therapy for women who underwent
35
36 91 cervical cerclage indicated by ultrasound(11) or physical(10) examination was found to be
37
38 92 associated with decreased rates of PTB and admission to the neonatal intensive care unit
39
40 93 (NICU). Given these recent promising findings and the lack of guidance on this topic, we
41
42 94 sought to determine the effect of combining both cerclage and progesterone on PTB by
43
44 95 conducting a systematic review and meta-analysis. This paper describes the proposed protocol
45
46 96 for this meta-analysis.
47
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51 97

52 98 **Aim**

53
54 99 This systematic review has two aims: 1) to compare the use of cerclage alone to cerclage and
55
56 100 vaginal progesterone combined, and 2) to compare progesterone alone to the combined use of
57
58
59
60

1
2
3 101 cerclage and vaginal progesterone in order to determine which of these is
4
5 102 associated better maternal and neonatal outcomes in relation to PTB. Our proposed review will
6
7 103 answer the questions *in women requiring prophylactic treatment for short cervix is combined*
8
9 104 *treatment favourable to cerclage alone? And in women requiring prophylactic treatment for*
10
11 105 *short cervix is combined treatment favourable to vaginal progesterone alone?*
12
13
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16

17 107 **Methods**

18 19 108 ***Registration:***

20
21 109 This systematic review protocol was submitted to the International Prospective Register of
22
23 110 Systematic Reviews (PROSPERO) on the 8th of October 2020 and was last updated on this
24
25 111 date (registration number CRD42020195975). This review and meta-analysis will be
26
27 112 completed in accordance using the recommendations of both Preferred Reporting Items for
28
29 113 Systematic Reviews and Meta-Analyses Protocol (PRISMA-P)(17) and the Cochrane
30
31 114 Handbook for Systematic Reviews of Interventions(18).
32
33

34
35 115 Information regarding registration can be accessed
36
37 116 from <http://www.crd.york.ac.uk/PROSPERO>.
38
39

40 41 42 118 ***Eligibility Criteria:***

43
44 119 The eligibility of studies included will be based on inclusion and exclusion criteria applied to
45
46 120 the domains of participant, exposure, comparator, study type, and outcome.
47
48
49

50 51 122 ***Participants:***

52
53 123 The review will consider all studies which include women who are undergoing ultrasound or
54
55 124 history indicated cerclage, vaginal progesterone, or both for the prevention of PTB. Only
56
57 125 singleton pregnancies will be assessed.
58
59
60

126

127 *Intervention:*

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

130

131 Cerclage

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

141

142 Vaginal Progesterone

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

149

150 Combined Treatment

1
2
3 151 Cervical cerclage (McDonald or Shirodkar technique) used in combination with vaginal
4
5 152 progesterone.
6
7

8 153

9
10 154 *Outcomes:*

11
12 155 The primary outcome is PTB, defined as birth <37 weeks gestation. Secondary dichotomous
13
14 156 outcomes will be PTB <34 weeks, <32 weeks, <28 weeks; PPRM; caesarean section; and
15
16 157 neonatal complications: NICU admission, intubation, and neonatal mortality. The continuous
17
18 158 secondary outcomes will be gestational age at delivery; birthweight; and number of days
19
20 159 between intervention and delivery.
21
22

23 160

24
25
26 161 *Types of studies:*

27
28 162 The review will include randomised and pseudo-randomised control trials, non-randomised
29
30 163 experimental control trials, and cohort studies. All included papers must compare cerclage to
31
32 164 combined treatment and/or vaginal progesterone to combined treatment.
33
34 165 Those studies which also presented a control group will be included.
35
36

37 166

38
39
40 167 *Search strategy:*

41
42 168 Electronic bibliographic databases will be searched for eligible, peer-reviewed
43
44 169 literature including: Medline (Ovid), EMBASE (Ovid), PsycINFO (Ovid), Scopus, CINAHL
45
46 170 (EBSCOhost) and Cochrane Library (Wiley). Reference lists of included studies will also be
47
48 171 screened for eligible papers. Studies recommended by experts, the references of textbooks, and
49
50 172 grey literature will also be reviewed for this purpose. We will place no restriction on the length
51
52 173 of study follow-up time or on country, year, or language of publication. All studies will be
53
54 174 human trials.
55
56

57
58 175
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1
2
3 176 The search strategy will be developed through discussion with experts and academics, pilot
4
5 177 searches, and by assessing systematic reviews with similar questions. The search strategy will
6
7
8 178 focus on identifying relevant interventions with no population or outcome related keywords
9
10 179 used. The intervention search terms will be: cervical OR cervix OR rescue; stitch OR cerclage
11
12 180 OR suture; progesterone OR progestin OR prometrium OR progest. Medical subject headings
13
14 181 (MeSH) will be used when relevant and present databases.
15
16

