

Interventions for preventing preterm birth in multiple gestations with short cervix – a systematic review and network meta-analysis

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Abstract

Background: Multiple gestation has a higher incidence of preterm birth (PTB), especially in the presence of a short cervix. **Objectives:** To perform a systematic review and network meta-analysis (NMA) evaluating the effect of progesterone, cerclage, cervical pessary and their combination as treatments for preventing PTB < 34 weeks. **Search strategy:** PubMed, MEDLINE, Cochrane Library, EMBASE, Web of Science, BVS, Scopus, and grey literature were explored. **Selection criteria:** We included randomized controlled trials that compared an intervention with a control group or another intervention to prevent PTB in women with a twin pregnancy and a short cervix < 40mm. **Data collection and Analysis:** Studies were checked for trustworthiness. We presented summary relative effect sizes (Odds Ratios) for each possible pair of interventions and we used the surface under the cumulative ranking curves (SUCRA) to rank all interventions. **Main Results:** A total of 20 studies participated in NMA. We found no evidence that the combined treatment of pessary and vaginal progesterone reduced the risk of spontaneous PTB < 34 weeks when compared to no intervention (OR 0.68; 95%CI 0.16 to 2.9). Also, pessary (OR 0.78; 95%CI 0.49 to 1.3), vaginal progesterone (OR 0.79; CI95% 0.45 to 1.4) and injectable 17-OH progesterone alone (OR 0.85; CI95% 0.26 to 2.8) did not show a statistically significant reduction in spontaneous PTB. For overall PTB < 34 weeks, findings were similar. **Conclusions:** We found no evidence that progesterone, cervical pessary, cerclage or their combination reduce PTB < 34 weeks. There is an urgent need for randomized trials assessing these treatments in women with a multiple pregnancy and a short cervix.

Introduction

Preterm birth (PTB) is a worldwide challenge and a major public health problem¹. PTB leads to short and long-term consequences for newborns and families, including cerebral palsy, blindness, and neurodevelopment problems².

In women with multiple gestations, nowadays seen more often due to assisted reproductive treatments and due to a rising maternal age, the prevalence of PTB is increased. In the presence of a mid-gestation short uterine cervix, an independent predictor for prematurity, the rate of spontaneous PTB in twins < 32 weeks increases exponentially as shorter is the cervical length measure^{3,4}. For women with a singleton pregnancy, progesterone is useful to reduce PTB < 34 weeks in women with a previous PTB or mid-trimester short cervix (vaginal progesterone vs no treatment RR 0.78; CI 0.68 to 0.90)⁵. Other preventative interventions include cerclage and cervical pessary with good efficacy. When considering only multiple gestations, interventions such as progesterone, cerclage or cervical pessary are also possible options to decrease PTB.

In fact, the uncertainty of evidence can be related to small sample sizes and different study designs and outcomes. Recently, a network meta-analysis (NMA) looking for effective treatments for preventing PTB in women with multiple gestations did not show a significant effect in reducing the rate of PTB or perinatal morbidity in twins, either when these interventions are applied to an unselected population of twins or in pregnancies with a short cervix⁶. One issue is that this NMA did not assess the integrity of the included studies, which is worrisome as some studies recently have been retracted⁷ it has recently become more clear that . Also, the P5 trial⁸ (n = 71 twins) and PESSAREONE study⁹ (n = 310) have been recently published, which warrants new updates for the evidence.

The aim of this study is to perform a systematic review and NMA evaluating the effectiveness of progesterone, cerclage and cervical pessary and their combination as possible treatments for preventing PTB in multiple gestations according to cervical length. We specifically tried to assess the trustworthiness of the underlying studies.

Materials and Methods

This systematic review and NMA was performed according to the PRISMA statement¹⁰. This review was registered on the PROSPERO database (CRD42020204486). The research question was “Which interventions for preventing preterm birth improve the gestational age at birth in women with twin gestation regarding cervical length?”.

We performed a Systematic Review of randomized clinical trials searching for studies on PubMed, MEDLINE, Cochrane Library, EMBASE, Web of Science, BVS, Scopus, and grey literature in May 2022. The search strategy used a combination of specific terms using Boolean connectors for each database with no exclusion criteria regarding period or language. The basic search strategy was composed by the following: “twin” **OR** “multiple gestation” **OR** “multiple pregnancy” **AND** “progesterone” **OR** “cervical cerclage” **OR** “pessary” **OR** “hydroxyprogesterone”. (Complete search strategy is available in Appendix 1).

We included randomized controlled trials comparing intervention treatment (progesterone, cerclage or pessary) with a control group or another intervention to prevent spontaneous preterm delivery in women with a twin pregnancy and a short cervix. Short cervical length was defined as a cervical length lower than 40mm¹¹.

The primary outcome was spontaneous preterm birth (sPTB) <34 weeks. Secondary outcome was PTB<34 weeks from any cause.

