BMJ Open

Risk of Recurrent Spontaneous Preterm Birth: A Systematic Review and Meta-Analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-015402
Article Type:	Research
Date Submitted by the Author:	01-Dec-2016
Complete List of Authors:	Phillips, Courtney; University of Calgary Velji, Zain; University of Calgary Hanly, Ciara; University of British Columbia Metcalfe, Amy; University of Calgary, Obstetrics and Gynecology
Primary Subject Heading:	Obstetrics and gynaecology
Secondary Subject Heading:	Obstetrics and gynaecology, Epidemiology, Evidence based practice, Paediatrics
Keywords:	EPIDEMIOLOGY, NEONATOLOGY, OBSTETRICS, PAEDIATRICS

Risk of Recurrent Spontaneous Preterm Birth: A Systematic Review and Meta-Analysis

Ms. Courtney PHILLIPS[1] BSc, Ms. Zain VELJI[2] BSc, Ms. Ciara HANLY[3], Dr. Amy METCALFE[4,5] PhD

[1]Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada
[2]Faculty of Nursing, University of Calgary, Calgary, Alberta, Canada
[3]School of Kinesiology, University of British Columbia, Vancouver, British Columbia, Canada
[4]Department of Obstetrics and Gynecology, University of Calgary, Calgary, Alberta, Canada
[5]Department of Community Health Sciences, University of Calgary, Calgary, Alberta, Canada

Address for Correspondence:
Amy Metcalfe
Foothills Medical Centre, 4th Floor North Tower
1403 29 St NW
Calgary, Alberta, Canada
T2N 2T9
Email: amy.metcalfe@albertahealthservices.ca
Phone: 403-944-8458

Short Title: Risk of Recurrent Spontaneous Preterm Birth

Condensation: The risk of recurrent spontaneous preterm birth is high, and tends to reoccur more frequently following preterm labor than preterm premature rupture of membranes.

Conflict of Interest: The authors have no conflicts of interest to report

Contributorship Statement: All authors made a substantial contribution to this study. CP, ZV and CH conducted the systematic review. CP drafted the manuscript. AM designed the study and conducted the meta-analysis. All authors critically reviewed the manuscript, interpreted the findings, and approved the final version. All authors had full access to all of the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. As the senior author AM affirms that the manuscript is an honest, accurate, and transparent account of the study being reported, that no important aspects of the study have been omitted, and that any discrepancies from the study as planned have been explained.

Data Sharing Agreement: No additional data is available

inclusion of electronic links from the Contribution to third party material where-ever it may be located; and, vi) licence any third party to do any or all of the above.

Funding: This study was funded by the Alberta Children's Hospital Research Institute. Amy Metcalfe is supported by a New Investigator Award from the Canadian Institutes of Health Research. The funder had no role in study design, execution, or publication decisions.

Word Count (Abstract): 236
Word Count (Manuscript): 1959
Number of References: 51
Number of Tables: 0
Number of Figures: 3
Number of Appendices: 3

Abstract

Objective: To determine the risk of recurrent spontaneous preterm birth following spontaneous preterm birth in singleton pregnancies.

Design: Systematic review and meta-analysis using random effects models.

Data Sources: An electronic literature search was conducted in OVID Medline (1948-2016), Embase (1980-2016), and ClinicalTrials.gov (completed studies effective 2016), supplemented by hand-searching bibliographies of included studies, to find all studies with original data concerning recurrent spontaneous preterm birth.

Study Eligibility Criteria: Studies had to include women with at least one spontaneous preterm singleton live birth (<37 weeks) and at least one subsequent pregnancy resulting in a singleton live birth. The Newcastle-Ottawa Scale and Jadad Scale were used to assess the study quality of cohort studies and randomized controlled trials respectively.

Results: Overall, 31 articles involving 55,016 women, met all inclusion criteria. Generally studies were well conducted and had a low risk of bias. The absolute risk of recurrent spontaneous preterm birth at <37 weeks gestation was 30.0% (95% CI: 27.0-34.0%). The risk of recurrence due to preterm premature rupture of membranes (PPROPM) at <37 weeks gestation was 7.0% (95% CI: 6.0-9.0%), while the risk of recurrence due to preterm labor at <37 weeks gestation was 23.0% (95% CI: 13.0-33.0%).

Conclusions: The risk of recurrent spontaneous preterm birth is high and is influenced by the underlying clinical pathway leading to the birth. This information is important for clinicians when discussing the recurrence risk of spontaneous preterm birth with their patients.

Key Words: preterm birth, preterm labor, preterm premature rupture of membranes, recurrence, systematic review

Article Summary – Strengths and Limitations of This Study:

- Spontaneous preterm birth has a tendency to reoccur in subsequent pregnancies; however, wide variation in the rate of recurrence has been reported in observational studies. Our study suggests that the rate of recurrence of spontaneous preterm birth is approximately 30%, and that the underlying etiology of the index spontaneous preterm birth (i.e. preterm labor or preterm premature rupture of membranes) influences the recurrence risk
- Study strengths include the comprehensive search strategy with no language restrictions used in the nature of the systematic review.
- Limitations primarily relate to the underlying data that was available on this top. Most of the included studies were observational in nature. Additionally, many primary studies examining the recurrence risk of preterm birth had to be excluded as they did not clearly differentiate between spontaneous and indicated preterm delivery.

Introduction

Preterm birth (PTB) is defined as any live birth occurring before 37 completed weeks of gestation; this can be subdivided into extremely preterm (<28 weeks), very preterm (28-<32 weeks), moderately preterm (32-<34 weeks) and late preterm (34-<37 weeks) birth based on the gestational age at delivery (1). This sub-categorization is important as gestational age is inversely associated with increased mortality, morbidity and the intensity of neonatal care required at birth (2). Worldwide, 11.1% of infants are born preterm every year (2). Preterm birth is the leading cause of perinatal morbidity and mortality, and second most common cause of death, after pneumonia, in children under five years of age (3, 4).

Indicated preterm births (iPTB) are those induced for medical reasons, such a pre-eclampsia, intrauterine growth restriction or fetal distress. However, approximately 70% of PTB occur spontaneously (sPTB) (5). The clinical pathways that lead to sPTB include both preterm labor (PTL) and preterm premature rupture of membranes (PPROM). PTL is defined as regular contractions and cervical changes at less than 37 weeks gestation, and PPROM is defined as spontaneous rupture of membranes at least one hour before contractions at less than 37 weeks gestation (5). Known risk factors for spontaneous preterm birth include a previous preterm birth, black race, low maternal body-mass index, comorbidities, a short cervical length and a raised fetal fibronectin concentration (5, 6). Despite knowing these risk factors, our understanding of the etiology behind sPTB is poor and sPTB is considered to be multifactorial in nature (6, 7).

Although sPTB has a tendency to recur, little is known about the recurrence risk (7). This is of concern because sPTB is a leading cause of neonatal morbidity and mortality, and it also has a large economic burden (8). Further, women who have had a previous sPTB are likely to be anxious during their subsequent pregnancies, which itself can lead to sPTB and other adverse pregnancy outcomes (9-11). Therefore, we conducted a systematic review and meta-analysis to

investigate the absolute risk of recurrent sPTB following sPTB in singleton pregnancies. By better understanding the recurrence risk of sPTB, healthcare workers may be better equipped to manage patient needs and anxieties, as well as develop and apply preventative treatments.

Methods

Two study authors (ZV and CH) executed a comprehensive literature search of Medline (from 1946 to 2015) and Embase (from 1980 to 2015) to identify publications that contained key terms related to recurrent sPTB in June 2015. The search was updated in July 2016, and expanded to included completed studies identified through ClinicalTrials.gov. PPROM, PTL and related terms were included in the search. For the full search strategy, please refer to Appendix A. Titles and abstracts of these articles were screened for relevance to determine which articles were to undergo full-text review. Two independent reviewers (ZV and CP) assessed the final eligibility of the full-text reviewed articles. We resolved disagreements in full-text eligibility or data abstraction by involvement of a third party (AM). The bibliographies of included studies were reviewed to identify additional publications not found through the database search. A complete summary of the search strategy can be found in Figure 1. No patients were directly involved in this study. As this study only used published data, it was exempt from Institutional Review Board approval.

All studies with original data concerning recurrent sPTB and N≥20 were considered for inclusion. No language restrictions were used. Conference abstracts were not considered. To be included, studies had to include women with at least one spontaneous preterm live birth (delivery <37 weeks of gestation) in their obstetric history and at least one subsequent pregnancy resulting in a live birth. Only studies looking at singleton pregnancies were included. Animal studies,

studies that only included iPTB, studies that combined iPTB and sPTB, and studies on PPROM or PTL where it was not clear if it resulted in sPTB were excluded.

The data extraction was completed independently by ZV and CP using a standardized data extraction form. Data was reviewed by AM prior to analysis to ensure completeness. Information on the authors, title, publication year, data year, location of study, study design, definitions of preterm birth, and inclusion and exclusion criteria were all extracted. In addition, information was extracted on the number of women with spontaneous preterm birth in their initial pregnancy, whether due to PPROM or PTL, number of women with term births in subsequent pregnancies, and number of women with preterm births in subsequent pregnancies, whether due to PPROM, PTL or indicated causes. For studies that reported on total reproductive history, only data on the first 2 consecutive pregnancies were extracted. The Newcastle-Ottawa Scale (12) and the Jadad Scale (13) were used to assess study quality of cohort studies and randomized controlled trials respectively.

The primary outcome measured was the recurrence rate of sPTB at <37 weeks gestation. Secondary outcomes were recurrence rate of sPTB due to PPROM at <37 weeks (following sPTB due to PPROM in the index pregnancy), recurrence rate of sPTB due to PTL at <37 weeks (following sPTB due to PTL in the index pregnancy), the recurrence of sPTB by gestational age, and occurrence of iPTB at <37 weeks after a previous sPTB.

For our analysis, we reported the pooled risk of recurrent preterm birth and accompanying 95% confidence interval (CIs) for sPTB <37 weeks gestation, by iPTB, by gestational age overall, and for PPROM and PTL. An a priori decision was made to use a random-effects model for all models in anticipation of clinical heterogeneity between studies. Forest plots were used to graphically represent the data. Heterogeneity between studies was

assessed using I^2, the Cochrane Q statistic, and accompanying p-values. All analysis was conducted using Stata SE Version 14 (College Station, Texas).

Results

The search returned 11,079 articles, of which 104 met criteria for full-text review (Figure 1). Overall 31 articles met all of the inclusion criteria and were included in the review (14-44). A summary of all of the studies' data can be found in Appendix B. The included studies were almost entirely cohort studies, with only five randomized controlled trials (22, 26, 28, 35, 40). The sample sizes in the studies ranged from 33 to 17,334 women and the rate of recurrent sPTB at <37 weeks gestation ranged from 15.4% to 85.5%. Many of the studies had different definitions of sPTB and therefore they could not be combined for meta-analysis. The majority of the studies were of high quality (Appendix C), although cohort studies typically traded off between being generalizable to the broader patient population not seen in a tertiary center or having detailed clinical data available.

The overall risk of recurrent sPTB at <37 weeks gestation (n=24 studies, 51,889 women) was 30.0% (95% CI: 27.0-34.0%) with a significant Q (P=0.00) and I^2 of 98.7%, indicating between-study heterogeneity (Figure 2). The risk of iPTB at <37 weeks gestation after a previous spontaneous preterm birth (n=6 studies, 18,355 women) was 5.0% (95% CI: 3.0-7.0%) with an I^2 of 98.0%.

Few studies looked specifically at the recurrence of PPROM and PTL resulting in sPTB in singleton pregnancies following prior PPROM or PTL respectively. However, the identified risk of recurrent PPROM at <37 weeks gestation (n=4 studies, 3,138 women) was 7.0% (95% CI: 6.0-9.0%) with an I^2 of 51.0% and the risk of recurrent PTL at <37 weeks gestation (n=3 studies, 2,852 women) was 23.0% (95% CI: 13.0-33.0%) with an I^2 of 97.3% (Figure 3).

Discussion

This meta-analysis provides an overview of the overall risk of recurrent spontaneous preterm birth. We found that the absolute risk of recurrent sPTB at less than 37 weeks gestation in pregnancies was 30%. Interestingly, the risk of recurrent PTL was found to be 23%, similar to the overall risk of recurrent sPTB. Conversely, if a woman has a sPTB due to PPROM, she is less likely to have recurrent PPROM leading to sPTB, with a risk of only 7%. Thus the clinical pathway that leads to sPTB appears to influence the risk of recurrence.

In a 2014 systematic review by Kazemier et al., they found that the risk of recurrence of preterm birth is influenced by the singleton/twin order in both pregnancies. When they looked at spontaneous preterm singleton births after a previous singleton pregnancy, they found that the risk of recurrence of sPTB was 20.2% (45). In contrast to ours, their search strategy was exceedingly complex and included only cohort studies. Ultimately after abstract review they were left with only six studies that looked at singleton-singleton pregnancies, which could explain the difference in our recurrence risk. Further, our study is novel as we differentiated risk by clinical pathway leading to sPTB, whether PTL or PPROM. Ultimately, we found that while all sPTB tends to recur, the clinical pathway of the first sPTB is important in determining that recurrence risk. Previous studies tend to combine these underlying pathways together, but our results suggest that perhaps they should not be pooled. Some studies also suggest that children born following PPROM have increased mortality (46-48) and worse health outcomes (49) compared to children born after PTL, which further supports the premise that these should be looked at as separate clinical conditions.

However, new evidence suggests that PTB and the underlying pathologies that lead to PTB are not mutually exclusive, thus spontaneous and indicated PTB should perhaps not be

considered completely separate phenomena. Basso and Wilcox estimated that mortality due to immaturity itself was about 51%, whereas underlying pathologies that led to PTB accounted for approximately half of mortality (50). Similarly, in a recent study by Brown et al., the authors found that gestational age is on the causal path between biological determinants of preterm birth and neonatal outcomes (51). Infants who were exposed to both pathological intrauterine conditions and early delivery had increased risk for poor neonatal outcomes. As such a pathological intrauterine environment, for instance, one characterized by infection, placental ischemia and other biological determinants, acts through early delivery to produce poor outcomes. Ananth et al. found that women with a sPTB were not only likely to experience recurrent sPTB, but they were also associated with increased medically indicated PTB, and vice versa (7). Prevention of preterm mortality requires more than the resolution of PTB, but must also address the underlying etiologies.

Strengths of our systematic review and meta-analysis include our broad search strategy with no language restrictions, which resulted in a large sample size of pooled data. Limitations include the fact that most of the studies were observational cohort studies and thus prone to bias, and there was significant between-study heterogeneity. While both small and large studies were identified and included, publication bias cannot be entirely ruled out. Although we were able to identify a large number of studies, many of them used different definitions for preterm birth and most did not identify the clinical pathway to PTB; as a consequence, these data could not be pooled and not all of the existing evidence could be summarized in this review.

In conclusion, our study reaffirmed that a previous spontaneous preterm birth is a significant risk factor for recurrence in subsequent pregnancies, placing that risk at 30%. However, substantial heterogeneity in underlying studies speaks to the need for common

definitions and further work in this area. Additionally, the absolute risk of recurrence appears to be substantially higher if the underlying etiology is PTL as opposed to PPROM. Clinically, this information will help with risk stratification and patient counseling. Interventions to prevent PTB need to be focused and designed for specific clinical conditions. Further studies need to be done that look at the efficacy of preventative treatments in the prevention of PTL and PPROM. Knowledge of the etiology of previous sPTB may help identify women at increased risk of sPTB for participation in future clinical trials.

References

1. March of Dimes, PMNCH, Save the Children, WHO. The global action report on preterm birth. Geneva: World Health Organization, 2012.
2. Blencowe H, Cousens S, Oestergaard MZ, Chou D, Moller AB, Narwal R, et al. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. Lancet. 2012;379(9832):2162-72.
3. Lawn JE, Cousens S, Zupan J, Lancet Neonatal Survival Steering T. 4 million neonatal deaths: when? Where? Why? Lancet. 2005;365(9462):891-900.
4. Liu L, Johnson HL, Cousens S, Perin J, Scott S, Lawn JE, et al. Global, regional, and national causes of child mortality: an updated systematic analysis for 2010 with time trends since 2000. Lancet. 2012;379(9832):2151-61.
5. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. Lancet. 2008;371(9606):75-84.
6. Mazaki-Tovi S, Romero R, Kusanovic JP, Erez O, Pineles BL, Gotsch F, et al. Recurrent preterm birth. Semin Perinatol. 2007;31(3):142-58.
7. Ananth CV, Vintzileos AM. Epidemiology of preterm birth and its clinical subtypes. J Matern Fetal Neonatal Med. 2006;19(12):773-82.
8. Lim G, Tracey J, Boom N, Karmakar S, Wang J, Berthelot JM, et al. CIHI survey: Hospital costs for preterm and small-for-gestational age babies in Canada. Healthc Q. 2009;12(4):20-4.
9. McDonald SW, Kingston D, Bayrampour H, Dolan SM, Tough SC. Cumulative psychosocial stress, coping resources, and preterm birth. Arch Womens Ment Health. 2014;17(6):559-68.
10. Shapiro GD, Fraser WD, Frasch MG, Seguin JR. Psychosocial stress in pregnancy and preterm birth: associations and mechanisms. J Perinat Med. 2013;41(6):631-45.
11. Loomans EM, van Dijk AE, Vrijkotte TG, van Eijsden M, Stronks K, Gemke RJ, et al. Psychosocial stress during pregnancy is related to adverse birth outcomes: results from a large multi-ethnic community-based birth cohort. Eur J Public Health. 2013;23(3):485-91.
12. Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analysis Ottawa: Ottawa Hospital Research Institute; 2014 [Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
13. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials. 1996;17(1):1-12.
14. Ananth CV, Getahun D, Peltier MR, Salihu HM, Vintzileos AM. Recurrence of spontaneous versus medically indicated preterm birth. Am J Obstet Gynecol. 2006;195(3):643-50.
15. Asrat T, Lewis DF, Garite TJ, Major CA, Nageotte MP, Towers CV, et al. Rate of recurrence of preterm premature rupture of membranes in consecutive pregnancies. Am J Obstet Gynecol. 1991;165(4 Pt 1):1111-5.
16. Care AG, Sharp AN, Lane S, Roberts D, Watkins L, Alfirevic Z. Predicting preterm birth in women with previous preterm birth and cervical length >/= 25 mm. Ultrasound Obstet Gynecol. 2014;43(6):681-6.

17. Carr-Hill RA, Hall MH. The repetition of spontaneous preterm labour. Br J Obstet Gynaecol. 1985;92(9):921-8.
18. Coleman S, Wallace L, Alexander J, Istwan N. Recurrent preterm birth in women treated with 17 alpha-hydroxyprogesterone caproate: the contribution of risk factors in the penultimate pregnancy. J Matern Fetal Neonatal Med. 2012;25(7):1034-8.
19. Crane JM, Hutchens D. Use of transvaginal ultrasonography to predict preterm birth in women with a history of preterm birth. Ultrasound Obstet Gynecol. 2008;32(5):640-5.
20. Drassinower D, Obican SG, Siddiq Z, Heller D, Gyamfi-Bannerman C, Friedman AM. Does the clinical presentation of a prior preterm birth predict risk in a subsequent pregnancy? Am J Obstet Gynecol. 2015;213(5):686 e1-7.
21. Ekwo E, Moawad A. The risk for recurrence of premature births to African-American and white women. J Assoc Acad Minor Phys. 1998;9(1):16-21.
22. Elimian A, Smith K, Williams M, Knudtson E, Goodman JR, Escobedo MB. A randomized controlled trial of intramuscular versus vaginal progesterone for the prevention of recurrent preterm birth. Int J Gynaecol Obstet. 2016;134(2):169-72.
23. Esplin MS, O'Brien E, Fraser A, Kerber RA, Clark E, Simonsen SE, et al. Estimating recurrence of spontaneous preterm delivery. Obstet Gynecol. 2008;112(3):516-23.
24. Getahun D, Strickland D, Ananth CV, Fassett MJ, Sacks DA, Kirby RS, et al. Recurrence of preterm premature rupture of membranes in relation to interval between pregnancies. Am J Obstet Gynecol. 2010;202(6):570 e1-6.
25. Glover MM, McKenna DS, Downing CM, Smith DB, Croom CS, Sonek JD. A randomized trial of micronized progesterone for the prevention of recurrent preterm birth. Am J Perinatol. 2011;28(5):377-81.
26. Goldenberg RL, Andrews WW, Faye-Petersen O, Cliver S, Goepfert AR, Hauth JC. The Alabama Preterm Birth Project: placental histology in recurrent spontaneous and indicated preterm birth. Am J Obstet Gynecol. 2006;195(3):792-6.
27. Gonzalez-Quintero VH, Cordova YC, Istwan NB, Tudela F, Rhea DJ, Romary LM, et al. Influence of gestational age and reason for prior preterm birth on rates of recurrent preterm delivery. Am J Obstet Gynecol. 2011;205(3):275 e1-5.
28. Harper M, Thom E, Klebanoff MA, Thorp J, Jr., Sorokin Y, Varner MW, et al. Omega-3 fatty acid supplementation to prevent recurrent preterm birth: a randomized controlled trial. Obstet Gynecol. 2010;115(2 Pt 1):234-42.
29. Himes KP, Simhan HN. Risk of recurrent preterm birth and placental pathology. Obstet Gynecol. 2008;112(1):121-6.
30. Hsieh TT, Chen SF, Shau WY, Hsieh CC, Hsu JJ, Hung TH. The impact of interpregnancy interval and previous preterm birth on the subsequent risk of preterm birth. J Soc Gynecol Investig. 2005;12(3):202-7.
31. Laughon SK, Albert PS, Leishear K, Mendola P. The NICHD Consecutive Pregnancies Study: recurrent preterm delivery by subtype. Am J Obstet Gynecol. 2014;210(2):131 e1-8.
32. Lykke JA, Paidas MJ, Langhoff-Roos J. Recurring complications in second pregnancy. Obstet Gynecol. 2009;113(6):1217-24.
33. Manuck TA, Henry E, Gibson J, Varner MW, Porter TF, Jackson GM, et al. Pregnancy outcomes in a recurrent preterm birth prevention clinic. Am J Obstet Gynecol. 2011;204(4):320 e1-6.
34. Markham KB, Walker H, Lynch CD, Iams JD. Preterm birth rates in a prematurity prevention clinic after adoption of progestin prophylaxis. Obstet Gynecol. 2014;123(1):34-9.

35. Meis PJ, Klebanoff M, Thom E, Dombrowski MP, Sibai B, Moawad AH, et al. Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. N Engl J Med. 2003;348(24):2379-85.
36. Mercer BM, Goldenberg RL, Moawad AH, Meis PJ, Iams JD, Das AF, et al. The preterm prediction study: effect of gestational age and cause of preterm birth on subsequent obstetric outcome. National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. Am J Obstet Gynecol. 1999;181(5 Pt 1):1216-21.
37. Owen J, Yost N, Berghella V, Thom E, Swain M, Dildy GA, 3rd, et al. Mid-trimester endovaginal sonography in women at high risk for spontaneous preterm birth. JAMA. 2001;286(11):1340-8.
38. Rittenberg C, Newman RB, Istwan NB, Rhea DJ, Stanziano GJ. Preterm birth prevention by 17 alpha-hydroxyprogesterone caproate vs. daily nursing surveillance. J Reprod Med. 2009;54(2):47-52.
39. Turitz AL, Bastek JA, Purisch SE, Elovitz MA, Levine LD. Patient characteristics associated with 17-alpha hydroxyprogesterone caproate use among a high-risk cohort. Am J Obstet Gynecol. 2016;214(4):536 e1-5.
40. Vermeulen GM, Bruinse HW. Prophylactic administration of clindamycin 2% vaginal cream to reduce the incidence of spontaneous preterm birth in women with an increased recurrence risk: a randomised placebo-controlled double-blind trial. Br J Obstet Gynaecol. 1999;106(7):652-7.
41. Vogel I, Goepfert AR, Thorsen P, Skogstrand K, Hougaard DM, Curry AH, et al. Early second-trimester inflammatory markers and short cervical length and the risk of recurrent preterm birth. J Reprod Immunol. 2007;75(2):133-40.
42. Wallace JM, Bhattacharya S, Campbell DM, Horgan GW. Inter-Pregnancy Weight Change and the Risk of Recurrent Pregnancy Complications. PLoS One. 2016;11(5):e0154812.
43. Yamashita M, Hayashi S, Endo M, Okuno K, Fukui O, Mimura K, et al. Incidence and risk factors for recurrent spontaneous preterm birth: A retrospective cohort study in Japan. J Obstet Gynaecol Res. 2015;41(11):1708-14.
44. Yang J, Baer RJ, Berghella V, Chambers C, Chung P, Coker T, et al. Recurrence of Preterm Birth and Early Term Birth. Obstet Gynecol. 2016;128(2):364-72.
45. Kazemier BM, Buijs PE, Mignini L, Limpens J, de Groot CJ, Mol BW, et al. Impact of obstetric history on the risk of spontaneous preterm birth in singleton and multiple pregnancies: a systematic review. BJOG. 2014;121(10):1197-208; discussion 209.
46. Kamath-Rayne BD, DeFranco EA, Chung E, Chen A. Subtypes of preterm birth and the risk of postneonatal death. J Pediatr. 2013;162(1):28-34 e2.
47. Villar J, Abalos E, Carroli G, Giordano D, Wojdyla D, Piaggio G, et al. Heterogeneity of perinatal outcomes in the preterm delivery syndrome. Obstet Gynecol. 2004;104(1):78-87.
48. Chen A, Feresu SA, Barsoom MJ. Heterogeneity of preterm birth subtypes in relation to neonatal death. Obstet Gynecol. 2009;114(3):516-22.
49. Newman DE, Paamoni-Keren O, Press F, Wiznitzer A, Mazor M, Sheiner E. Neonatal outcome in preterm deliveries between 23 and 27 weeks' gestation with and without preterm premature rupture of membranes. Arch Gynecol Obstet. 2009;280(1):7-11.
50. Basso O, Wilcox A. Mortality risk among preterm babies: immaturity versus underlying pathology. Epidemiology. 2010;21(4):521-7.