17 182

183 ***Data collection and analysis***

184 *Study Selection*

185 Identified titles and abstracts will be downloaded into Endnote(25) where duplicated studies
186 will be removed. Remaining papers will then be uploaded to Covidence(26) and then screened
187 against the eligibility criteria outlined above. Full texts of remaining studies will be sourced
188 and screened before undergoing critical appraisal and data extraction. All screening will be
189 performed by two independent reviewers and any disagreements will be addressed by a senior
190 research moderator. No reviewers or moderators will be blinded to titles, authors, journals, or
191 institutions.
192

193 *Data management*

194 The search will be uploaded to Covidence(26), an Internet-based software which allows
195 collaboration between multiple reviewers during the study selection process, backup copies of
196 all studies will also be kept in an Endnote library(25).
197

198 *Data collection*

199 Two reviewers will extract data through Covidence(26) using a standardised electronic form
200 consistent with data collection items recommended by the Cochrane Handbook for Systematic
201

1
2
3 201 Reviews of Interventions(18). This process will be piloted prior to use and any discrepancies
4
5 202 will be moderated by a third senior research moderator. Once extracted, upon reviewer
6
7 203 agreement, data will be transferred from Covidence(26) into Review Manager data-analysis
8
9 204 software(27).
10
11
12
13

205

14 206 The following data will be extracted:

- 15
16
17 207 • Study characteristics: authors; publication date; study design; country of
18
19 208 study; sample size; confounding factors of participants; publication status; trial size;
20
21 209 funding; and risk of bias information.
22
23
24 210 • Intervention characteristics: type of intervention used; reason for
25
26 211 intervention; patient characteristics (maternal age, gravity, parity), and any co-
27
28 212 interventions received.
29
30
31 213 • Outcomes: maternal, fetal and neonatal outcome data and definitions of
32
33 214 each of the outcomes as described below.
34
35
36

215

216 **Outcomes and prioritisation:**

217 *Primary outcome*

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

220 For outcomes which report this data as “*greater than*” *X weeks gestation*, data extractors will
221 manually invert the figure to less than.
222

223

223 *Secondary outcomes*

224 Dichotomous

- 225 1. PPRM

226

- 226 2. Caesarean section
- 227 3. NICU admission
- 228 4. Intubation
- 229 5. Neonatal mortality
- 230 Continuous
- 231 6. Gestational age at delivery
- 232 7. Birthweight
- 233 8. Number of days between intervention and delivery

234

235 *Assessment of risk of bias*

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

244

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

1
2
3 251 Randomised trials will be assessed with the Risk of Bias in Randomised Studies of
4
5 252 Interventions (RoB2)(28). This tool assesses five domains which are (1) the randomisation
6
7
8 253 process; (2) deviations from intended interventions; (3) missing outcome data; (4)
9
10 254 measurement of the outcome, and (5) selection of the reported results. Studies which score a
11
12 255 high risk of bias in one or more domains or which have concerns for several domains will be
13
14
15 256 judged as at serious risk of bias.
16

17 257

19 258 Cochrane GRADE Assessment

21 259 The GRADE tool will be used to assess quality of evidence for the primary outcome(30). The
22
23 260 outcome will be assessed in terms of bias risk, consistency, directness, precision, and
24
25
26 261 publication bias. The primary outcome's quality will be judged to be (i) high quality - we are
27
28 262 very confident the true effect is close to that of the estimated effect; (ii) moderate - it is possible
29
30 263 that there is a substantial difference but we are moderately confident the true effect is close to
31
32 264 that of the estimated effect; (iii) low - we are limited in our confidence that the estimated effect
33
34 265 and true effect reflect each other; and (iv) very low - we have very little confidence that the
35
36 266 true and estimated effect align, the true effect is likely to be substantially different to our
37
38 267 estimate. GRADE will be conducted by two independent reviewers and discrepancies will be
39
40 268 resolved through discussion, disagreements which cannot be resolved will be mediated by a
41
42 269 third reviewer.
43
44
45

46
47 270 Graphic representations of potential bias within and across the studies will be calculated
48
49 271 using RevMan 5.3 (Review Manager 5.3)(27). All items in the risk of bias assessment will be
50
51 272 considered independently without an attempt to collate and assign an overarching score.
52
53

54 273

56 274 **Data synthesis**

1
2
3 275 Meta-analysis will be constructed by pooling studies using Covidence(26) and RevMan 5.3
4
5 276 software(27). Forest plots and I^2 values will be used to explore the heterogeneity of
6
7 277 data. Heterogeneity of data will be examined using forest plots and quantified throughout using
8
9
10 278 the calculation of the I^2 value. An I^2 of greater than or equal to 50% will be used to indicate
11
12 279 substantial heterogeneity and a random-effects model will be used. For all I^2 less than 50%, a
13
14 280 fixed effects model will be used. Outcomes with less than five studies will be analysed using a
15
16 281 fixed effects models(31). For reporting consistency between outcomes, the monotherapy
17
18 282 (cerclage or progesterone respectively) intervention was made the reference set for all analyses,
19
20 283 standardising the direction of effect across all primary and secondary outcomes.
21
22
23
24 284