We included studies reporting on natural or 17-alpha hydroxyprogesterone caproate with any administration route (oral, rectal, vaginal and intramuscular), cervical cerclage (McDonald or Shirodkar) and cervical pessary. We also included studies in which women received a combination of these interventions. The comparison group could have received a different treatment strategy, placebo or standard treatment. We excluded studies if they reported on women with preterm labor or previously threatened preterm labor, interventions for preterm premature rupture of membranes and treatment for women with cervical dilatation. No language restrictions were considered. If needed we contacted the authors to obtain additional data not presented in the papers.

Studies’ references were imported to the Endnote web reference manager, and duplicates were excluded. Two authors (TV and ABP) evaluated titles and abstracts from the selected papers. If there were conflicting decisions, a third author (RCP) makes the final decision. Finally, two authors (TV and ABP) independently accessed the full texts of potentially eligible articles, retrieved and reviewed studies for eligibility. A third author evaluated any conflicted decision. All excluded articles after full-text analysis were described according to the reason why they were excluded. The included articles were submitted to a quality assessment using RoB2 tool¹² and we considered risk of bias if the study presented two or more concerns in the components. We assessed integrity using a screening checklist to assess data integrity of Randomized Clinical Trials¹³.

Descriptive statistical analyses were performed using Stata 17.0 and overall confidence in the results of NMA were assessed using the CINeMA tool¹⁴. We performed random-effect NMA to synthesize evidence from the entire network by integrating direct and indirect estimates for each intervention into a single summary

effect, using the statistical package ‘network’ in Stata, version 17.0. League tables with summary relative effect sizes (Odds Ratios) for each possible pair of interventions were presented. We used the surface under the cumulative ranking curves (SUCRA) to rank all interventions. We assessed global inconsistency by using a design-by-treatment interaction model and local inconsistency through the side-splitting approach.

Results

Our search strategy identified 978 studies. We selected 33 papers for assessment of the full paper (Figure S1). We excluded 13 studies: 5 studies without CL measurement¹⁵⁻¹⁹, 2 studies with the wrong population^{20,21}, 2 studies considered duplicate patient population^{22,23}, and 1 study included patients with a previous episode of threatened preterm labor²⁴. For three studies, there was concern about trustworthiness of the data^{25,26,27}. Two studies^{25,26} had not shared data in an individual participant data meta-analysis⁵, of which one study had been retracted by the journal as it was not performed under the appropriate ethics²⁵. A third author did not respond on our request for additional information²⁶ (Table S1). Two studies involving cerclage presented combined results for singleton and twins only and were excluded because the authors could not be contacted to assess only twins data^{28,29}. Thus, we included 20 studies (Table S2).

Study characteristics

A total of 20 studies participated in NMA comprising 4461 women (vaginal progesterone 1081, 17-OH progesterone 530, pessary 828, pessary plus progesterone 43, control group 1979). Twelve studies had progesterone as the main intervention: seven studies compared vaginal progesterone (varied between 90mg, 200mg, 400mg and 600mg) vs control group (placebo or standard treatment).³⁰⁻³⁶ Five studies compared intramuscular progesterone vs control group. The 17-OH progesterone dose varied between 250 to 1000mcg³⁷⁻⁴¹.

Eight studies had cervical pessary as the main intervention: six studies compared pessary vs control group^{9,42-46}, one study compared vaginal progesterone vs pessary⁴⁷ and one study compared the combined intervention pessary + vaginal progesterone vs progesterone⁸. Table 1 shows the descriptive characteristics of the included studies. The full quality assessment result of the included studies using Rob2 is reported in Table S2.

Considering the study’s results including participants with a CL cut-off point (total sample or specific a subgroup), one study included women with CL [?] 15mm³⁰, three studies included CL [?] 25mm^{41,43,44}, one study included CL < 30mm³⁶, two studies included CL [?] 30mm^{8,45}, studies included CL < 35mm^{9,40}, one study included CL [?] 35mm⁴⁶, one study included CL < 38mm⁴⁰ and eight studies included CL < 40mm^{31-35,37-39}.

Table 1 - Main characteristics of studies included in network meta-analysis

Overall analysis

On pairwise comparison, the combined treatment of pessary and vaginal progesterone did not reduce the risk of sPTB < 34 weeks when compared to no intervention (OR 0.68; 95%CI 0.16-2.91). Also, pessary alone (OR 0.78; 95%CI 0.49-1.25), vaginal progesterone alone (OR 0.79; CI95% 0.45-1.41) and injectable 17-OH progesterone alone (OR 0.85; CI95% 0.26-2.75) did not showed reduction in PTB. None of the pairwise comparisons reached statistical significance. (Table 2 & Figure 1) Compared to the control group, pessary + vaginal progesterone ranked first according to the SUCRA values, with pessary, vaginal progesterone and 17-OH progesterone ranked second, third, and fourth respectively (Table S3).

For overall PTB < 34 weeks, the combined treatment pessary + vaginal progesterone did not show a statistically significant reduction in PTB (OR 0.56; 95%CI 0.17-1.82) compared to the control group. Pessary alone (OR 0.76; 95%CI 0.55-1.06) and vaginal progesterone alone (OR 0.88; CI95% 0.63-1.22) also did not show reduction in PTB. Injectable 17-OH progesterone showed a non-statistically significant increase on risk of PTB < 34 (OR 1.42; CI95% 0.92-2.20). Again, none of the pairwise comparisons did reach statistical significance. (Table 2 & Figure 1) Compared to the control group, the rank according to the SUCRA values was pessary + vaginal progesterone, pessary, vaginal progesterone and 17-OH progesterone (Table S3).