51. Brown HK, Speechley KN, Macnab J, Natale R, Campbell MK. Neonatal morbidity associated with late preterm and early term birth: the roles of gestational age and biological determinants of preterm birth. Int J Epidemiol. 2014;43(3):802-14.

Figure 1: Flow diagram of included studies

Figure 2. Forest plot of the rate of recurrent spontaneous preterm birth at <37 weeks gestation

Figure 3. Forest plots of the rate of (a) recurrent spontaneous preterm birth (sPTB) due to preterm premature rupture of membranes (PPROM) following sPTB due to PPROM in the index pregnancy at <37 weeks gestation and (b) recurrent sPTB due to preterm labor (PTL) following sPTB due to PTL in the index pregnancy at <37 weeks gestation

Appendix A. Search Strategy

Search Strategy:

1. Premature Birth
2. ((preterm or pre-term or premature or pre-mature) and (birth* or childbirth* or deliver* or parturit*))
3. Fetal Membranes, Premature Rupture
4. pprom
5. Obstetric Labor, Premature
6. ((preterm or pre-term or premature or pre-mature) and (labor or labour))
7. Recurrence
8. recur* or repeat
9. (1 or 2 or 3 or 4 or 5 or 6) and (7 or 8)

Initial Search Run on June 17, 2015
Updated Search Run on July 29, 2016

Appendix B. Included studies

Author	Time Period	Country	Gestational Age at Spontaneous Preterm Birth (weeks)		Recurrence Rate
			Pregnancy 1	Pregnancy 2	
Ananth 2006 (14)	1989-1997	USA	<37	<37	2,626/12,670 (20.7%)
				<35	698/12,670 (5.5%)
				<32	164/12,670 (1.3%)
			<35	<35	698/4,463 (15.6%)
			<32	<32	164/2,022 (8.1%)
Asrat 1991 (15)		USA	<36	<36	39/121 (32.2%)
Care 2014 (16)	2010-2012	UK	<34	<37	53/196 (27.0%)
				<34	32/196 (16.3%)
Carr-Hill 1985 (17)	unspecified	UK	<37	<37	76/494 (15.4%)
Coleman 2012 (18)	2007-2010	USA	<37	<37	426/1,183 (36.0%)
				<35	156/1,183 (13.2%)
				<32	61/1,183 (5.2%)
Crane 2008 (19)	2000-2006	Canada	<37	<37	21/90 (23.3%)
				<35	11/90 (12.2%)
				<34	8/90 (8.9%)
Drassinower 2015 (20)	2009-2014	USA	<37	<37	178/522 (34.1%)
				<34	78/522 (14.9%)
				<28	34/522 (6.5%)
Ekwo 1998 (21)	1988-1993	USA	<37	<37	56/108 (51.9%)
Elimian 2016 (22)	2007-2010	USA	<37	<37	59/145 (40.7%)
				<34	27/145 (18.6%)
				<28	15/145 (10.3%)
Esplin 2008 (23)	1989-2001	USA	<37	<37	1663/6,199 (26.8%)
			<34	<37	587/1,669 (35.2%)
				<34	299/1,669 (17.9%)
Getahun 2010 (24) *PPROM only	1989-1997	USA	<37	<37	157/2,259 (6.9%)
			<34	<34	97/1,071 (9.1%)
			<32	<32	67/697 (9.6%)
			<28	<28	22/323 (6.8%)

Author	Time Period	Country	Gestational Age at Spontaneous Preterm Birth (weeks)		Recurrence Rate
			Pregnancy 1	Pregnancy 2	
Glover 2011 (25)	2006-2009	USA	<37	<37	13/33 (39.4%)
Goldenberg 2006 (26)	1996-2001	USA	<32	<37	71/83 (85.5%)
Gonzalez-Quintero 2011 (27)	2006-2009	USA	<37	<37	597/2,123 (28.1%)
				<35	274/2,123 (12.9%)
				<32	113/2,123 (5.3%)
Harper 2010 (28)	2005-2006	USA	<37	<37	292/852 (34.3%)
Himes 2008 (29)	2001-2006	USA	<37	<37	102/245 (41.6%)
Hsieh 2005 (30)	1991-1997	Taiwan	<37	<37	52/228 (22.8%)
Laughon 2014 (31)	2002-2010	USA	<37	<37	921/3,139 (29.3%)
Lykke 2009 (32)	1978-2007	Denmark	<37	<37	2742/17,334 (15.8%)
			<33		444/1,734 (25.6%)
			<28		139/535 (26.0%)
Manuck 2011 (33)	2002-2010	USA	<35	<37	131/223 (58.7%)
				<32	25/223 (11.2%)
Markham 2014 (34)	1998-2012	USA	<37	<37	459/1,066 (43.1%)
				<35	269/1,066 (25.2%)
				<32	139/1,066 (13.0%)
Meis 2003 (35)	1999-2002	USA	<37	<37	159/463 (34.3%)
Mercer 1999 (36)	1992-1994	USA	<37	<37	89/410 (21.7%)
				<35	55/410 (13.4%)
				<32	21/410 (5.1%)
				<30	12/410 (2.9%)
				<28	10/410 (2.4%)
Owen 2001 (37)	1997-1999	USA	<32	<35	48/183 (26.2%)
				<32	35/183 (19.1%)
				<28	29/183 (15.8%)
				<24	20/183 (10.9%)
Rittenberg 2009 (38)	1995-2005	USA	<37	<37	185/684 (27.0%)
				<35	78/684 (11.4%)
				<32	30/684 (4.4%)
Turitz 2016 (39)	2009-2013	USA	<37	<37	80/218 (36.7%)

Author	Time Period	Country	Gestational Age at Spontaneous Preterm Birth (weeks)		Recurrence Rate
			Pregnancy 1	Pregnancy 2	
Vermeulen 1999 (40)	1994-1996	Netherlands	<37	<37	41/168 (24.4%)
				<34	14/168 (8.3%)
Vogel 2007 (41)	2000-2001	USA	<30	<37	20/62 (32.3%)
				<35	15/62 (24.2%)
Wallace 2016 (42)	1986-2013	UK	<37	<37	449/1,900 (23.6%)
Yamashita 2015 (43)	2008-2012	Japan	<37	<37	89/547 (16.3%)
				<34	28/547 (5.1%)
				<28	10/547 (1.8%)
Yang 2016 (44)	2005-2011	USA	<37	<37	588/1,068 (55.1%)
				<32	71/1,068 (6.6%)
			<32	<32	43/177 (24.3%)

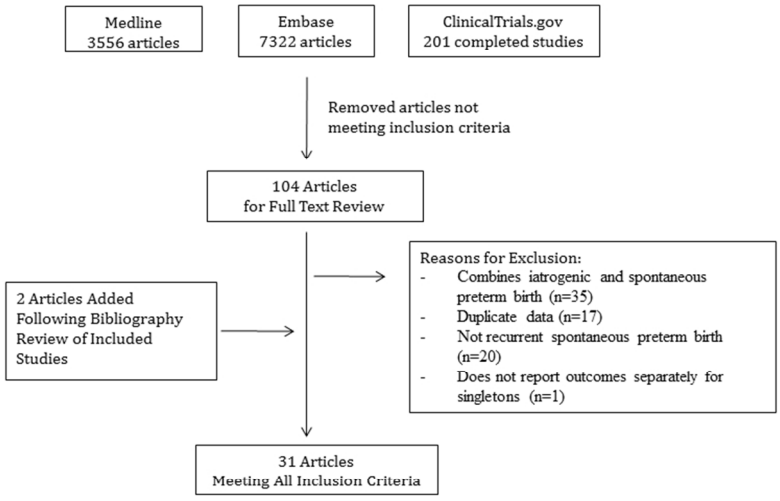
Appendix C: Quality Assessment

Author	Cohort Studies (Newcastle Ottawa Scale (12))							
	Representatives of the exposed cohort (0, 1)	Selection of the non-exposed cohort (0, 1)	Ascertainment of exposure (0, 1)	Demonstration that outcome of interest was not present at start of study (0, 1)	Comparability of cohorts on the basis of design or analysis (0, 1)	Assessment of outcome (0, 1)	Was follow-up long enough for outcomes to occur (0, 1)	Adequacy of follow-up of cohorts (0, 1)
Ananth 2006 (14)	1	N/A	0	1	N/A	0	1	1
Asrat 1991 (15)	0	N/A	1	1	N/A	1	1	1
Care 2014 (16)	0	N/A	1	1	N/A	1	1	1
Carr-Hill 1985 (17)	1	N/A	0	1	N/A	0	1	1
Coleman 2012 (18)	0	N/A	1	1	N/A	1	1	1
Crane 2008 (19)	0	N/A	1	1	N/A	1	1	1
Drassinower 2015 (20)	0	N/A	1	1	N/A	1	1	1
Ekwo 1998 (21)	0	N/A	1	1	N/A	1	1	1
Esplin 2008 (23)	1	N/A	0	1	N/A	0	1	1

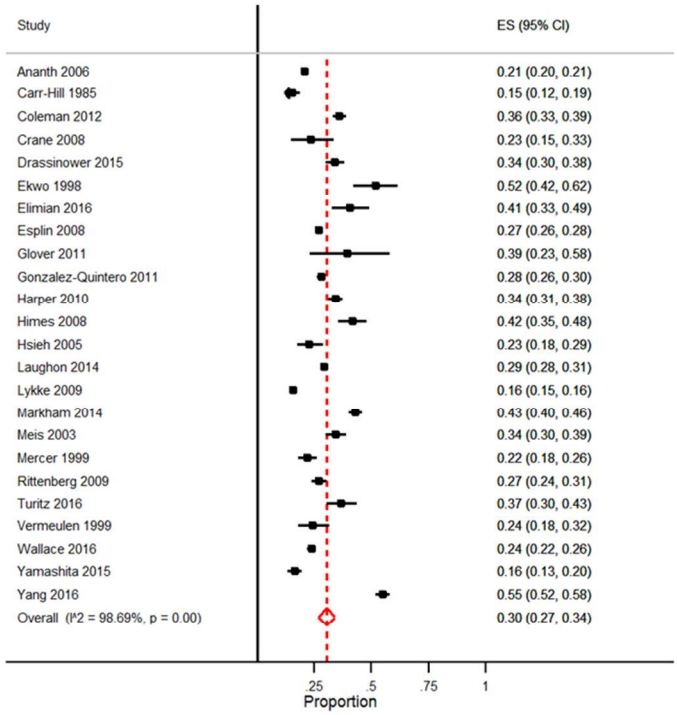
Author	Cohort Studies (Newcastle Ottawa Scale (12))							
	Representatives of the exposed cohort (0, 1)	Selection of the non-exposed cohort (0, 1)	Ascertainment of exposure (0, 1)	Demonstration that outcome of interest was not present at start of study (0, 1)	Comparability of cohorts on the basis of design or analysis (0, 1)	Assessment of outcome (0, 1)	Was follow-up long enough for outcomes to occur (0, 1)	Adequacy of follow-up of cohorts (0, 1)
Getahun 2010 (24) *PPROM only	1	N/A	0	1	N/A	0	1	1
Goldenberg 2006 (26)	0	N/A	1	1	N/A	1	1	1
Gonzalez-Quintero 2011 (27)	0	N/A	1	1	N/A	1	1	1
Himes 2008 (29)	0	N/A	1	1	N/A	1	1	1
Hsieh 2005 (30)	0	N/A	1	1	N/A	1	1	1
Laughon 2014 (31)	1	N/A	0	1	N/A	0	1	1
Lykke 2009 (32)	1	N/A	0	1	N/A	0	1	1
Manuck 2011 (33)	0	N/A	1	1	N/A	1	1	1
Markham 2014 (34)	0	N/A	1	1	N/A	1	1	1

Author	Cohort Studies (Newcastle Ottawa Scale (12))							
	Representatives of the exposed cohort (0, 1)	Selection of the non-exposed cohort (0, 1)	Ascertainment of exposure (0, 1)	Demonstration that outcome of interest was not present at start of study (0, 1)	Comparability of cohorts on the basis of design or analysis (0, 1)	Assessment of outcome (0, 1)	Was follow-up long enough for outcomes to occur (0, 1)	Adequacy of follow-up of cohorts (0, 1)
Mercer 1999 (36)	0	N/A	1	1	N/A	1	1	1
Owen 2001 (37)	0	N/A	1	1	N/A	1	1	1
Rittenberg 2009 (38)	0	N/A	1	1	N/A	1	1	1
Turitz 2016 (39)	0	N/A	1	1	N/A	1	1	1
Vogel 2007 (41)	0	N/A	1	1	N/A	1	1	1
Wallace 2016 (42)	1	N/A	0	1	N/A	0	1	1
Yamashita 2015 (43)	0	N/A	1	1	N/A	1	1	1
Yang 2016 (44)	1	N/A	0	1	N/A	0	1	1

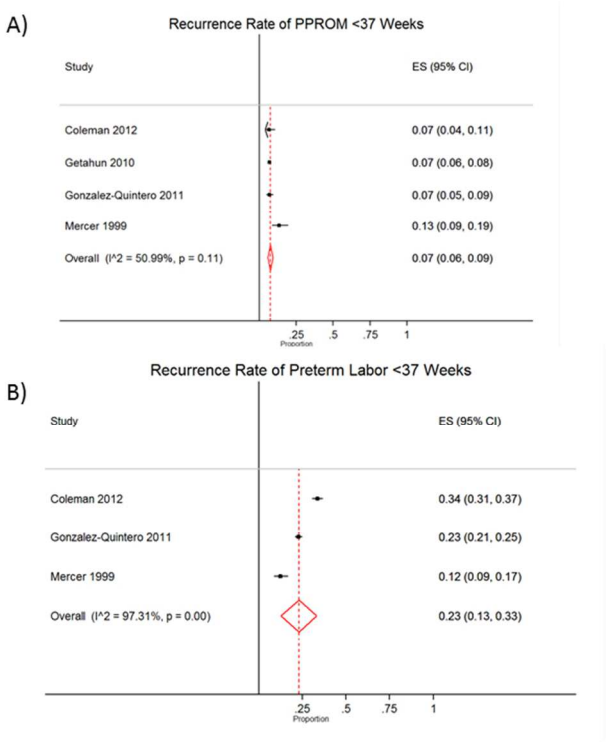
Randomized Controlled Trials (Jadad Scale (13))			
Author	Randomization (0, 1, 2)	Blinding (0, 1, 2)	An account of all patients (0, 1)
Elimian 2016 (22)	2	0	0
Glover 2011 (25)	1	2	1
Harper 2010 (28)	2	2	1
Meis 2003 (35)	2	2	1
Vermeulen 1999 (40)	2	2	0



254x190mm (96 x 96 DPI)



254x190mm (96 x 96 DPI)



254x190mm (96 x 96 DPI)

BMJ Open

Risk of Recurrent Spontaneous Preterm Birth: A Systematic Review and Meta-Analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-015402.R1
Article Type:	Research
Date Submitted by the Author:	30-Mar-2017
Complete List of Authors:	Phillips, Courtney; University of Calgary Velji, Zain; University of Calgary Hanly, Ciara; University of British Columbia Metcalfe, Amy; University of Calgary, Obstetrics and Gynecology
Primary Subject Heading:	Obstetrics and gynaecology
Secondary Subject Heading:	Obstetrics and gynaecology, Epidemiology, Evidence based practice, Paediatrics
Keywords:	EPIDEMIOLOGY, NEONATOLOGY, OBSTETRICS, PAEDIATRICS

Risk of Recurrent Spontaneous Preterm Birth: A Systematic Review and Meta-Analysis

Ms. Courtney PHILLIPS[1] BSc, Ms. Zain VELJI[2] BSc, Ms. Ciara HANLY[3], Dr. Amy METCALFE[4,5] PhD

[1]Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada
[2]Faculty of Nursing, University of Calgary, Calgary, Alberta, Canada
[3]School of Kinesiology, University of British Columbia, Vancouver, British Columbia, Canada
[4]Department of Obstetrics and Gynecology, University of Calgary, Calgary, Alberta, Canada
[5]Department of Community Health Sciences, University of Calgary, Calgary, Alberta, Canada

Address for Correspondence:
Amy Metcalfe
Foothills Medical Centre, 4th Floor North Tower
1403 29 St NW
Calgary, Alberta, Canada
T2N 2T9
Email: amy.metcalfe@albertahealthservices.ca
Phone: 403-944-8458

Short Title: Risk of Recurrent Spontaneous Preterm Birth

Condensation: The risk of recurrent spontaneous preterm birth is high, and tends to reoccur more frequently following preterm labor than preterm premature rupture of membranes.

Conflict of Interest: The authors have no conflicts of interest to report

Contributorship Statement: All authors made a substantial contribution to this study. CP, ZV and CH conducted the systematic review. CP drafted the manuscript. AM designed the study and conducted the meta-analysis. All authors critically reviewed the manuscript, interpreted the findings, and approved the final version. All authors had full access to all of the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. As the senior author AM affirms that the manuscript is an honest, accurate, and transparent account of the study being reported, that no important aspects of the study have been omitted, and that any discrepancies from the study as planned have been explained.

Data Sharing Agreement: No additional data is available

inclusion of electronic links from the Contribution to third party material where-ever it may be located; and, vi) licence any third party to do any or all of the above.

Funding: This study was funded by the Alberta Children's Hospital Research Institute. Amy Metcalfe is supported by a New Investigator Award from the Canadian Institutes of Health Research. The funder had no role in study design, execution, or publication decisions.

Word Count (Abstract): 236
Word Count (Manuscript): 2540
Number of References: 53
Number of Tables: 0
Number of Figures: 3
Number of Appendices: 3

Abstract

Objective: To determine the risk of recurrent spontaneous preterm birth following spontaneous preterm birth in singleton pregnancies.

Design: Systematic review and meta-analysis using random effects models.

Data Sources: An electronic literature search was conducted in OVID Medline (1948-2016), Embase (1980-2016), and ClinicalTrials.gov (completed studies effective 2016), supplemented by hand-searching bibliographies of included studies, to find all studies with original data concerning recurrent spontaneous preterm birth.

Study Eligibility Criteria: Studies had to include women with at least one spontaneous preterm singleton live birth (<37 weeks) and at least one subsequent pregnancy resulting in a singleton live birth. The Newcastle-Ottawa Scale and Jadad Scale were used to assess the study quality of cohort studies and randomized controlled trials respectively.

Results: Overall, 31 articles involving 55,016 women, met all inclusion criteria. Generally studies were well conducted and had a low risk of bias. The absolute risk of recurrent spontaneous preterm birth at <37 weeks gestation was 30.0% (95% CI: 27.0-34.0%). The risk of recurrence due to preterm premature rupture of membranes (PPROM) at <37 weeks gestation was 7.0% (95% CI: 6.0-9.0%), while the risk of recurrence due to preterm labor at <37 weeks gestation was 23.0% (95% CI: 13.0-33.0%).

Conclusions: The risk of recurrent spontaneous preterm birth is high and is influenced by the underlying clinical pathway leading to the birth. This information is important for clinicians when discussing the recurrence risk of spontaneous preterm birth with their patients.

Key Words: preterm birth, preterm labor, preterm premature rupture of membranes, recurrence, systematic review

Article Summary – Strengths and Limitations of This Study:

- Study strengths include the comprehensive search strategy with no language restrictions used in the nature of the systematic review.
- Limitations primarily relate to the underlying data that was available on this top. Most of the included studies were observational in nature. Additionally, many primary studies examining the recurrence risk of preterm birth had to be excluded as they did not clearly differentiate between spontaneous and indicated preterm delivery. There was a high degree of heterogeneity in the studies included in the meta-analysis.

Introduction

Preterm birth (PTB) is defined as any live birth occurring before 37 completed weeks of gestation; this can be subdivided into extremely preterm (<28 weeks), very preterm (28-<32 weeks), moderately preterm (32-<34 weeks) and late preterm (34-<37 weeks) birth based on the gestational age at delivery (1). This sub-categorization is important as gestational age is inversely associated with increased mortality, morbidity and the intensity of neonatal care required at birth (2). Worldwide, 11.1% of infants are born preterm every year (2). Preterm birth is the leading cause of perinatal morbidity and mortality, and second most common cause of death, after pneumonia, in children under five years of age (3, 4).

Indicated preterm births (iPTB) are those induced for medical reasons, such a pre-eclampsia, intrauterine growth restriction or fetal distress. However, approximately 70% of PTB occur spontaneously (sPTB) (5). The clinical pathways that lead to sPTB typically include preterm labor (PTL) and preterm premature rupture of membranes (PPROM), although these occur on a spectrum and may co-occur in the same clinical setting. PTL is defined as regular contractions and cervical changes at less than 37 weeks gestation, and PPROM is defined as spontaneous rupture of membranes at least one hour before contractions at less than 37 weeks gestation (5). Known risk factors for spontaneous preterm birth include a previous preterm birth, black race, low maternal body-mass index, comorbidities, a short cervical length and a raised fetal fibronectin concentration (5, 6). Despite knowing these risk factors, our understanding of the etiology behind sPTB is poor and sPTB is considered to be multifactorial in nature (6, 7).

Although sPTB has a tendency to recur, little is known about the recurrence risk (7). This is of concern because sPTB is a leading cause of neonatal morbidity and mortality, and it also has a large economic burden (8). Further, women who have had a previous sPTB are likely to be anxious during their subsequent pregnancies, which itself can lead to sPTB and other adverse

pregnancy outcomes (9-11). Therefore, we conducted a systematic review and meta-analysis to investigate the absolute risk of recurrent sPTB following sPTB in singleton pregnancies. By better understanding the recurrence risk of sPTB, healthcare workers may be better equipped to manage patient needs and anxieties, as well as develop and apply preventative treatments.

Methods

Two study authors (ZV and CH) executed a comprehensive literature search of Medline (from 1946 to 2015) and Embase (from 1980 to 2015) to identify publications that contained key terms related to recurrent sPTB in June 2015. The search was updated in July 2016, and expanded to included completed studies identified through ClinicalTrials.gov. PPROM, PTL and related terms were included in the search. For the full search strategy, please refer to Appendix A. Titles and abstracts of these articles were screened for relevance to determine which articles were to undergo full-text review. Two independent reviewers (ZV and CP) assessed the final eligibility of the full-text reviewed articles. We resolved disagreements in full-text eligibility or data abstraction by involvement of a third party (AM). The bibliographies of included studies were reviewed to identify additional publications not found through the database search. A complete summary of the search strategy can be found in Figure 1. No patients were directly involved in this study. As this study only used published data, it was exempt from Institutional Review Board approval.

All studies with original data concerning recurrent sPTB and N≥20 were considered for inclusion. No language restrictions were used. Conference abstracts were not considered. To be included, studies had to include women with at least one spontaneous preterm live birth (delivery <37 weeks of gestation) in their obstetric history and at least one subsequent pregnancy resulting in a live birth. Only studies looking at singleton pregnancies were included. Animal studies,

studies that only included iPTB, studies that combined iPTB and sPTB, and studies on PPROM or PTL where it was not clear if it resulted in sPTB were excluded. In the case of duplicate data, the study with the largest sample size was included.

The data extraction was completed independently by ZV and CP using a standardized data extraction form. Data was reviewed by AM prior to analysis to ensure completeness. Information on the authors, title, publication year, data year, location of study, study design, definitions of preterm birth, and inclusion and exclusion criteria were all extracted. In addition, information was extracted on the number of women with spontaneous preterm birth in their initial pregnancy, whether due to PPROM or PTL, number of women with term births in subsequent pregnancies, and number of women with preterm births in subsequent pregnancies, whether due to PPROM, PTL or indicated causes. For studies that reported on total reproductive history, only data on the first 2 consecutive pregnancies were extracted. The Newcastle-Ottawa Scale (12) and the Jadad Scale (13) were used to assess study quality of cohort studies and randomized controlled trials respectively.

The primary outcome measured was the recurrence rate of sPTB at <37 weeks gestation. Secondary outcomes were recurrence rate of sPTB due to PPROM at <37 weeks (following sPTB due to PPROM in the index pregnancy), recurrence rate of sPTB due to PTL at <37 weeks (following sPTB due to PTL in the index pregnancy), the recurrence of sPTB by gestational age, and occurrence of iPTB at <37 weeks after a previous sPTB.

For our analysis, we reported the pooled risk of recurrent preterm birth and accompanying 95% confidence interval (CIs) for sPTB <37 weeks gestation, by iPTB, by gestational age overall, and for PPROM and PTL. Stratified analysis was used to examine the recurrence rate of sPTB <37 weeks gestation by study design and quality. An a priori decision

was made to use a random-effects model for all models in anticipation of clinical heterogeneity between studies. Forest plots were used to graphically represent the data. Heterogeneity between studies was assessed using I^2, the Cochrane Q statistic, and accompanying p-values. All analysis was conducted using Stata SE Version 14 (College Station, Texas).

Results

The search returned 11,079 articles, of which 104 met criteria for full-text review (Figure 1). Overall 31 articles met all of the inclusion criteria and were included in the review (14-44). A summary of all of the studies' data can be found in Appendix B (recurrence risk of sPTB is located in Table B1 and occurrence risk of iPTB following sPTB is located in Table B2). The included studies were almost entirely cohort studies, with only five randomized controlled trials (22, 26, 28, 35, 40). The sample sizes in the studies ranged from 33 to 17,334 women and the rate of recurrent sPTB at <37 weeks gestation ranged from 15.4% to 85.5%. Many of the studies had different definitions of sPTB and therefore they could not be combined for meta-analysis. There was only a sufficient number of studies that defined preterm birth as occurring prior to 37 weeks in both the index and subsequent pregnancy to create pooled estimates.

The overall risk of recurrent sPTB at <37 weeks gestation (n=24 studies, 51,889 women) was 30.0% (95% CI: 27.0-34.0%) with a significant Q (P=0.00) and I^2 of 98.7%, indicating between-study heterogeneity (Figure 2). The recurrence rate did not significantly differ between randomized controlled trials (34.0%, 95% CI: 29.0-38.0%; n=5 studies, 1,661 women) and cohort studies (30.0%, 95% CI: 26.0-34.0%, n=19 studies, 50,228 women). The risk of iPTB at <37 weeks gestation after a previous spontaneous preterm birth (n=6 studies, 18,355 women) was 5.0% (95% CI: 3.0-7.0%) with an I^2 of 98.0%.

