# The past, present, and future of progestogens in the prevention of preterm birth: an evidence-based review

**Background/Synopsis:** Preterm birth is the most important obstetrical problem and many past attempts have been made to prevent recurrent spontaneous preterm birth (SPTB). In 2011, after several small trials showed that 17α-hydroxyprogesterone caproate reduced the rate of SPTB, this drug received FDA contingent approval for this indication. In April 2023, based on the results of the largest randomized controlled trial of 17α-hydroxyprogesterone caproate that showed it was ineffective in preventing SPTB, the FDA removed its approval. This presentation is a thorough review of the pertinent literature regarding the past and present role of progestogens in preventing SPTB and will conclude with recommendations for future research avenues to develop better preventative strategies for the future. The author is an established investigator in this field, has conducted pertinent clinical trials related to SPTB, and has been an FDA expert reviewer for more than 35 years.
**Objective/Purpose:** To perform a critical review of the pertinent publications on this topic and to present recommendations for future research avenues addressing the prevention of SPTB.
**Methods:** Searches were performed in MEDLINE, Ovid, ClinicalTrials.gov, the International Prospective Register of Systematic Reviews (PROSPERO), and the Cochrane Central Register of Controlled Trials (CENTRAL) with the use of a combination of keywords and text words related to "preterm birth," "preterm delivery," "singleton," "progesterone," "progestogens," "17-alpha-hydroxy-progesterone caproate," and randomized controlled trials from the inception of each database to April 2023.
**Results:** 83 articles met the primary search criteria and, of these, 17 were randomized controlled trials (RCTs) of 17α-hydroxyprogesterone caproate versus placebo to prevent recurrent SPTB. Of these only two were adequately powered and only one demonstrated benefit. Conversely, five showed no benefit and possible harm as a meta-analysis found an increased incidence of gestational diabetes following administration of 17α-hydroxyprogesterone caproate. There were an additional 15 RCTs of vaginally administered natural progesterone versus placebo and 7 RCTs of 17α-hydroxyprogesterone caproate versus natural progesterone. The largest meta-analysis to date, EPPPIC (Evaluating Hormone Treatments for Women at Increased Risk for Preterm Birth) included 31 RCTs involving progestogens and showed possible benefit from natural progesterone in reducing risk of SPTB < 34 weeks but no benefits from either natural progesterone or 17α-hydroxyprogesterone caproate for patients with prior PTB and cervical length > 30 mm or twin gestations without other complications.
**Conclusions:** On the basis of the foregoing studies, 17α-hydroxyprogesterone caproate will no longer be used by the obstetric community to prevent recurrent SPTB. Other pharmacological interventions such as vaginal micronized progesterone show promise but still require larger RCTs to establish reliability, efficacy and safety. Future approaches to preventing and/or reducing the rate of SPTB should include development of robust, artificial-intelligence-aided patient risk-scoring systems, genomic assessment of patients at risk for SPTB (including progesterone-receptor polymorphisms and inflammatory proteins), and adequately powered trials of probiotics and lifestyle modifications.