Table 2. Comparative treatment effect of intervention to prevent preterm birth in twin gestations compared to control group for spontaneous PTB<34 weeks and overall PTB<34 weeks

Figure 1 - Treatment effect of intervention compared to control to prevent preterm birth in twin gestations compared to control group for spontaneous PTB<34 weeks and overall PTB<34 weeks

Figure 2 - Evidence network diagram of network meta-analysis comparisons for spontaneous PTB<34 weeks and overall PTB<34. The width of each edge is proportional to the number of randomized controlled trials comparing each pair of treatments, and the size of each treatment node is proportional to the number of randomized participants

For overall PTB<34 weeks, the p value for overall network consistency test was 0.489, indicating overall satisfactory consistency. When performing node splitting test, the p values for each comparison ranged between 0.489 and 0.998, suggesting minimal local inconsistency. The network consistency test was not possible for sPTB<34 weeks because there was no closed loop in the network (Figure 2).

Discussion

Main Findings

This network meta-analysis including 20 clinical trials for preventing PTB in multiple gestation identified that considering cervical length, neither progesterone or cervical pessary achieved a statistic significant reduction in spontaneous PTB<34 or any PTB<34 weeks.

Interpretation

Recently, a network meta-analysis developed by D'Antonio et al. to determine the role of progesterone, cerclage and vaginal pessary for decreasing the risk of PTB in an unselected population of twin pregnancies did not find an association between these treatments and a reduction in PTB or adverse maternal and perinatal outcomes⁶. However, differently from D'Antonio et al, in our NMA we identified a non-statistical reduction in PTB<34 when comparing pessary vs control (0.76; CI 0.55-1.06). In our study, a similar trend was also identified when considering only sPTB<34 (0.78; CI 0.49-1.25). It is important to clarify that our NMA included six studies comparing pessary vs control, a considerably large sample size when compared to previous studies and D'Antonio. This result raises the possibility that, with a powerful sample size, a significant decrease in PTB would be possible using a cervical pessary in twins.

Strengths and Limitations

This is the first NMA including a study with the combined intervention pessary + vaginal progesterone and, despite the small subgroup sample size, the interesting reduction results for PTB and sPTB<34 illustrates the lack amid RCT involving combined interventions and highlights the need for new trials adequately powered to strength the results.

In limitations, this NMA includes a large number of studies and different cervical length cutoff points create heterogeneity among included studies. Moreover, we used 40mm as a cervical length cut off point to identify a mid-trimester short uterine cervix, considering previous studies that identified a similar measure for the 25th percentile of uterine cervix in twins³⁹. It allowed us to include a large number of patients in the control group when we had access to previous IPD meta-analysis data. However, it was not possible for all studies, which we also consider a limitation in our research.

In women with multiple gestation and a short cervical length, neither progesterone, cerclage or cervical pessary achieved a statistically significant reduction in sPTB<34 or PTB<34 weeks. More trials are needed to identify whether treatment is effective.

Disclosure of Interests

The authors declare that they have no competing interests. BWM is supported by a NHMRC Investigator grant (GNT1176437). BWM reports consultancy for ObsEva and Merck and travel support from Merck.

Contribution to Authorship

Role in the conception: TVS, RCP, BWM

Planning: BWM and RCP

Carrying out: TVS, ABP, VC, RCP and WL

Analyzing data: WL, RCP and BWM

Writing first draft: TVS, ABP and RCP

Review and writing: BWM, RCP and WL

Details of Ethics Approval

Ethics and dissemination: As this is an overview of randomized clinical trials, no ethical approval is needed. The results of the proposed systematic review will be presented in national and international scientific meetings.

