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REVIEW ARTICLE

A systematic review and meta-analysis of progestogen use for maintenance tocolysis after preterm labor in women with intact membranes

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ABSTRACT

Background: The use of progestogens for maintenance tocolysis remains controversial, with randomized controlled trials having conflicting results on their efficacy. *Objectives:* To evaluate the use of progestational agents for maintenance tocolysis after preterm labor in a systematic review of randomized controlled trials. *Search strategy:* Electronic databases were searched for reports published before December 2014. Keywords included "tocolysis," "progesterone," "preterm labor," "17-alpha-hydroxyprogesterone," and "vaginal progesterone." *Selection criteria:* Only randomized controlled trials involving progestational agents for maintenance tocolysis were included. *Data collection and analysis:* Outcomes were analyzed on an intent-to-treat basis and meta-analysis was performed where appropriate. Relative risks and mean differences with 95% confidence intervals were calculated. *Main results:* Four studies (362 women) were included. There were no significant differences between progestational agents and placebo/no treatment in terms of delivery before 34 weeks or before 37 weeks of pregnancy, time from randomization to delivery, and respiratory distress syndrome. Progestogens were associated with an increase in the neonatal birth weight (mean difference 203.32 g, 95% confidence interval 110.85-295.80; $P = 0.032$). *Conclusions:* The current evidence does not support the routine use of progestational agents for maintenance tocolysis after an episode of preterm labor.

1. Introduction

Preterm birth remains a significant public health problem and a leading cause of long-term disability [1]. However, the preterm birth rate continues to decrease. According to 2013 data from the Centers for Disease Control and Prevention [2], the preterm birth rate in the USA has dropped to 11.39%, with the vast majority (approximately 75%) of preterm births occurring spontaneously. It has been hypothesized that the decrease in the preterm birth rate could be attributable to lower rates of multiple pregnancies owing to improvements in assisted reproductive technology techniques, decreases in teen births, better use of cervical cerclage, and—most importantly—the use of progesterone for the prevention of preterm birth [3]. The effect of progesterone has been confirmed by studies reported in 2003 and 2011 [4–6]. Interestingly, however, the use of progestogens as uterine tocolytic agents in this context has been studied for several decades with conflicting results [7,8].

The role of progestogens in the maintenance of uterine quiescence was initially reported in 1954, at which time it was suggested that they could be tocolytic agents [9,10]. Several mechanisms of action have since been proposed. Current evidence favors two major mechanisms: an increase in the progesterone concentration in gestational tissues that counteracts the functional progesterone withdrawal associated with preterm birth; and anti-inflammatory effects that counteract the inflammatory process in pregnancies complicated by preterm labor [11]. These anti-inflammatory effects are mediated by: stimulation of the transcription of the genes encoding the Zinc finger E-box-binding homeobox 1 and 2 proteins, which inhibit expression of the genes encoding connexin 43 (an abundant gap junction protein that helps to harmonize contractile activity) and the oxytocin receptor [12]; a reduced synthesis of prostaglandins (infection-mediated cytokine production by fetal membranes/the placenta) [11]; a decreased ratio of progesterone receptor-A to progesterone receptor-B (membrane-bound progesterone receptors within the myometrium that, when activated by progesterone, stimulate gene promotion and prevent the binding of other factors to ultimately reduce uterine contractions); attenuation of

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the response to inflammation and bleeding in the decidua; and selective nongenomic pathways [13,14].

Randomized clinical trials investigating the use of progesterone for maintenance tocolysis after an episode of preterm labor have produced conflicting data. Some reported a benefit, whereas others did not. Four randomized controlled trials [15–18] have assessed progesterone supplementation in this setting. In three of the four trials [15,17,18], progesterone maintenance therapy after successful parenteral tocolysis did not significantly reduce the rate of preterm birth. However, one trial [16] reported a considerable reduction in the rate of preterm delivery, and another trial [17] described a significantly longer latency period (time from randomization to delivery: 36.1 ± 17.9 vs 24.5 ± 27.2 days). The largest of these progesterone trials [15] was a multicenter randomized controlled trial in which women with a singleton pregnancy between 24 and 31 weeks and preterm labor successfully inhibited by tocolytic treatment were randomly assigned to receive 500 mg of intramuscular 17α-hydroxyprogesterone caproate versus no treatment twice weekly until week 36 of pregnancy. The administration of 17α-hydroxyprogesterone caproate did not significantly increase the time to delivery or reduce the rates of preterm birth before 32 weeks, 34 weeks, or 37 weeks.

