

## Progestogen maintenance therapy to prevent preterm birth after an episode of preterm labor: a systematic review and meta-analysis

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### INTRODUCTION

- The effectiveness of progestogen maintenance therapy after an episode of pretem labor (PTL) is subject of debate.
- The objective of this study was to conduct a meta-analysis of progestogen maintenance therapy after an episode of PTL.

### **METHODS**

- Systematic review and meta-analysis
- Inclusion criteria:
  - Randomized controlled trials (RCT)
  - Women with gestational age (GA) between 16<sup>+0</sup> and 37<sup>+0</sup> weeks. who remained pregnant after an episode of PTL
  - Randomization between (any type of) progestogen maintenance therapy compared to a control group
- Primary outcome was time to delivery in days (latency time), defined as timing of randomization to delivery
- Secondary neonatal and maternal outcomes are consistent with the core outcome set of preterm Birth studies<sup>2</sup>
- Studies were extensively assessed for data trustworthiness (data integrity) and risk of bias.

## Progestogen maintenance therapy might have a modest effect on prolongation of latency time.

# However, this effect is **not** demonstrated when analyzing low risk

## of bias studies only.

	Progestogens			Control				Mean Difference	Mean Difference	
Study or Subgroup	Mean	<b>SD</b>	Total	Mean	<b>SD</b>	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl	
Arikan 2011	32.1	17.8	43	21.2	16.3	40	10.1%	10.90 [3.56, 18.24]		
Borna 2008	36.1	17.9	37	24.5	27.2	33	7.1%	11.60 [0.67, 22.53]		
Briery 2014	23	17.5	22	16	12.1	23	8.7%	7.00 [-1.83, 15.83]	_ <b></b>	
Choudhary 2014	33.3	22.2	45	23.1	15.4	45	9.6%	10.20 [2.31, 18.09]		
Facchinetti 2007	35.3	19.1	30	25.5	15.1	30	8.8%	9.80 [1.09, 18.51]	_ <b></b>	
Facchinetti 2017	61.9	27.3	158	65.5	21.3	77	11.1%	-3.60 [-9.98, 2.78]		
Frey 2022	32.5	21.2	18	34.8	23.2	18	5.0%	-2.30 [-16.82, 12.22]		
Kashanian 2020	28.8	3.4	80	21.2	4.6	80	15.4%	7.60 [6.35, 8.85]	-	
Martinez de Tejada 2015	45.9	27.9	193	49.9	27.5	186	11.9%	-4.00 [-9.58, 1.58]		
Rozenberg 2012	61	29.1	94	63	29.1	94	9.2%	-2.00 [-10.32, 6.32]		
Wood 2017	44.5	35.6	19	46.6	29.9	22	3.0%	-2.10 [-22.41, 18.21]		
Total (95% CI)			739			648	100.0%	4.32 [0.40, 8.24]	<b>◆</b>	
Heterogeneity: Tau <sup>2</sup> = 25.51; Chi <sup>2</sup> = 35.79, df = 10 (P < 0.0001); l <sup>2</sup> = 72%										
Test for overall effect: Z = 2.16 (P = 0.03)									Favours [Control] Favours [Progestogens]	
									Tavours [Control] Tavours [Trogestogens]	

#### Figure 1: Latency time from randomization to delivery in all included studies

Progest	Progestogens		ntrol		Mean Difference	Mean Difference						
Study or Subgroup Mean	SD Total	Mean	SD Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI						
24.1.1 High risk of bias												
Arikan 2011 32.1 17	7.8 43	21.2 1	16.3 40	10.1%	10.90 [3.56, 18.24]							
Borna 2008 36.1 17	7.9 37	24.5 2	27.2 33	7.1%	11.60 [0.67, 22.53]							
Facchinetti 2007 35.3 19	9.1 30	25.5 1	15.1 30	8.8%	9.80 [1.09, 18.51]							
Facchinetti 2017 61.9 27	7.3 158	65.5 2	21.3 77	11.1%	-3.60 [-9.98, 2.78]							
Kashanian 2020 28.8 3	3.4 80	21.2	4.6 80	15.4%	7.60 [6.35, 8.85]	-						
Rozenberg 2012 61 29		63 2	29.1 94	9.2%	-2.00 [-10.32, 6.32]							
Subtotal (95% CI)	442		354	61.8%	5.47 [0.66, 10.29]	$\bullet$						
Heterogeneity: Tau² = 22.98; Chi² = 18.03, df = 5 (P = 0.003); l² = 72%												
Test for overall effect: $Z = 2.23$ (P = 0.03)												
24.1.2 Low risk of bias												
Briery 2014 23 17	7.5 22	16 1	12.1 23	8.7%	7.00 [-1.83, 15.83]	+						
Choudhary 2014 33.3 22	2.2 45	23.1 1	15.4 45	9.6%	10.20 [2.31, 18.09]							
Frey 2022 32.5 21	1.2 18	34.8 2	23.2 18	5.0%	-2.30 [-16.82, 12.22]							
Martinez de Tejada 2015 45.9 27	7.9 193	49.9 2	27.5 186	11.9%	-4.00 [-9.58, 1.58]							
Wood 2017 44.5 35		46.6 2	29.9 22	3.0%	-2.10 [-22.41, 18.21]							
Subtotal (95% CI)	297		294	38.2%	2.44 [-4.55, 9.42]	<b>+</b>						
Heterogeneity: Tau <sup>2</sup> = 35.17; Chi <sup>2</sup> = 10.27, df = 4 (P = 0.04); l <sup>2</sup> = 61%												
Test for overall effect: $Z = 0.68$ (P = 0.49)												
Total (95% CI)	739		648	100.0%	4.32 [0.40, 8.24]	◆						
Heterogeneity: Tau <sup>2</sup> = 25.51; Chi <sup>2</sup> = 35.79, df = 10 (P < 0.0001); l <sup>2</sup> = 72%												
Test for overall effect: Z = 2.16 (P = 0.03) Favours [control] Favours [Progestogens]												
Test for subgroup differences: Chi <sup>2</sup> = 0.49, df = 1 (P = 0.48), l <sup>2</sup> = 0%												

Figure 2: High risk of bias versus low risk of bias in studies; outcome latency time, comparing treatment with progestogens to controls

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## RESULTS

- Thirteen RCTs including a total of 1.722 women (910 progestogen maintenance group, 812 control group) were included
- Progestogen maintenance therapy demonstrated a longer latency time of 4.32 days (mean difference, 95% CI 0.40-8.24) compared to controls (Figure 1).
- Neonates were born with a high birth weight (mean difference 124.25 grams, 95% CI 8.99-239.51).
- No difference were found for any other perinatal outcomes
- When analysing studies with low risk of bias only (5 RCTs, 591 women), a significant longer latency time could not be demonstrated (Figure 2)

### DISCUSSION

- Progestogen maintenance therapy after PTL might have a modest effect on prolongation of pregnancy
- When analysing low risk of bias studies only, this effect was not demonstrated
- Validation through further research, preferably by an individual patient data meta-analysis is highly recommended.

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2. Van t' Hooft et al. Preventing preterm birth with progesterone in women with short cervical length, outcomes in children at 24 months of age. AJOG 2017.