References

1. March of Dimes, PMNCH, Save the Children, WHO. Born Too Soon: The Global Action Report on Preterm Birth. Geneva; 2012.
2. Collins J. Global epidemiology of multiple birth. *Reprod Biomed Online*. 2007;15 Suppl 3:45–52.
3. Goldenberg RL, Iams JD, Miodovnik M, Van Dorsten JP, Thurnau G, Bottoms S, et al. The preterm prediction study: risk factors in twin gestations. National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. *Am J Obstet Gynecol*. 1996 Oct;175(4 Pt 1):1047–53.
4. Souka AP, Heath V, Flint S, Sevastopoulou I, Nicolaides KH. Cervical length at 23 weeks in twins in predicting spontaneous preterm delivery. *Obstet Gynecol*. 1999 Sep;94(3):450-4. doi: 10.1016/s0029-7844(99)00277-x. PMID: 10472876.
5. EPPPIC Group. Evaluating Progestogens for Preventing Preterm birth International Collaborative (EPPPIC): meta-analysis of individual participant data from randomized controlled trials. *Lancet* 2021 Mar;397(10280):1183–94. doi: 10.1016/S0140-6736(21)00217-8. Erratum in: *Lancet*. 2021 Apr 17;397(10283):1446. PMID: 33773630.
6. D’Antonio F, Berghella V, Di Mascio D, Saccone G, Sileo F, Flacco ME, et al. Role of progesterone, cerclage and pessary in preventing preterm birth in twin pregnancies: A systematic review and network meta-analysis. *Eur J Obstet Gynecol Reprod Biol*. 2021 Jun;261:166–77
7. El-Refaie W, Abdelhafez MS, Badawy A. Retraction Note: Vaginal progesterone for prevention of preterm labor in asymptomatic twin pregnancies with sonographic short cervix: a randomized clinical trial of efficacy and safety. *Arch Gynecol Obstet*. 2021 Oct;304(4):1113.
8. Pacagnella RC, Silva TV, Cecatti JG, Passini R Jr, Fanton TF, Borovac-Pinheiro A, et al. Pessary Plus Progesterone to Prevent Preterm Birth in Women With Short Cervixes: A Randomized Controlled Trial. *Obstet Gynecol*. 2022 Jan 1;139(1):41-51. doi: 10.1097/AOG.0000000000004634. PMID: 34856583.
9. Groussolles M, Winer N, Sentilhes L, Biquart F, Massoud M, Vivanti AJ, et al. Arabin pessary to prevent adverse perinatal outcomes in twin pregnancies with a short cervix: a multicenter randomized controlled trial (PESSARONE). *Am J Obstet Gynecol*. 2022 Aug;227(2):271.e1-271.e13. doi: 10.1016/j.ajog.2022.01.038. Epub 2022 Feb 3. PMID: 35123930.
10. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021 Mar 29;372:n71. doi: 10.1136/bmj.n71. PMID: 33782057; PMCID: PMC8005924.

11. Liem S, Schuit E, Hegeman M, Bais J, de Boer K, Bloemenkamp K, et al. Cervical pessaries for prevention of preterm birth in women with a multiple pregnancy (ProTWIN): a multicentre, open-label randomised controlled trial. *Lancet*. 2013 Oct 19;382(9901):1341-9. doi: 10.1016/S0140-6736(13)61408-7. Epub 2013 Aug 5. PMID: 23924878.
12. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019; 366: 14898
13. Ben W. Mol, Shimona Lai, Ayesha Rahim, Wentao Li. A Screening Checklist to Assess Data Integrity and Fabrication in Randomized Clinical Trials. Ninth International Congress on Peer Review and Scientific Publication, September 8-10, 2022.
14. Nikolakopoulou A, Higgins JPT, Papakonstantinou T, Chaimani A, Del Giovane C, Egger M, et al. CINeMA: An approach for assessing confidence in the results of a network meta-analysis. *PLoS Med*. 2020 Apr 3;17(4):e1003082. doi: 10.1371/journal.pmed.1003082. PMID: 32243458; PMCID: PMC7122720.
15. Rouse DJ, Caritis SN, Peaceman AM, Sciscione A, Thom EA, Spong CY, et al. A trial of 17 alpha-hydroxyprogesterone caproate to prevent prematurity in twins. *N Engl J Med*. 2007 Aug 2;357(5):454-61. doi: 10.1056/NEJMoa070641. PMID: 17671253.
16. Awwad J, Usta IM, Ghazeeri G, Yacoub N, Succar J, Hayek S, et al. A randomised controlled double-blind clinical trial of 17-hydroxyprogesterone caproate for the prevention of preterm birth in twin gestation (PRO-GESTWIN): evidence for reduced neonatal morbidity. *BJOG*. 2015 Jan;122(1):71-9. doi: 10.1111/1471-0528.13031. Epub 2014 Aug 27. PMID: 25163819.
17. Crowther CA, Ashwood P, McPhee AJ, Flenady V, Tran T, Dodd JM, et al. Vaginal progesterone pessaries for pregnant women with a previous preterm birth to prevent neonatal respiratory distress syndrome (the PROGRESS Study): A multicentre, randomised, placebo-controlled trial. *PLoS Med*. 2017 Sep 26;14(9):e1002390. doi: 10.1371/journal.pmed.1002390. PMID: 28949973; PMCID: PMC5614421.
18. Aboulghar MM, El-Faissal Y, Kamel A, Mansour R, Serour G, Aboulghar M, et al. The effect of early administration of rectal progesterone in IVF/ICSI twin pregnancies on the preterm birth rate: a randomized trial. *BMC Pregnancy Childbirth*. 2020 Jun 9;20(1):351. doi: 10.1186/s12884-020-03033-4. PMID: 32517660; PMCID: PMC7285559.
19. Norman JE, Mackenzie F, Owen P, Mactier H, Hanretty K, Cooper S, et al. Progesterone for the prevention of preterm birth in twin pregnancy (STOPPIT): a randomised, double-blind, placebo-controlled study and meta-analysis. *Lancet*. 2009 Jun 13;373(9680):2034-40. doi: 10.1016/S0140-6736(09)60947-8. PMID: 19523680.
20. Combs CA, Garite T, Maurel K, Das A, Porto M; Obstetrix Collaborative Research Network. Failure of 17-hydroxyprogesterone to reduce neonatal morbidity or prolong triplet pregnancy: a double-blind, randomized clinical trial. *Am J Obstet Gynecol*. 2010 Sep;203(3):248.e1-9. doi: 10.1016/j.ajog.2010.06.016. Erratum in: *Am J Obstet Gynecol*. 2011 Feb;204(2):166. PMID: 20816146.
21. Hajizadeh N, Saharkhiz N, Hosseini S, Arabzadeh B. Comparison of cerclage and pessary in prevention of preterm birth in twin pregnancies. *Med J Islam Repub Iran*. 2020 Jul 6;34:74. doi: 10.34171/mjiri.34.74. PMID: 33306065; PMCID: PMC7711049.
22. Klein K, Rode L, Nicolaides KH, Krampl-Bettelheim E, Tabor A; PREDICT Group. Vaginal micronized progesterone and risk of preterm delivery in high-risk twin pregnancies: secondary analysis of a placebo-controlled randomized trial and meta-analysis. *Ultrasound Obstet Gynecol*. 2011 Sep;38(3):281-7. doi: 10.1002/uog.9092. PMID: 21739499.
23. Caritis SN, Simhan HN, Zhao Y, Rouse DJ, Peaceman AM, Sciscione A, et al. Relationship between 17-hydroxyprogesterone caproate concentrations and gestational age at delivery in twin gestation. *Am J*