Few studies looked specifically at the recurrence of PPROM and PTL resulting in sPTB in singleton pregnancies following prior PPROM or PTL respectively. However, the identified risk of recurrent PPROM at <37 weeks gestation (n=4 studies, 3,138 women) was 7.0% (95% CI: 6.0-9.0%) with an I^2 of 51.0% and the risk of recurrent PTL at <37 weeks gestation (n=3 studies, 2,852 women) was 23.0% (95% CI: 13.0-33.0%) with an I^2 of 97.3% (Figure 3).

The majority of the studies were of high quality (Appendix C – cohort studies are located in Table C1 and randomized controlled trials in Table C2). As this study exclusively examined the recurrence risk of spontaneous preterm birth, two elements of the Newcastle Ottawa Scale relating to the selection of the unexposed cohort and the comparability of the exposed and unexposed cohorts were unable to be assessed. Cohort studies typically traded off between being generalizable to the broader patient population not seen in a tertiary center or having detailed clinical data available. All cohort studies had a quality score of 4 or 5 out of a possible 6 points. No statistically significant differences in the recurrence rate of sPTB prior to 37 weeks was observed based on quality score in cohort studies (Score 4: 27.0%, 95% CI: 21.0-32.0%; Score 5: 32.0%, 95% CI: 26.0-37.0%). All but one randomized controlled trial was deemed to be high quality (Jahad score ≥4/5) (22). This low-quality trial did report a higher recurrence risk (41.0%, 95% CI: 33.0-49.0) than the pooled estimated generated from high quality trials (32.0%, 95% CI: 28.0-37.0); however, as evidenced by the overlapping confidence intervals, these estimates are not statistically different.

Discussion

This meta-analysis provides an overview of the overall risk of recurrent spontaneous preterm birth. We found that the absolute risk of recurrent sPTB at less than 37 weeks gestation in

pregnancies was 30%; this estimate was consistent across study designs and study quality. Interestingly, the risk of recurrent PTL was found to be 23%, similar to the overall risk of recurrent sPTB. Conversely, if a woman has a sPTB due to PPROM, she is less likely to have recurrent PPROM leading to sPTB, with a risk of only 7%. Thus the clinical pathway that leads to sPTB appears to influence the risk of recurrence.

In a 2014 systematic review by Kazemier et al., they found that the risk of recurrence of preterm birth is influenced by the singleton/twin order in both pregnancies. When they looked at spontaneous preterm singleton births after a previous singleton pregnancy, they found that the risk of recurrence of sPTB was 20.2% (45). In contrast to ours, their search strategy was exceedingly complex and included only cohort studies. Ultimately after abstract review they were left with only six studies that looked at singleton-singleton pregnancies, which could explain the difference in our recurrence risk. Further, our study is novel as we differentiated risk by clinical pathway leading to sPTB, whether PTL or PPROM. Ultimately, we found that while all sPTB tends to recur, the clinical pathway of the first sPTB is important in determining that recurrence risk. Previous studies tend to combine these underlying pathways together, but our results suggest that perhaps they should not be pooled. Some studies also suggest that children born following PPROM have increased mortality (46-48) and worse health outcomes (49) compared to children born after PTL, which further supports the premise that these should be looked at as separate clinical conditions.

However, new evidence suggests that PTB and the underlying pathologies that lead to PTB are not mutually exclusive, thus spontaneous and indicated PTB should perhaps not be considered completely separate phenomena. Basso and Wilcox estimated that mortality due to immaturity itself was about 51%, whereas underlying pathologies that led to PTB accounted for

approximately half of mortality (50). Similarly, in a recent study by Brown et al., the authors found that gestational age is on the causal path between biological determinants of preterm birth and neonatal outcomes (51). Infants who were exposed to both pathological intrauterine conditions and early delivery had increased risk for poor neonatal outcomes. As such a pathological intrauterine environment, for instance, one characterized by infection, placental ischemia and other biological determinants, acts through early delivery to produce poor outcomes. Ananth et al. found that women with a sPTB were not only likely to experience recurrent sPTB, but they were also associated with increased medically indicated PTB, and vice versa (7). Prevention of preterm mortality requires more than the resolution of PTB, but must also address the underlying etiologies.

Strengths of our systematic review and meta-analysis include our broad search strategy with no language restrictions, which resulted in a large sample size of pooled data. Limitations include the fact that most of the studies were observational cohort studies and thus prone to bias, and there was significant between-study heterogeneity. This is important as many women included in this body of literature would have been offered some form of therapy to reduce their risks of recurrent preterm birth. Strategies to prevent preterm birth are varied and evidence of their effectiveness are mixed (52). Effective strategies to prevent preterm birth can be implemented at the individual level (i.e. progesterone supplementation, cervical cerclage, smoking cessation), the clinic/hospital level (i.e. hard-stop policies to prevent non-medically indicated late preterm and early term birth, preterm birth prevention clinics) and the societal level (i.e. smoke-free legislation to reduce environmental tobacco smoke, legislation regarding single-embryo transfer during in vitro fertilization) (52). As documentation of specific treatment strategies was not consistently reported in this body of literature, we were not able to synthesize

these results according to specific types of treatment. While both small and large studies were identified and included, publication bias cannot be entirely ruled out. While the decision to only include studies with a minimum sample size of 20 was used to exclude case studies of rare cases that may not be generalizable, this may have inadvertently resulted in the exclusion of some small case series. Additionally, we only searched 3 independent sources and reviewed the bibliographies of included articles, thus articles in journals that were not indexed in either Medline or Embase or studies that were not registered on clinicialtrials.gov or were not cited by articles that were ultimately included in this review would not have been identified. We anticipate that the impact of this would be minimal as a study examining the effectiveness of different databases to identify studies related to maternal morbidity and mortality concluded that Medline and Embase has the highest yield in identifying unique studies, and that over 60% of all studies were identified by multiple sources (53). Although we were able to identify a large number of studies, many of them used different definitions for preterm birth and most did not identify the clinical pathway to PTB; as a consequence, these data could not be pooled and not all of the existing evidence could be summarized in this review.

In conclusion, our study reaffirmed that a previous spontaneous preterm birth is a significant risk factor for recurrence in subsequent pregnancies, placing that risk at 30%. However, substantial heterogeneity in underlying studies speaks to the need for common definitions and further work in this area. Additionally, the absolute risk of recurrence appears to be substantially higher if the underlying etiology is PTL as opposed to PPROM. Clinically, this information will help with risk stratification and patient counseling. Interventions to prevent PTB need to be focused and designed for specific clinical conditions. Further studies need to be done that look at the efficacy of preventative treatments in the prevention of PTL and PPROM.

Knowledge of the etiology of previous sPTB may help identify women at increased risk of sPTB for participation in future clinical trials.

References

1. March of Dimes, PMNCH, Save the Children, WHO. The global action report on preterm birth. Geneva: World Health Organization, 2012.
2. Blencowe H, Cousens S, Oestergaard MZ, Chou D, Moller AB, Narwal R, et al. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. Lancet. 2012;379(9832):2162-72.
3. Lawn JE, Cousens S, Zupan J, Lancet Neonatal Survival Steering T. 4 million neonatal deaths: when? Where? Why? Lancet. 2005;365(9462):891-900.
4. Liu L, Johnson HL, Cousens S, Perin J, Scott S, Lawn JE, et al. Global, regional, and national causes of child mortality: an updated systematic analysis for 2010 with time trends since 2000. Lancet. 2012;379(9832):2151-61.
5. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. Lancet. 2008;371(9606):75-84.
6. Mazaki-Tovi S, Romero R, Kusanovic JP, Erez O, Pineles BL, Gotsch F, et al. Recurrent preterm birth. Semin Perinatol. 2007;31(3):142-58.
7. Ananth CV, Vintzileos AM. Epidemiology of preterm birth and its clinical subtypes. J Matern Fetal Neonatal Med. 2006;19(12):773-82.
8. Lim G, Tracey J, Boom N, Karmakar S, Wang J, Berthelot JM, et al. CIHI survey: Hospital costs for preterm and small-for-gestational age babies in Canada. Healthc Q. 2009;12(4):20-4.
9. McDonald SW, Kingston D, Bayrampour H, Dolan SM, Tough SC. Cumulative psychosocial stress, coping resources, and preterm birth. Arch Womens Ment Health. 2014;17(6):559-68.
10. Shapiro GD, Fraser WD, Frasch MG, Seguin JR. Psychosocial stress in pregnancy and preterm birth: associations and mechanisms. J Perinat Med. 2013;41(6):631-45.
11. Loomans EM, van Dijk AE, Vrijkotte TG, van Eijsden M, Stronks K, Gemke RJ, et al. Psychosocial stress during pregnancy is related to adverse birth outcomes: results from a large multi-ethnic community-based birth cohort. Eur J Public Health. 2013;23(3):485-91.
12. Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analysis Ottawa: Ottawa Hospital Research Institute; 2014 [Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
13. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials. 1996;17(1):1-12.
14. Ananth CV, Getahun D, Peltier MR, Salihu HM, Vintzileos AM. Recurrence of spontaneous versus medically indicated preterm birth. Am J Obstet Gynecol. 2006;195(3):643-50.
15. Asrat T, Lewis DF, Garite TJ, Major CA, Nageotte MP, Towers CV, et al. Rate of recurrence of preterm premature rupture of membranes in consecutive pregnancies. Am J Obstet Gynecol. 1991;165(4 Pt 1):1111-5.
16. Care AG, Sharp AN, Lane S, Roberts D, Watkins L, Alfirevic Z. Predicting preterm birth in women with previous preterm birth and cervical length >/= 25 mm. Ultrasound Obstet Gynecol. 2014;43(6):681-6.

17. Carr-Hill RA, Hall MH. The repetition of spontaneous preterm labour. Br J Obstet Gynaecol. 1985;92(9):921-8.
18. Coleman S, Wallace L, Alexander J, Istwan N. Recurrent preterm birth in women treated with 17 alpha-hydroxyprogesterone caproate: the contribution of risk factors in the penultimate pregnancy. J Matern Fetal Neonatal Med. 2012;25(7):1034-8.
19. Crane JM, Hutchens D. Use of transvaginal ultrasonography to predict preterm birth in women with a history of preterm birth. Ultrasound Obstet Gynecol. 2008;32(5):640-5.
20. Drassinower D, Obican SG, Siddiq Z, Heller D, Gyamfi-Bannerman C, Friedman AM. Does the clinical presentation of a prior preterm birth predict risk in a subsequent pregnancy? Am J Obstet Gynecol. 2015;213(5):686 e1-7.
21. Ekwo E, Moawad A. The risk for recurrence of premature births to African-American and white women. J Assoc Acad Minor Phys. 1998;9(1):16-21.
22. Elimian A, Smith K, Williams M, Knudtson E, Goodman JR, Escobedo MB. A randomized controlled trial of intramuscular versus vaginal progesterone for the prevention of recurrent preterm birth. Int J Gynaecol Obstet. 2016;134(2):169-72.
23. Esplin MS, O'Brien E, Fraser A, Kerber RA, Clark E, Simonsen SE, et al. Estimating recurrence of spontaneous preterm delivery. Obstet Gynecol. 2008;112(3):516-23.
24. Getahun D, Strickland D, Ananth CV, Fassett MJ, Sacks DA, Kirby RS, et al. Recurrence of preterm premature rupture of membranes in relation to interval between pregnancies. Am J Obstet Gynecol. 2010;202(6):570 e1-6.
25. Glover MM, McKenna DS, Downing CM, Smith DB, Croom CS, Sonek JD. A randomized trial of micronized progesterone for the prevention of recurrent preterm birth. Am J Perinatol. 2011;28(5):377-81.
26. Goldenberg RL, Andrews WW, Faye-Petersen O, Cliver S, Goepfert AR, Hauth JC. The Alabama Preterm Birth Project: placental histology in recurrent spontaneous and indicated preterm birth. Am J Obstet Gynecol. 2006;195(3):792-6.
27. Gonzalez-Quintero VH, Cordova YC, Istwan NB, Tudela F, Rhea DJ, Romary LM, et al. Influence of gestational age and reason for prior preterm birth on rates of recurrent preterm delivery. Am J Obstet Gynecol. 2011;205(3):275 e1-5.
28. Harper M, Thom E, Klebanoff MA, Thorp J, Jr., Sorokin Y, Varner MW, et al. Omega-3 fatty acid supplementation to prevent recurrent preterm birth: a randomized controlled trial. Obstet Gynecol. 2010;115(2 Pt 1):234-42.
29. Himes KP, Simhan HN. Risk of recurrent preterm birth and placental pathology. Obstet Gynecol. 2008;112(1):121-6.
30. Hsieh TT, Chen SF, Shau WY, Hsieh CC, Hsu JJ, Hung TH. The impact of interpregnancy interval and previous preterm birth on the subsequent risk of preterm birth. J Soc Gynecol Investig. 2005;12(3):202-7.
31. Laughon SK, Albert PS, Leishear K, Mendola P. The NICHD Consecutive Pregnancies Study: recurrent preterm delivery by subtype. Am J Obstet Gynecol. 2014;210(2):131 e1-8.
32. Lykke JA, Paidas MJ, Langhoff-Roos J. Recurring complications in second pregnancy. Obstet Gynecol. 2009;113(6):1217-24.
33. Manuck TA, Henry E, Gibson J, Varner MW, Porter TF, Jackson GM, et al. Pregnancy outcomes in a recurrent preterm birth prevention clinic. Am J Obstet Gynecol. 2011;204(4):320 e1-6.
34. Markham KB, Walker H, Lynch CD, Iams JD. Preterm birth rates in a prematurity prevention clinic after adoption of progestin prophylaxis. Obstet Gynecol. 2014;123(1):34-9.

35. Meis PJ, Klebanoff M, Thom E, Dombrowski MP, Sibai B, Moawad AH, et al. Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. N Engl J Med. 2003;348(24):2379-85.
36. Mercer BM, Goldenberg RL, Moawad AH, Meis PJ, Iams JD, Das AF, et al. The preterm prediction study: effect of gestational age and cause of preterm birth on subsequent obstetric outcome. National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. Am J Obstet Gynecol. 1999;181(5 Pt 1):1216-21.
37. Owen J, Yost N, Berghella V, Thom E, Swain M, Dildy GA, 3rd, et al. Mid-trimester endovaginal sonography in women at high risk for spontaneous preterm birth. JAMA. 2001;286(11):1340-8.
38. Rittenberg C, Newman RB, Istwan NB, Rhea DJ, Stanziano GJ. Preterm birth prevention by 17 alpha-hydroxyprogesterone caproate vs. daily nursing surveillance. J Reprod Med. 2009;54(2):47-52.
39. Turitz AL, Bastek JA, Purisch SE, Elovitz MA, Levine LD. Patient characteristics associated with 17-alpha hydroxyprogesterone caproate use among a high-risk cohort. Am J Obstet Gynecol. 2016;214(4):536 e1-5.
40. Vermeulen GM, Bruinse HW. Prophylactic administration of clindamycin 2% vaginal cream to reduce the incidence of spontaneous preterm birth in women with an increased recurrence risk: a randomised placebo-controlled double-blind trial. Br J Obstet Gynaecol. 1999;106(7):652-7.
41. Vogel I, Goepfert AR, Thorsen P, Skogstrand K, Hougaard DM, Curry AH, et al. Early second-trimester inflammatory markers and short cervical length and the risk of recurrent preterm birth. J Reprod Immunol. 2007;75(2):133-40.
42. Wallace JM, Bhattacharya S, Campbell DM, Horgan GW. Inter-Pregnancy Weight Change and the Risk of Recurrent Pregnancy Complications. PLoS One. 2016;11(5):e0154812.
43. Yamashita M, Hayashi S, Endo M, Okuno K, Fukui O, Mimura K, et al. Incidence and risk factors for recurrent spontaneous preterm birth: A retrospective cohort study in Japan. J Obstet Gynaecol Res. 2015;41(11):1708-14.
44. Yang J, Baer RJ, Berghella V, Chambers C, Chung P, Coker T, et al. Recurrence of Preterm Birth and Early Term Birth. Obstet Gynecol. 2016;128(2):364-72.
45. Kazemier BM, Buijs PE, Mignini L, Limpens J, de Groot CJ, Mol BW, et al. Impact of obstetric history on the risk of spontaneous preterm birth in singleton and multiple pregnancies: a systematic review. BJOG. 2014;121(10):1197-209.
46. Kamath-Rayne BD, DeFranco EA, Chung E, Chen A. Subtypes of preterm birth and the risk of postneonatal death. J Pediatr. 2013;162(1):28-34 e2.
47. Villar J, Abalos E, Carroli G, Giordano D, Wojdyla D, Piaggio G, et al. Heterogeneity of perinatal outcomes in the preterm delivery syndrome. Obstet Gynecol. 2004;104(1):78-87.
48. Chen A, Feresu SA, Barsoom MJ. Heterogeneity of preterm birth subtypes in relation to neonatal death. Obstet Gynecol. 2009;114(3):516-22.
49. Newman DE, Paamoni-Keren O, Press F, Wiznitzer A, Mazor M, Sheiner E. Neonatal outcome in preterm deliveries between 23 and 27 weeks' gestation with and without preterm premature rupture of membranes. Arch Gynecol Obstet. 2009;280(1):7-11.
50. Basso O, Wilcox A. Mortality risk among preterm babies: immaturity versus underlying pathology. Epidemiology. 2010;21(4):521-7.

51. Brown HK, Speechley KN, Macnab J, Natale R, Campbell MK. Neonatal morbidity associated with late preterm and early term birth: the roles of gestational age and biological determinants of preterm birth. Int J Epidemiol. 2014;43(3):802-14.
52. Newnham JP, Dickinson JE, Hart RJ, Pennell CE, Arrese CA, Keelan JA. Strategies to prevent preterm birth. Front Immunol. 2014;5:584.
53. Betran AP, Say L, Gulmezoglu AM, Allen T, Hampson L. Effectiveness of different databases in identifying studies for systematic reviews: experience from the WHO systematic review of maternal morbidity and mortality. BMC Med Res Methodol. 2005;5(1):6.

Figure 1: Flow diagram of included studies

Figure 2. Forest plot of the rate of recurrent spontaneous preterm birth at <37 weeks gestation

Figure 3. Forest plots of the rate of (a) recurrent PPROM and (b) recurrent PTL at <37 weeks gestation

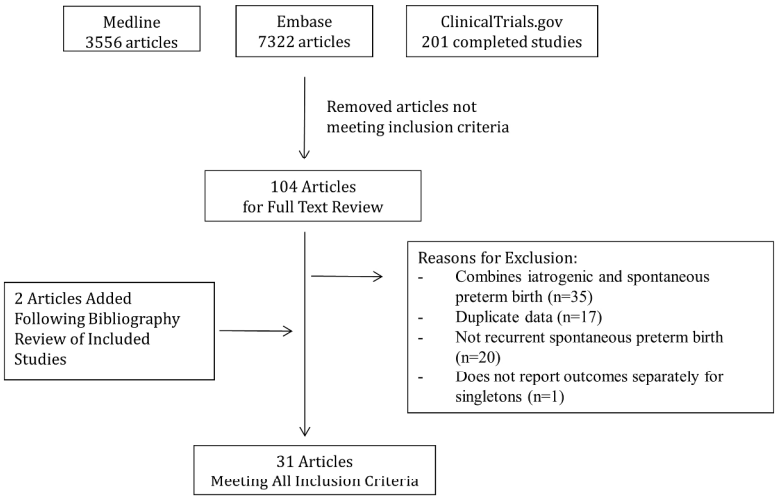


Figure 1

254x190mm (300 x 300 DPI)

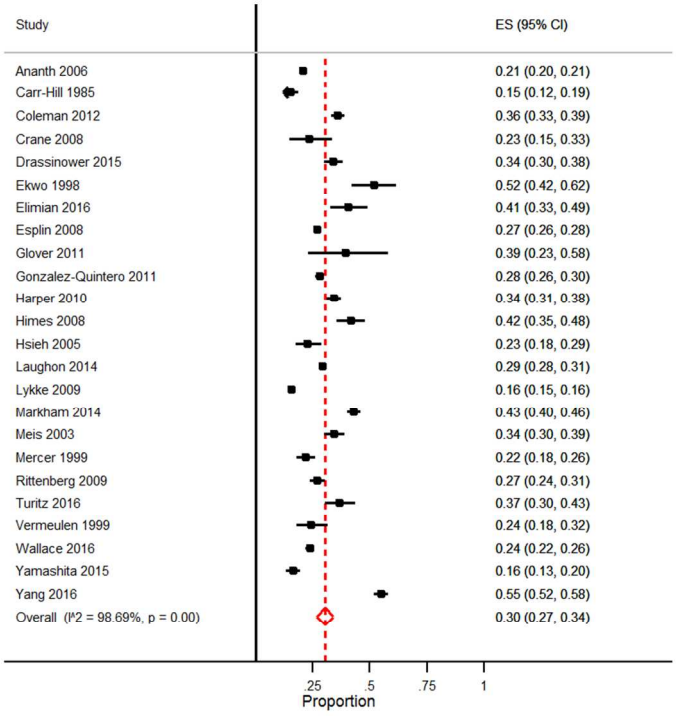


Figure 2

254x190mm (300 x 300 DPI)

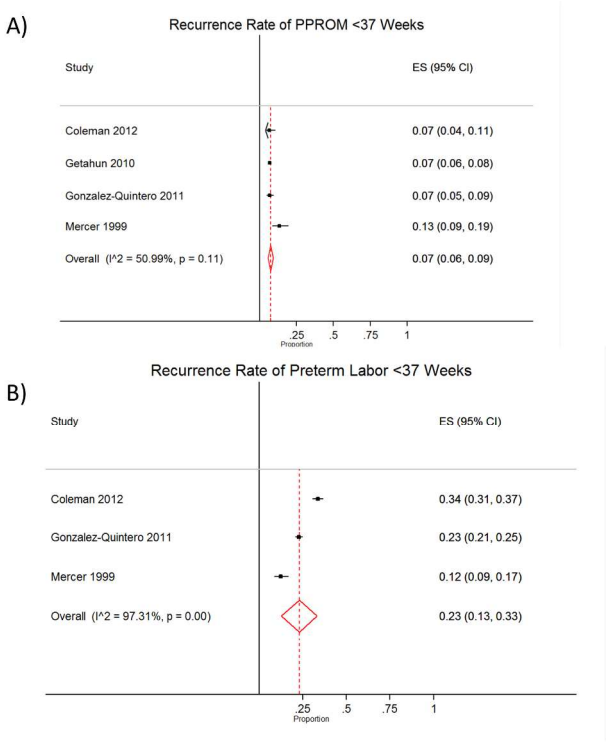


Figure 3

254x190mm (300 x 300 DPI)

Appendix A. Search Strategy

Search Strategy:

1. Premature Birth
2. ((preterm or pre-term or premature or pre-mature) and (birth* or childbirth* or deliver* or parturit*))
3. Fetal Membranes, Premature Rupture
4. pprom
5. Obstetric Labor, Premature
6. ((preterm or pre-term or premature or pre-mature) and (labor or labour))
7. Recurrence
8. recur* or repeat
9. (1 or 2 or 3 or 4 or 5 or 6) and (7 or 8)

Initial Search Run on June 17, 2015
Updated Search Run on July 29, 2016

Appendix B. Included studies

Table B1 – Recurrence rate of spontaneous preterm birth

Author	Time Period	Country	Study Design	Inclusion/Exclusion Criteria	Gestational Age at Spontaneous Preterm Birth (weeks) Pregnancy 1	Gestational Age at Spontaneous Preterm Birth (weeks) Pregnancy 2	Recurrence Rate of Spontaneous Preterm Birth
Ananth 2006 (14)	1989-1997	USA	Cohort	*Inclusion:* Prior sPTB *Exclusion:* Multiple gestation pregnancies	<37	<37	2,626/12,670 (20.7%)
						<35	698/12,670 (5.5%)
						<32	164/12,670 (1.3%)
					<35	<35	698/4,463 (15.6%)
					<32	<32	164/2,022 (8.1%)
Asrat 1991 (15)		USA	Cohort	*Inclusion:* Prior PPROM *Exclusion:* Incompetent cervix, uterine anomalies, diethelstilbestrol exposure, multiple gestations, and neonates with congenital anomalies	<36	<36	39/121 (32.2%)
Care 2014 (16)	2010-2012	UK	Cohort	*Inclusion:* Prior sPTB or PROM; cervical length >25mm at 20-24 weeks *Exclusion:* Prior cervical surgery, non-viable pregnancy, history of iPTB, cerclage, uterine anomalies, Ehlers-Danlos syndrome, intrauterine death, twins, congenital abnormalities	<34	<37	53/196 (27.0%)
						<34	32/196 (16.3%)
Carr-Hill 1985 (17)	unspecified	UK	Cohort	*Inclusion:* Prior sPTB, singleton *Exclusion:* Multiple gestation, stillbirth, induced labor	<37	<37	76/494 (15.4%)

Author	Time Period	Country	Study Design	Inclusion/Exclusion Criteria	Gestational Age at Spontaneous Preterm Birth (weeks) Pregnancy 1	Gestational Age at Spontaneous Preterm Birth (weeks) Pregnancy 2	Recurrence Rate of Spontaneous Preterm Birth
Coleman 2012 (18)	2007-2010	USA	Cohort	*Inclusion:* Prior sPTB, received 17P injections *Exclusion:* Non-compliance with 17P injections	<37	<37	426/1,183 (36.0%)
						<35	156/1,183 (13.2%)
						<32	61/1,183 (5.2%)
Crane 2008 (19)	2000-2006	Canada	Cohort	*Inclusion:* Prior sPTB *Exclusion:* Cervical cerclage	<37	<37	21/90 (23.3%)
						<35	11/90 (12.2%)
						<34	8/90 (8.9%)
Drassinower 2015 (20)	2009-2014	USA	Cohort	*Inclusion:* Prior sPTB, singleton *Exclusion:* Multiple gestations, major fetal anomalies, cerclage, history of iPTB or placental abruption	<37	<37	178/522 (34.1%)
						<34	78/522 (14.9%)
						<28	34/522 (6.5%)
Ekwo 1998 (21)	1988-1993	USA	Cohort	*Inclusion:* Prior sPTB *Exclusion:* Fetal loss, multiple gestation	<37	<37	56/108 (51.9%)
Elimian 2016 (22)	2007-2010	USA	RCT	*Inclusion:* Prior sPTB *Exclusion:* Multiple gestation, major fetal anomaly or chromosomal anomalies, prior progesterone use in the current pregnancy, use of heparin in the current pregnancy, uterine anomaly, maternal medical conditions, no ultrasound before 20^{+6} in the current pregnancy	<37	<37	59/145 (40.7%)
						<34	27/145 (18.6%)
						<28	15/145 (10.3%)
Esplin 2008 (23)	1989-2001	USA	Cohort	*Inclusion:* First live birth in Utah and a subsequent live birth in the study period	<37	<37	1663/6,199 (26.8%)
					<34	<37	587/1,669 (35.2%)