25 26 285 *Measures of treatment effect*

27
28 286 Dichotomous outcomes will be assessed and reported using risk ratios (RR) while continuous
29
30 287 data will be reported on using mean difference (MD) or standardised mean difference (SMD),
31
32 288 95% confidence intervals (CI) will be used for all data sets. A SMD will be used when studies
33
34 289 report a comparable but not identical measure for the same outcome. To avoid discarding
35
36 290 important data from papers that do not report the mean and SD of continuous data we will
37
38 291 attempt to calculate means and SDs using known parameters. For papers which
39
40 292 reported median and range, the Hozo's approach will be used(32). For papers which
41
42 293 reported median and interquartile range, the Wan's approach will be employed(33). Data
43
44 294 that are too positivity or negatively skewed renders the mean and standard deviated unsuitable
45
46 295 for these approaches, particularly when the standard deviation is large(34). For this reason, data
47
48 296 which are not suitable to be estimated with mean and standard deviation will be excluded as
49
50 297 per the Cochrane Handbook(34). Where meta-analysis is not possible alternative synthesis
51
52 298 methods, including summarising effect estimates and combining p-values, will be used as
53
54 299 recommended by the Cochrane Handbook for Systematic Reviews of Interventions(18).
55
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3 3004
5 301 *Missing data*

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8 302 For studies which presented missing data we will attempt to contact authors. However, if this
9
10 303 is not possible, we will conduct sensitivity analysis which will exclude trials with >30%
11
12 304 missing data (18).

13
14
15 30516
17 306 *Meta-bias(es)*

18
19 307 To determine reporting bias, we will attempt to investigate to see if protocols for included
20
21 308 studies were published prior to those studies being started.

22
23
24 30925
26 310 *Sensitivity analysis*

27
28 311 Sensitivity analysis will be conducted on the primary outcome for birth <37 weeks gestation
29
30 312 for dual interventions (cerclage vs combined and progesterone vs combined). This will be done
31
32 313 by removing studies which are judged to have an overall critical risk of bias, allowing us to
33
34 314 examine their impact on the effect estimate of the primary outcome.

35
36 315 Additional sensitivity analysis will be conducted excluding studies which assessed combined
37
38 316 therapy in a sequential manner. For this sensitivity analysis we will define ‘stepwise’ as
39
40 317 cerclage that is placed >14 days following the failure of progesterone to prevent further
41
42 318 cervical shortening, or as progesterone that is initiated >14 days following the failure of
43
44 319 cerclage wherein the initial intervention has been ineffective in preventing cervical
45
46 320 shortening.

47
48
49 32150
51
52 322 **Discussion**

53
54 323 This systematic review and meta-analysis will determine the differences in effectiveness of
55
56 324 cerclage alone versus combined treatment, as well as the differences in effectiveness between
57
58
59
60

1
2
3 325 progesterone alone versus combined treatment. These results will provide valuable synthesis
4
5 326 of information to specialists in their clinical decisions for women at risk of PTB. It is hoped
6
7 327 that women at high risk of sPTB and its complications benefit from these findings. The results
8
9 328 of this paper could potentially bring updates to clinical management guidelines and reduce the
10
11 329 short and long-term negative health outcomes of preterm birth for women and their children.
12
13
14
15

330

331 **Patient and public involvement**

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

334

335 **Ethics approval and consent to participate**

336 Not applicable.

337

338 **Consent for publication**

339 Not applicable.

340

341 **Availability of data and materials**

342 Not applicable.

343

344 **Competing interests**

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

346 The authors declare they have no other competing interests.

347

348 **Author's contributions**

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60

1
2
3 349 R.D., A.I., K. P. W., L.M., A-M.A., and J.E.M. led the development of this manuscript. C.W.
4
5 350 and J.E.M. provided guidance on the statistical plan, J.P. and C.E.P. provided expertise relating
6
7 351 to obstetric care. All authors read and approved the final manuscript.
8
9

10 352

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12
13
14 354 The authors would like to thank Ms Joanne Davies for her editing and advice.
15
16

17 355

18 356 **List of abbreviations**

19
20
21 357 CI Confidence interval

22
23
24 358 CINAHL Cumulative Index of Nursing and Allied Health Literature.