Obstet Gynecol. 2012 Nov;207(5):396.e1-8. doi: 10.1016/j.ajog.2012.08.001. Epub 2012 Aug 6. PMID: 22959763; PMCID: PMC3484214.

24. Merced C, Goya M, Pratorcorona L, Rodó C, Llurba E, Higuera T, et al. Cervical pessary for preventing preterm birth in twin pregnancies with maternal short cervix after an episode of threatened preterm labor: randomised controlled trial. *Am J Obstet Gynecol*. 2019 Jul;221(1):55.e1-55.e14. doi: 10.1016/j.ajog.2019.02.035. Epub 2019 Feb 28. Erratum in: *Am J Obstet Gynecol*. 2021 May;224(5):532. PMID: 30826339.

25. El-Refaie W, Abdelhafez MS, Badawy A. Vaginal progesterone for prevention of preterm labor in asymptomatic twin pregnancies with sonographic short cervix: a randomized clinical trial of efficacy and safety. *Arch Gynecol Obstet*. 2016 Jan;293(1):61-67. doi: 10.1007/s00404-015-3767-1. Epub 2015 Jun 5. Retraction in: *Arch Gynecol Obstet*. 2021 Oct;304(4):1113. PMID: 26044148.

26. Cetingoz E, Cam C, Sakalli M, Karateke A, Celik C, Sancak A. Progesterone effects on preterm birth in high-risk pregnancies: a randomized placebo-controlled trial. *Arch Gynecol Obstet*. 2011 Mar;283(3):423-9. doi: 10.1007/s00404-009-1351-2. Epub 2010 Jan 22. PMID: 20091317.

27. Abdel Wahab AS, Abdelmonaem MI, Mahmoud WM, Mansour AE. A randomized controlled trial of two-doses of vaginal progesterone 400 vs. 200 mg for prevention of preterm labor in twin gestations. *J Perinat Med*. 2021 Sep 14. doi: 10.1515/jpm-2021-0131. Epub ahead of print. PMID: 34523303.

28. Rust OA, Atlas RO, Jones KJ, Benham BN, Balducci J. A randomized trial of cerclage versus no cerclage among patients with ultrasonographically detected second-trimester preterm dilatation of the internal os. *Am J Obstet Gynecol*. 2000 Oct;183(4):830-5. doi: 10.1067/mob.2000.109040. PMID: 11035321.

29. Berghella V, Odibo AO, Tolosa JE. Cerclage for prevention of preterm birth in women with a short cervix found on transvaginal ultrasound examination: a randomized trial. *Am J Obstet Gynecol*. 2004 Oct;191(4):1311-7. doi: 10.1016/j.ajog.2004.06.054. PMID: 15507959.

30. Fonseca EB, Celik E, Parra M, Singh M, Nicolaides KH; Fetal Medicine Foundation Second Trimester Screening Group. Progesterone and the risk of preterm birth among women with a short cervix. *N Engl J Med*. 2007 Aug 2;357(5):462-9. doi: 10.1056/NEJMoa067815. PMID: 17671254.

31. Rode L, Klein K, Nicolaides KH, Krampl-Bettelheim E, Tabor A; PREDICT Group. Prevention of preterm delivery in twin gestations (PREDICT): a multicenter, randomized, placebo-controlled trial on the effect of vaginal micronized progesterone. *Ultrasound Obstet Gynecol*. 2011 Sep;38(3):272-80. doi: 10.1002/uog.9093. PMID: 21739497.

32. Aboulghar MM, Aboulghar MA, Amin YM, Al-Inany HG, Mansour RT, Serour GI. The use of vaginal natural progesterone for prevention of preterm birth in IVF/ICSI pregnancies. *Reprod Biomed Online*. 2012 Aug;25(2):133-8. doi: 10.1016/j.rbmo.2012.03.013. Epub 2012 Apr 3. PMID: 22695310.