Author	Time Period	Country	Study Design	Inclusion/Exclusion Criteria	Gestational Age at Spontaneous Preterm Birth (weeks) Pregnancy 1	Pregnancy 2	Recurrence Rate of Spontaneous Preterm Birth
						<34	299/1,669 (17.9%)
Getahun 2010 (24) *PPROM only	1989-1997	USA	Cohort	*Inclusion:* Prior PPROM *Exclusion:* Multiple gestations, births <20 weeks, non White or Black race, >1 pregnancy before 1989	<37	<37	157/2,259 (6.9%)
					<34	<34	97/1,071 (9.1%)
					<32	<32	67/697 (9.6%)
					<28	<28	22/323 (6.8%)
Glover 2011 (25)	2006-2009	USA	RCT	*Inclusion:* Prior sPTB, initiated prenatal care prior to 20 weeks gestation *Exclusion:* Multiple gestations, major fetal anomaly	<37	<37	13/33 (39.4%)
Goldenberg 2006 (26)	1996-2001	USA	Cohort	*Inclusion:* Prior sPTB	<32	<37	71/83 (85.5%)
Gonzalez-Quintero 2011 (27)	2006-2009	USA	Cohort	*Inclusion:* Prior sPTB, singleton *Exclusion:* iPTB, >1 prior PTB, cerclage in current pregnancy	<37	<37	597/2,123 (28.1%)
						<35	274/2,123 (12.9%)
						<32	113/2,123 (5.3%)

Author	Time Period	Country	Study Design	Inclusion/Exclusion Criteria	Gestational Age at Spontaneous Preterm Birth (weeks)		Recurrence Rate of Spontaneous Preterm Birth
					Pregnancy 1	Pregnancy 2	
Harper 2010 (28)	2005-2006	USA	RCT	*Inclusion:* Prior sPTB, singleton *Exclusion:* Major fetal anomaly, intake of a fish oil supplement >500mg/week at any time during the preceding month, allergy to fish, anticoagulation therapy, hypertension, White's classification D or higher diabetes, drug or alcohol abuse, seizure disorder, uncontrolled thyroid disease, clotting disorder, current or planned cerclage, or a plan to deliver either elsewhere or before 37 weeks of gestation	<37	<37	292/852 (34.3%)
Himes 2008 (29)	2001-2006	USA	Cohort	*Inclusion:* Prior sPTB placenta pathology information available	<37	<37	102/245 (41.6%)
Hsieh 2005 (30)	1991-1997	Taiwan	Cohort	*Exclusion:* Multiple gestation, fetal anomaly, cervical incompetence, stillbirth, iPTB	<37	<37	52/228 (22.8%)
Laughon 2014 (31)	2002-2010	USA	Cohort	*Inclusion:* Singleton pregnancies	<37	<37	921/3,139 (29.3%)
Lykke 2009 (32)	1978-2007	Denmark	Cohort	*Inclusion:* Maternal age between 15-50 *Exclusion:* Women with cardiovascular disease, type 1 or 2 diabetes, women who emigrated within 3 months of 2nd delivery	<37 <33 <28	<37	2742/17,334 (15.8%) 444/1,734 (25.6%) 139/535 (26.0%)

Author	Time Period	Country	Study Design	Inclusion/Exclusion Criteria	Gestational Age at Spontaneous Preterm Birth (weeks) Pregnancy 1	Gestational Age at Spontaneous Preterm Birth (weeks) Pregnancy 2	Recurrence Rate of Spontaneous Preterm Birth
Manuck 2011 (33)	2002-2010	USA	Cohort	*Inclusion:* Prior sPTB, singleton *Exclusion:* History of iPTB or incompetent cervix	<35	<37	131/223 (58.7%)
						<32	25/223 (11.2%)
Markham 2014 (34)	1998-2012	USA	Cohort	*Inclusion:* Prior sPTB *Exclusion:* Multiple gestations, known uterine anomalies,	<37	<37	459/1,066 (43.1%)
						<35	269/1,066 (25.2%)
						<32	139/1,066 (13.0%)
Meis 2003 (35)	1999-2002	USA	RCT	*Inclusion:* Prior sPTB *Exclusion:* Multiple gestations, fetal anomaly, progesterone or heparin treatment during the current pregnancy, current or planned cervical cerclage, hypertension requiring medication, seizure disorder, or a plan to deliver elsewhere	<37	<37	159/463 (34.3%)
Mercer 1999 (36)	1992-1994	USA	Cohort	*Inclusion:* Singleton *Exclusion:* Placenta previa, major fetal malformations, cervical cerclage, polyhydramnios, oligohydramnios, cervical dilatation of ≥2 cm for nulliparous women and ≥3 cm for multiparous women.	<37	<37	89/410 (21.7%)
						<35	55/410 (13.4%)
						<32	21/410 (5.1%)
						<30	12/410 (2.9%)
						<28	10/410 (2.4%)
Owen 2001 (37)	1997-1999	USA	Cohort	*Inclusion:* Prior sPTB, singleton *Exclusion:* chronic medical or obstetrical problems, history of	<32	<35	48/183 (26.2%)
						<32	35/183 (19.1%)
						<28	29/183 (15.8%)

Author	Time Period	Country	Study Design	Inclusion/Exclusion Criteria	Gestational Age at Spontaneous Preterm Birth (weeks) Pregnancy 1	Gestational Age at Spontaneous Preterm Birth (weeks) Pregnancy 2	Recurrence Rate of Spontaneous Preterm Birth
				substance abuse, uterine anomalies, cerclage		<24	20/183 (10.9%)
Rittenberg 2009 (38)	1995-2005	USA	Cohort	*Inclusion:* Prior sPTB, singleton pregnancies, referred for weekly 17P administration *Exclusion:* Diagnosis of preterm labour, cerclage or vaginal bleeding at enrollment	<37	<37	185/684 (27.0%)
						<35	78/684 (11.4%)
						<32	30/684 (4.4%)
Turitz 2016 (39)	2009-2013	USA	Cohort	*Inclusion:* Prior sPTB	<37	<37	80/218 (36.7%)
Vermeulen 1999 (40)	1994-1996	Netherlands	RCT	*Inclusion:* Prior sPTB *Exclusion:* Fetal anomaly, previous iPTB, known allergy to clindamycin	<37	<37	41/168 (24.4%)
						<34	14/168 (8.3%)
Vogel 2007 (41)	2000-2001	USA	Cohort	*Inclusion:* Prior sPTB *Exclusion:* Multiple gestations, ruptured membranes, cerclage in a previous pregnancy	<30	<37	20/62 (32.3%)
						<35	15/62 (24.2%)
Wallace 2016 (42)	1986-2013	UK	Cohort		<37	<37	449/1,900 (23.6%)
Yamashita 2015 (43)	2008-2012	Japan	Cohort	*Inclusion:* Prior sPTB *Exclusion:* First antenatal visit after 14 weeks, previous iPTB, placenta previa, placental abruption, multiple gestation, fetal anomaly, antepartum fetal demise	<37	<37	89/547 (16.3%)
						<34	28/547 (5.1%)
						<28	10/547 (1.8%)

Author	Time Period	Country	Study Design	Inclusion/Exclusion Criteria	Gestational Age at Spontaneous Preterm Birth (weeks)		Recurrence Rate of Spontaneous Preterm Birth
					Pregnancy 1	Pregnancy 2	
Yang 2016 (44)	2005-2011	USA	Cohort		<37	<37	588/1,068 (55.1%)
						<32	71/1,068 (6.6%)
					<32	<32	43/177 (24.3%)

Table B2 – Occurrence of Indicated Preterm Birth Following Spontaneous Preterm Birth

Author	Time Period	Country	Study Design	Inclusion/Exclusion Criteria	Gestational Age at Preterm Birth (weeks) Pregnancy 1	Gestational Age at Preterm Birth (weeks) Pregnancy 2	Occurrence Rate of Indicated Preterm Birth Following a Prior Spontaneous Preterm Birth
Ananth 2006 (14)	1989-1997	USA	Cohort	*Inclusion:* Prior sPTB *Exclusion:* Multiple gestation pregnancies	<37	<37	342/12,670 (2.70%)
						<35	121/12,670 (0.96%)
						<32	40/12,670 (0.32%)
					<35	<35	121/4,463 (2.71%)
					<32	<32	40/2,022 (1.98%)
Harper 2010 (28)	2005-2006	USA	RCT	*Inclusion:* Prior sPTB, singleton *Exclusion:* Major fetal anomaly, intake of a fish oil supplement >500mg/week at any time during the preceding month, allergy to fish, anticoagulation therapy, hypertension, White's classification D or higher diabetes, drug or alcohol abuse, seizure disorder, uncontrolled thyroid disease, clotting disorder, current or planned cerclage, or a plan to deliver either elsewhere or before 37 weeks of gestation	<37	<37	46/852 (5.63%)
Laughon 2014 (31)	2002-2010	USA	Cohort	*Inclusion:* Singleton pregnancies	<37	<37	17/3,139 (0.54%)

Author	Time Period	Country	Study Design	Inclusion/Exclusion Criteria	Gestational Age at Preterm Birth (weeks) Pregnancy 1	Gestational Age at Preterm Birth (weeks) Pregnancy 2	Occurrence Rate of Indicated Preterm Birth Following a Prior Spontaneous Preterm Birth
Meis 2003 (35)	1999-2002	USA	RCT	*Inclusion:* Prior sPTB *Exclusion:* Multiple gestations, fetal anomaly, progesterone or heparin treatment during the current pregnancy, current or planned cervical cerclage, hypertension requiring medication, seizure disorder, or a plan to deliver elsewhere	<37	<37	36/463 (7.78%)
Owen 2001 (37)	1997-1999	USA	Cohort	*Inclusion:* Prior sPTB, singleton *Exclusion:* chronic medical or obstetrical problems, history of substance abuse, uterine anomalies, cerclage	<32	<35	5/183 (2.73%)
Rittenberg 2009 (38)	1995-2005	USA	Cohort	*Inclusion:* Prior sPTB, singleton pregnancies, referred for weekly 17P administration *Exclusion:* Diagnosis of preterm labour, cerclage or vaginal bleeding at enrollment	<37	<37	84/684 (12.28%)

Author	Time Period	Country	Study Design	Inclusion/Exclusion Criteria	Gestational Age at Preterm Birth (weeks)		Occurrence Rate of Indicated Preterm Birth Following a Prior Spontaneous Preterm Birth
					Pregnancy 1	Pregnancy 2	
Yamashita 2015 (43)	2008-2012	Japan	Cohort	*Inclusion:* Prior sPTB *Exclusion:* First antenatal visit after 14 weeks, previous iPTB, placenta previa, placental abruption, multiple gestation, fetal anomaly, antepartum fetal demise	<37	<37	23/547 (4.20%)

Appendix C: Quality Assessment

Table C1 – Quality Scores for Included Cohort Studies

Author	Cohort Studies (Newcastle Ottawa Scale (12)) Representatives of the exposed cohort (0, 1)	Selection of the non-exposed cohort (0, 1)	Ascertainment of exposure (0, 1)	Demonstration that outcome of interest was not present at start of study (0, 1)	Comparability of cohorts on the basis of design or analysis (0, 1)	Assessment of outcome (0, 1)	Was follow-up long enough for outcomes to occur (0, 1)	Adequacy of follow-up of cohorts (0, 1)
Ananth 2006 (14) *Score: 4/6*	1	N/A	0	1	N/A	0	1	1
Asrat 1991 (15) *Score: 5/6*	0	N/A	1	1	N/A	1	1	1
Care 2014 (16) *Score: 5/6*	0	N/A	1	1	N/A	1	1	1
Carr-Hill 1985 (17) *Score: 4/6*	1	N/A	0	1	N/A	0	1	1
Coleman 2012 (18) *Score: 5/6*	0	N/A	1	1	N/A	1	1	1
Crane 2008 (19) *Score: 5/6*	0	N/A	1	1	N/A	1	1	1

Author	Cohort Studies (Newcastle Ottawa Scale (12)) Representatives of the exposed cohort (0, 1)	Selection of the non-exposed cohort (0, 1)	Ascertainment of exposure (0, 1)	Demonstration that outcome of interest was not present at start of study (0, 1)	Comparability of cohorts on the basis of design or analysis (0, 1)	Assessment of outcome (0, 1)	Was follow-up long enough for outcomes to occur (0, 1)	Adequacy of follow-up of cohorts (0, 1)
Drassinower 2015 (20) *Score: 5/6*	0	N/A	1	1	N/A	1	1	1
Ekwo 1998 (21) *Score: 5/6*	0	N/A	1	1	N/A	1	1	1
Esplin 2008 (23) *Score: 4/6*	1	N/A	0	1	N/A	0	1	1
Getahun 2010 (24) *PPROM only *Score: 4/6*	1	N/A	0	1	N/A	0	1	1
Goldenberg 2006 (26) *Score: 5/6*	0	N/A	1	1	N/A	1	1	1
Gonzalez-Quintero 2011 (27) *Score: 5/6*	0	N/A	1	1	N/A	1	1	1

Author	Cohort Studies (Newcastle Ottawa Scale (12)) Representatives of the exposed cohort (0, 1)	Selection of the non-exposed cohort (0, 1)	Ascertainment of exposure (0, 1)	Demonstration that outcome of interest was not present at start of study (0, 1)	Comparability of cohorts on the basis of design or analysis (0, 1)	Assessment of outcome (0, 1)	Was follow-up long enough for outcomes to occur (0, 1)	Adequacy of follow-up of cohorts (0, 1)
Himes 2008 (29) *Score: 5/6*	0	N/A	1	1	N/A	1	1	1
Hsieh 2005 (30) *Score: 5/6*	0	N/A	1	1	N/A	1	1	1
Laughon 2014 (31) *Score: 4/6*	1	N/A	0	1	N/A	0	1	1
Lykke 2009 (32) *Score: 4/6*	1	N/A	0	1	N/A	0	1	1
Manuck 2011 (33) *Score: 5/6*	0	N/A	1	1	N/A	1	1	1
Markham 2014 (34) *Score: 5/6*	0	N/A	1	1	N/A	1	1	1
Mercer 1999 (36) *Score: 5/6*	0	N/A	1	1	N/A	1	1	1

Author	Cohort Studies (Newcastle Ottawa Scale (12)) Representatives of the exposed cohort (0, 1)	Selection of the non-exposed cohort (0, 1)	Ascertainment of exposure (0, 1)	Demonstration that outcome of interest was not present at start of study (0, 1)	Comparability of cohorts on the basis of design or analysis (0, 1)	Assessment of outcome (0, 1)	Was follow-up long enough for outcomes to occur (0, 1)	Adequacy of follow-up of cohorts (0, 1)
Owen 2001 (37) *Score: 5/6*	0	N/A	1	1	N/A	1	1	1
Rittenberg 2009 (38) *Score: 5/6*	0	N/A	1	1	N/A	1	1	1
Turitz 2016 (39) *Score: 5/6*	0	N/A	1	1	N/A	1	1	1
Vogel 2007 (41) *Score: 5/6*	0	N/A	1	1	N/A	1	1	1
Wallace 2016 (42) *Score: 4/6*	1	N/A	0	1	N/A	0	1	1
Yamashita 2015 (43) *Score: 5/6*	0	N/A	1	1	N/A	1	1	1
Yang 2016 (44) *Score: 4/6*	1	N/A	0	1	N/A	0	1	1

Table C2 – Quality Scores of Included Randomized Controlled Trials

Randomized Controlled Trials (Jadad Scale (13))			
Author	**Randomization (0, 1, 2)**	**Blinding (0, 1, 2)**	**An account of all patients (0, 1)**
Elimian 2016 (22) *Score: 2/5*	2	0	0
Glover 2011 (25) *Score: 4/5*	1	2	1
Harper 2010 (28) *Score: 5/5*	2	2	1
Meis 2003 (35) *Score: 5/5*	2	2	1
Vermeulen 1999 (40) *Score: 4/5*	2	2	0

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.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
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.	n/a
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.	6-8
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.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix A
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).	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.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7-8
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.	7-8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
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.	8

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).	7-8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
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.	Figure 1, page 8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Appendix B
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).	Appendix C, pages 9-10
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.	Figures 2, 3, page 8-9
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Figures 2, 3, page 8-9
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Appendix C, pages 9-10
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	9
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).	10
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).	12-13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13
FUNDING			

PRISMA 2009 Checklist

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.	2

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

For more information, visit: **www.prisma-statement.org**.

BMJ Open

Risk of Recurrent Spontaneous Preterm Birth: A Systematic Review and Meta-Analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-015402.R2
Article Type:	Research
Date Submitted by the Author:	31-May-2017
Complete List of Authors:	Phillips, Courtney; University of Calgary Velji, Zain; University of Calgary Hanly, Ciara; University of British Columbia Metcalfe, Amy; University of Calgary, Obstetrics and Gynecology
Primary Subject Heading:	Obstetrics and gynaecology
Secondary Subject Heading:	Obstetrics and gynaecology, Epidemiology, Evidence based practice, Paediatrics
Keywords:	EPIDEMIOLOGY, NEONATOLOGY, OBSTETRICS, PAEDIATRICS

Risk of Recurrent Spontaneous Preterm Birth: A Systematic Review and Meta-Analysis

Ms. Courtney PHILLIPS[1] BSc, Ms. Zain VELJI[2] BSc, Ms. Ciara HANLY[3], Dr. Amy METCALFE[4,5] PhD

[1]Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada
[2]Faculty of Nursing, University of Calgary, Calgary, Alberta, Canada
[3]School of Kinesiology, University of British Columbia, Vancouver, British Columbia, Canada
[4]Department of Obstetrics and Gynecology, University of Calgary, Calgary, Alberta, Canada
[5]Department of Community Health Sciences, University of Calgary, Calgary, Alberta, Canada

Address for Correspondence:
Amy Metcalfe
Foothills Medical Centre, 4th Floor North Tower
1403 29 St NW
Calgary, Alberta, Canada
T2N 2T9
Email: amy.metcalfe@albertahealthservices.ca
Phone: 403-944-8458

Short Title: Risk of Recurrent Spontaneous Preterm Birth

Condensation: The risk of recurrent spontaneous preterm birth is high, and tends to reoccur more frequently following preterm labor than preterm premature rupture of membranes.

Conflict of Interest: The authors have no conflicts of interest to report

Contributorship Statement: All authors made a substantial contribution to this study. CP, ZV and CH conducted the systematic review. CP drafted the manuscript. AM designed the study and conducted the meta-analysis. All authors critically reviewed the manuscript, interpreted the findings, and approved the final version. All authors had full access to all of the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. As the senior author AM affirms that the manuscript is an honest, accurate, and transparent account of the study being reported, that no important aspects of the study have been omitted, and that any discrepancies from the study as planned have been explained.

Data Sharing Agreement: No additional data is available

inclusion of electronic links from the Contribution to third party material where-ever it may be located; and, vi) licence any third party to do any or all of the above.

Funding: This study was funded by the Alberta Children's Hospital Research Institute. Amy Metcalfe is supported by a New Investigator Award from the Canadian Institutes of Health Research. The funder had no role in study design, execution, or publication decisions.

Word Count (Abstract): 236
Word Count (Manuscript): 2656
Number of References: 55
Number of Tables: 0
Number of Figures: 3
Number of Appendices: 3

Abstract

Objective: To determine the risk of recurrent spontaneous preterm birth following spontaneous preterm birth in singleton pregnancies.

Design: Systematic review and meta-analysis using random effects models.

Data Sources: An electronic literature search was conducted in OVID Medline (1948-2017), Embase (1980-2017), and ClinicalTrials.gov (completed studies effective 2017), supplemented by hand-searching bibliographies of included studies, to find all studies with original data concerning recurrent spontaneous preterm birth.

Study Eligibility Criteria: Studies had to include women with at least one spontaneous preterm singleton live birth (<37 weeks) and at least one subsequent pregnancy resulting in a singleton live birth. The Newcastle-Ottawa Scale and Jadad Scale were used to assess the study quality of cohort studies and randomized controlled trials respectively.

Results: Overall, 32 articles involving 55,197 women, met all inclusion criteria. Generally studies were well conducted and had a low risk of bias. The absolute risk of recurrent spontaneous preterm birth at <37 weeks gestation was 30.0% (95% CI: 27.0-34.0%). The risk of recurrence due to preterm premature rupture of membranes (PPROM) at <37 weeks gestation was 7.0% (95% CI: 6.0-9.0%), while the risk of recurrence due to preterm labor at <37 weeks gestation was 23.0% (95% CI: 13.0-33.0%).

Conclusions: The risk of recurrent spontaneous preterm birth is high and is influenced by the underlying clinical pathway leading to the birth. This information is important for clinicians when discussing the recurrence risk of spontaneous preterm birth with their patients.

Key Words: preterm birth, preterm labor, preterm premature rupture of membranes, recurrence, systematic review

Article Summary – Strengths and Limitations of This Study:

- Study strengths include the comprehensive search strategy with no language restrictions used in the nature of the systematic review.
- Limitations primarily relate to the underlying data that was available on this topic. Most of the included studies were observational in nature. Additionally, many primary studies examining the recurrence risk of preterm birth had to be excluded as they did not clearly differentiate between spontaneous and indicated preterm delivery. There was a high degree of heterogeneity in the studies included in the meta-analysis.

Introduction

Preterm birth (PTB) is defined as any live birth occurring before 37 completed weeks of gestation; this can be subdivided into extremely preterm (<28 weeks), very preterm (28-<32 weeks), moderately preterm (32-<34 weeks) and late preterm (34-<37 weeks) birth based on the gestational age at delivery (1). This sub-categorization is important as gestational age is inversely associated with increased mortality, morbidity and the intensity of neonatal care required at birth (2). Worldwide, 11.1% of infants are born preterm every year (2). Preterm birth is the leading cause of perinatal morbidity and mortality, and second most common cause of death, after pneumonia, in children under five years of age (3, 4).

Indicated preterm births (iPTB) are those induced for medical reasons, such a pre-eclampsia, intrauterine growth restriction, or fetal distress. However, approximately 70% of PTB occur spontaneously (sPTB) (5). The clinical pathways that lead to sPTB typically include preterm labor (PTL) and preterm premature rupture of membranes (PPROM), although these occur on a spectrum and may co-occur in the same clinical setting. PTL is defined as regular contractions and cervical changes at less than 37 weeks gestation, and PPROM is defined as spontaneous rupture of membranes at least one hour before contractions at less than 37 weeks gestation (5). Known risk factors for spontaneous preterm birth include a previous preterm birth, black race, low maternal body-mass index, comorbidities, a short cervical length and a raised fetal fibronectin concentration (5, 6). Despite knowing these risk factors, our understanding of the etiology behind sPTB is poor and sPTB is considered to be multifactorial in nature (6, 7).

Although sPTB has a tendency to recur, little is known about the recurrence risk (7). This is of concern because sPTB is a leading cause of neonatal morbidity and mortality, and it also has a large economic burden (8). Further, women who have had a previous sPTB are likely to be anxious during their subsequent pregnancies, which itself can lead to sPTB and other adverse

pregnancy outcomes (9-11). Therefore, we conducted a systematic review and meta-analysis to investigate the absolute risk of recurrent sPTB following sPTB in singleton pregnancies. By better understanding the recurrence risk of sPTB, healthcare workers may be better equipped to manage patient needs and anxieties, as well as develop and apply preventative treatments.

Methods

Two study authors (ZV and CH) executed a comprehensive literature search of Medline (from 1946 to 2015) and Embase (from 1980 to 2015) to identify publications that contained key terms related to recurrent sPTB in June 2015. The search was updated in July 2016, and expanded to included completed studies identified through ClinicalTrials.gov. The search was further updated in May 2017. PPROM, PTL and related terms were included in the search. For the full search strategy, please refer to Appendix A. Titles and abstracts of these articles were screened for relevance to determine which articles were to undergo full-text review. Two independent reviewers (ZV and CP) jointly assessed the final eligibility of the full-text reviewed articles. We resolved disagreements in full-text eligibility or data abstraction by involvement of a third party (AM). The bibliographies of included studies were reviewed to identify additional publications not found through the database search. A complete summary of the search strategy can be found in Figure 1. No patients were directly involved in this study. As this study only used published data, it was exempt from Institutional Review Board approval.

All studies with original data concerning recurrent sPTB and N≥20 were considered for inclusion. No language restrictions were used. Conference abstracts were not considered. To be included, studies had to include women with at least one spontaneous preterm live birth (delivery <37 weeks of gestation) in their obstetric history and at least one subsequent pregnancy resulting in a live birth. Only studies looking at singleton pregnancies were included. Animal studies,

studies that only included iPTB, studies that combined iPTB and sPTB, and studies on PPROM or PTL where it was not clear if it resulted in sPTB were excluded. In the case of duplicate data, the study with the largest sample size was included.

The data extraction was completed independently by ZV and CP using a standardized data extraction form. Data was reviewed by AM prior to analysis to ensure completeness. Information on the authors, title, publication year, data year, location of study, study design, definitions of preterm birth, and inclusion and exclusion criteria were all extracted. In addition, information was extracted on the number of women with spontaneous preterm birth in their initial pregnancy, whether due to PPROM or PTL, number of women with term births in subsequent pregnancies, and number of women with preterm births in subsequent pregnancies, whether due to PPROM, PTL or indicated causes. For studies that reported on total reproductive history, only data on the first 2 consecutive pregnancies were extracted. The Newcastle-Ottawa Scale (12) and the Jadad Scale (13) were used to assess study quality of cohort studies and randomized controlled trials respectively. Given the observational nature of this review, the quality of randomized controlled trials was additionally assessed using the criteria found in the Newcastle-Ottawa Scale.

