



## Systematic review

# Progesterone for prevention of preterm delivery: A meta-analysis after the dust has settled

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### ABSTRACT

**Objective:** In November 2003 The American College of Obstetricians and Gynecologists (ACOG) recommended the use of progesterone to prevent preterm delivery (PTD) in women at high risk. Aim of this review is to investigate whether subsequent literature supports the use of progesterone.

**Data sources:** A search in PubMed, Medline, EMBASE, and the Cochrane Trials Register from January 2003 to October 2008 was conducted. Search terms were preterm delivery, preterm labor, preterm birth, progesterone, 17 $\alpha$ -hydroxyprogesterone caproate, pregnancy.

**Review methods:** Randomized clinical trials that assessed high-risk women were considered. PTD rates and neonatal outcomes were compared between groups. Odds Ratio (OR) and 95% Confidence Intervals (CI) were calculated using the Mantel-Haenszel fixed-effects model and the DerSimonian-Laird random-effects model.

**Results:** Four articles were included in analysis. PTD was significantly reduced by progesterone (276/812, 34% vs. controls; 272/650, 42%,  $p=0.01$ ; OR=0.49; 95% CI: 0.24-0.84). Neonatal outcomes were different between progesterone and controls in regard to birth weight <1500g (44/426, 10% vs. 48/276, 17% respectively,  $p=0.02$ , OR=0.60, 95% CI: 0.38-0.93) and neonatal death (16/740, 2% vs. 23/580, 4%, respectively,  $p=0.04$ , OR=0.50, 95% CI: 0.26-0.96).

**Conclusion:** The administration of progesterone provides beneficial effects for the prevention of PTD in women at high risk.

**Key words:** Preterm delivery, progesterone, prevention, prophylaxis.

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## Introduction

Preterm delivery (PTD) represents a major challenge for obstetricians, since it is the leading cause of perinatal morbidity/mortality [1] and long-term neurological handicaps [2]. Progesterone had been offered as a preventive approach for women at high risk. The proposed rationale to use exogenous progesterone is that the hormone inhibits the onset of premature uterine contractions through multiple physiological mechanisms, enhances the barrier to ascending infection via cervical mucus production, and improves resistance to cervical stromal degradation [3]. In November 2003 The American College of Obstetricians and Gynecologists (ACOG) recommended the use of progesterone in pregnant women with a history of spontaneous PTD [4]. This recommendation was largely based on two trials that were highly criticized in the English literature [5]. After the

ACOG statement ensuing studies showed that less than 60% of eligible patients are offered progesterone because of physician behavior or institution guidelines rather than patients' demographic characteristics [6]. In addition, a more recent survey assessed that non-use of progesterone by physicians was due to concerns about efficacy, safety, long-term neonatal outcomes, and need for more data [7]. The aim of this meta-analysis was to review whether subsequent studies (2003-2008) support the use of progesterone to prevent PTD.

## Materials and methods

A search in PubMed, Medline, EMBASE, and the Cochrane Trials Register from January 2003 to October 2008 was conducted to find relevant articles that investigated the role of progesterone (**Figure 1**). The two authors indepen-



dently evaluated the pertinent studies to determine eligibility. Key words were preterm delivery, preterm labor, preterm birth, progesterone, 17 $\alpha$ -hydroxyprogesterone caproate, pregnancy. Inclusion criteria were prophylaxis of PTD in patients at elevated risk, singleton pregnancy, randomized controlled trial, definition of preterm delivery, definition of risk factors for PTD, and data reported exactly in tables or text. Exclusion criteria were omitting at least one of the inclusion criteria, threatened preterm labor, PTD following premature rupture of membranes (PROM), and data reported in graphs or percentage. Personal communications, letters, and non-English language publications were also excluded. Outcomes of interest were PTD rate, neonatal morbidity and mortality rate, birth weight <2500g and <1500g, necessity of tocolysis in spite of prevention for PTD. Whenever possible, spontaneous PTD was distinguished from iatrogenic PTD. When more than one cut-off was used to define PTD, we selected outcomes associated with the latest gestational age. In cases of missed data, an effort to contact the principal investigator and/or the corresponding author was made in order to obtain unpublished outcomes.