25
26 359 GRADE Grading of Recommendations, Assessment, Development and Evaluations

27
28 360 MD Mean difference

29
30 361 MeSH Medical subject headings

31
32 362 NICU Neonatal intensive care unit

33
34 363 PTB Preterm birth

35
36 364 P value Probability value

37
38 365 PRISMA-P Preferred Reporting Items or Systematic Reviews and Meta-Analyses Protocol

39
40 366 PROM Premature rupture of membranes

41
42 367 PPRM Preterm premature rupture of membranes

43
44 368 PROSPERO International Prospective Register of Systematic Reviews

45
46 369 RCT Randomised control trial

47
48 370 RDS Respiratory distress syndrome

49
50 371 RevMan Review Manager 5.3

51
52 372 ROBINS I Risk of Bias in Non-Randomised Studies of Interventions

53
54 373 ROBINS II Risk of Bias in Randomised Studies of Interventions
55
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59
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1
2
3 374 RR Risk ratio
4
5 375 SPTB Spontaneous preterm birth
6
7
8 376 SMD Standardised mean difference
9

10 377

11
12 378 **References**

- 13
14
15 379 1.WHO: recommended definitions terminology format for statistical tables related to the
16
17 380 perinatal period use of a new certificate for cause of perinatal deaths. Modifications
18
19 381 recommended by FIGO as amended October 14, 1976.
20
21 382 *Acta Obstetrica et Gynecologica Scandinavica*. 1977;56:247-53.
22
23
24 383 2.Blencowe H, Cousens S, Oestergaard MZ, Chou D, Moller A-B, Narwal R, et al.
25
26 384 National, regional, and worldwide estimates of preterm birth rates in the year 2010 with
27
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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, PICCOs, 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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BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-050086.R1
Article Type:	Protocol
Date Submitted by the Author:	06-May-2021
Complete List of Authors:	<p>Diacci, Rosanna; The University of Newcastle School of Medicine and Public Health Issah, Ashad; The University of Newcastle School of Medicine and Public Health Williams, Kimberley P; The University of Newcastle School of Medicine and Public Health McAuliffe, Liam; The University of Newcastle School of Medicine and Public Health Aubin, Anne-Marie; The University of Newcastle School of Medicine and Public Health McAuliffe, Jack E; Not Applicable Phung, Jason; The University of Newcastle School of Medicine and Public Health; The University of Newcastle Hunter Medical Research Institute, Mothers and Babies Research Centre Wang, Carol; The University of Newcastle School of Medicine and Public Health; The University of Newcastle Hunter Medical Research Institute, Mothers and Babies Research Centre Pennell, Craig; The University of Newcastle School of Medicine and Public Health; The University of Newcastle Hunter Medical Research Institute, Mothers and Babies Research Centre</p>
Primary Subject Heading:	Obstetrics and gynaecology
Secondary Subject Heading:	Surgery
Keywords:	OBSTETRICS, Maternal medicine < OBSTETRICS, Fetal medicine < OBSTETRICS, Prenatal diagnosis < OBSTETRICS

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3 1 **The effectiveness of combined vaginal progesterone and cervical cerclage in preventing**
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5 2 **preterm birth: a systematic review and meta-analysis protocol**
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1
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3 26 Abstract: 255
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10 29 **Abstract**

11
12 30 **Introduction:** Preterm birth (PTB) is the leading cause of death in children under five.
13
14 31 Preventive therapies targeted towards women with risk factors such as a prior PTB or a short
15
16 32 cervix reduce the rate of PTB. Cervical cerclage, vaginal progesterone, and a combination of
17
18 33 the two have been used with no consensus as to whether combined treatment is more
19
20 34 effective than any single treatment alone. The objective of this review is to determine the
21
22 35 efficacy of combined treatment compared to cerclage alone, and combined treatment compared
23
24 36 to progesterone alone. **Methods and analysis:** Studies will be sourced from the electronic
25
26 37 databases Medline (Ovid), EMBASE (Ovid), PsycINFO (Ovid), Scopus, CINAHL
27
28 38 (EBSCOhost) and Cochrane Library (Wiley) and reference lists. We will not exclude any
29
30 39 papers due to publication date. Randomised control trials (RCTs), non-randomised control
31
32 40 trials, and cohort studies assessing single therapy (either progesterone or cerclage) versus
33
34 41 combined therapy in women with a singleton pregnancy will be included. Two independent
35
36 42 reviewers will conduct study screening (at abstract and full text level), data extraction and risk
37
38 43 of bias assessment with disagreements resolved by an experienced researcher. Random or fixed
39
40 44 effects models will be used depending on data heterogeneity and data will be presented as Risk
41
42 45 Ratio (RR) for dichotomous data or Mean Difference (MD) for continuous data with a
43
44 46 Confidence Interval (CI) of 95% used for all outcomes.. **Ethics and dissemination:** not
45
46 47 applicable due to nature of the study type. **Registration:** PROSPERO on 8th of October, 2020
47
48 48 with registration number CRD42020195975 **Key words:** Cervical, Stitch, Cerclage,
49
50 49 Progesterone, Preterm Birth.
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51 **Strengths and limitations:**

- 52 • The systematic review will follow the rigorous methods outlined in this protocol which
- 53 have been written as per Cochrane guidelines.
- 54 • This will be the first systematic review to answer this question.
- 55 • Data will be screened and extracted by two reviewers.
- 56 • Lack of reviewer and moderator blinding at inclusion/exclusion level.
- 57 • Lack of blinding of reviewers and moderators for papers at quality assessment Robins
- 58 1, Rob 2, and GRADE.

