The More, the Better? Combining Interventions to Prevent Preterm Birth in Women at Risk: a Systematic Review and Meta-Analysis

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Abstract

Objectives: To systematically examine the evidence around the combination of interventions to prevent preterm birth.

Methods: Without language restrictions, we searched clinicaltrials.gov and five electronic databases (Medline, EMBASE, CINAHL, Cochrane CENTRAL, and Web of Science) up to July 7, 2016. We included randomized and non-randomized studies where asymptomatic women at risk of preterm birth received any combination of progesterone, cerclage, or pessary compared with either one or no intervention. Primary outcomes were preterm birth <34 and <37 weeks and neonatal death. Two independent reviewers extracted data using a piloted form and assessed risk and direction of bias. We pooled data with unlikely or unclear bias using random-effects meta-analyses. Comparisons with likely bias (e.g., confounding by indication) were not pooled.

Results: We screened 1335 results and assessed 154 full texts, including seven studies. In singletons, we found no differences in preterm birth <34 weeks when comparing pessary & progesterone with pessary alone (RR 1.30, 95% CI 0.70–2.42) or progesterone alone (RR 1.16, 95% CI 0.79–1.72). Similarly, we found no differences in preterm birth <37 weeks when comparing cerclage & progesterone with cerclage alone (RR 1.04, 95% CI 0.56–1.93) or with progesterone alone (RR 0.82, 95% CI 0.57–1.19) nor between pessary & progesterone and pessary alone (RR 1.04, 95% CI 0.62–1.74). No data were available for neonatal death in singletons.

Conclusions: Despite being a common clinical practice, evidence to support the combined use of multiple versus single interventions for preventing preterm birth is scarce.

Key Words: Cervical cerclage, pessaries, combined intervention, premature birth, progesterone

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Competing interests: None declared.

Received on March 10, 2017

Accepted on July 4, 2017

Résumé

Objectifs : Mener un examen systématique des données probantes sur la combinaison d'interventions pour prévenir un accouchement prématuré.

Méthodologie : Nous avons interrogé, jusqu'au 7 juillet 2016, le site Web clinicaltrials.gov ainsi que cinq bases de données électroniques (Medline, Embase, CINAHL, Cochrane CENTRAL et Web of Science). Aucune restriction de langue n'a été utilisée. Nous avons retenu les études randomisées et non randomisées dans lesquelles des femmes asymptomatiques à risque d'accouchement prématuré ont reçu n'importe quelle combinaison de progestérone, de cerclage ou de pessaire, et ont été comparées à des femmes ayant fait l'objet d'une seule ou d'aucune intervention. Les indicateurs de résultats principaux étaient la naissance prématurée survenant avant 34 semaines et avant 37 semaines, ainsi que le décès néonatal. Deux évaluateurs indépendants ont extrait les données en se servant d'un formulaire uniformisé et ont évalué les risques et les tendances de biais. Nous nous sommes servis de méta-analyses à effets aléatoires pour rassembler les données pour lesquelles un biais était peu probable ou incertain. Les données probablement biaisées (p. ex. biais d'indication) ont été exclues.

Résultats : Nous avons étudié 1 335 résultats et évalué 154 textes complets, dont sept études. Aucune différence n'a été notée dans les naissances prématurées survenant avant 34 semaines entre la combinaison pessaire-progestérone et le pessaire seul (RR : 1,30; IC à 95 % : 0,70–2,42) ou la progestérone seule (RR : 1,16; IC à 95 % : 0,79–1,72) en ce qui concerne les grossesses monofœtales. De même, aucune différence n'a été notée dans les naissances prématurées survenant avant 37 semaines entre la combinaison cerclage-progestérone et le cerclage seul (RR : 1,04; IC à 95 % : 0,56–1,93) ou la progestérone seule (RR : 0,82; IC à 95 % : 0,57–1,19), ni entre la combinaison pessaire-progestérone et le pessaire seul (RR : 1,04; IC à 95 % : 0,62–1,74). Aucune donnée sur les décès néonataux n'était disponible pour les grossesses monofœtales.