The primary outcome measured was the recurrence rate of sPTB at <37 weeks gestation. Secondary outcomes were recurrence rate of sPTB due to PPROM at <37 weeks (following sPTB due to PPROM in the index pregnancy), recurrence rate of sPTB due to PTL at <37 weeks (following sPTB due to PTL in the index pregnancy), the recurrence of sPTB by gestational age, and occurrence of iPTB at <37 weeks after a previous sPTB.

For our analysis, we reported the pooled risk of recurrent preterm birth and accompanying 95% confidence interval (CIs) for sPTB <37 weeks gestation, by iPTB, by

gestational age overall, and for PPROM and PTL. Stratified analysis was used to examine the recurrence rate of sPTB <37 weeks gestation by study design and quality. An a priori decision was made to use a random-effects model for all models in anticipation of clinical heterogeneity between studies. The metaprop command in Stata was used to conduct the analysis and exact confidence intervals were reported (14). Forest plots were used to graphically represent the data. Heterogeneity between studies was assessed using I^2, the Cochrane Q statistic, and accompanying p-values. All analyses were conducted using Stata SE Version 14 (College Station, Texas).

Results

The search returned 11,775 articles, of which 118 met criteria for full-text review (Figure 1). Overall 32 articles met all of the inclusion criteria and were included in the review (15-46). A summary of all of the studies' data can be found in Appendix B (recurrence risk of sPTB is located in Table B1 and occurrence risk of iPTB following sPTB is located in Table B2). The included studies were almost entirely cohort studies, with only five randomized controlled trials (23, 27, 29, 36, 41). The sample sizes in the studies ranged from 33 to 17,334 women and the rate of recurrent sPTB at <37 weeks gestation ranged from 15.4% to 85.5%. Many of the studies had different definitions of sPTB and therefore they could not be combined for meta-analysis. There were only a sufficient number of studies that defined preterm birth as occurring prior to 37 weeks in both the index and subsequent pregnancy to create pooled estimates.

The overall risk of recurrent sPTB at <37 weeks gestation (n=25 studies, 52,070 women) was 30.0% (95% CI: 27.0-34.0%) with a significant Q (P=0.00) and I^2 of 98.6%, indicating between-study heterogeneity (Figure 2). The recurrence rate did not significantly differ between randomized controlled trials (34.0%, 95% CI: 29.0-38.0%; n=5 studies, 1,661 women) and

cohort studies (29.0%, 95% CI: 26.0-33.0%, n=20 studies, 50,409 women). The risk of iPTB at <37 weeks gestation after a previous spontaneous preterm birth (n=6 studies, 18,355 women) was 5.0% (95% CI: 3.0-7.0%) with an I^2 of 98.0%.

Few studies looked specifically at the recurrence of PPROM and PTL resulting in sPTB in singleton pregnancies following prior PPROM or PTL respectively. However, the identified risk of recurrent PPROM at <37 weeks gestation (n=4 studies, 3,138 women) was 7.0% (95% CI: 6.0-9.0%) with an I^2 of 51.0% and the risk of recurrent PTL at <37 weeks gestation (n=3 studies, 2,852 women) was 23.0% (95% CI: 13.0-33.0%) with an I^2 of 97.3% (Figure 3).

The majority of the studies were of high quality (Appendix C – cohort studies are located in Table C1 and randomized controlled trials in Tables C2 and C3). As this study exclusively examined the recurrence risk of spontaneous preterm birth, two elements of the Newcastle Ottawa Scale relating to the selection of the unexposed cohort and the comparability of the exposed and unexposed cohorts were unable to be assessed. Cohort studies typically traded off between being generalizable to the broader patient population not seen in a tertiary center or having detailed clinical data available. All cohort studies had a quality score of 4 or 5 out of a possible 6 points. No statistically significant differences in the recurrence rate of sPTB prior to 37 weeks was observed based on quality score in cohort studies (Score 4: 27.0%, 95% CI: 21.0-32.0%; Score 5: 31.0%, 95% CI: 26.0-36.0%). All but one randomized controlled trial was deemed to be high quality (Jahad score ≥4/5) (23). This low-quality trial did report a higher recurrence risk (41.0%, 95% CI: 33.0-49.0) than the pooled estimated generated from high quality trials (32.0%, 95% CI: 28.0-37.0); however, as evidenced by the overlapping confidence intervals, these estimates are not statistically different.

Discussion

This meta-analysis provides an overview of the overall risk of recurrent spontaneous preterm birth. We found that the absolute risk of recurrent sPTB at less than 37 weeks gestation in pregnancies was 30%; this estimate was consistent across study designs and study quality. Interestingly, the risk of recurrent PTL was found to be 23%, similar to the overall risk of recurrent sPTB. Conversely, if a woman has a sPTB due to PPROM, she is less likely to have recurrent PPROM leading to sPTB, with a risk of only 7%. Thus the clinical pathway that leads to sPTB appears to influence the risk of recurrence.

In a 2014 systematic review by Kazemier et al., they found that the risk of recurrence of preterm birth is influenced by the singleton/twin order in both pregnancies. When they looked at spontaneous preterm singleton births after a previous singleton pregnancy, they found that the risk of recurrence of sPTB was 20.2% (47). In contrast to ours, their search strategy was exceedingly complex and included only cohort studies. Ultimately after abstract review they were left with only six studies that looked at singleton-singleton pregnancies, which could explain the difference in our recurrence risk. Further, our study is novel as we differentiated risk by clinical pathway leading to sPTB, whether PTL or PPROM. Ultimately, we found that while all sPTB tends to recur, the clinical pathway of the first sPTB is important in determining that recurrence risk. Previous studies tend to combine these underlying pathways together, but our results suggest that perhaps they should not be pooled. Some studies also suggest that children born following PPROM have increased mortality (48-50) and worse health outcomes (51) compared to children born after PTL, which further supports the premise that these should be looked at as separate clinical conditions.

However, new evidence suggests that PTB and the underlying pathologies that lead to PTB are not mutually exclusive, thus spontaneous and indicated PTB should perhaps not be

considered completely separate phenomena. Basso and Wilcox estimated that mortality due to immaturity itself was about 51%, whereas underlying pathologies that led to PTB accounted for approximately half of mortality (52). Similarly, in a recent study by Brown et al., the authors found that gestational age is on the causal path between biological determinants of preterm birth and neonatal outcomes (53). Infants who were exposed to both pathological intrauterine conditions and early delivery had increased risk for poor neonatal outcomes. As such a pathological intrauterine environment, for instance, one characterized by infection, placental ischemia and other biological determinants, acts through early delivery to produce poor outcomes. Ananth et al. found that women with a sPTB were not only likely to experience recurrent sPTB, but they were also associated with increased risks of having a medically indicated PTB, and vice versa (7). Prevention of preterm mortality requires more than the resolution of PTB, but must also address the underlying etiologies.

Strengths of our systematic review and meta-analysis include our broad search strategy with no language restrictions, which resulted in a large sample size of pooled data. Limitations include the fact that most of the studies were observational cohort studies and thus prone to bias, and there was significant between-study heterogeneity. This is important as many women included in this body of literature would have been offered some form of therapy to reduce their risks of recurrent preterm birth. In a similar vein, we also included participants from both the treated and control arms of the included randomized controlled trials. With the exception of the trial lead by Meis et al, which found a statistically significant reduction in the incidence of sPTB in women treated with progesterone (RR=0.66, 95% CI: 0.54-0.81) (36), the other trials had null findings. Strategies to prevent preterm birth are varied and evidence of their effectiveness are mixed (54). Effective strategies to prevent preterm birth can be implemented at the individual

level (i.e. progesterone supplementation, cervical cerclage, smoking cessation), the clinic/hospital level (i.e. hard-stop policies to prevent non-medically indicated late preterm and early term birth, preterm birth prevention clinics) and the societal level (i.e. smoke-free legislation to reduce environmental tobacco smoke, legislation regarding single-embryo transfer during in vitro fertilization) (54). As documentation of specific treatment strategies was not consistently reported in this body of literature, we were not able to synthesize these results according to specific types of treatment. While both small and large studies were identified and included, publication bias cannot be entirely ruled out. While the decision to only include studies with a minimum sample size of 20 was used to exclude case studies of rare cases that may not be generalizable, this may have inadvertently resulted in the exclusion of some small case series. Additionally, we only searched 3 independent sources and reviewed the bibliographies of included articles, thus articles in journals that were not indexed in either Medline or Embase or studies that were not registered on clinicialtrials.gov or were not cited by articles that were ultimately included in this review would not have been identified. We anticipate that the impact of this would be minimal as a study examining the effectiveness of different databases to identify studies related to maternal morbidity and mortality concluded that Medline and Embase has the highest yield in identifying unique studies, and that over 60% of all studies were identified by multiple sources (55). Although we were able to identify a large number of studies, many of them used different definitions for preterm birth and most did not identify the clinical pathway to PTB; as a consequence, these data could not be pooled and not all of the existing evidence could be summarized in this review.

In conclusion, our study reaffirmed that a previous spontaneous preterm birth is a significant risk factor for recurrence in subsequent pregnancies, placing that risk at 30%.

However, substantial heterogeneity in underlying studies speaks to the need for common definitions and further work in this area. Additionally, the absolute risk of recurrence appears to be substantially higher if the underlying etiology is PTL as opposed to PPROM. Clinically, this information will help with risk stratification and patient counseling. Interventions to prevent PTB need to be focused and designed for specific clinical conditions. Further studies need to be done that look at the efficacy of preventative treatments in the prevention of PTL and PPROM. Knowledge of the etiology of previous sPTB may help identify women at increased risk of sPTB for participation in future clinical trials.

References

1. March of Dimes, PMNCH, Save the Children, WHO. The global action report on preterm birth. Geneva: World Health Organization; 2012.
2. Blencowe H, Cousens S, Oestergaard MZ, Chou D, Moller AB, Narwal R, et al. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. Lancet. 2012;379(9832):2162-72.
3. Lawn JE, Cousens S, Zupan J, Lancet Neonatal Survival Steering T. 4 million neonatal deaths: when? Where? Why? Lancet. 2005;365(9462):891-900.
4. Liu L, Johnson HL, Cousens S, Perin J, Scott S, Lawn JE, et al. Global, regional, and national causes of child mortality: an updated systematic analysis for 2010 with time trends since 2000. Lancet. 2012;379(9832):2151-61.
5. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. Lancet. 2008;371(9606):75-84.
6. Mazaki-Tovi S, Romero R, Kusanovic JP, Erez O, Pineles BL, Gotsch F, et al. Recurrent preterm birth. Semin Perinatol. 2007;31(3):142-58.
7. Ananth CV, Vintzileos AM. Epidemiology of preterm birth and its clinical subtypes. J Matern Fetal Neonatal Med. 2006;19(12):773-82.
8. Lim G, Tracey J, Boom N, Karmakar S, Wang J, Berthelot JM, et al. CIHI survey: Hospital costs for preterm and small-for-gestational age babies in Canada. Healthc Q. 2009;12(4):20-4.
9. McDonald SW, Kingston D, Bayrampour H, Dolan SM, Tough SC. Cumulative psychosocial stress, coping resources, and preterm birth. Arch Womens Ment Health. 2014;17(6):559-68.
10. Shapiro GD, Fraser WD, Frasch MG, Seguin JR. Psychosocial stress in pregnancy and preterm birth: associations and mechanisms. J Perinat Med. 2013;41(6):631-45.
11. Loomans EM, van Dijk AE, Vrijkotte TG, van Eijsden M, Stronks K, Gemke RJ, et al. Psychosocial stress during pregnancy is related to adverse birth outcomes: results from a large multi-ethnic community-based birth cohort. Eur J Public Health. 2013;23(3):485-91.
12. Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analysis Ottawa: Ottawa Hospital Research Institute; 2014 [Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
13. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials. 1996;17(1):1-12.
14. Nyaga VN, Arbyn M, Aerts M. Metaprop: a Stata command to perform meta-analysis of binomial data. Arch Public Health. 2014;72(1):39.
15. Ananth CV, Getahun D, Peltier MR, Salihu HM, Vintzileos AM. Recurrence of spontaneous versus medically indicated preterm birth. Am J Obstet Gynecol. 2006;195(3):643-50.
16. Asrat T, Lewis DF, Garite TJ, Major CA, Nageotte MP, Towers CV, et al. Rate of recurrence of preterm premature rupture of membranes in consecutive pregnancies. Am J Obstet Gynecol. 1991;165(4 Pt 1):1111-5.

17. Care AG, Sharp AN, Lane S, Roberts D, Watkins L, Alfirevic Z. Predicting preterm birth in women with previous preterm birth and cervical length >/= 25 mm. Ultrasound Obstet Gynecol. 2014;43(6):681-6.
18. Carr-Hill RA, Hall MH. The repetition of spontaneous preterm labour. Br J Obstet Gynaecol. 1985;92(9):921-8.
19. Coleman S, Wallace L, Alexander J, Istwan N. Recurrent preterm birth in women treated with 17 alpha-hydroxyprogesterone caproate: the contribution of risk factors in the penultimate pregnancy. J Matern Fetal Neonatal Med. 2012;25(7):1034-8.
20. Crane JM, Hutchens D. Use of transvaginal ultrasonography to predict preterm birth in women with a history of preterm birth. Ultrasound Obstet Gynecol. 2008;32(5):640-5.
21. Drassinower D, Obican SG, Siddiq Z, Heller D, Gyamfi-Bannerman C, Friedman AM. Does the clinical presentation of a prior preterm birth predict risk in a subsequent pregnancy? Am J Obstet Gynecol. 2015;213(5):686 e1-7.
22. Ekwo E, Moawad A. The risk for recurrence of premature births to African-American and white women. J Assoc Acad Minor Phys. 1998;9(1):16-21.
23. Elimian A, Smith K, Williams M, Knudtson E, Goodman JR, Escobedo MB. A randomized controlled trial of intramuscular versus vaginal progesterone for the prevention of recurrent preterm birth. Int J Gynaecol Obstet. 2016;134(2):169-72.
24. Esplin MS, O'Brien E, Fraser A, Kerber RA, Clark E, Simonsen SE, et al. Estimating recurrence of spontaneous preterm delivery. Obstet Gynecol. 2008;112(3):516-23.
25. Getahun D, Strickland D, Ananth CV, Fassett MJ, Sacks DA, Kirby RS, et al. Recurrence of preterm premature rupture of membranes in relation to interval between pregnancies. Am J Obstet Gynecol. 2010;202(6):570 e1-6.
26. Glover MM, McKenna DS, Downing CM, Smith DB, Croom CS, Sonek JD. A randomized trial of micronized progesterone for the prevention of recurrent preterm birth. Am J Perinatol. 2011;28(5):377-81.
27. Goldenberg RL, Andrews WW, Faye-Petersen O, Cliver S, Goepfert AR, Hauth JC. The Alabama Preterm Birth Project: placental histology in recurrent spontaneous and indicated preterm birth. Am J Obstet Gynecol. 2006;195(3):792-6.
28. Gonzalez-Quintero VH, Cordova YC, Istwan NB, Tudela F, Rhea DJ, Romary LM, et al. Influence of gestational age and reason for prior preterm birth on rates of recurrent preterm delivery. Am J Obstet Gynecol. 2011;205(3):275 e1-5.
29. Harper M, Thom E, Klebanoff MA, Thorp J, Jr., Sorokin Y, Varner MW, et al. Omega-3 fatty acid supplementation to prevent recurrent preterm birth: a randomized controlled trial. Obstet Gynecol. 2010;115(2 Pt 1):234-42.
30. Himes KP, Simhan HN. Risk of recurrent preterm birth and placental pathology. Obstet Gynecol. 2008;112(1):121-6.
31. Hsieh TT, Chen SF, Shau WY, Hsieh CC, Hsu JJ, Hung TH. The impact of interpregnancy interval and previous preterm birth on the subsequent risk of preterm birth. J Soc Gynecol Investig. 2005;12(3):202-7.
32. Laughon SK, Albert PS, Leishear K, Mendola P. The NICHD Consecutive Pregnancies Study: recurrent preterm delivery by subtype. Am J Obstet Gynecol. 2014;210(2):131 e1-8.
33. Lykke JA, Paidas MJ, Langhoff-Roos J. Recurring complications in second pregnancy. Obstet Gynecol. 2009;113(6):1217-24.

34. Manuck TA, Henry E, Gibson J, Varner MW, Porter TF, Jackson GM, et al. Pregnancy outcomes in a recurrent preterm birth prevention clinic. Am J Obstet Gynecol. 2011;204(4):320 e1-6.
35. Markham KB, Walker H, Lynch CD, Iams JD. Preterm birth rates in a prematurity prevention clinic after adoption of progestin prophylaxis. Obstet Gynecol. 2014;123(1):34-9.
36. Meis PJ, Klebanoff M, Thom E, Dombrowski MP, Sibai B, Moawad AH, et al. Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. N Engl J Med. 2003;348(24):2379-85.
37. Mercer BM, Goldenberg RL, Moawad AH, Meis PJ, Iams JD, Das AF, et al. The preterm prediction study: effect of gestational age and cause of preterm birth on subsequent obstetric outcome. National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. Am J Obstet Gynecol. 1999;181(5 Pt 1):1216-21.
38. Owen J, Yost N, Berghella V, Thom E, Swain M, Dildy GA, 3rd, et al. Mid-trimester endovaginal sonography in women at high risk for spontaneous preterm birth. JAMA. 2001;286(11):1340-8.
39. Rittenberg C, Newman RB, Istwan NB, Rhea DJ, Stanziano GJ. Preterm birth prevention by 17 alpha-hydroxyprogesterone caproate vs. daily nursing surveillance. J Reprod Med. 2009;54(2):47-52.
40. Turitz AL, Bastek JA, Purisch SE, Elovitz MA, Levine LD. Patient characteristics associated with 17-alpha hydroxyprogesterone caproate use among a high-risk cohort. Am J Obstet Gynecol. 2016;214(4):536 e1-5.
41. Vermeulen GM, Bruinse HW. Prophylactic administration of clindamycin 2% vaginal cream to reduce the incidence of spontaneous preterm birth in women with an increased recurrence risk: a randomised placebo-controlled double-blind trial. Br J Obstet Gynaecol. 1999;106(7):652-7.
42. Vogel I, Goepfert AR, Thorsen P, Skogstrand K, Hougaard DM, Curry AH, et al. Early second-trimester inflammatory markers and short cervical length and the risk of recurrent preterm birth. J Reprod Immunol. 2007;75(2):133-40.
43. Wallace JM, Bhattacharya S, Campbell DM, Horgan GW. Inter-Pregnancy Weight Change and the Risk of Recurrent Pregnancy Complications. PLoS One. 2016;11(5):e0154812.
44. Yamashita M, Hayashi S, Endo M, Okuno K, Fukui O, Mimura K, et al. Incidence and risk factors for recurrent spontaneous preterm birth: A retrospective cohort study in Japan. J Obstet Gynaecol Res. 2015;41(11):1708-14.
45. Yang J, Baer RJ, Berghella V, Chambers C, Chung P, Coker T, et al. Recurrence of Preterm Birth and Early Term Birth. Obstet Gynecol. 2016;128(2):364-72.
46. Uquillas KR, Fox NS, Rebarber A, Saltzman DH, Klauser CK, Roman AS. A comparison of cervical length measurement techniques for the prediction of spontaneous preterm birth. J Matern Fetal Neonatal Med. 2017;30(1):50-3.
47. Kazemier BM, Buijs PE, Mignini L, Limpens J, de Groot CJ, Mol BW, et al. Impact of obstetric history on the risk of spontaneous preterm birth in singleton and multiple pregnancies: a systematic review. BJOG. 2014;121(10):1197-209.
48. Kamath-Rayne BD, DeFranco EA, Chung E, Chen A. Subtypes of preterm birth and the risk of postneonatal death. J Pediatr. 2013;162(1):28-34 e2.
49. Villar J, Abalos E, Carroli G, Giordano D, Wojdyla D, Piaggio G, et al. Heterogeneity of perinatal outcomes in the preterm delivery syndrome. Obstet Gynecol. 2004;104(1):78-87.

50. Chen A, Feresu SA, Barsoom MJ. Heterogeneity of preterm birth subtypes in relation to neonatal death. Obstet Gynecol. 2009;114(3):516-22.
51. Newman DE, Paamoni-Keren O, Press F, Wiznitzer A, Mazor M, Sheiner E. Neonatal outcome in preterm deliveries between 23 and 27 weeks' gestation with and without preterm premature rupture of membranes. Arch Gynecol Obstet. 2009;280(1):7-11.
52. Basso O, Wilcox A. Mortality risk among preterm babies: immaturity versus underlying pathology. Epidemiology. 2010;21(4):521-7.
53. Brown HK, Speechley KN, Macnab J, Natale R, Campbell MK. Neonatal morbidity associated with late preterm and early term birth: the roles of gestational age and biological determinants of preterm birth. Int J Epidemiol. 2014;43(3):802-14.
54. Newnham JP, Dickinson JE, Hart RJ, Pennell CE, Arrese CA, Keelan JA. Strategies to prevent preterm birth. Front Immunol. 2014;5:584.
55. Betran AP, Say L, Gulmezoglu AM, Allen T, Hampson L. Effectiveness of different databases in identifying studies for systematic reviews: experience from the WHO systematic review of maternal morbidity and mortality. BMC Med Res Methodol. 2005;5(1):6.

Figure 1: Flow diagram of included studies

Figure 2. Forest plot of the rate of recurrent spontaneous preterm birth at <37 weeks gestation

Figure 3. Forest plots of the rate of (a) recurrent PPROM and (b) recurrent PTL at <37 weeks gestation

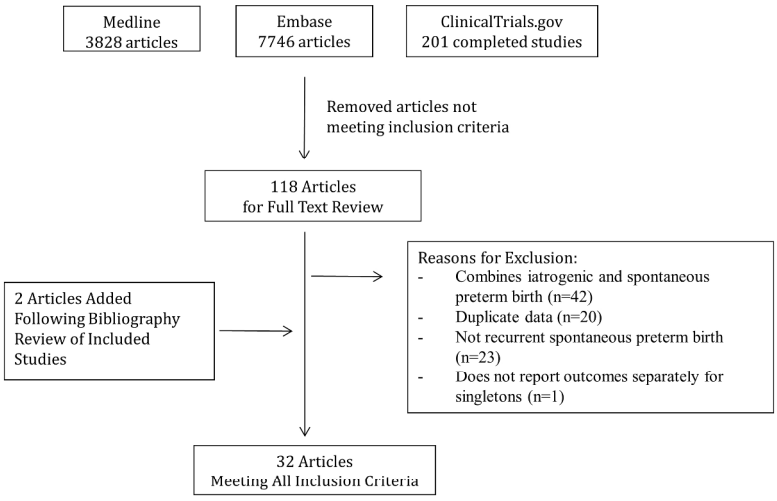


Figure 1: Flow diagram of included studies

254x190mm (300 x 300 DPI)

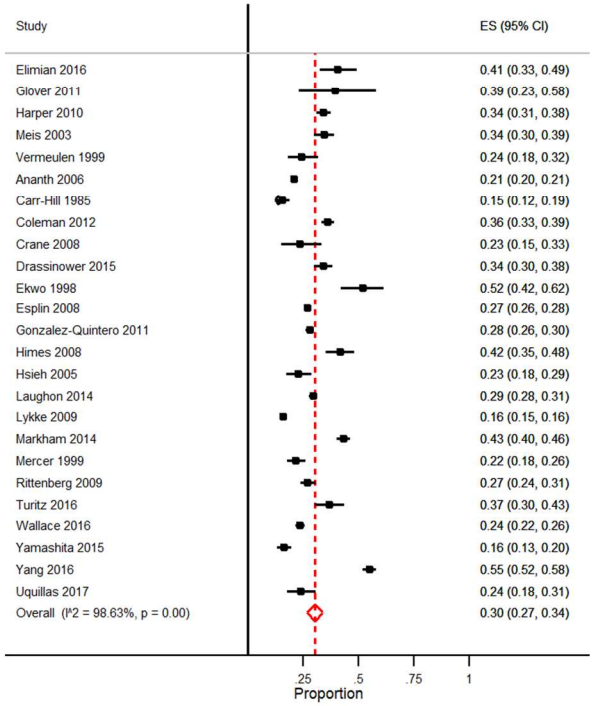


Figure 2. Forest plot of the rate of recurrent spontaneous preterm birth at <37 weeks gestation

254x190mm (300 x 300 DPI)

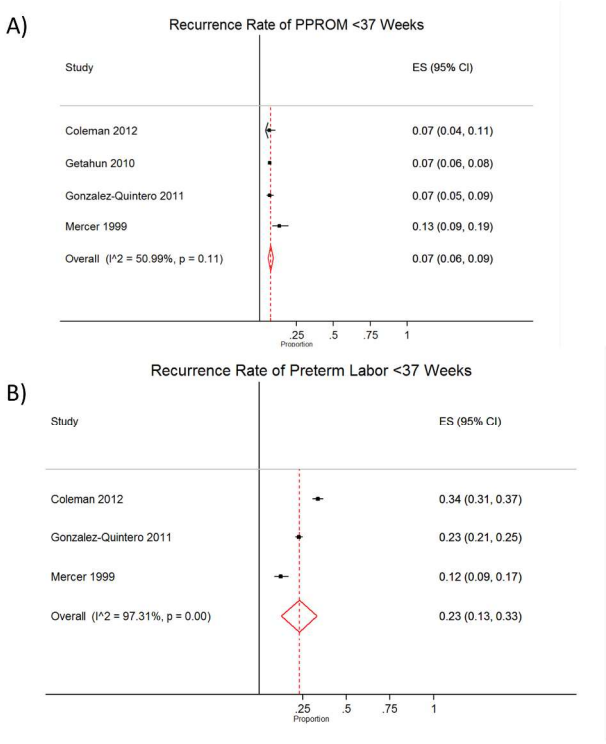


Figure 3. Forest plots of the rate of (a) recurrent PPROM and (b) recurrent PTL at <37 weeks gestation