33. Wood S, Ross S, Tang S, Miller L, Sauve R, Brant R. Vaginal progesterone to prevent preterm birth in multiple pregnancy: a randomized controlled trial. *J Perinat Med*. 2012 Nov;40(6):593-9. doi: 10.1515/jpm-2012-0057. PMID: 23093256.

34. Serra V, Perales A, Meseguer J, Parrilla JJ, Lara C, Bellver J, et al. Increased doses of vaginal progesterone for the prevention of preterm birth in twin pregnancies: a randomised controlled double-blind multicentre trial. *BJOG*. 2013 Jan;120(1):50-7. doi: 10.1111/j.1471-0528.2012.03448.x. Epub 2012 Aug 13. PMID: 22882759.

35. Brizot ML, Hernandez W, Liao AW, Bittar RE, Francisco RPV, Krebs VLJ, et al. Vaginal progesterone for the prevention of preterm birth in twin gestations: a randomized placebo-controlled double-blind study. *Am J Obstet Gynecol*. 2015 Jul;213(1):82.e1-82.e9. doi: 10.1016/j.ajog.2015.02.021. Epub 2015 Feb 27. PMID: 25731690.

36. Rehal A, Benkő Z, De Paco Matallana C, Syngelaki A, Janga D, Cicero S, et al. Early vaginal progesterone versus placebo in twin pregnancies for the prevention of spontaneous preterm birth: a randomized, double-blind trial. *Am J Obstet Gynecol.* 2021 Jan;224(1):86.e1-86.e19. doi: 10.1016/j.ajog.2020.06.050. Epub 2020 Jun 26. PMID: 32598909.
37. Briery CM, Veillon EW, Klauser CK, Martin RW, Magann EF, Chauhan SP, et al. Women with preterm premature rupture of the membranes do not benefit from weekly progesterone. *Am J Obstet Gynecol.* 2011 Jan;204(1):54.e1-5. doi: 10.1016/j.ajog.2010.08.022. PMID: 20869038.
38. Durnwald CP, Momirova V, Rouse DJ, Caritis SN, Peaceman AM, Sciscione A. Se, et al. Second trimester cervical length and risk of preterm birth in women with twin gestations treated with 17- α hydroxyprogesterone caproate. *J Matern Fetal Neonatal Med.* 2010 Dec;23(12):1360-4. doi: 10.3109/14767051003702786. Epub 2010 May 4. PMID: 20441408; PMCID: PMC2999406.
39. Combs CA, Garite T, Maurel K, Das A, Porto M; Obstetrix Collaborative Research Network. 17-hydroxyprogesterone caproate for twin pregnancy: a double-blind, randomized clinical trial. *Am J Obstet Gynecol.* 2011 Mar;204(3):221.e1-8. doi: 10.1016/j.ajog.2010.12.042. PMID: 21376161.
40. Lim AC, Schuit E, Bloemenkamp K, Bernardus RE, Duvekot JJ, Erwich JJHM, et al. 17 α -hydroxyprogesterone caproate for the prevention of adverse neonatal outcome in multiple pregnancies: a randomized controlled trial. *Obstet Gynecol.* 2011 Sep;118(3):513-520. doi: 10.1097/AOG.0b013e31822ad6aa. PMID: 21860279.
41. Senat MV, Porcher R, Winer N, Vayssière C, Deruelle P, Capelle M, et al. Prevention of preterm delivery by 17 alpha-hydroxyprogesterone caproate in asymptomatic twin pregnancies with a short cervix: a randomized controlled trial. *Am J Obstet Gynecol.* 2013 Mar;208(3):194.e1-8. doi: 10.1016/j.ajog.2013.01.032. PMID: 23433324.
42. Liem S, Schuit E, Hegeman M, Bais J, de Boer K, Bloemenkamp K, et al. Cervical pessaries for prevention of preterm birth in women with a multiple pregnancy (ProTWIN): a multicentre, open-label randomised controlled trial. *Lancet.* 2013 Oct 19;382(9901):1341-9. doi: 10.1016/S0140-6736(13)61408-7. Epub 2013 Aug 5. PMID: 23924878.
43. Nicolaides KH, Syngelaki A, Poon LC, de Paco Matallana C, Plasencia W, Molina FS, et al. Cervical pessary placement for prevention of preterm birth in unselected twin pregnancies: a randomized controlled trial. *Am J Obstet Gynecol.* 2016 Jan;214(1):3.e1-9. doi: 10.1016/j.ajog.2015.08.051. Epub 2015 Aug 28. PMID: 26321037.
44. Goya M, de la Calle M, Pratcorona L, Merced C, Rodó C, Muñoz B, et al; PECEP-Twins Trial Group. Cervical pessary to prevent preterm birth in women with twin gestation and sonographic short cervix: a multicenter randomized controlled trial (PECEP-Twins). *Am J Obstet Gynecol.* 2016 Feb;214(2):145-152. doi: 10.1016/j.ajog.2015.11.012. Epub 2015 Nov 25. PMID: 26627728.
45. Berghella V, Dugoff L, Ludmir J. Prevention of preterm birth with pessary in twins (PoPPT): a randomized controlled trial. *Ultrasound Obstet Gynecol.* 2017 May;49(5):567-572. doi: 10.1002/uog.17430. PMID: 28170117.
46. Norman JE, Norrie J, MacLennan G, Cooper D, Whyte S, Chowdhry S, et al. Evaluation of the Arabin cervical pessary for prevention of preterm birth in women with a twin pregnancy and short cervix (STOPPIT-2): An open-label randomised trial and updated meta-analysis. *PLoS Med.* 2021 Mar 29;18(3):e1003506. doi: 10.1371/journal.pmed.1003506. PMID: 33780463; PMCID: PMC8041194.
47. Dang VQ, Nguyen LK, Pham TD, He YTN, Vu KN, Phan MTN, et al. Pessary Compared With Vaginal Progesterone for the Prevention of Preterm Birth in Women With Twin Pregnancies and Cervical Length Less Than 38 mm: A Randomized Controlled Trial. *Obstet Gynecol.* 2019 Mar;133(3):459-467. doi: 10.1097/AOG.0000000000003136. PMID: 30741812.