The reporting of this meta-analysis was performed according to the QUORUM (Quality of Reporting of Meta-analyses) [8] guidelines. Heterogeneity between studies defined according to Higgins and Thompson [9] as the percentage of total variation across studies due to heterogeneity rather than chance ( $I^2$ ), was tested with chi-squared test for heterogeneity at a significance level of  $P=0.10$ . A random effects model was applied whenever the  $I^2$  statistics was greater than 25%. Categorical variables were examined with calculation of pooled odds ratios (OR) with 95% Con-

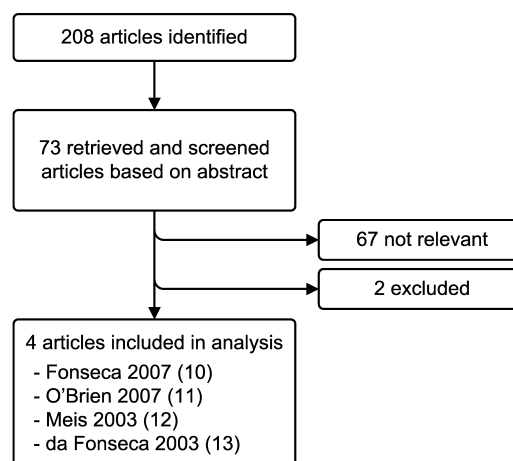


Figure 1. Search strategy

fidence Interval (CI). Inter-groups comparison was considered statistically significant at an alpha level of 2-tailed  $P<0.05$ . Meta-analysis was performed with RevMan (Revision Manager, Version 4.2 for Windows. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration 2003).

### Results

From January 2003 to October 2008, four articles were included for analysis. These articles [10-13] provided 812 (55%) women in the progesterone group and 650 (45%) in the placebo group. All of the four studies randomized women who were considered at high risk for PTD. The

Table 1. Characteristics of the included studies.

Author	Year	Risk factors	Type of administration	Sample size	Definition of PTD (weeks)	Rate of PTD	BW <2500	BW <1500	Neonatal morbidity	Neonatal death
Fonseca	2007	cervix <15 mm at 20-25 wks)	200 mg/daily (24 to 34 wks) intravaginal capsules	treatment: 125, placebo: 125	<34	26 (21)	56 (41)	18 (13)	11 (8)	2 (1)
						45 (36)	59 (43)	27 (20)	19 (14)	7 (5)
					<37	129 (41)	NA	NA	43 (14)	6 (2)
						123 (40)	NA	NA	46 (15)	7 (2)
O'Brien	2007	recurrent PTD	8%/daily gel (18-22 to 37 wks)	treatment: 309, placebo: 302	<35	70 (23)				
						80 (26)				
					<32	31 (10)				
						34 (11)				
					<28	10 (3)				
					9 (3)					
Meis	2003	recurrent PTD	i.m. (16-20 weeks)	treatment: 306, placebo: 153	<37	111 (36)	82 (27)	26 (9)	58 (19)	8 (3)
						84 (55)	62 (41)	21 (14)	57 (38)	9 (6)
					<35	63 (20)				
					47 (30)					
					35 (11)					
					30 (20)					
da Fonseca	2003	recurrent PTD, previous prophylactic cervical cerclage, uterine malformations	100 mg daily (24 to 34 wks)	treatment: 72, placebo: 70	<37	10 (14)	NA	NA	NA	NA
						20 (3)	NA	NA	NA	NA
					<34	2 (3)				
					13 (19)					

PTD, preterm delivery; BW, Birthweight; NA, not available

definition of high risk was consisted of recurrent PTD in two studies [11, 12], cervical length <15 mm in one study [10], and recurrent PTD, uterine malformation and previous pregnancies affected with cervical incompetence in one study [13]. Three studies administered progesterone by intravaginal gel or capsules [10, 11, 13] and by intramuscular injection in one study [12]. Characteristics of each study are given in **Table 1**.