60 **Introduction**

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

66
67 The majority of PTB occurs either spontaneously or following preterm premature rupture of
68 membranes (PPROM)(5). It is well established that a cervical length of less than 25mm,
69 measured between 18 and 25 weeks, is a good predictor -of spontaneous PTB (sPTB) with rates
70 of 31.2% to 41.3%(6, 7). Vaginal progesterone(8) and cervical cerclage(6, 9) are effective
71 single treatments for the prevention of sPTB in these women, as well as those with a prior
72 history of PTB.

73
74 Cervical cerclage is a treatment proven to prevent PTB and reduce neonatal morbidity
75 and mortality(10, 11, 12) by mechanically maintaining a long and closed cervix. In contrast,

1
2
3 76 progesterone has an inhibitory action on uterine contractility by inhibiting the production of
4
5 77 stimulatory prostaglandins and expression of contraction associated protein genes in
6
7 78 the myometrium(13, 14). It has been shown to play an important role in maintaining a
8
9 79 pregnancy until term(15).
10
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12
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14 80
15 81 More recently, studies have assessed the combination of the cervical cerclage and vaginal
16
17 82 progesterone to improve PTB prevention (10, 11). To our knowledge, only one systematic
18
19 83 review published in 2013 has addressed progesterone as an adjunctive therapy to
20
21 84 cerclage; however, the included studies were not randomised and assessed synthetic progestin
22
23 85 17-hydroxyprogesterone caproate (17-OHPC), which found no difference in the outcome of
24
25 86 PTB (13). To our knowledge, there has not been any systematic review addressing combined
26
27 87 treatment of progesterone and cerclage versus singular treatment since 2017 (16); with no
28
29 88 review specifically assessing vaginal progesterone in combined treatment. More recently,
30
31 89 adjuvant vaginal progesterone therapy for women who underwent cervical cerclage indicated
32
33 90 by ultrasound(11) or physical(10) examination was found to be associated with decreased rates
34
35 91 of PTB and admission to the neonatal intensive care unit (NICU). Given these recent
36
37 92 promising findings and the lack of guidance on this topic, we sought to determine the effect of
38
39 93 combining both cerclage and progesterone on PTB by conducting a systematic review and
40
41 94 meta-analysis. This paper describes the proposed protocol for this meta-analysis.
42
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49 96 **Aim**

50
51 97 This systematic review has two aims: 1) to compare the use of cerclage alone to cerclage and
52
53 98 vaginal progesterone combined, and 2) to compare progesterone alone to the combined use of
54
55 99 cerclage and vaginal progesterone in order to determine which of these is
56
57 100 associated better maternal and neonatal outcomes in relation to PTB. Our proposed review will
58
59
60

1
2
3 101 answer the questions *in women requiring prophylactic treatment for short cervix is combined*
4
5 102 *treatment favourable to cerclage alone? And in women requiring prophylactic treatment for*
6
7 103 *short cervix is combined treatment favourable to vaginal progesterone alone?*
8
9

10 104

11 105 **Methods**

12 106 ***Registration:***

13
14
15 107 This systematic review protocol was submitted to the International Prospective Register of
16
17 108 Systematic Reviews (PROSPERO) on the 8th of October 2020 and was last updated on this
18
19 109 date (registration number CRD42020195975). This review and meta-analysis will be
20
21 110 completed in accordance using the recommendations of both Preferred Reporting Items for
22
23 111 Systematic Reviews and Meta-Analyses Protocol (PRISMA-P)(17) and the Cochrane
24
25 112 Handbook for Systematic Reviews of Interventions(18).

26
27 113 Information regarding registration can be accessed
28
29 114 from <http://www.crd.york.ac.uk/PROSPERO>.

30 115

31 116 ***Eligibility Criteria:***

32
33 117 The eligibility of studies included will be based on inclusion and exclusion criteria applied to
34
35 118 the domains of participant, exposure, comparator, study type, and outcome.
36
37 119

38 120 ***Participants:***

39
40 121 The review will consider all studies which include women who are undergoing ultrasound or
41
42 122 history indicated cerclage, vaginal progesterone, or both for the prevention of PTB. Only
43
44 123 singleton pregnancies will be assessed.
45
46

47 124

48 125 ***Intervention:***

1
2
3 126 Studies comparing combined cerclage and vaginal progesterone treatment with vaginal
4
5 127 progesterone alone or cerclage alone.
6
7
8 128