Table/Figure Caption List

Figure 1 - Treatment effect of intervention compared to control to prevent preterm birth in twin gestations compared to control group for spontaneous PTB<34 weeks and overall PTB<34 weeks

Figure 2 - Evidence network diagram of network meta-analysis comparisons for spontaneous PTB<34 weeks and overall PTB<34. The width of each edge is proportional to the number of randomized controlled trials comparing each pair of treatments, and the size of each treatment node is proportional to the number of randomized participants

Table 1 - Main characteristics of studies included in network meta-analysis

Table 2. Comparative treatment effect of intervention to prevent preterm birth in twin gestations compared to control group for spontaneous PTB<34 weeks and overall PTB<34 weeks

Table S1 – Excluded articles classified according to exclusion reasons

Table S2- Risk assessment of included studies using Rob2 tool

Table S3 - Effectiveness of progesterone (vaginal and injectable 17-OHPC), pessary and pessary plus progesterone compared with control in women with a twin pregnancy at spontaneous and overall risk of preterm birth in women with cervical length under 40 mm

Table 1 - Main characteristics of studies included in network meta-analysis

Study/year	Country	Cervical length cutoff	GA at intervention	Design intervention x comparison	Primary outcome	Total sample (n=4461)	Intervention sample size	Comparison sample size	Cr Ap pr (R
Liem 2013 ⁴²	The Netherlands	<38mm*	16-22	Pes X NoI	Composite neonatal adverse outcomes	133	78	55	Lo ris
Nicolaides 2016 ⁴³	United Kingdom	[?]25mm*	20-24	Pes X NoI	sPTB<34	214	106	108	Lo ris
Goya 2016 ⁴⁴	Spain	[?]25mm	18-22	Pes X NoI	sPTB<34	134	68	66	Lo ris
Berghella 2017 ⁴⁵	United States	[?]30mm	18-27	Pes X NoI	PTB<34	46	23	23	Lo ris
Dang 2019 ⁴⁷	Vietnam	<38mm	16-22	Pes X	PTB<34	297	149	148	Lo ris
P5 trial 2021 ⁸	Brazil	[?]30mm	18-22	Prog _v PP X Prog _{v200}	Composite neonatal adverse outcomes	71	43	28	Lo ris
STOPPIT-2 2021 ⁴⁶	Belgium, United Kingdom	[?]35mm	18-20	Pes X NoI	PTB<34	503	250	253	Lo ris

Study/year	Country	Cervical length cutoff	GA at intervention	Design intervention x comparison	Primary outcome	Total sample (n=4461)	Intervention sample size	Comparison sample size	Cr pr (R)
PESSARONE 2022 ⁹	France	<35mm	16-24	Pes X NoI	Composite neonatal adverse outcomes	310	155	155	Ris
Fonseca 2007 ³⁰	United Kingdom	[?]15mm	20-25	Prog _v 200 X NoI	sPTB<34	24	11	13	Lo ris
Briery 2009 ³⁷	United States	<40mm	20-30	Prog _{IM} 250 X NoI	PTB<35	30	16	14	Lo ris
SSTARS 2010 ³⁸	United States	<40mm	16-20w3d	Prog _{IM} 250 X NoI	PTB or fetal death <35	565	235	330	Lo ris
PREDICT 2011 ³¹	Austria/Denmark/United Kingdom	<40mm	18-24	Prog _v 200 X NoI	PTB<34	675	334	341	Lo ris
Combs 2011 ³⁹	United States	<40mm	15-23	Prog _{IM} 250 X NoI	Composite neonatal adverse outcomes	238	160	78	Lo ris
AMPHIA 2011 ⁴⁰	The Netherlands	<35mm*	16-20	Prog _{IM} 250 X NoI	Composite neonatal adverse outcomes	61	37	24	Lo ris
Aboulghar 2012 ³²	Egypt	<40mm	18-24	Prog _v 400 X NoI	PTB<37 and <34	91	49	42	Ris
Wood 2012 ³³	Canada	<40mm	16-21	Prog _v 90g X NoI	GA at birth	84	42	42	Lo ris
Serra 2012 ³⁴	Spain	<40mm	20w	Prog _v 200/400 X NoI	PTB<37	289	194	95	Lo ris
PHENIX 2013 ⁴¹	France	<25mm	20-31w6d	Prog _{IM} 1000C	Time from randomization to delivery	161	82	79	Lo ris