254x190mm (300 x 300 DPI)

Appendix A. Search Strategy

Search Strategy:

1. Premature Birth
2. ((preterm or pre-term or premature or pre-mature) and (birth* or childbirth* or deliver* or parturit*))
3. Fetal Membranes, Premature Rupture
4. pprom
5. Obstetric Labor, Premature
6. ((preterm or pre-term or premature or pre-mature) and (labor or labour))
7. Recurrence
8. recur* or repeat
9. (1 or 2 or 3 or 4 or 5 or 6) and (7 or 8)

Initial Search Run on June 17, 2015
Updated Search Run on July 29, 2016
Updated Search Run on May 24, 2017

Appendix B. Included studies

Table B1 – Recurrence rate of spontaneous preterm birth

Author	Time Period	Country	Study Design	Inclusion/Exclusion Criteria	Gestational Age at Spontaneous Preterm Birth (weeks) Pregnancy 1	Gestational Age at Spontaneous Preterm Birth (weeks) Pregnancy 2	Recurrence Rate of Spontaneous Preterm Birth
Ananth 2006 (15)	1989-1997	USA	Cohort	*Inclusion:* Prior sPTB *Exclusion:* Multiple gestation pregnancies	<37	<37	2,626/12,670 (20.7%)
						<35	698/12,670 (5.5%)
						<32	164/12,670 (1.3%)
					<35	<35	698/4,463 (15.6%)
					<32	<32	164/2,022 (8.1%)
Asrat 1991 (16)		USA	Cohort	*Inclusion:* Prior PPROM *Exclusion:* Incompetent cervix, uterine anomalies, diethelstilbestrol exposure, multiple gestations, and neonates with congenital anomalies	<36	<36	39/121 (32.2%)
Care 2014 (17)	2010-2012	UK	Cohort	*Inclusion:* Prior sPTB or PROM; cervical length >25mm at 20-24 weeks *Exclusion:* Prior cervical surgery, non-viable pregnancy, history of iPTB, cerclage, uterine anomalies, Ehlers-Danlos syndrome, intrauterine death, twins, congenital abnormalities	<34	<37	53/196 (27.0%)
						<34	32/196 (16.3%)
Carr-Hill 1985 (18)	unspecified	UK	Cohort	*Inclusion:* Prior sPTB, singleton *Exclusion:* Multiple gestation, stillbirth, induced labor	<37	<37	76/494 (15.4%)

Author	Time Period	Country	Study Design	Inclusion/Exclusion Criteria	Gestational Age at Spontaneous Preterm Birth (weeks) Pregnancy 1	Gestational Age at Spontaneous Preterm Birth (weeks) Pregnancy 2	Recurrence Rate of Spontaneous Preterm Birth
Coleman 2012 (19)	2007-2010	USA	Cohort	*Inclusion:* Prior sPTB, received 17P injections *Exclusion:* Non-compliance with 17P injections	<37	<37	426/1,183 (36.0%)
						<35	156/1,183 (13.2%)
						<32	61/1,183 (5.2%)
Crane 2008 (20)	2000-2006	Canada	Cohort	*Inclusion:* Prior sPTB *Exclusion:* Cervical cerclage	<37	<37	21/90 (23.3%)
						<35	11/90 (12.2%)
						<34	8/90 (8.9%)
Drassinower 2015 (21)	2009-2014	USA	Cohort	*Inclusion:* Prior sPTB, singleton *Exclusion:* Multiple gestations, major fetal anomalies, cerclage, history of iPTB or placental abruption	<37	<37	178/522 (34.1%)
						<34	78/522 (14.9%)
						<28	34/522 (6.5%)
Ekwo 1998 (22)	1988-1993	USA	Cohort	*Inclusion:* Prior sPTB *Exclusion:* Fetal loss, multiple gestation	<37	<37	56/108 (51.9%)
Elimian 2016 (23)	2007-2010	USA	RCT	*Inclusion:* Prior sPTB *Exclusion:* Multiple gestation, major fetal anomaly or chromosomal anomalies, prior progesterone use in the current pregnancy, use of heparin in the current pregnancy, uterine anomaly, maternal medical conditions, no ultrasound before 20^{+6} in the current pregnancy	<37	<37	59/145 (40.7%)
						<34	27/145 (18.6%)
						<28	15/145 (10.3%)
Esplin 2008 (24)	1989-2001	USA	Cohort	*Inclusion:* First live birth in Utah and a subsequent live birth in the study period	<37	<37	1663/6,199 (26.8%)
					<34	<37	587/1,669 (35.2%)

Author	Time Period	Country	Study Design	Inclusion/Exclusion Criteria	Gestational Age at Spontaneous Preterm Birth (weeks) Pregnancy 1	Gestational Age at Spontaneous Preterm Birth (weeks) Pregnancy 2	Recurrence Rate of Spontaneous Preterm Birth
						<34	299/1,669 (17.9%)
Getahun 2010 (25) *PPROM only	1989-1997	USA	Cohort	*Inclusion:* Prior PPROM *Exclusion:* Multiple gestations, births <20 weeks, non White or Black race, >1 pregnancy before 1989	<37	<37	157/2,259 (6.9%)
					<34	<34	97/1,071 (9.1%)
					<32	<32	67/697 (9.6%)
					<28	<28	22/323 (6.8%)
Glover 2011 (26)	2006-2009	USA	RCT	*Inclusion:* Prior sPTB, initiated prenatal care prior to 20 weeks gestation *Exclusion:* Multiple gestations, major fetal anomaly	<37	<37	13/33 (39.4%)
Goldenberg 2006 (27)	1996-2001	USA	Cohort	*Inclusion:* Prior sPTB	<32	<37	71/83 (85.5%)
Gonzalez-Quintero 2011 (28)	2006-2009	USA	Cohort	*Inclusion:* Prior sPTB, singleton *Exclusion:* iPTB, >1 prior PTB, cerclage in current pregnancy	<37	<37	597/2,123 (28.1%)
						<35	274/2,123 (12.9%)
						<32	113/2,123 (5.3%)

Author	Time Period	Country	Study Design	Inclusion/Exclusion Criteria	Gestational Age at Spontaneous Preterm Birth (weeks)		Recurrence Rate of Spontaneous Preterm Birth
					Pregnancy 1	Pregnancy 2	
Harper 2010 (29)	2005-2006	USA	RCT	*Inclusion:* Prior sPTB, singleton *Exclusion:* Major fetal anomaly, intake of a fish oil supplement >500mg/week at any time during the preceding month, allergy to fish, anticoagulation therapy, hypertension, White's classification D or higher diabetes, drug or alcohol abuse, seizure disorder, uncontrolled thyroid disease, clotting disorder, current or planned cerclage, or a plan to deliver either elsewhere or before 37 weeks of gestation	<37	<37	292/852 (34.3%)
Himes 2008 (30)	2001-2006	USA	Cohort	*Inclusion:* Prior sPTB placenta pathology information available	<37	<37	102/245 (41.6%)
Hsieh 2005 (31)	1991-1997	Taiwan	Cohort	*Exclusion:* Multiple gestation, fetal anomaly, cervical incompetence, stillbirth, iPTB	<37	<37	52/228 (22.8%)
Laughon 2014 (32)	2002-2010	USA	Cohort	*Inclusion:* Singleton pregnancies	<37	<37	921/3,139 (29.3%)
Lykke 2009 (33)	1978-2007	Denmark	Cohort	*Inclusion:* Maternal age between 15-50 *Exclusion:* Women with cardiovascular disease, type 1 or 2 diabetes, women who emigrated within 3 months of 2nd delivery	<37 <33 <28	<37	2742/17,334 (15.8%) 444/1,734 (25.6%) 139/535 (26.0%)

Author	Time Period	Country	Study Design	Inclusion/Exclusion Criteria	Gestational Age at Spontaneous Preterm Birth (weeks) Pregnancy 1	Gestational Age at Spontaneous Preterm Birth (weeks) Pregnancy 2	Recurrence Rate of Spontaneous Preterm Birth
Manuck 2011 (34)	2002-2010	USA	Cohort	*Inclusion:* Prior sPTB, singleton *Exclusion:* History of iPTB or incompetent cervix	<35	<37	131/223 (58.7%)
						<32	25/223 (11.2%)
Markham 2014 (35)	1998-2012	USA	Cohort	*Inclusion:* Prior sPTB *Exclusion:* Multiple gestations, known uterine anomalies,	<37	<37	459/1,066 (43.1%)
						<35	269/1,066 (25.2%)
						<32	139/1,066 (13.0%)
Meis 2003 (36)	1999-2002	USA	RCT	*Inclusion:* Prior sPTB *Exclusion:* Multiple gestations, fetal anomaly, progesterone or heparin treatment during the current pregnancy, current or planned cervical cerclage, hypertension requiring medication, seizure disorder, or a plan to deliver elsewhere	<37	<37	159/463 (34.3%)
Mercer 1999 (37)	1992-1994	USA	Cohort	*Inclusion:* Singleton *Exclusion:* Placenta previa, major fetal malformations, cervical cerclage, polyhydramnios, oligohydramnios, cervical dilatation of ≥2 cm for nulliparous women and ≥3 cm for multiparous women.	<37	<37	89/410 (21.7%)
						<35	55/410 (13.4%)
						<32	21/410 (5.1%)
						<30	12/410 (2.9%)
						<28	10/410 (2.4%)
Owen 2001 (38)	1997-1999	USA	Cohort	*Inclusion:* Prior sPTB, singleton *Exclusion:* chronic medical or obstetrical problems, history of	<32	<35	48/183 (26.2%)
						<32	35/183 (19.1%)
						<28	29/183 (15.8%)

Author	Time Period	Country	Study Design	Inclusion/Exclusion Criteria	Gestational Age at Spontaneous Preterm Birth (weeks) Pregnancy 1	Gestational Age at Spontaneous Preterm Birth (weeks) Pregnancy 2	Recurrence Rate of Spontaneous Preterm Birth
				substance abuse, uterine anomalies, cerclage		<24	20/183 (10.9%)
Rittenberg 2009 (39)	1995-2005	USA	Cohort	*Inclusion:* Prior sPTB, singleton pregnancies, referred for weekly 17P administration *Exclusion:* Diagnosis of preterm labour, cerclage or vaginal bleeding at enrollment	<37	<37	185/684 (27.0%)
						<35	78/684 (11.4%)
						<32	30/684 (4.4%)
Turitz 2016 (40)	2009-2013	USA	Cohort	*Inclusion:* Prior sPTB	<37	<37	80/218 (36.7%)
Uquillas 2017 (46)	2005-2011	USA	Cohort	*Inclusion:* Prior sPTB *Exclusion:* Current cerclage, prior iPTB	<37	<37	43/181 (23.7%)
						<32	6/181 (3.3%)
Vermeulen 1999 (41)	1994-1996	Netherlands	RCT	*Inclusion:* Prior sPTB *Exclusion:* Fetal anomaly, previous iPTB, known allergy to clindamycin	<37	<37	41/168 (24.4%)
						<34	14/168 (8.3%)
Vogel 2007 (42)	2000-2001	USA	Cohort	*Inclusion:* Prior sPTB *Exclusion:* Multiple gestations, ruptured membranes, cerclage in a previous pregnancy	<30	<37	20/62 (32.3%)
						<35	15/62 (24.2%)
Wallace 2016 (43)	1986-2013	UK	Cohort		<37	<37	449/1,900 (23.6%)
Yamashita 2015 (44)	2008-2012	Japan	Cohort	*Inclusion:* Prior sPTB *Exclusion:* First antenatal visit after	<37	<37	89/547 (16.3%)
						<34	28/547 (5.1%)

Author	Time Period	Country	Study Design	Inclusion/Exclusion Criteria	Gestational Age at Spontaneous Preterm Birth (weeks)		Recurrence Rate of Spontaneous Preterm Birth
					Pregnancy 1	Pregnancy 2	
				14 weeks, previous iPTB, placenta previa, placental abruption, multiple gestation, fetal anomaly, antepartum fetal demise		<28	10/547 (1.8%)
Yang 2016 (45)	2005-2011	USA	Cohort		<37	<37	588/1,068 (55.1%)
						<32	71/1,068 (6.6%)
					<32	<32	43/177 (24.3%)

Table B2 – Occurrence of Indicated Preterm Birth Following Spontaneous Preterm Birth

Author	Time Period	Country	Study Design	Inclusion/Exclusion Criteria	Gestational Age at Preterm Birth (weeks) Pregnancy 1	Gestational Age at Preterm Birth (weeks) Pregnancy 2	Occurrence Rate of Indicated Preterm Birth Following a Prior Spontaneous Preterm Birth
Ananth 2006 (15)	1989-1997	USA	Cohort	*Inclusion:* Prior sPTB *Exclusion:* Multiple gestation pregnancies	<37	<37	342/12,670 (2.70%)
						<35	121/12,670 (0.96%)
						<32	40/12,670 (0.32%)
					<35	<35	121/4,463 (2.71%)
					<32	<32	40/2,022 (1.98%)
Harper 2010 (29)	2005-2006	USA	RCT	*Inclusion:* Prior sPTB, singleton *Exclusion:* Major fetal anomaly, intake of a fish oil supplement >500mg/week at any time during the preceding month, allergy to fish, anticoagulation therapy, hypertension, White's classification D or higher diabetes, drug or alcohol abuse, seizure disorder, uncontrolled thyroid disease, clotting disorder, current or planned cerclage, or a plan to deliver either elsewhere or before 37 weeks of gestation	<37	<37	46/852 (5.63%)
Laughon 2014 (32)	2002-2010	USA	Cohort	*Inclusion:* Singleton pregnancies	<37	<37	17/3,139 (0.54%)

Author	Time Period	Country	Study Design	Inclusion/Exclusion Criteria	Gestational Age at Preterm Birth (weeks) Pregnancy 1	Gestational Age at Preterm Birth (weeks) Pregnancy 2	Occurrence Rate of Indicated Preterm Birth Following a Prior Spontaneous Preterm Birth
Meis 2003 (36)	1999-2002	USA	RCT	*Inclusion:* Prior sPTB *Exclusion:* Multiple gestations, fetal anomaly, progesterone or heparin treatment during the current pregnancy, current or planned cervical cerclage, hypertension requiring medication, seizure disorder, or a plan to deliver elsewhere	<37	<37	36/463 (7.78%)
Owen 2001 (38)	1997-1999	USA	Cohort	*Inclusion:* Prior sPTB, singleton *Exclusion:* chronic medical or obstetrical problems, history of substance abuse, uterine anomalies, cerclage	<32	<35	5/183 (2.73%)
Rittenberg 2009 (39)	1995-2005	USA	Cohort	*Inclusion:* Prior sPTB, singleton pregnancies, referred for weekly 17P administration *Exclusion:* Diagnosis of preterm labour, cerclage or vaginal bleeding at enrollment	<37	<37	84/684 (12.28%)

Author	Time Period	Country	Study Design	Inclusion/Exclusion Criteria	Gestational Age at Preterm Birth (weeks)		Occurrence Rate of Indicated Preterm Birth Following a Prior Spontaneous Preterm Birth
					Pregnancy 1	Pregnancy 2	
Yamashita 2015 (44)	2008-2012	Japan	Cohort	*Inclusion:* Prior sPTB *Exclusion:* First antenatal visit after 14 weeks, previous iPTB, placenta previa, placental abruption, multiple gestation, fetal anomaly, antepartum fetal demise	<37	<37	23/547 (4.20%)

Appendix C: Quality Assessment

Table C1 – Quality Scores for Included Cohort Studies

Author	Cohort Studies (Newcastle Ottawa Scale (12)) Representatives of the exposed cohort (0, 1)	Selection of the non-exposed cohort (0, 1)	Ascertainment of exposure (0, 1)	Demonstration that outcome of interest was not present at start of study (0, 1)	Comparability of cohorts on the basis of design or analysis (0, 1)	Assessment of outcome (0, 1)	Was follow-up long enough for outcomes to occur (0, 1)	Adequacy of follow-up of cohorts (0, 1)
Ananth 2006 (15) *Score: 4/6*	1	N/A	0	1	N/A	0	1	1
Asrat 1991 (16) *Score: 5/6*	0	N/A	1	1	N/A	1	1	1
Care 2014 (17) *Score: 5/6*	0	N/A	1	1	N/A	1	1	1
Carr-Hill 1985 (18) *Score: 4/6*	1	N/A	0	1	N/A	0	1	1
Coleman 2012 (19) *Score: 5/6*	0	N/A	1	1	N/A	1	1	1
Crane 2008 (20) *Score: 5/6*	0	N/A	1	1	N/A	1	1	1

Author	Cohort Studies (Newcastle Ottawa Scale (12)) Representatives of the exposed cohort (0, 1)	Selection of the non-exposed cohort (0, 1)	Ascertainment of exposure (0, 1)	Demonstration that outcome of interest was not present at start of study (0, 1)	Comparability of cohorts on the basis of design or analysis (0, 1)	Assessment of outcome (0, 1)	Was follow-up long enough for outcomes to occur (0, 1)	Adequacy of follow-up of cohorts (0, 1)
Drassinower 2015 (21) *Score: 5/6*	0	N/A	1	1	N/A	1	1	1
Ekwo 1998 (22) *Score: 5/6*	0	N/A	1	1	N/A	1	1	1
Esplin 2008 (24) *Score: 4/6*	1	N/A	0	1	N/A	0	1	1
Getahun 2010 (25) *PPROM only *Score: 4/6*	1	N/A	0	1	N/A	0	1	1
Goldenberg 2006 (27) *Score: 5/6*	0	N/A	1	1	N/A	1	1	1
Gonzalez-Quintero 2011 (28) *Score: 5/6*	0	N/A	1	1	N/A	1	1	1

Author	Cohort Studies (Newcastle Ottawa Scale (12)) Representatives of the exposed cohort (0, 1)	Selection of the non-exposed cohort (0, 1)	Ascertainment of exposure (0, 1)	Demonstration that outcome of interest was not present at start of study (0, 1)	Comparability of cohorts on the basis of design or analysis (0, 1)	Assessment of outcome (0, 1)	Was follow-up long enough for outcomes to occur (0, 1)	Adequacy of follow-up of cohorts (0, 1)
Himes 2008 (30) *Score: 5/6*	0	N/A	1	1	N/A	1	1	1
Hsieh 2005 (31) *Score: 5/6*	0	N/A	1	1	N/A	1	1	1
Laughon 2014 (32) *Score: 4/6*	1	N/A	0	1	N/A	0	1	1
Lykke 2009 (33) *Score: 4/6*	1	N/A	0	1	N/A	0	1	1
Manuck 2011 (34) *Score: 5/6*	0	N/A	1	1	N/A	1	1	1
Markham 2014 (35) *Score: 5/6*	0	N/A	1	1	N/A	1	1	1
Mercer 1999 (37) *Score: 5/6*	0	N/A	1	1	N/A	1	1	1

Author	Cohort Studies (Newcastle Ottawa Scale (12)) Representatives of the exposed cohort (0, 1)	Selection of the non-exposed cohort (0, 1)	Ascertainment of exposure (0, 1)	Demonstration that outcome of interest was not present at start of study (0, 1)	Comparability of cohorts on the basis of design or analysis (0, 1)	Assessment of outcome (0, 1)	Was follow-up long enough for outcomes to occur (0, 1)	Adequacy of follow-up of cohorts (0, 1)
Owen 2001 (38) *Score: 5/6*	0	N/A	1	1	N/A	1	1	1
Rittenberg 2009 (39) *Score: 5/6*	0	N/A	1	1	N/A	1	1	1
Turitz 2016 (40) *Score: 5/6*	0	N/A	1	1	N/A	1	1	1
Uquillas 2017 (46) *Score: 5/6*	0	N/A	1	1	N/A	1	1	1
Vogel 2007 (42) *Score: 5/6*	0	N/A	1	1	N/A	1	1	1
Wallace 2016 (43) *Score: 4/6*	1	N/A	0	1	N/A	0	1	1
Yamashita 2015 (44) *Score: 5/6*	0	N/A	1	1	N/A	1	1	1

Author	Cohort Studies (Newcastle Ottawa Scale (12)) Representatives of the exposed cohort (0, 1)	Selection of the non-exposed cohort (0, 1)	Ascertainment of exposure (0, 1)	Demonstration that outcome of interest was not present at start of study (0, 1)	Comparability of cohorts on the basis of design or analysis (0, 1)	Assessment of outcome (0, 1)	Was follow-up long enough for outcomes to occur (0, 1)	Adequacy of follow-up of cohorts (0, 1)
Yang 2016 (45) *Score: 4/6*	1	N/A	0	1	N/A	0	1	1

Table C2 – Quality Scores of Included Randomized Controlled Trials – Jadad Scale

Author	Randomized Controlled Trials (Jadad Scale (13)) Randomization (0, 1, 2)	Blinding (0, 1, 2)	An account of all patients (0, 1)
Elimian 2016 (23) *Score: 2/5*	2	0	0
Glover 2011 (26) *Score: 4/5*	1	2	1
Harper 2010 (29) *Score: 5/5*	2	2	1
Meis 2003 (36) *Score: 5/5*	2	2	1
Vermeulen 1999 (41) *Score: 4/5*	2	2	0

Table C3 – Quality Scores of Included Randomized Controlled Trials – Newcastle Ottawa Scale

Author	Representatives of the exposed cohort (0, 1)	Selection of the non-exposed cohort (0, 1)	Ascertainment of exposure (0, 1)	Demonstration that outcome of interest was not present at start of study (0, 1)	Comparability of cohorts on the basis of design or analysis (0, 1)	Assessment of outcome (0, 1)	Was follow-up long enough for outcomes to occur (0, 1)	Adequacy of follow-up of cohorts (0, 1)
Elimian 2016 (23) *Score: 2/5*	0	1	1	1	1	1	1	1
Glover 2011 (26) *Score: 4/5*	0	1	1	1	1	1	1	1
Harper 2010 (29) *Score: 5/5*	0	1	1	1	1	1	1	1
Meis 2003 (36) *Score: 5/5*	0	1	1	1	1	1	1	1
Vermeulen 1999 (41) *Score: 4/5*	0	1	1	1	1	1	1	1

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.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
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.	n/a
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.	6-8
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.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix A
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).	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.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7-8
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.	7-8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
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.	8

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).	7-8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
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.	Figure 1, page 8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Appendix B
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).	Appendix C, pages 9-10
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.	Figures 2, 3, page 8-9
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Figures 2, 3, page 8-9
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Appendix C, pages 9-10
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	9
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).	10
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).	12-13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13
FUNDING			

PRISMA 2009 Checklist

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.	2

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

For more information, visit: **www.prisma-statement.org**.

BMJ Open

Risk of Recurrent Spontaneous Preterm Birth: A Systematic Review and Meta-Analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-015402.R3
Article Type:	Research
Date Submitted by the Author:	07-Jun-2017
Complete List of Authors:	Phillips, Courtney; University of Calgary Velji, Zain; University of Calgary Hanly, Ciara; University of British Columbia Metcalfe, Amy; University of Calgary, Obstetrics and Gynecology
Primary Subject Heading:	Obstetrics and gynaecology
Secondary Subject Heading:	Obstetrics and gynaecology, Epidemiology, Evidence based practice, Paediatrics
Keywords:	EPIDEMIOLOGY, NEONATOLOGY, OBSTETRICS, PAEDIATRICS

Risk of Recurrent Spontaneous Preterm Birth: A Systematic Review and Meta-Analysis

Ms. Courtney PHILLIPS[1] BSc, Ms. Zain VELJI[2] BSc, Ms. Ciara HANLY[3], Dr. Amy METCALFE[4,5] PhD

[1]Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada
[2]Faculty of Nursing, University of Calgary, Calgary, Alberta, Canada
[3]School of Kinesiology, University of British Columbia, Vancouver, British Columbia, Canada
[4]Department of Obstetrics and Gynecology, University of Calgary, Calgary, Alberta, Canada
[5]Department of Community Health Sciences, University of Calgary, Calgary, Alberta, Canada

Address for Correspondence:
Amy Metcalfe
Foothills Medical Centre, 4th Floor North Tower
1403 29 St NW
Calgary, Alberta, Canada
T2N 2T9
Email: amy.metcalfe@albertahealthservices.ca
Phone: 403-944-8458

Short Title: Risk of Recurrent Spontaneous Preterm Birth

Condensation: The risk of recurrent spontaneous preterm birth is high, and tends to reoccur more frequently following preterm labor than preterm premature rupture of membranes.

Conflict of Interest: The authors have no conflicts of interest to report

Contributorship Statement: All authors made a substantial contribution to this study. CP, ZV and CH conducted the systematic review. CP drafted the manuscript. AM designed the study and conducted the meta-analysis. All authors critically reviewed the manuscript, interpreted the findings, and approved the final version. All authors had full access to all of the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. As the senior author AM affirms that the manuscript is an honest, accurate, and transparent account of the study being reported, that no important aspects of the study have been omitted, and that any discrepancies from the study as planned have been explained.

Data Sharing Agreement: No additional data is available

inclusion of electronic links from the Contribution to third party material where-ever it may be located; and, vi) licence any third party to do any or all of the above.

Funding: This study was funded by the Alberta Children's Hospital Research Institute. Amy Metcalfe is supported by a New Investigator Award from the Canadian Institutes of Health Research. The funder had no role in study design, execution, or publication decisions.

Word Count (Abstract): 224
Word Count (Manuscript): 2596
Number of References: 54
Number of Tables: 0
Number of Figures: 3
Number of Appendices: 3

Abstract

Objective: To determine the risk of recurrent spontaneous preterm birth following spontaneous preterm birth in singleton pregnancies.

Design: Systematic review and meta-analysis using random effects models.

Data Sources: An electronic literature search was conducted in OVID Medline (1948-2017), Embase (1980-2017), and ClinicalTrials.gov (completed studies effective 2017), supplemented by hand-searching bibliographies of included studies, to find all studies with original data concerning recurrent spontaneous preterm birth.

Study Eligibility Criteria: Studies had to include women with at least one spontaneous preterm singleton live birth (<37 weeks) and at least one subsequent pregnancy resulting in a singleton live birth. The Newcastle-Ottawa Scale was used to assess study quality.