A Cochrane systematic review published in 2014 [19] evaluated the use of progestational agents for acute tocolysis of preterm labor. However, a systematic review/meta-analysis on the use of progestogens for maintenance tocolysis does not seem to have been performed previously, despite the availability of randomized trials on this topic. Therefore, a systematic review and meta-analysis were performed to evaluate the efficacy and safety of the use of progestational agents for maintenance tocolysis after an episode of preterm labor.

2. Materials and methods

The present systematic review and meta-analysis was conducted in agreement with the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines for reporting systematic reviews and meta-analyses of randomized controlled trials [20].

2.1. Literature search

Literature searches were performed in the Cochrane Central Register of Controlled Trials, PubMed, African Journals Online, Embase, Medline, Literature in the Health Sciences in Latin America and the Caribbean, Cumulative Index to Nursing and Allied Health Literature, Web of Science, registers of ongoing trials (http://www.ukctg.nihr.ac.uk, https://www.clinicaltrials.gov, http://www.umin.ac.jp/ctr, http://www.anzctr.org.au, http://www.controlled-trials.com, and http://www.centerwatch.com), and Google Scholar (all from database inception to December 15, 2014). Keywords including "tocolysis," "progesterone," "progestogen," "preterm labor," "17-alpha-hydroxyprogesterone," "vaginal progesterone" were used during the search process. Additional publications were found by reviewing the proceedings of international society meetings in perinatology and international meetings on preterm birth and tocolysis, and by reviewing the bibliographies of identified studies and review articles. For studies with several publications, the data from the most complete report were used and supplemented if additional information—including secondary data analyses—appeared in other publications. No language restrictions were used in the search.

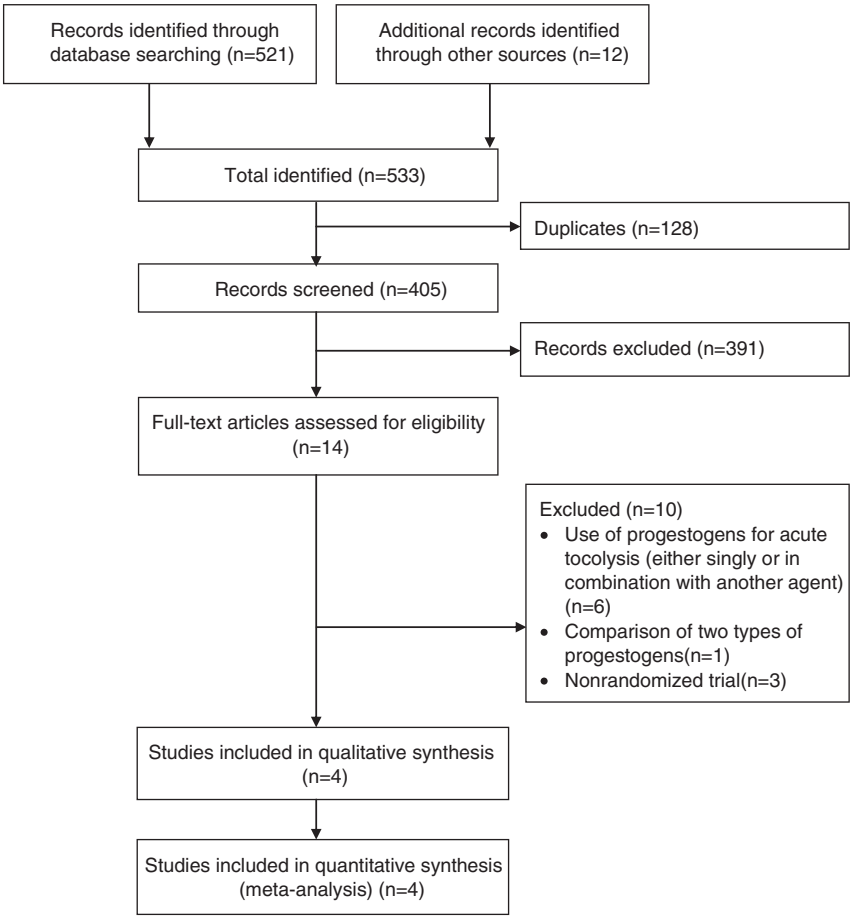

Fig. 1. Study flow diagram.