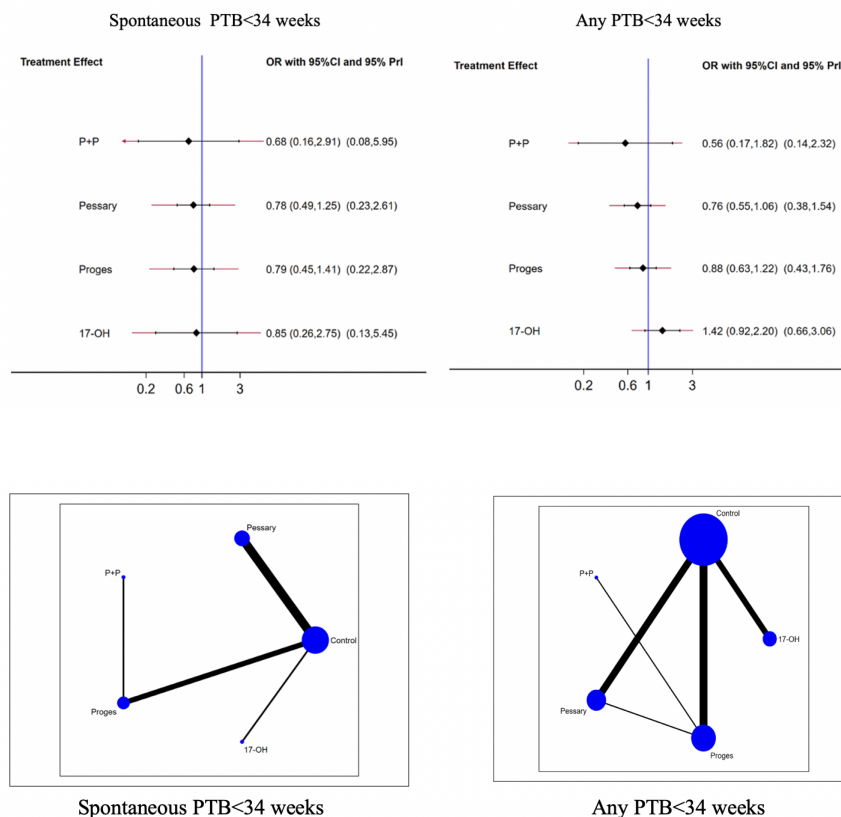
Study/year	Country	Cervical length cutoff	GA at intervention	Design intervention x comparison	Primary outcome	Total sample (n=4461)	Intervention sample size	Comparison sample size	Cr pr (R
Brizot 2015 ³⁵	Brazil	<40mm	18-21	Prog _v 200NoI	Difference in mean GA at birth	380	189	191	Lo ris
Rehal 2021 ³⁶	Belgium/ Bul- garia/ France/ Italy/ Spain/ United Kingdom	<30mm*	11-14	Prog _v 600NoI	sPTB<34	155	85	70	Lo ris

*Subgroup results considering cervical length cutoff point

Prog_v=vaginal progesterone 90mg/200mg/400mg; Pes=pessary; NoI=control (placebo/no intervention); PP= Pessary+Progesterone, C=cerclage; Prog_{IM}=17-OH; GA = gestational age

Table 2. Comparative treatment effect of intervention to prevent preterm birth in twin gestations compared to control group for spontaneous PTB<34 weeks and overall PTB<34 weeks

	sPTB<34 weeks	sPTB<34 weeks	sPTB<34 weeks	PTB<34 w
Comparison	No. of studies with direct comparison	NMA OR (95% CI)	Confidence in result	No. of stud
Progesterone vs. control	3 ^{29, 33,34}	0.79 (0.45,1.41)	Very low	7 ²⁸⁻³⁴
Pessary vs. control	5 ^{8,41-44}	0.78 (0.49,1.25)	Low	6 ^{8,40-44}
P+P vs. control	—	0.68 (0.16,2.91)	Very low	—
17-OH vs. control	1 ³⁷	0.85 (0.26,2.75)	Low	5 ³⁵⁻³⁹
Progesterone vs. pessary	—	1.01 (0.48,2.12)	Low	1 ⁴⁵
Progesterone vs. P+P	1 ⁷	1.16 (0.31,4.40)	Very low	1 ⁷
Progesterone vs. 17-OH	—	0.93 (0.25,3.44)	Low	—
Pessary vs. P+P	—	1.15 (0.25,5.25)	Very low	—
Pessary vs. 17-OH	—	0.92 (0.26,3.25)	Low	—
P+P vs. 17-OH	—	0.80 (0.12,5.17)	Very low	—



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Supporting informationBJOG.docx available at <https://authorea.com/users/437751/articles/617191-interventions-for-preventing-preterm-birth-in-multiple-gestations-with-short-cervix-a-systematic-review-and-network-meta-analysis>