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Risk of recurrent spontaneous preterm birth: a systematic review and meta-analysis

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ABSTRACT

Objective To determine the risk of recurrent spontaneous preterm birth (sPTB) following sPTB 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 sPTB.

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 sPTB at <37 weeks' gestation was 30% (95% CI 27% to 34%). The risk of recurrence due to preterm premature rupture of membranes (PPROM) at <37 weeks gestation was 7% (95% CI 6% to 9%), while the risk of recurrence due to preterm labour (PTL) at <37 weeks gestation was 23% (95% CI 13% to 33%).

Conclusions The risk of recurrent sPTB 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 sPTB with their patients.

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 subcategorisation 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] PTB is the leading cause of perinatal morbidity and mortality and second most common cause of death, after pneumonia, in children under 5 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.[5] The clinical pathways that lead to spontaneous preterm birth (sPTB) typically include preterm labour (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 1 hour before contractions at less than 37 weeks gestation.[5] Known risk factors for sPTB include a previous PTB, 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 aetiology 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's 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 online supplementary appendix A. Titles and abstracts of these articles were screened for relevance by two 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.

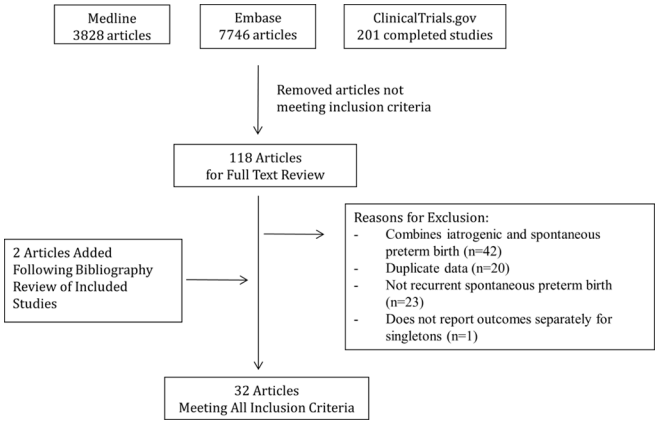

Figure 1 Flow diagram of included studies.

The data extraction were completed independently by ZV and CP using a standardised data extraction form. Data were 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 PTB, and inclusion and exclusion criteria were all extracted. In addition, information was extracted on the number of women with sPTB in their initial pregnancy, whether due to PPROM or PTL, number of women with term births in subsequent pregnancies, and number of women with PTB in subsequent pregnancies, whether due to PPROM, PTL or indicated causes. For studies that reported on total reproductive history, only data on the first two 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 randomised 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 PTB and accompanying 95% 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 CIs 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 V.14.

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 study data can be found in online supplementary 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 randomised controlled trials.[22 26 28 35 40] The sample sizes in the studies ranged from 33 to 17 334 women and the

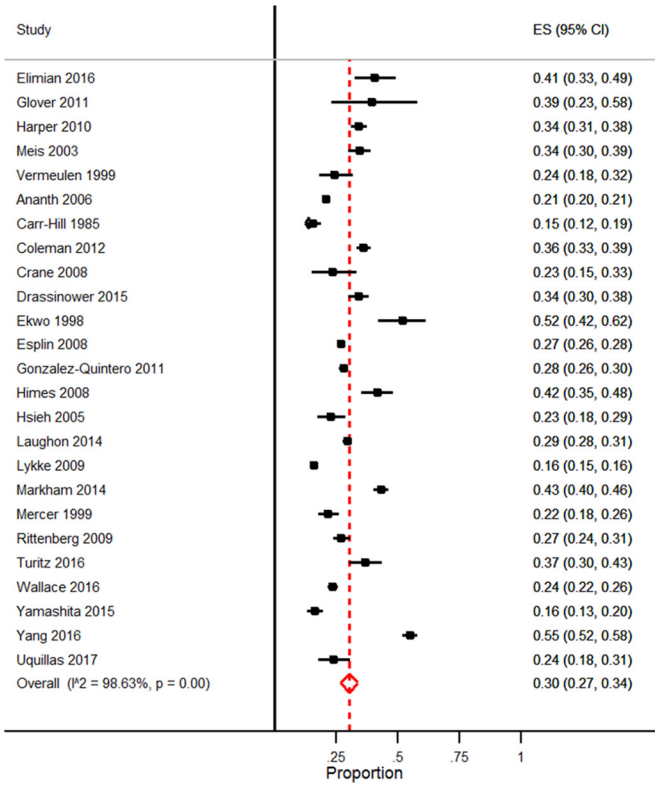

Figure 2 Forest plot of the rate of recurrent spontaneous preterm birth at <37 weeks' gestation. ES, effect size.