9
10 129 Cerclage

11
12 130 There are two commonly performed vaginal cerclage procedures which were first described by
13
14 131 Shirodkar and McDonald. In the McDonald approach a suture is placed around the cervix in
15
16 132 purse-string fashion and securely tied anteriorly. The McDonald approach requires no
17
18 133 dissection into para-cervical tissues (19, 20). The Shirodkar technique involves a
19
20 134 transverse anterior colpotomy, dissection of the bladder up to the internal cervical os and a
21
22 135 posterior colpotomy with dissection of peritoneum upwards to the internal os. The suture is
23
24 136 placed subcutaneously and the knot tied in the posterior defect and buried under the
25
26 137 vaginal epithelium (19, 21, 22) or tied exterior to the epithelium in the modified approach. Both
27
28 138 Shirodkar techniques will be considered.
29
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34
35 140 Vaginal Progesterone

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37 141 Vaginal progesterone is available as a gel, suppository, or pessary (14). It is the most
38
39 142 bioavailable form of progesterone for uterine and cervical effects with the fewest side effects.
40
41 143 Its micronized form decreases particle size and increases surface area resulting in improved
42
43 144 absorption with less metabolic and vascular side effects (23). The vaginal route also allows
44
45 145 rapid absorption and avoids first pass hepatic metabolism, resulting in high bioavailability in
46
47 146 the uterus (24).
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51 147

52
53 148 Combined Treatment

54
55 149 Cervical cerclage (McDonald or Shirodkar technique) used in combination with vaginal
56
57 150 progesterone.
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151

152 *Outcomes:*

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

158

159 *Types of studies:*

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

164

165 *Search strategy:*

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

173

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

1
2
3 176 focus on identifying relevant interventions with no population or outcome related keywords
4
5 177 used. The intervention search terms will be: cervical OR cervix OR rescue; stitch OR cerclage
6
7
8 178 OR suture; progesterone OR progestin OR prometrium OR progest. Medical subject headings
9
10 179 (MeSH) will be used when relevant and present databases.
11

12 180

15 181 ***Data collection and analysis***

17 182 *Study Selection*

19 183 Identified titles and abstracts will be downloaded into Endnote(25) where duplicated studies
20
21 184 will be removed. Remaining papers will then be uploaded to Covidence(26) and then screened
22
23 185 against the eligibility criteria outlined above. Full texts of remaining studies will be sourced
24
25 186 and screened before undergoing critical appraisal and data extraction. All screening will be
26
27 187 performed by two independent reviewers and any disagreements will be addressed by a senior
28
29 188 research moderator. No reviewers or moderators will be blinded to titles, authors, journals, or
30
31 189 institutions.
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33
34

35 190

37 191 *Data management*

39 192 The search will be uploaded to Covidence(26), an Internet-based software which allows
40
41 193 collaboration between multiple reviewers during the study selection process, backup copies of
42
43 194 all studies will also be kept in an Endnote library(25).
44
45
46

47 195

49 196 *Data collection*

51 197 Two reviewers will extract data through Covidence(26) using a standardised electronic form
52
53 198 consistent with data collection items recommended by the Cochrane Handbook for Systematic
54
55 199 Reviews of Interventions(18). This process will be piloted prior to use and any discrepancies
56
57 200 will be moderated by a third senior research moderator. Once extracted, upon reviewer
58
59
60

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

203

204 The following data will be extracted:

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

213

214 **Outcomes and prioritisation:**

215 *Primary outcome*

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

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

220

221 *Secondary outcomes*

222 **Dichotomous**

- 223 1. PPRM
- 224 2. Caesarean section
- 225 3. NICU admission

- 1
- 2
- 3 226 4. Intubation
- 4
- 5 227 5. Neonatal mortality
- 6
- 7
- 8 228 Continuous
- 9
- 10 229 6. Gestational age at delivery
- 11
- 12 230 7. Birthweight
- 13
- 14
- 15 231 8. Number of days between intervention and delivery
- 16
- 17 232
- 18

19 233 *Assessment of risk of bias*

21 234 Each paper will be assessed for risk of bias using the Cochrane Collaboration tool for assessing
22
23 risk of bias (ROBINS I and RoB-2)(28, 29). Each study will be reviewed independently by two
24 235 assessors and disagreements will be resolved through mediation with a third reviewer. High
25
26 236 quality studies are those which achieve a score of seven or eight, average are scored four to six,
27
28 237 and below four will be considered low quality. We will not be excluding any study based on
29
30 238 these scores, however risk of bias will be taken into account when outcomes are assessed in
31
32 239 regard to impact as per the Grade of Recommendation, Assessment, Development and
33
34 240 Evaluations (GRADE)(30).
35
36 241