Results: Overall, 32 articles involving 55,197 women, met all inclusion criteria. Generally studies were well conducted and had a low risk of bias. The absolute risk of recurrent spontaneous preterm birth at <37 weeks gestation was 30.0% (95% CI: 27.0-34.0%). The risk of recurrence due to preterm premature rupture of membranes (PPROM) at <37 weeks gestation was 7.0% (95% CI: 6.0-9.0%), while the risk of recurrence due to preterm labor at <37 weeks gestation was 23.0% (95% CI: 13.0-33.0%).

Conclusions: The risk of recurrent spontaneous preterm birth is high and is influenced by the underlying clinical pathway leading to the birth. This information is important for clinicians when discussing the recurrence risk of spontaneous preterm birth with their patients.

Key Words: preterm birth, preterm labor, preterm premature rupture of membranes, recurrence, systematic review

Article Summary – Strengths and Limitations of This Study:

- Study strengths include the comprehensive search strategy with no language restrictions used in the nature of the systematic review.
- Limitations primarily relate to the underlying data that was available on this topic. Most of the included studies were observational in nature. Additionally, many primary studies examining the recurrence risk of preterm birth had to be excluded as they did not clearly differentiate between spontaneous and indicated preterm delivery. There was a high degree of heterogeneity in the studies included in the meta-analysis.

Introduction

Preterm birth (PTB) is defined as any live birth occurring before 37 completed weeks of gestation; this can be subdivided into extremely preterm (<28 weeks), very preterm (28-<32 weeks), moderately preterm (32-<34 weeks) and late preterm (34-<37 weeks) birth based on the gestational age at delivery (1). This sub-categorization is important as gestational age is inversely associated with increased mortality, morbidity and the intensity of neonatal care required at birth (2). Worldwide, 11.1% of infants are born preterm every year (2). Preterm birth is the leading cause of perinatal morbidity and mortality, and second most common cause of death, after pneumonia, in children under five years of age (3, 4).

Indicated preterm births (iPTB) are those induced for medical reasons, such a pre-eclampsia, intrauterine growth restriction, or fetal distress. However, approximately 70% of PTB occur spontaneously (sPTB) (5). The clinical pathways that lead to sPTB typically include preterm labor (PTL) and preterm premature rupture of membranes (PPROM), although these occur on a spectrum and may co-occur in the same clinical setting. PTL is defined as regular contractions and cervical changes at less than 37 weeks gestation, and PPROM is defined as spontaneous rupture of membranes at least one hour before contractions at less than 37 weeks gestation (5). Known risk factors for spontaneous preterm birth include a previous preterm birth, black race, low maternal body-mass index, comorbidities, a short cervical length and a raised fetal fibronectin concentration (5, 6). Despite knowing these risk factors, our understanding of the etiology behind sPTB is poor and sPTB is considered to be multifactorial in nature (6, 7).

Although sPTB has a tendency to recur, little is known about the recurrence risk (7). This is of concern because sPTB is a leading cause of neonatal morbidity and mortality, and it also has a large economic burden (8). Further, women who have had a previous sPTB are likely to be anxious during their subsequent pregnancies, which itself can lead to sPTB and other adverse

pregnancy outcomes (9-11). Therefore, we conducted a systematic review and meta-analysis to investigate the absolute risk of recurrent sPTB following sPTB in singleton pregnancies. By better understanding the recurrence risk of sPTB, healthcare workers may be better equipped to manage patient needs and anxieties, as well as develop and apply preventative treatments.

Methods

Two study authors (ZV and CH) executed a comprehensive literature search of Medline (from 1946 to 2015) and Embase (from 1980 to 2015) to identify publications that contained key terms related to recurrent sPTB in June 2015. The search was updated in July 2016, and expanded to included completed studies identified through ClinicalTrials.gov. The search was further updated in May 2017. PPROM, PTL and related terms were included in the search. For the full search strategy, please refer to Appendix A. Titles and abstracts of these articles were screened for relevance by 2 reviewers (ZV and CH) to determine which articles were to undergo full-text review. Articles identified by either reviewer at this stage as potentially relevant moved onto full text review. Two independent reviewers (ZV and CP) jointly assessed the final eligibility of the full-text reviewed articles. We resolved disagreements in full-text eligibility or data abstraction by involvement of a third party (AM). The bibliographies of included studies were reviewed to identify additional publications not found through the database search. A complete summary of the search strategy can be found in Figure 1. No patients were directly involved in this study. As this study only used published data, it was exempt from Institutional Review Board approval.

All studies with original data concerning recurrent sPTB and N≥20 were considered for inclusion. No language restrictions were used. Conference abstracts were not considered. To be included, studies had to include women with at least one spontaneous preterm live birth (delivery <37 weeks of gestation) in their obstetric history and at least one subsequent pregnancy resulting

in a live birth. Only studies looking at singleton pregnancies were included. Animal studies, studies that only included iPTB, studies that combined iPTB and sPTB, and studies on PPROM or PTL where it was not clear if it resulted in sPTB were excluded. In the case of duplicate data, the study with the largest sample size was included.

The data extraction was completed independently by ZV and CP using a standardized data extraction form. Data was reviewed by AM prior to analysis to ensure completeness. Information on the authors, title, publication year, data year, location of study, study design, definitions of preterm birth, and inclusion and exclusion criteria were all extracted. In addition, information was extracted on the number of women with spontaneous preterm birth in their initial pregnancy, whether due to PPROM or PTL, number of women with term births in subsequent pregnancies, and number of women with preterm births in subsequent pregnancies, whether due to PPROM, PTL or indicated causes. For studies that reported on total reproductive history, only data on the first 2 consecutive pregnancies were extracted. Given the observational nature of this review, the Newcastle-Ottawa Scale (12) was used to assess study quality of both cohort studies and randomized controlled trials.

The primary outcome measured was the recurrence rate of sPTB at <37 weeks gestation. Secondary outcomes were recurrence rate of sPTB due to PPROM at <37 weeks (following sPTB due to PPROM in the index pregnancy), recurrence rate of sPTB due to PTL at <37 weeks (following sPTB due to PTL in the index pregnancy), the recurrence of sPTB by gestational age, and occurrence of iPTB at <37 weeks after a previous sPTB.

For our analysis, we reported the pooled risk of recurrent preterm birth and accompanying 95% confidence interval (CIs) for sPTB <37 weeks gestation, by iPTB, by gestational age overall, and for PPROM and PTL. Stratified analysis was used to examine the

recurrence rate of sPTB <37 weeks gestation by study design and quality. An a priori decision was made to use a random-effects model for all models in anticipation of clinical heterogeneity between studies. The metaprop command in Stata was used to conduct the analysis and exact confidence intervals were reported (13). Forest plots were used to graphically represent the data. Heterogeneity between studies was assessed using I^2, the Cochrane Q statistic, and accompanying p-values. All analyses were conducted using Stata SE Version 14 (College Station, Texas).

Results

The search returned 11,775 articles, of which 118 met criteria for full-text review (Figure 1). Overall 32 articles met all of the inclusion criteria and were included in the review (14-45). A summary of all of the studies' data can be found in Appendix B (recurrence risk of sPTB is located in Table B1 and occurrence risk of iPTB following sPTB is located in Table B2). The included studies were almost entirely cohort studies, with only five randomized controlled trials (22, 26, 28, 35, 40). The sample sizes in the studies ranged from 33 to 17,334 women and the rate of recurrent sPTB at <37 weeks gestation ranged from 15.4% to 85.5%. Many of the studies had different definitions of sPTB and therefore they could not be combined for meta-analysis. There were only a sufficient number of studies that defined preterm birth as occurring prior to 37 weeks in both the index and subsequent pregnancy to create pooled estimates.

The overall risk of recurrent sPTB at <37 weeks gestation (n=25 studies, 52,070 women) was 30.0% (95% CI: 27.0-34.0%) with a significant Q (P=0.00) and I^2 of 98.6%, indicating between-study heterogeneity (Figure 2). The recurrence rate did not significantly differ between randomized controlled trials (34.0%, 95% CI: 29.0-38.0%; n=5 studies, 1,661 women) and cohort studies (29.0%, 95% CI: 26.0-33.0%, n=20 studies, 50,409 women). The risk of iPTB at

<37 weeks gestation after a previous spontaneous preterm birth (n=6 studies, 18,355 women) was 5.0% (95% CI: 3.0-7.0%) with an I^2 of 98.0%.

Few studies looked specifically at the recurrence of PPROM and PTL resulting in sPTB in singleton pregnancies following prior PPROM or PTL respectively. However, the identified risk of recurrent PPROM at <37 weeks gestation (n=4 studies, 3,138 women) was 7.0% (95% CI: 6.0-9.0%) with an I^2 of 51.0% and the risk of recurrent PTL at <37 weeks gestation (n=3 studies, 2,852 women) was 23.0% (95% CI: 13.0-33.0%) with an I^2 of 97.3% (Figure 3).

The majority of the studies were of high quality (Appendix C). As this study exclusively examined the recurrence risk of spontaneous preterm birth, two elements of the Newcastle Ottawa Scale relating to the selection of the unexposed cohort and the comparability of the exposed and unexposed cohorts were unable to be assessed. Cohort studies typically traded off between being generalizable to the broader patient population not seen in a tertiary center or having detailed clinical data available. All cohort studies had a quality score of 4 or 5 out of a possible 6 points. No statistically significant differences in the recurrence rate of sPTB prior to 37 weeks was observed based on quality score in cohort studies (Score 4: 27.0%, 95% CI: 21.0-32.0%; Score 5: 31.0%, 95% CI: 26.0-36.0%). All randomized controlled trials were deemed to be high quality (score 7/8).

Discussion

This meta-analysis provides an overview of the overall risk of recurrent spontaneous preterm birth. We found that the absolute risk of recurrent sPTB at less than 37 weeks gestation in pregnancies was 30%; this estimate was consistent across study designs and study quality. Interestingly, the risk of recurrent PTL was found to be 23%, similar to the overall risk of recurrent sPTB. Conversely, if a woman has a sPTB due to PPROM, she is less likely to have

recurrent PPROM leading to sPTB, with a risk of only 7%. Thus the clinical pathway that leads to sPTB appears to influence the risk of recurrence.

In a 2014 systematic review by Kazemier et al., they found that the risk of recurrence of preterm birth is influenced by the singleton/twin order in both pregnancies. When they looked at spontaneous preterm singleton births after a previous singleton pregnancy, they found that the risk of recurrence of sPTB was 20.2% (46). In contrast to ours, their search strategy was exceedingly complex and included only cohort studies. Ultimately after abstract review they were left with only six studies that looked at singleton-singleton pregnancies, which could explain the difference in our recurrence risk. Further, our study is novel as we differentiated risk by clinical pathway leading to sPTB, whether PTL or PPROM. Ultimately, we found that while all sPTB tends to recur, the clinical pathway of the first sPTB is important in determining that recurrence risk. Previous studies tend to combine these underlying pathways together, but our results suggest that perhaps they should not be pooled. Some studies also suggest that children born following PPROM have increased mortality (47-49) and worse health outcomes (50) compared to children born after PTL, which further supports the premise that these should be looked at as separate clinical conditions.

However, new evidence suggests that PTB and the underlying pathologies that lead to PTB are not mutually exclusive, thus spontaneous and indicated PTB should perhaps not be considered completely separate phenomena. Basso and Wilcox estimated that mortality due to immaturity itself was about 51%, whereas underlying pathologies that led to PTB accounted for approximately half of mortality (51). Similarly, in a recent study by Brown et al., the authors found that gestational age is on the causal path between biological determinants of preterm birth and neonatal outcomes (52). Infants who were exposed to both pathological intrauterine

conditions and early delivery had increased risk for poor neonatal outcomes. As such a pathological intrauterine environment, for instance, one characterized by infection, placental ischemia and other biological determinants, acts through early delivery to produce poor outcomes. Ananth et al. found that women with a sPTB were not only likely to experience recurrent sPTB, but they were also associated with increased risks of having a medically indicated PTB, and vice versa (7). Prevention of preterm mortality requires more than the resolution of PTB, but must also address the underlying etiologies.

Strengths of our systematic review and meta-analysis include our broad search strategy with no language restrictions, which resulted in a large sample size of pooled data. Limitations include the fact that most of the studies were observational cohort studies and thus prone to bias, and there was significant between-study heterogeneity. This is important as many women included in this body of literature would have been offered some form of therapy to reduce their risks of recurrent preterm birth. In a similar vein, we also included participants from both the treated and control arms of the included randomized controlled trials. With the exception of the trial lead by Meis et al, which found a statistically significant reduction in the incidence of sPTB in women treated with progesterone (RR=0.66, 95% CI: 0.54-0.81) (35), the other trials had null findings. Strategies to prevent preterm birth are varied and evidence of their effectiveness are mixed (53). Effective strategies to prevent preterm birth can be implemented at the individual level (i.e. progesterone supplementation, cervical cerclage, smoking cessation), the clinic/hospital level (i.e. hard-stop policies to prevent non-medically indicated late preterm and early term birth, preterm birth prevention clinics) and the societal level (i.e. smoke-free legislation to reduce environmental tobacco smoke, legislation regarding single-embryo transfer during in vitro fertilization) (53). As documentation of specific treatment strategies was not

consistently reported in this body of literature, we were not able to synthesize these results according to specific types of treatment. While both small and large studies were identified and included, publication bias cannot be entirely ruled out. While the decision to only include studies with a minimum sample size of 20 was used to exclude case studies of rare cases that may not be generalizable, this may have inadvertently resulted in the exclusion of some small case series. Additionally, we only searched 3 independent sources and reviewed the bibliographies of included articles, thus articles in journals that were not indexed in either Medline or Embase or studies that were not registered on clinicialtrials.gov or were not cited by articles that were ultimately included in this review would not have been identified. We anticipate that the impact of this would be minimal as a study examining the effectiveness of different databases to identify studies related to maternal morbidity and mortality concluded that Medline and Embase has the highest yield in identifying unique studies, and that over 60% of all studies were identified by multiple sources (54). Although we were able to identify a large number of studies, many of them used different definitions for preterm birth and most did not identify the clinical pathway to PTB; as a consequence, these data could not be pooled and not all of the existing evidence could be summarized in this review.

In conclusion, our study reaffirmed that a previous spontaneous preterm birth is a significant risk factor for recurrence in subsequent pregnancies, placing that risk at 30%. However, substantial heterogeneity in underlying studies speaks to the need for common definitions and further work in this area. Additionally, the absolute risk of recurrence appears to be substantially higher if the underlying etiology is PTL as opposed to PPROM. Clinically, this information will help with risk stratification and patient counseling. Interventions to prevent PTB need to be focused and designed for specific clinical conditions. Further studies need to be done

that look at the efficacy of preventative treatments in the prevention of PTL and PPROM. Knowledge of the etiology of previous sPTB may help identify women at increased risk of sPTB for participation in future clinical trials.

References

1. March of Dimes, PMNCH, Save the Children, WHO. The global action report on preterm birth. Geneva: World Health Organization; 2012.
2. Blencowe H, Cousens S, Oestergaard MZ, Chou D, Moller AB, Narwal R, et al. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. Lancet. 2012;379(9832):2162-72.
3. Lawn JE, Cousens S, Zupan J, Lancet Neonatal Survival Steering T. 4 million neonatal deaths: when? Where? Why? Lancet. 2005;365(9462):891-900.
4. Liu L, Johnson HL, Cousens S, Perin J, Scott S, Lawn JE, et al. Global, regional, and national causes of child mortality: an updated systematic analysis for 2010 with time trends since 2000. Lancet. 2012;379(9832):2151-61.
5. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. Lancet. 2008;371(9606):75-84.
6. Mazaki-Tovi S, Romero R, Kusanovic JP, Erez O, Pineles BL, Gotsch F, et al. Recurrent preterm birth. Semin Perinatol. 2007;31(3):142-58.
7. Ananth CV, Vintzileos AM. Epidemiology of preterm birth and its clinical subtypes. J Matern Fetal Neonatal Med. 2006;19(12):773-82.
8. Lim G, Tracey J, Boom N, Karmakar S, Wang J, Berthelot JM, et al. CIHI survey: Hospital costs for preterm and small-for-gestational age babies in Canada. Healthc Q. 2009;12(4):20-4.
9. McDonald SW, Kingston D, Bayrampour H, Dolan SM, Tough SC. Cumulative psychosocial stress, coping resources, and preterm birth. Arch Womens Ment Health. 2014;17(6):559-68.
10. Shapiro GD, Fraser WD, Frasch MG, Seguin JR. Psychosocial stress in pregnancy and preterm birth: associations and mechanisms. J Perinat Med. 2013;41(6):631-45.
11. Loomans EM, van Dijk AE, Vrijkotte TG, van Eijsden M, Stronks K, Gemke RJ, et al. Psychosocial stress during pregnancy is related to adverse birth outcomes: results from a large multi-ethnic community-based birth cohort. Eur J Public Health. 2013;23(3):485-91.
12. Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analysis Ottawa: Ottawa Hospital Research Institute; 2014 [Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
13. Nyaga VN, Arbyn M, Aerts M. Metaprop: a Stata command to perform meta-analysis of binomial data. Arch Public Health. 2014;72(1):39.
14. Ananth CV, Getahun D, Peltier MR, Salihu HM, Vintzileos AM. Recurrence of spontaneous versus medically indicated preterm birth. Am J Obstet Gynecol. 2006;195(3):643-50.
15. Asrat T, Lewis DF, Garite TJ, Major CA, Nageotte MP, Towers CV, et al. Rate of recurrence of preterm premature rupture of membranes in consecutive pregnancies. Am J Obstet Gynecol. 1991;165(4 Pt 1):1111-5.
16. Care AG, Sharp AN, Lane S, Roberts D, Watkins L, Alfirevic Z. Predicting preterm birth in women with previous preterm birth and cervical length >/= 25 mm. Ultrasound Obstet Gynecol. 2014;43(6):681-6.
17. Carr-Hill RA, Hall MH. The repetition of spontaneous preterm labour. Br J Obstet Gynaecol. 1985;92(9):921-8.

18. Coleman S, Wallace L, Alexander J, Istwan N. Recurrent preterm birth in women treated with 17 alpha-hydroxyprogesterone caproate: the contribution of risk factors in the penultimate pregnancy. J Matern Fetal Neonatal Med. 2012;25(7):1034-8.
19. Crane JM, Hutchens D. Use of transvaginal ultrasonography to predict preterm birth in women with a history of preterm birth. Ultrasound Obstet Gynecol. 2008;32(5):640-5.
20. Drassinower D, Obican SG, Siddiq Z, Heller D, Gyamfi-Bannerman C, Friedman AM. Does the clinical presentation of a prior preterm birth predict risk in a subsequent pregnancy? Am J Obstet Gynecol. 2015;213(5):686 e1-7.
21. Ekwo E, Moawad A. The risk for recurrence of premature births to African-American and white women. J Assoc Acad Minor Phys. 1998;9(1):16-21.
22. Elimian A, Smith K, Williams M, Knudtson E, Goodman JR, Escobedo MB. A randomized controlled trial of intramuscular versus vaginal progesterone for the prevention of recurrent preterm birth. Int J Gynaecol Obstet. 2016;134(2):169-72.
23. Esplin MS, O'Brien E, Fraser A, Kerber RA, Clark E, Simonsen SE, et al. Estimating recurrence of spontaneous preterm delivery. Obstet Gynecol. 2008;112(3):516-23.
24. Getahun D, Strickland D, Ananth CV, Fassett MJ, Sacks DA, Kirby RS, et al. Recurrence of preterm premature rupture of membranes in relation to interval between pregnancies. Am J Obstet Gynecol. 2010;202(6):570 e1-6.
25. Glover MM, McKenna DS, Downing CM, Smith DB, Croom CS, Sonek JD. A randomized trial of micronized progesterone for the prevention of recurrent preterm birth. Am J Perinatol. 2011;28(5):377-81.
26. Goldenberg RL, Andrews WW, Faye-Petersen O, Cliver S, Goepfert AR, Hauth JC. The Alabama Preterm Birth Project: placental histology in recurrent spontaneous and indicated preterm birth. Am J Obstet Gynecol. 2006;195(3):792-6.
27. Gonzalez-Quintero VH, Cordova YC, Istwan NB, Tudela F, Rhea DJ, Romary LM, et al. Influence of gestational age and reason for prior preterm birth on rates of recurrent preterm delivery. Am J Obstet Gynecol. 2011;205(3):275 e1-5.
28. Harper M, Thom E, Klebanoff MA, Thorp J, Jr., Sorokin Y, Varner MW, et al. Omega-3 fatty acid supplementation to prevent recurrent preterm birth: a randomized controlled trial. Obstet Gynecol. 2010;115(2 Pt 1):234-42.
29. Himes KP, Simhan HN. Risk of recurrent preterm birth and placental pathology. Obstet Gynecol. 2008;112(1):121-6.
30. Hsieh TT, Chen SF, Shau WY, Hsieh CC, Hsu JJ, Hung TH. The impact of interpregnancy interval and previous preterm birth on the subsequent risk of preterm birth. J Soc Gynecol Investig. 2005;12(3):202-7.
31. Laughon SK, Albert PS, Leishear K, Mendola P. The NICHD Consecutive Pregnancies Study: recurrent preterm delivery by subtype. Am J Obstet Gynecol. 2014;210(2):131 e1-8.
32. Lykke JA, Paidas MJ, Langhoff-Roos J. Recurring complications in second pregnancy. Obstet Gynecol. 2009;113(6):1217-24.
33. Manuck TA, Henry E, Gibson J, Varner MW, Porter TF, Jackson GM, et al. Pregnancy outcomes in a recurrent preterm birth prevention clinic. Am J Obstet Gynecol. 2011;204(4):320 e1-6.
34. Markham KB, Walker H, Lynch CD, Iams JD. Preterm birth rates in a prematurity prevention clinic after adoption of progestin prophylaxis. Obstet Gynecol. 2014;123(1):34-9.

35. Meis PJ, Klebanoff M, Thom E, Dombrowski MP, Sibai B, Moawad AH, et al. Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. N Engl J Med. 2003;348(24):2379-85.
36. Mercer BM, Goldenberg RL, Moawad AH, Meis PJ, Iams JD, Das AF, et al. The preterm prediction study: effect of gestational age and cause of preterm birth on subsequent obstetric outcome. National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. Am J Obstet Gynecol. 1999;181(5 Pt 1):1216-21.
37. Owen J, Yost N, Berghella V, Thom E, Swain M, Dildy GA, 3rd, et al. Mid-trimester endovaginal sonography in women at high risk for spontaneous preterm birth. JAMA. 2001;286(11):1340-8.
38. Rittenberg C, Newman RB, Istwan NB, Rhea DJ, Stanziano GJ. Preterm birth prevention by 17 alpha-hydroxyprogesterone caproate vs. daily nursing surveillance. J Reprod Med. 2009;54(2):47-52.
39. Turitz AL, Bastek JA, Purisch SE, Elovitz MA, Levine LD. Patient characteristics associated with 17-alpha hydroxyprogesterone caproate use among a high-risk cohort. Am J Obstet Gynecol. 2016;214(4):536 e1-5.
40. Vermeulen GM, Bruinse HW. Prophylactic administration of clindamycin 2% vaginal cream to reduce the incidence of spontaneous preterm birth in women with an increased recurrence risk: a randomised placebo-controlled double-blind trial. Br J Obstet Gynaecol. 1999;106(7):652-7.
41. Vogel I, Goepfert AR, Thorsen P, Skogstrand K, Hougaard DM, Curry AH, et al. Early second-trimester inflammatory markers and short cervical length and the risk of recurrent preterm birth. J Reprod Immunol. 2007;75(2):133-40.
42. Wallace JM, Bhattacharya S, Campbell DM, Horgan GW. Inter-Pregnancy Weight Change and the Risk of Recurrent Pregnancy Complications. PLoS One. 2016;11(5):e0154812.
43. Yamashita M, Hayashi S, Endo M, Okuno K, Fukui O, Mimura K, et al. Incidence and risk factors for recurrent spontaneous preterm birth: A retrospective cohort study in Japan. J Obstet Gynaecol Res. 2015;41(11):1708-14.
44. Yang J, Baer RJ, Berghella V, Chambers C, Chung P, Coker T, et al. Recurrence of Preterm Birth and Early Term Birth. Obstet Gynecol. 2016;128(2):364-72.
45. Uquillas KR, Fox NS, Rebarber A, Saltzman DH, Klauser CK, Roman AS. A comparison of cervical length measurement techniques for the prediction of spontaneous preterm birth. J Matern Fetal Neonatal Med. 2017;30(1):50-3.
46. Kazemier BM, Buijs PE, Mignini L, Limpens J, de Groot CJ, Mol BW, et al. Impact of obstetric history on the risk of spontaneous preterm birth in singleton and multiple pregnancies: a systematic review. BJOG. 2014;121(10):1197-208; discussion 209.
47. Kamath-Rayne BD, DeFranco EA, Chung E, Chen A. Subtypes of preterm birth and the risk of postneonatal death. J Pediatr. 2013;162(1):28-34 e2.
48. Villar J, Abalos E, Carroli G, Giordano D, Wojdyla D, Piaggio G, et al. Heterogeneity of perinatal outcomes in the preterm delivery syndrome. Obstet Gynecol. 2004;104(1):78-87.
49. Chen A, Feresu SA, Barsoom MJ. Heterogeneity of preterm birth subtypes in relation to neonatal death. Obstet Gynecol. 2009;114(3):516-22.
50. Newman DE, Paamoni-Keren O, Press F, Wiznitzer A, Mazor M, Sheiner E. Neonatal outcome in preterm deliveries between 23 and 27 weeks' gestation with and without preterm premature rupture of membranes. Arch Gynecol Obstet. 2009;280(1):7-11.

51. Basso O, Wilcox A. Mortality risk among preterm babies: immaturity versus underlying pathology. Epidemiology. 2010;21(4):521-7.
52. Brown HK, Speechley KN, Macnab J, Natale R, Campbell MK. Neonatal morbidity associated with late preterm and early term birth: the roles of gestational age and biological determinants of preterm birth. Int J Epidemiol. 2014;43(3):802-14.
53. Newnham JP, Dickinson JE, Hart RJ, Pennell CE, Arrese CA, Keelan JA. Strategies to prevent preterm birth. Front Immunol. 2014;5:584.
54. Betran AP, Say L, Gulmezoglu AM, Allen T, Hampson L. Effectiveness of different databases in identifying studies for systematic reviews: experience from the WHO systematic review of maternal morbidity and mortality. BMC Med Res Methodol. 2005;5(1):6.