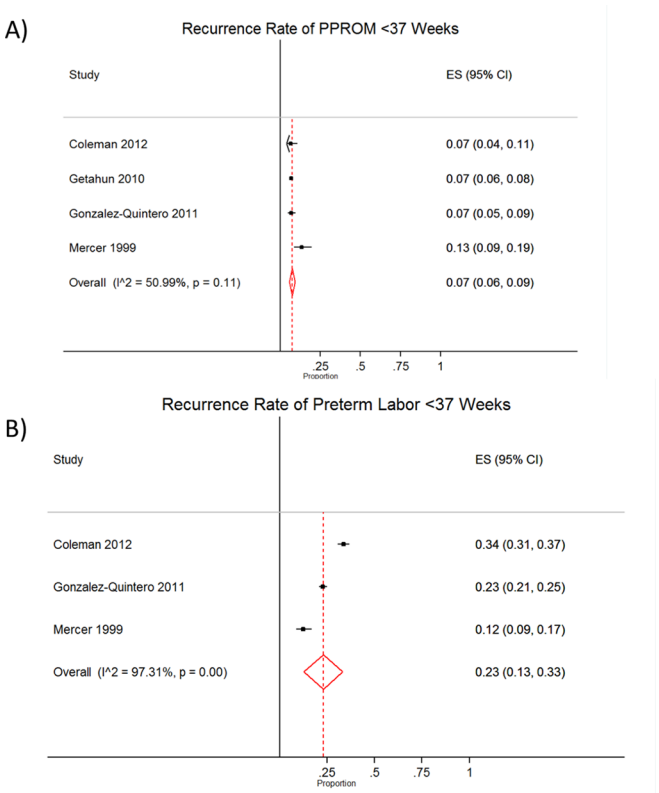

Figure 3 Forest plots of the rate of (A) recurrent preterm premature rupture of membranes (PPROM) and (B) recurrent preterm labour (PTL) at <37 weeks' gestation. ES, effect size.

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 PTB 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% (95% CI27% to 34%) 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 randomised controlled trials (34%, 95% CI 29% to 38%; n=5 studies, 1661 women) and cohort studies (29%, 95% CI 26% to 33%, n=20 studies, 50 409 women). The risk of iPTB at <37 weeks' gestation after a previous sPTB (n=6 studies, 18 355 women) was 5% (95% CI 3% to 7%) 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, 3138 women) was 7% (95% CI 6% to 9%) with an I^2 of 51% and the risk of recurrent PTL at <37 weeks' gestation (n=3 studies, 2852 women) was 23% (95% CI 13% to 33%) with an I^2 of 97.3% (figure 3).

The majority of the studies were of high quality (see online supplementary appendix C). As this study exclusively examined the recurrence risk of sPTB, 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 generalisable to the broader patient population not seen in a tertiary centre or having detailed clinical data available. All cohort studies had a quality score of four or five out of a possible six 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%, 95% CI 21% to 32%; Score 5: 31%, 95% CI 26% to 36%). All randomised controlled trials were deemed to be high quality (score 7/8).

DISCUSSION

This meta-analysis provides an overview of the overall risk of recurrent sPTB. 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 PTB 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 with 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, sPTB and iPTB 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 PTB 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 characterised by infection, placental ischaemia 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 aetiologies.

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 PTB. In a similar vein, we also included participants from both the treated and control arms of the included randomised 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 to 0.81),[35] the other trials had null findings. Strategies to prevent PTB are varied and evidence of their effectiveness are mixed.[53] Effective strategies to prevent PTB can be implemented at the individual level (ie, progesterone supplementation, cervical cerclage, smoking cessation), the clinic/hospital level (ie, hard-stop policies to prevent non-medically indicated late preterm and early term birth, PTB prevention clinics) and the societal level (ie, smoke-free legislation to reduce environmental tobacco smoke, legislation regarding single-embryo transfer during in vitro fertilisation).[53] As documentation of specific treatment strategies was not consistently reported in this body of literature, we were not able to synthesise 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 generalisable, this may have inadvertently resulted in the exclusion of some small case series. Additionally, we only searched three 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 clinicaltrials.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 PTB 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 summarised in this review.

In conclusion, our study reaffirmed that a previous sPTB 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 aetiology is PTL as opposed to PPROM. Clinically, this information will help with risk stratification and patient counselling. 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 aetiology of previous sPTB may help to identify women at increased risk of sPTB for participation in future clinical trials.

Correction notice This article has been corrected since it first published. The word 'TEST' has been removed from the first line of the Introduction.

Contributors 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.

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