Conclusions : Même si la combinaison d'interventions est une pratique répandue, peu de données montrent qu'elle est plus efficace que les interventions uniques pour prévenir l'accouchement prématuré.

J Obstet Gynaecol Can 2017;39(12):1192–1202
https://doi.org/10.1016/j.jogc.2017.07.007

INTRODUCTION

Preterm birth affects about 8% of pregnant women in Canada[1] and is a leading cause of mortality[2] and morbidity in children.[3] Three common interventions are used to prevent preterm birth in women considered to be at increased risk, including progesterone, cervical cerclage, and vaginal pessary. Common risk factors for preterm birth include previous preterm birth, shortening of the cervix in the current pregnancy, or both, among other factors.

Although previous systematic reviews have found benefit with a single intervention (Dodd et al.[4] for progesterone, Alfirevic et al.[5] for cerclage, Abdel-Aleem et al.[6] for pessary), it is not unusual in clinical practice to combine more than one intervention or supplement one with another.[7] However, there is little evidence regarding a cumulative effect of the interventions.

The aim of this systematic review was to comprehensively synthesize the literature on all combinations of progesterone, cerclage, and pessary compared with individual interventions or no intervention in women considered to be at increased risk for preterm birth, but in the absence of symptoms or signs of preterm labour.

METHODS

The protocol for this systematic review was published in PROSPERO (CRD42016033946).

Information Sources and Search Strategy

We executed our search strategy (see online for Appendix A) without language restrictions in five electronic databases (Medline, EMBASE, CINAHL, Cochrane Central Register of Controlled Trials, and ISI Web of Science) from their inception to July 7, 2016. In addition, we searched clinicaltrials.gov for ongoing trials. Reference lists of previous reviews were screened.

Eligibility Criteria

We included randomized and non-randomized studies (cohort and case-control studies) that reported at least one of our outcomes of interest in asymptomatic women considered to be at increased risk of preterm birth (i.e., prior preterm birth or cervical shortening) where women received any combination of progesterone, cerclage, or pessary compared with women who received any of these interventions individually or no intervention.

We excluded conference abstracts, posters, or any non–peer-reviewed literature, cross-sectional studies or review articles and studies in which women presented with uterine activity or other symptoms or signs of threatened preterm labour (including visible membranes or cervical dilation) or studies that included women who were considered to require emergency cerclage.

Our primary outcomes of interest were preterm birth <34 weeks, preterm birth <37 weeks, and neonatal death.

Infant secondary outcomes included any other cut-off week for defining preterm birth, GA at birth (continuous outcome), low birth weight <2500 g, birth weight (continuous outcome), SGA (defined as <10th, <5th, or <3rd percentile for GA and sex), congenital anomalies, masculinization of a female fetus, miscarriage (intrauterine fetal death before 20 weeks of gestation), stillbirth (intrauterine fetal death after 20 weeks of gestation), perinatal death (stillbirth or death in the first 7 days of life), 5-minute Apgar score, umbilical cord pH <7.1, cystic periventricular leukomalacia, respiratory problems (respiratory distress syndrome, mechanical ventilation, continuous positive airway pressure, bronchopulmonary dysplasia), intraventricular hemorrhage (grades I–IV and III/IV), necrotizing enterocolitis (stages II/III), retinopathy of prematurity (stages I–V and III–V), sepsis, NICU admission and length of stay, cerebral palsy, neurological defects, and any composite outcome reported in the studies.

Maternal secondary outcomes included mortality, length of inpatient antepartum stay, number of outpatient visits, CSs, preterm premature rupture of membranes, and intervention side effects.

Data Extraction

Two independent reviewers screened the titles and abstracts of the search results, as well as the full text of articles that were considered potentially relevant. A third assessor (S.M.) was available when the discrepancies could not be resolved by discussion. For each included article, the same reviewers independently extracted data on study characteristics, potential effect modifiers, outcomes, and