37
38
39
40 242

41
42 243 The Risk of Bias in Non-Randomised Studies of Interventions (ROBINS-I) tool(28) will be
43
44 244 used to assess the risk of bias in included observational studies. The risk of bias will be rated
45
46 245 as no information, low risk, moderate risk, serious risk, or critical risk across seven domains.
47
48 246 The seven domains of this tool are (1) confounding; (2) selection of participants; (3)
49
50 247 classification of intervention; (4) deviation from interventions; (5) missing outcome data; (6)
51
52 248 measurement of outcomes; and (7) selection of reported results overall.
53
54

55
56 249 Randomised trials will be assessed with the Risk of Bias in Randomised Studies of
57
58 250 Interventions (RoB2)(28). This tool assesses five domains which are (1) the randomisation
59
60

1
2
3 251 process; (2) deviations from intended interventions; (3) missing outcome data; (4)
4
5 252 measurement of the outcome, and (5) selection of the reported results. Studies which score a
6
7
8 253 high risk of bias in one or more domains or which have concerns for several domains will be
9
10 254 judged as at serious risk of bias.

11
12 255

14 256 Cochrane GRADE Assessment

16
17 257 The GRADE tool will be used to assess quality of evidence for the primary outcome(30). The
18
19 258 outcome will be assessed in terms of bias risk, consistency, directness, precision, and
20
21 259 publication bias. The primary outcome's quality will be judged to be (i) high quality - we are
22
23 260 very confident the true effect is close to that of the estimated effect; (ii) moderate - it is possible
24
25 261 that there is a substantial difference but we are moderately confident the true effect is close to
26
27 262 that of the estimated effect; (iii) low - we are limited in our confidence that the estimated effect
28
29 263 and true effect reflect each other; and (iv) very low - we have very little confidence that the
30
31 264 true and estimated effect align, the true effect is likely to be substantially different to our
32
33 265 estimate. GRADE will be conducted by two independent reviewers and discrepancies will be
34
35 266 resolved through discussion, disagreements which cannot be resolved will be mediated by a
36
37 267 third reviewer.

38
39 268 Graphic representations of potential bias within and across the studies will be calculated
40
41 269 using RevMan 5.3 (Review Manager 5.3)(27). All items in the risk of bias assessment will be
42
43 270 considered independently without an attempt to collate and assign an overarching score.
44
45
46
47
48

49 271

51 272 **Data synthesis**

52
53 273 Meta-analysis will be constructed by pooling studies using Covidence(26) and RevMan 5.3
54
55 274 software(27). Forest plots and I^2 values will be used to explore the heterogeneity of
56
57 275 data. Heterogeneity of data will be examined using forest plots and quantified throughout using
58
59
60

1
2
3 276 the calculation of the I^2 value. A Random Effects Model will be used when a data set meets
4
5 277 three of the following four criteria 1) there is an intention to use results beyond the included
6
7 278 studies, 2) number of included studies greater than five, 3) there is statistical heterogeneity
8
9 279 measured as an I^2 greater or equal to 50%, 4) it is reasonable to assume that included studies
10
11 280 estimate a different underlying true effect with normal distribution (31). If a data set does not
12
13 281 meet three or more criteria a Fixed Effects Model will be used. All outcomes for which a
14
15 282 Random Effects Model is used will undergo a second examination using the Hartung-Knapp-
16
17 283 Sidik-Jonkman method for random effects to ensure considerable heterogeneity does not
18
19 284 impact the data. For reporting consistency between outcomes, the monotherapy (cerclage or
20
21 285 progesterone respectively) intervention was made the reference set for all analyses,
22
23 286 standardising the direction of effect across all primary and secondary outcomes.
24
25
26
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30

31 *Measures of treatment effect*

32
33 289 Dichotomous outcomes will be assessed and reported using risk ratios (RR) while continuous
34
35 290 data will be reported on using mean difference (MD) or standardised mean difference (SMD),
36
37 291 95% confidence intervals (CI) will be used for all data sets. A SMD will be used when studies
38
39 292 report a comparable but not identical measure for the same outcome. To avoid discarding
40
41 293 important data from papers that do not report the mean and SD of continuous data we will
42
43 294 attempt to calculate means and SDs using known parameters. For papers which
44
45 295 reported median and range, the Hozo's approach will be used(32). For papers which
46
47 296 reported median and interquartile range, the Wan's approach will be employed(33). Data
48
49 297 that are too positivity or negatively skewed renders the mean and standard deviated unsuitable
50
51 298 for these approaches, particularly when the standard deviation is large(34). For this reason, data
52
53 299 which are not suitable to be estimated with mean and standard deviation will be excluded as
54
55 300 per the Cochrane Handbook(34). Where meta-analysis is not possible alternative synthesis
56
57
58
59
60

1
2
3 301 methods, including summarising effect estimates and combining p-values, will be used as
4
5 302 recommended by the Cochrane Handbook for Systematic Reviews of Interventions(18).
6
7
8 303