In all but one study [11], there was a lower incidence of PTD in the progesterone group as compared with placebo. Meta-analysis confirmed that PTD was significantly less likely to occur in women treated with progesterone (276/812, 34%) than women receiving placebo (272/650, 42%;  $Z=2.58$ ;  $P=0.01$ ;  $OR=0.49$ ; 95% CI: 0.24-0.84) (**Figure 2A**). Two studies [10, 12] analyzed spontaneous PTD and were concordant in finding that this outcome occurred less frequent among the progesterone than placebo group (progesterone: 114/418, 27%; vs. placebo: 112/267, 42%;  $Z=4.24$ ;  $P<0.0001$ ) (**Figure 2B**). Three studies [11-13] reported that tocolytic therapy was equally required in both groups (progesterone: 102/687, 15%; placebo: 77/525, 15%;  $Z=0.26$ ;  $P=0.80$ ).

Two studies [10, 11] reported that neonatal morbidity rate occurred equally in the two groups, whereas the third study [12] detected a lower incidence of neonatal morbidity in the progesterone group than placebo. Overall, no significant difference was noted for neonatal morbidity rate (progesterone: 112/739, 15%; placebo: 122/578, 21%;  $Z=1.88$ ;  $P=0.06$ ). The three studies were concordant in finding a not significant trend for reduced neonatal death in the progesterone group and such trend became significant when articles were pooled (progesterone: 16/740, 2%; placebo: 23/580, 4%;  $Z=2.09$ ;  $P=0.04$ ;  $OR=0.50$ ; 95% CI: 0.26-0.96) (**Figure 2C**).

Birth weight was assessed in two studies [10, 12] as infants weighting <2500g or <1500g. Considered as a whole, infants with birth weight <2500g were similar in the two groups (progesterone: 138/426, 56%; placebo: 121/276, 44%;  $Z=1.45$ ;  $P=0.15$ ), whereas infants in the progesterone group were less likely to weight <1500g at birth as compared with infants in the placebo group (progesterone: 44/426, 10%; placebo: 48/276, 17%;  $Z=2.25$ ;  $P=0.02$ ;  $OR=0.60$ ; 95% CI: 0.38-0.93).