Figure 1: Flow diagram of included studies

Figure 2. Forest plot of the rate of recurrent spontaneous preterm birth at <37 weeks gestation

Figure 3. Forest plots of the rate of (a) recurrent PPROM and (b) recurrent PTL at <37 weeks gestation

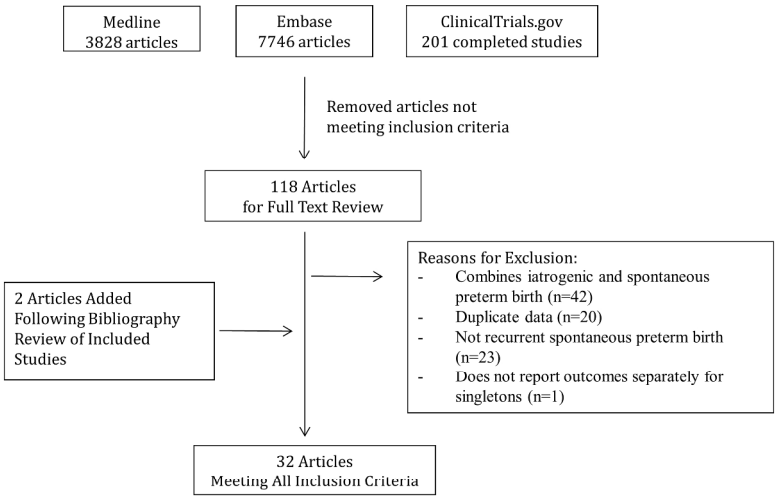


Figure 1: Flow diagram of included studies

254x190mm (300 x 300 DPI)

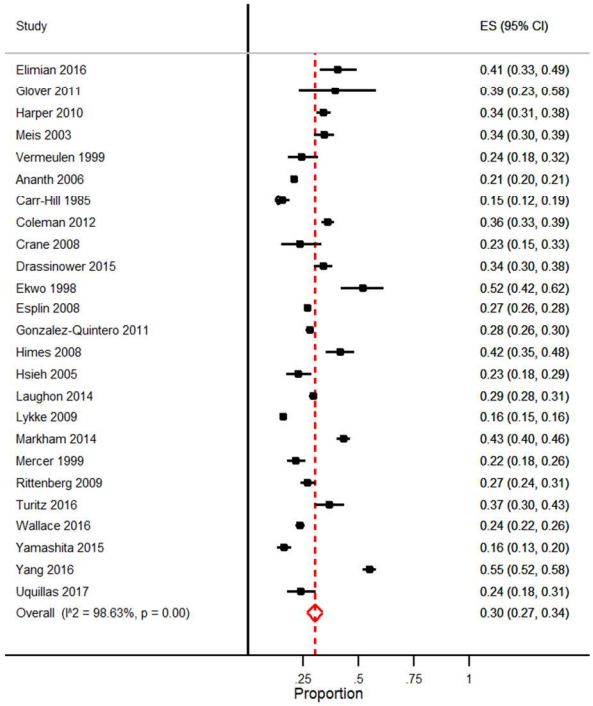


Figure 2. Forest plot of the rate of recurrent spontaneous preterm birth at <37 weeks gestation

254x190mm (300 x 300 DPI)

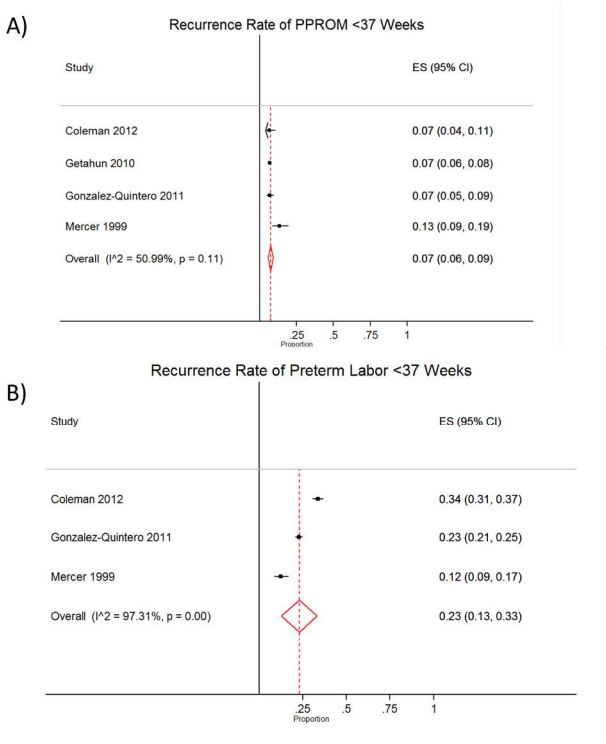


Figure 3. Forest plots of the rate of (a) recurrent PPROM and (b) recurrent PTL at <37 weeks gestation

254x190mm (300 x 300 DPI)

Appendix A. Search Strategy

Search Strategy:

1. Premature Birth
2. ((preterm or pre-term or premature or pre-mature) and (birth* or childbirth* or deliver* or parturit*))
3. Fetal Membranes, Premature Rupture
4. pprom
5. Obstetric Labor, Premature
6. ((preterm or pre-term or premature or pre-mature) and (labor or labour))
7. Recurrence
8. recur* or repeat
9. (1 or 2 or 3 or 4 or 5 or 6) and (7 or 8)

Initial Search Run on June 17, 2015
Updated Search Run on July 29, 2016
Updated Search Run on May 24, 2017

Appendix B. Included studies

Table B1 – Recurrence rate of spontaneous preterm birth

Author	Time Period	Country	Study Design	Inclusion/Exclusion Criteria	Gestational Age at Spontaneous Preterm Birth (weeks) Pregnancy 1	Gestational Age at Spontaneous Preterm Birth (weeks) Pregnancy 2	Recurrence Rate of Spontaneous Preterm Birth
Ananth 2006 (14)	1989-1997	USA	Cohort	*Inclusion:* Prior sPTB *Exclusion:* Multiple gestation pregnancies	<37	<37	2,626/12,670 (20.7%)
						<35	698/12,670 (5.5%)
						<32	164/12,670 (1.3%)
					<35	<35	698/4,463 (15.6%)
					<32	<32	164/2,022 (8.1%)
Asrat 1991 (15)		USA	Cohort	*Inclusion:* Prior PPROM *Exclusion:* Incompetent cervix, uterine anomalies, diethelstilbestrol exposure, multiple gestations, and neonates with congenital anomalies	<36	<36	39/121 (32.2%)
Care 2014 (16)	2010-2012	UK	Cohort	*Inclusion:* Prior sPTB or PROM; cervical length >25mm at 20-24 weeks *Exclusion:* Prior cervical surgery, non-viable pregnancy, history of iPTB, cerclage, uterine anomalies, Ehlers-Danlos syndrome, intrauterine death, twins, congenital abnormalities	<34	<37	53/196 (27.0%)
						<34	32/196 (16.3%)
Carr-Hill 1985 (17)	unspecified	UK	Cohort	*Inclusion:* Prior sPTB, singleton *Exclusion:* Multiple gestation, stillbirth, induced labor	<37	<37	76/494 (15.4%)

Author	Time Period	Country	Study Design	Inclusion/Exclusion Criteria	Gestational Age at Spontaneous Preterm Birth (weeks) Pregnancy 1	Gestational Age at Spontaneous Preterm Birth (weeks) Pregnancy 2	Recurrence Rate of Spontaneous Preterm Birth
Coleman 2012 (18)	2007-2010	USA	Cohort	*Inclusion:* Prior sPTB, received 17P injections *Exclusion:* Non-compliance with 17P injections	<37	<37	426/1,183 (36.0%)
						<35	156/1,183 (13.2%)
						<32	61/1,183 (5.2%)
Crane 2008 (19)	2000-2006	Canada	Cohort	*Inclusion:* Prior sPTB *Exclusion:* Cervical cerclage	<37	<37	21/90 (23.3%)
						<35	11/90 (12.2%)
						<34	8/90 (8.9%)
Drassinower 2015 (20)	2009-2014	USA	Cohort	*Inclusion:* Prior sPTB, singleton *Exclusion:* Multiple gestations, major fetal anomalies, cerclage, history of iPTB or placental abruption	<37	<37	178/522 (34.1%)
						<34	78/522 (14.9%)
						<28	34/522 (6.5%)
Ekwo 1998 (21)	1988-1993	USA	Cohort	*Inclusion:* Prior sPTB *Exclusion:* Fetal loss, multiple gestation	<37	<37	56/108 (51.9%)
Elimian 2016 (22)	2007-2010	USA	RCT	*Inclusion:* Prior sPTB *Exclusion:* Multiple gestation, major fetal anomaly or chromosomal anomalies, prior progesterone use in the current pregnancy, use of heparin in the current pregnancy, uterine anomaly, maternal medical conditions, no ultrasound before 20^{+6} in the current pregnancy	<37	<37	59/145 (40.7%)
						<34	27/145 (18.6%)
						<28	15/145 (10.3%)
Esplin 2008 (23)	1989-2001	USA	Cohort	*Inclusion:* First live birth in Utah and a subsequent live birth in the study period	<37	<37	1663/6,199 (26.8%)
					<34	<37	587/1,669 (35.2%)

Author	Time Period	Country	Study Design	Inclusion/Exclusion Criteria	Gestational Age at Spontaneous Preterm Birth (weeks) Pregnancy 1	Pregnancy 2	Recurrence Rate of Spontaneous Preterm Birth
						<34	299/1,669 (17.9%)
Getahun 2010 (24) *PPROM only	1989-1997	USA	Cohort	*Inclusion:* Prior PPROM *Exclusion:* Multiple gestations, births <20 weeks, non White or Black race, >1 pregnancy before 1989	<37	<37	157/2,259 (6.9%)
					<34	<34	97/1,071 (9.1%)
					<32	<32	67/697 (9.6%)
					<28	<28	22/323 (6.8%)
Glover 2011 (25)	2006-2009	USA	RCT	*Inclusion:* Prior sPTB, initiated prenatal care prior to 20 weeks gestation *Exclusion:* Multiple gestations, major fetal anomaly	<37	<37	13/33 (39.4%)
Goldenberg 2006 (26)	1996-2001	USA	Cohort	*Inclusion:* Prior sPTB	<32	<37	71/83 (85.5%)
Gonzalez-Quintero 2011 (27)	2006-2009	USA	Cohort	*Inclusion:* Prior sPTB, singleton *Exclusion:* iPTB, >1 prior PTB, cerclage in current pregnancy	<37	<37	597/2,123 (28.1%)
						<35	274/2,123 (12.9%)
						<32	113/2,123 (5.3%)

Author	Time Period	Country	Study Design	Inclusion/Exclusion Criteria	Gestational Age at Spontaneous Preterm Birth (weeks)		Recurrence Rate of Spontaneous Preterm Birth
					Pregnancy 1	Pregnancy 2	
Harper 2010 (28)	2005-2006	USA	RCT	*Inclusion:* Prior sPTB, singleton *Exclusion:* Major fetal anomaly, intake of a fish oil supplement >500mg/week at any time during the preceding month, allergy to fish, anticoagulation therapy, hypertension, White's classification D or higher diabetes, drug or alcohol abuse, seizure disorder, uncontrolled thyroid disease, clotting disorder, current or planned cerclage, or a plan to deliver either elsewhere or before 37 weeks of gestation	<37	<37	292/852 (34.3%)
Himes 2008 (29)	2001-2006	USA	Cohort	*Inclusion:* Prior sPTB placenta pathology information available	<37	<37	102/245 (41.6%)
Hsieh 2005 (30)	1991-1997	Taiwan	Cohort	*Exclusion:* Multiple gestation, fetal anomaly, cervical incompetence, stillbirth, iPTB	<37	<37	52/228 (22.8%)
Laughon 2014 (31)	2002-2010	USA	Cohort	*Inclusion:* Singleton pregnancies	<37	<37	921/3,139 (29.3%)
Lykke 2009 (32)	1978-2007	Denmark	Cohort	*Inclusion:* Maternal age between 15-50 *Exclusion:* Women with cardiovascular disease, type 1 or 2 diabetes, women who emigrated within 3 months of 2nd delivery	<37 <33 <28	<37	2742/17,334 (15.8%) 444/1,734 (25.6%) 139/535 (26.0%)

Author	Time Period	Country	Study Design	Inclusion/Exclusion Criteria	Gestational Age at Spontaneous Preterm Birth (weeks) Pregnancy 1	Gestational Age at Spontaneous Preterm Birth (weeks) Pregnancy 2	Recurrence Rate of Spontaneous Preterm Birth
Manuck 2011 (33)	2002-2010	USA	Cohort	*Inclusion:* Prior sPTB, singleton *Exclusion:* History of iPTB or incompetent cervix	<35	<37	131/223 (58.7%)
						<32	25/223 (11.2%)
Markham 2014 (34)	1998-2012	USA	Cohort	*Inclusion:* Prior sPTB *Exclusion:* Multiple gestations, known uterine anomalies,	<37	<37	459/1,066 (43.1%)
						<35	269/1,066 (25.2%)
						<32	139/1,066 (13.0%)
Meis 2003 (35)	1999-2002	USA	RCT	*Inclusion:* Prior sPTB *Exclusion:* Multiple gestations, fetal anomaly, progesterone or heparin treatment during the current pregnancy, current or planned cervical cerclage, hypertension requiring medication, seizure disorder, or a plan to deliver elsewhere	<37	<37	159/463 (34.3%)
Mercer 1999 (36)	1992-1994	USA	Cohort	*Inclusion:* Singleton *Exclusion:* Placenta previa, major fetal malformations, cervical cerclage, polyhydramnios, oligohydramnios, cervical dilatation of ≥2 cm for nulliparous women and ≥3 cm for multiparous women.	<37	<37	89/410 (21.7%)
						<35	55/410 (13.4%)
						<32	21/410 (5.1%)
						<30	12/410 (2.9%)
						<28	10/410 (2.4%)
Owen 2001 (37)	1997-1999	USA	Cohort	*Inclusion:* Prior sPTB, singleton *Exclusion:* chronic medical or obstetrical problems, history of	<32	<35	48/183 (26.2%)
						<32	35/183 (19.1%)
						<28	29/183 (15.8%)

Author	Time Period	Country	Study Design	Inclusion/Exclusion Criteria	Gestational Age at Spontaneous Preterm Birth (weeks) Pregnancy 1	Gestational Age at Spontaneous Preterm Birth (weeks) Pregnancy 2	Recurrence Rate of Spontaneous Preterm Birth
				substance abuse, uterine anomalies, cerclage		<24	20/183 (10.9%)
Rittenberg 2009 (38)	1995-2005	USA	Cohort	*Inclusion:* Prior sPTB, singleton pregnancies, referred for weekly 17P administration *Exclusion:* Diagnosis of preterm labour, cerclage or vaginal bleeding at enrollment	<37	<37	185/684 (27.0%)
						<35	78/684 (11.4%)
						<32	30/684 (4.4%)
Turitz 2016 (39)	2009-2013	USA	Cohort	*Inclusion:* Prior sPTB	<37	<37	80/218 (36.7%)
Uquillas 2017 (45)	2005-2011	USA	Cohort	*Inclusion:* Prior sPTB *Exclusion:* Current cerclage, prior iPTB	<37	<37	43/181 (23.7%)
						<32	6/181 (3.3%)
Vermeulen 1999 (40)	1994-1996	Netherlands	RCT	*Inclusion:* Prior sPTB *Exclusion:* Fetal anomaly, previous iPTB, known allergy to clindamycin	<37	<37	41/168 (24.4%)
						<34	14/168 (8.3%)
Vogel 2007 (41)	2000-2001	USA	Cohort	*Inclusion:* Prior sPTB *Exclusion:* Multiple gestations, ruptured membranes, cerclage in a previous pregnancy	<30	<37	20/62 (32.3%)
						<35	15/62 (24.2%)
Wallace 2016 (42)	1986-2013	UK	Cohort		<37	<37	449/1,900 (23.6%)
Yamashita 2015 (43)	2008-2012	Japan	Cohort	*Inclusion:* Prior sPTB *Exclusion:* First antenatal visit after	<37	<37	89/547 (16.3%)
						<34	28/547 (5.1%)

Author	Time Period	Country	Study Design	Inclusion/Exclusion Criteria	Gestational Age at Spontaneous Preterm Birth (weeks)		Recurrence Rate of Spontaneous Preterm Birth
					Pregnancy 1	Pregnancy 2	
				14 weeks, previous iPTB, placenta previa, placental abruption, multiple gestation, fetal anomaly, antepartum fetal demise		<28	10/547 (1.8%)
Yang 2016 (44)	2005-2011	USA	Cohort		<37	<37	588/1,068 (55.1%)
						<32	71/1,068 (6.6%)
					<32	<32	43/177 (24.3%)

Table B2 – Occurrence of Indicated Preterm Birth Following Spontaneous Preterm Birth

Author	Time Period	Country	Study Design	Inclusion/Exclusion Criteria	Gestational Age at Preterm Birth (weeks) Pregnancy 1	Gestational Age at Preterm Birth (weeks) Pregnancy 2	Occurrence Rate of Indicated Preterm Birth Following a Prior Spontaneous Preterm Birth
Ananth 2006 (14)	1989-1997	USA	Cohort	*Inclusion:* Prior sPTB *Exclusion:* Multiple gestation pregnancies	<37	<37	342/12,670 (2.70%)
						<35	121/12,670 (0.96%)
						<32	40/12,670 (0.32%)
					<35	<35	121/4,463 (2.71%)
					<32	<32	40/2,022 (1.98%)
Harper 2010 (28)	2005-2006	USA	RCT	*Inclusion:* Prior sPTB, singleton *Exclusion:* Major fetal anomaly, intake of a fish oil supplement >500mg/week at any time during the preceding month, allergy to fish, anticoagulation therapy, hypertension, White's classification D or higher diabetes, drug or alcohol abuse, seizure disorder, uncontrolled thyroid disease, clotting disorder, current or planned cerclage, or a plan to deliver either elsewhere or before 37 weeks of gestation	<37	<37	46/852 (5.63%)
Laughon 2014 (31)	2002-2010	USA	Cohort	*Inclusion:* Singleton pregnancies	<37	<37	17/3,139 (0.54%)

Author	Time Period	Country	Study Design	Inclusion/Exclusion Criteria	Gestational Age at Preterm Birth (weeks) Pregnancy 1	Gestational Age at Preterm Birth (weeks) Pregnancy 2	Occurrence Rate of Indicated Preterm Birth Following a Prior Spontaneous Preterm Birth
Meis 2003 (35)	1999-2002	USA	RCT	*Inclusion:* Prior sPTB *Exclusion:* Multiple gestations, fetal anomaly, progesterone or heparin treatment during the current pregnancy, current or planned cervical cerclage, hypertension requiring medication, seizure disorder, or a plan to deliver elsewhere	<37	<37	36/463 (7.78%)
Owen 2001 (37)	1997-1999	USA	Cohort	*Inclusion:* Prior sPTB, singleton *Exclusion:* chronic medical or obstetrical problems, history of substance abuse, uterine anomalies, cerclage	<32	<35	5/183 (2.73%)
Rittenberg 2009 (38)	1995-2005	USA	Cohort	*Inclusion:* Prior sPTB, singleton pregnancies, referred for weekly 17P administration *Exclusion:* Diagnosis of preterm labour, cerclage or vaginal bleeding at enrollment	<37	<37	84/684 (12.28%)

Author	Time Period	Country	Study Design	Inclusion/Exclusion Criteria	Gestational Age at Preterm Birth (weeks)		Occurrence Rate of Indicated Preterm Birth Following a Prior Spontaneous Preterm Birth
					Pregnancy 1	Pregnancy 2	
Yamashita 2015 (43)	2008-2012	Japan	Cohort	*Inclusion:* Prior sPTB *Exclusion:* First antenatal visit after 14 weeks, previous iPTB, placenta previa, placental abruption, multiple gestation, fetal anomaly, antepartum fetal demise	<37	<37	23/547 (4.20%)

Appendix C: Quality Assessment

Table C1 – Quality Scores for Included Studies

Author	Representatives of the exposed cohort (0, 1)	Selection of the non-exposed cohort (0, 1)	Ascertainment of exposure (0, 1)	Demonstration that outcome of interest was not present at start of study (0, 1)	Comparability of cohorts on the basis of design or analysis (0, 1)	Assessment of outcome (0, 1)	Was follow-up long enough for outcomes to occur (0, 1)	Adequacy of follow-up of cohorts (0, 1)
Ananth 2006 (14) *Score: 4/6*	1	N/A	0	1	N/A	0	1	1
Asrat 1991 (15) *Score: 5/6*	0	N/A	1	1	N/A	1	1	1
Care 2014 (16) *Score: 5/6*	0	N/A	1	1	N/A	1	1	1
Carr-Hill 1985 (17) *Score: 4/6*	1	N/A	0	1	N/A	0	1	1
Coleman 2012 (18) *Score: 5/6*	0	N/A	1	1	N/A	1	1	1
Crane 2008 (19) *Score: 5/6*	0	N/A	1	1	N/A	1	1	1

Author	Representatives of the exposed cohort (0, 1)	Selection of the non-exposed cohort (0, 1)	Ascertainment of exposure (0, 1)	Demonstration that outcome of interest was not present at start of study (0, 1)	Comparability of cohorts on the basis of design or analysis (0, 1)	Assessment of outcome (0, 1)	Was follow-up long enough for outcomes to occur (0, 1)	Adequacy of follow-up of cohorts (0, 1)
Drassinower 2015 (20) *Score: 5/6*	0	N/A	1	1	N/A	1	1	1
Ekwo 1998 (21) *Score: 5/6*	0	N/A	1	1	N/A	1	1	1
Elimian 2016 (22) *Score: 7/8*	0	1	1	1	1	1	1	1
Esplin 2008 (23) *Score: 4/6*	1	N/A	0	1	N/A	0	1	1
Getahun 2010 (24) *PPROM only *Score: 4/6*	1	N/A	0	1	N/A	0	1	1
Goldenberg 2006 (26) *Score: 5/6*	0	N/A	1	1	N/A	1	1	1
Glover 2011 (25) *Score: 7/8*	0	1	1	1	1	1	1	1

Author	Representatives of the exposed cohort (0, 1)	Selection of the non-exposed cohort (0, 1)	Ascertainment of exposure (0, 1)	Demonstration that outcome of interest was not present at start of study (0, 1)	Comparability of cohorts on the basis of design or analysis (0, 1)	Assessment of outcome (0, 1)	Was follow-up long enough for outcomes to occur (0, 1)	Adequacy of follow-up of cohorts (0, 1)
Gonzalez-Quintero 2011 (27) *Score: 5/6*	0	N/A	1	1	N/A	1	1	1
Harper 2010 (28) *Score: 7/8*	0	1	1	1	1	1	1	1
Himes 2008 (29) *Score: 5/6*	0	N/A	1	1	N/A	1	1	1
Hsieh 2005 (30) *Score: 5/6*	0	N/A	1	1	N/A	1	1	1
Laughon 2014 (31) *Score: 4/6*	1	N/A	0	1	N/A	0	1	1
Lykke 2009 (32) *Score: 4/6*	1	N/A	0	1	N/A	0	1	1
Manuck 2011 (33) *Score: 5/6*	0	N/A	1	1	N/A	1	1	1

Author	Representatives of the exposed cohort (0, 1)	Selection of the non-exposed cohort (0, 1)	Ascertainment of exposure (0, 1)	Demonstration that outcome of interest was not present at start of study (0, 1)	Comparability of cohorts on the basis of design or analysis (0, 1)	Assessment of outcome (0, 1)	Was follow-up long enough for outcomes to occur (0, 1)	Adequacy of follow-up of cohorts (0, 1)
Markham 2014 (34) *Score: 5/6*	0	N/A	1	1	N/A	1	1	1
Meis 2003 (35) *Score: 7/8*	0	1	1	1	1	1	1	1
Mercer 1999 (36) *Score: 5/6*	0	N/A	1	1	N/A	1	1	1
Owen 2001 (37) *Score: 5/6*	0	N/A	1	1	N/A	1	1	1
Rittenberg 2009 (38) *Score: 5/6*	0	N/A	1	1	N/A	1	1	1
Turitz 2016 (39) *Score: 5/6*	0	N/A	1	1	N/A	1	1	1
Uquillas 2017 (45) *Score: 5/6*	0	N/A	1	1	N/A	1	1	1

Author	Representatives of the exposed cohort (0, 1)	Selection of the non-exposed cohort (0, 1)	Ascertainment of exposure (0, 1)	Demonstration that outcome of interest was not present at start of study (0, 1)	Comparability of cohorts on the basis of design or analysis (0, 1)	Assessment of outcome (0, 1)	Was follow-up long enough for outcomes to occur (0, 1)	Adequacy of follow-up of cohorts (0, 1)
Vermeulen 1999 (40) *Score: 7/8*	0	1	1	1	1	1	1	1
Vogel 2007 (41) *Score: 5/6*	0	N/A	1	1	N/A	1	1	1
Wallace 2016 (42) *Score: 4/6*	1	N/A	0	1	N/A	0	1	1
Yamashita 2015 (43) *Score: 5/6*	0	N/A	1	1	N/A	1	1	1
Yang 2016 (44) *Score: 4/6*	1	N/A	0	1	N/A	0	1	1

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.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
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.	n/a
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.	6-8
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.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix A
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).	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.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7-8
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.	7-8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
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.	8

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).	7-8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
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.	Figure 1, page 8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Appendix B
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).	Appendix C, pages 9-10
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.	Figures 2, 3, page 8-9
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Figures 2, 3, page 8-9
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Appendix C, pages 9-10
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	9
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).	10
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).	12-13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13
FUNDING			

PRISMA 2009 Checklist

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.	2

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

For more information, visit: **www.prisma-statement.org**.