9
10 304 *Missing data*

11
12 305 For studies which presented missing data we will attempt to contact authors. However, if this
13
14 306 is not possible, we will conduct sensitivity analysis which will exclude trials with >30%
15
16 307 missing data (18).
17
18
19 308

20
21 309 *Meta-bias(es)*

22
23
24 310 To determine reporting bias, we will attempt to investigate to see if protocols for included
25
26 311 studies were published prior to those studies being started.
27
28 312

29
30 313 *Sensitivity analysis*

31
32 314 Sensitivity analysis will be conducted on the primary outcome for birth <37 weeks gestation
33
34 315 for dual interventions (cerclage vs combined and progesterone vs combined). This will be done
35
36 316 by removing studies which are judged to have an overall critical risk of bias, allowing us to
37
38 317 examine their impact on the effect estimate of the primary outcome.
39
40 318

41
42 319 Additional sensitivity analysis will be conducted excluding studies which assessed combined
43
44 320 therapy in a sequential manner. For this sensitivity analysis we will define 'stepwise' as
45
46 321 cerclage that is placed >14 days following the failure of progesterone to prevent further
47
48 322 cervical shortening, or as progesterone that is initiated >14 days following the failure of
49
50 323 cerclage wherein the initial intervention has been ineffective in preventing cervical
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1
2
3 324 Where individual patient data is available, neonatal outcomes and baseline maternal
4
5 325 characteristics will be extracted from studies and sub-analysis will be conducted if there is
6
7
8 326 found to be vast differences in these baseline characteristics.
9

10 327

11 328 **Discussion**

12
13
14 329 This systematic review and meta-analysis will determine the differences in effectiveness of
15
16 330 cerclage alone versus combined treatment, as well as the differences in effectiveness between
17
18 331 progesterone alone versus combined treatment. These results will provide valuable synthesis
19
20 332 of information to specialists in their clinical decisions for women at risk of PTB. It is hoped
21
22 333 that women at high risk of sPTB and its complications benefit from these findings. The results
23
24 334 of this paper could potentially bring updates to clinical management guidelines and reduce the
25
26 335 short and long-term negative health outcomes of preterm birth for women and their children.
27
28
29

30 336

31 337 **Patient and public involvement**

32
33 338 There was no patient or public involvement in this paper nor will there be in the systematic
34
35 339 review it describes.
36
37
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40 340

41 341 **Ethics approval and consent to participate**

42 342 Not applicable.
43
44
45
46
47 343

48 344 **Consent for publication**

49 345 Not applicable.
50
51
52
53
54 346

55 347 **Availability of data and materials**

56 348 Not applicable.
57
58
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6 350 **Data sharing**

7
8 351 Not applicable.
9

10 352

11
12 353 **Competing interests**

13
14 354 JP is supported by the Hunter New England Health Clinical and Health Research Fellowship.

15
16 355 The authors declare they have no other competing interests.
17
18

19 356

20
21 357 **Author's contributions**

22
23 358 R.D., A.I., K. P. W., L.M., A-M.A., and J.E.M. led the development of this manuscript. C.W.

24
25 359 and J.E.M. provided guidance on the statistical plan, J.P. and C.E.P. provided expertise relating

26
27 360 to obstetric care. All authors read and approved the final manuscript.
28
29

30 361

31
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33
34 363 Not applicable
35
36

37 364

38
39 365 **Acknowledgements**

40
41 366 The authors would like to thank Ms Joanne Davies for her editing and advice.
42
43

44 367

45
46 368 **List of abbreviations**

47
48 369 CI Confidence interval

49
50 370 CINAHL Cumulative Index of Nursing and Allied Health Literature.

51
52 371 GRADE Grading of Recommendations, Assessment, Development and Evaluations

53
54 372 MD Mean difference
55
56

57
58 373 MeSH Medical subject headings
59
60

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3 374 NICU Neonatal intensive care unit
4
5 375 PTB Preterm birth
6
7
8 376 P value Probability value
9
10 377 PRISMA-P Preferred Reporting Items or Systematic Reviews and Meta-Analyses Protocol
11
12 378 PROM Premature rupture of membranes
13
14 379 PPRM Preterm premature rupture of membranes
15
16
17 380 PROSPERO International Prospective Register of Systematic Reviews
18
19 381 RCT Randomised control trial
20
21 382 RDS Respiratory distress syndrome
22
23
24 383 RevMan Review Manager 5.3
25
26 384 ROBINS I Risk of Bias in Non-Randomised Studies of Interventions
27
28 385 ROBINS II Risk of Bias in Randomised Studies of Interventions
29
30
31 386 RR Risk ratio
32
33 387 SPTB Spontaneous preterm birth
34
35 388 SMD Standardised mean difference
36
37
38
39

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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.

For peer review only

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 Lines 204-286 methods of combining data from studies, including any planned exploration of consistency (such as I^2 , Kendall's τ)
	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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