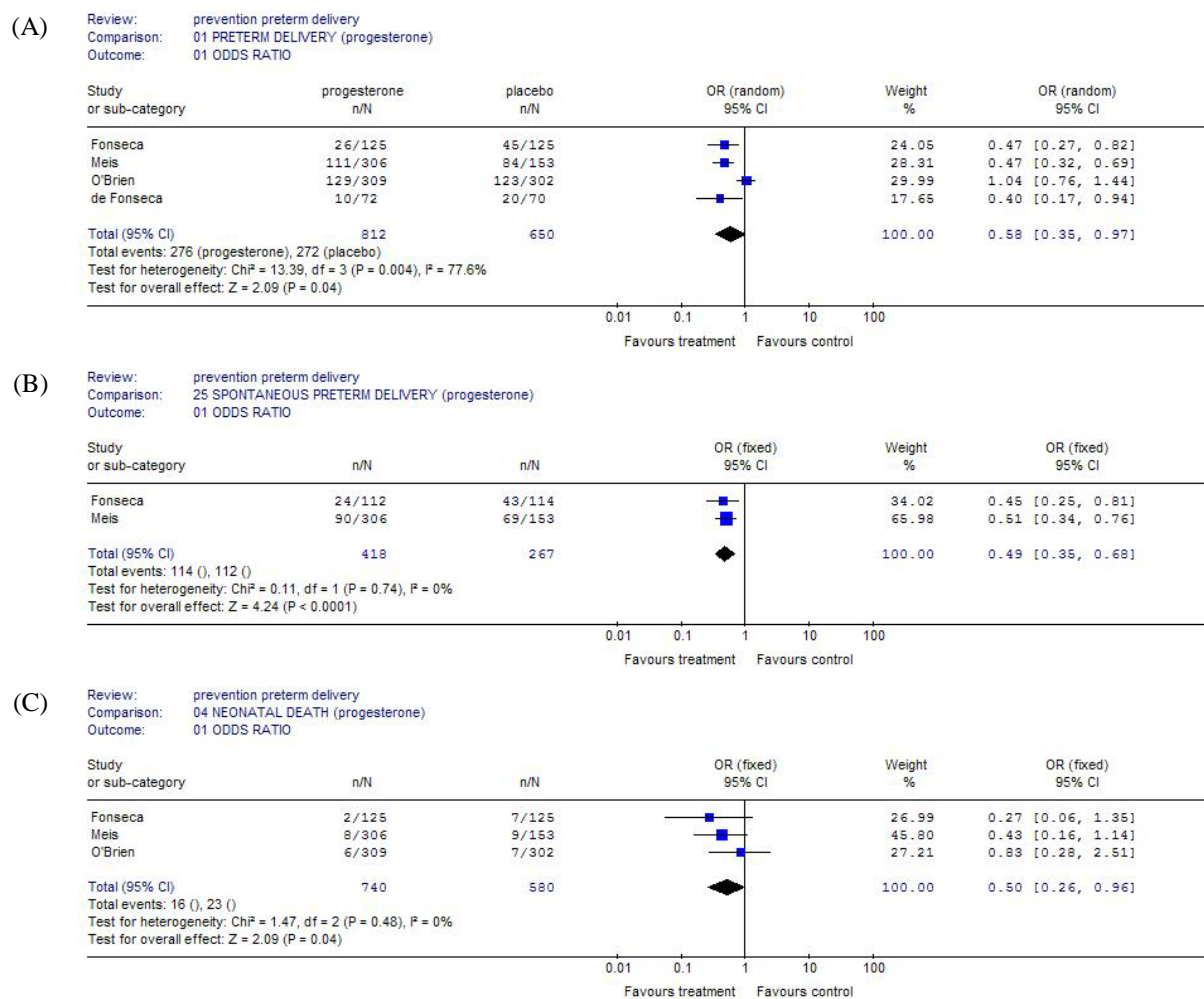


Figure 2. **A.** Comparison of preterm delivery between progesterone and placebo. **B.** Comparison of spontaneous preterm delivery between progesterone and placebo. **C.** Comparison of neonatal death between progesterone and placebo.

## Conclusion

This article reviewed the English literature in the last 5 years concerning the efficacy of prophylaxis for PTD with progesterone. It showed that the administration of progesterone in women at high risk for PTD was efficacious in reducing the incidence of PTD. Our review also highlights that a significant decrease of very low birth weight (<1500g) and neonatal death is achieved following prophylaxis with progesterone.

In the reviewed articles, progesterone was investigated in women at high risk for PTD, which was defined in all but one study [10] as a positive history of preterm birth in previous pregnancies. However, a previous PTD is responsible for 15-50% of spontaneous PTD, dependent on number and gestational age of previous delivery [14], and is not applicable in women in their first pregnancy. Because there is paucity of studies aimed to investigate the benefit of progesterone in women with other risk factors, such as ethnicity, age, number of previous PTD, smoking, short interval between pregnancies, and prepregnancy weight [15], a better identification of candidate women for preventing PTD is advocated.

A potential limitation of our results consists in that we pooled articles that did not use the same progestational agent and dosage. However ideal formulation and optimal route of delivery are still undetermined [4]. In addition, gestational age at time of recruitment also differed across studies, but such heterogeneity is unlikely to affect our results, since no significant differences in outcomes were observed between women initiating progesterone at 16-20 weeks and those undergoing prophylaxis at 21-26 weeks [16].

Results of randomized studies can also be biased by the fact that women enrolled in randomized studies are motivated to adhere to the follow up, but it is unknown whether women in the general population are available to attend weekly clinic visits. Because early discontinuation of progesterone treatment is associated with an increased risk of PTD [17], the efficacy of progesterone in the general population may not reflect the efficacy reported in randomized studies. In addition, researches about maternal and neonatal adverse effects of progesterone use, such as gestational diabetes [17], have been poorly investigated.

An important limitation of current literature is the paucity of data emerged with regard to spontaneous versus iatrogenic PTD, PROM and tocolysis in women undergoing prophylaxis for PTD. A matter of heterogeneity across studies was represented by the low-gestational age cut-off of PTD, which, although it is defined as delivery at less than 37 weeks, varied by studies (**Table 1**). However, different cut-offs are unlikely to affect our results, since the risk of adverse neonatal outcomes are similar between infants delivered at 34-35 weeks and those who are delivered earlier.

In conclusion, gestational age at delivery is used as a surrogate marker for neonatal outcomes, assuming that the greater the gestational age the lower the risk of adverse outcomes. In this context, administration of progesterone in women with high risk is associated with a reduced incidence of PTD, small for gestational age newborns (<1500g), and neonatal death.

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