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UNIVERSITÀ DEGLI STUDI DI MODENA E REGGIO EMILIA

Bologna, 22 settembre 2018

Si può prevenire il parto pretermine?

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Dipartimento Materno-infantile
Università degli Studi di Modena e Reggio Emilia



PRETERM BIRTH: EPIDEMIOLOGY

15 million babies

1,1 million preterm babies die every year

World Health Organization

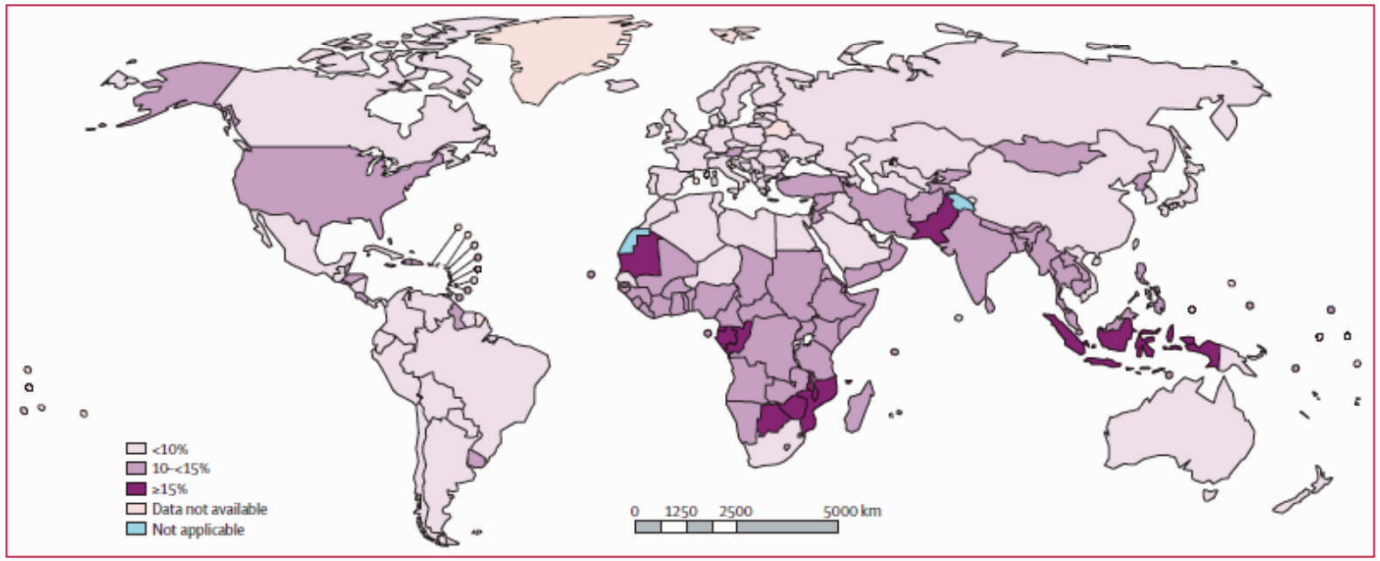


Figure 3: Estimated preterm birth rates by country for the year 2010

Italy: **6.5%** (data from WHO survey 2012)

Emilia-Romagna: **7.1%** (data from CedAP 2016-2017)



- Two-thirds: **spontaneous onset of labor or PPROM**
- one-third: **medically indicated** for maternal or fetal complications.

Blencowe et al. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. Lancet 2012; 379: 2162–72
WHO. Born too Soon: The Global Action Report on Preterm Birth. 2012

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Primary and Sercondary Prevention

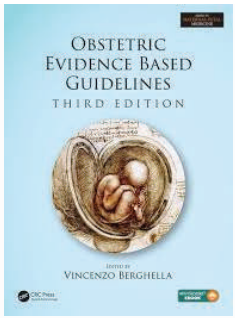
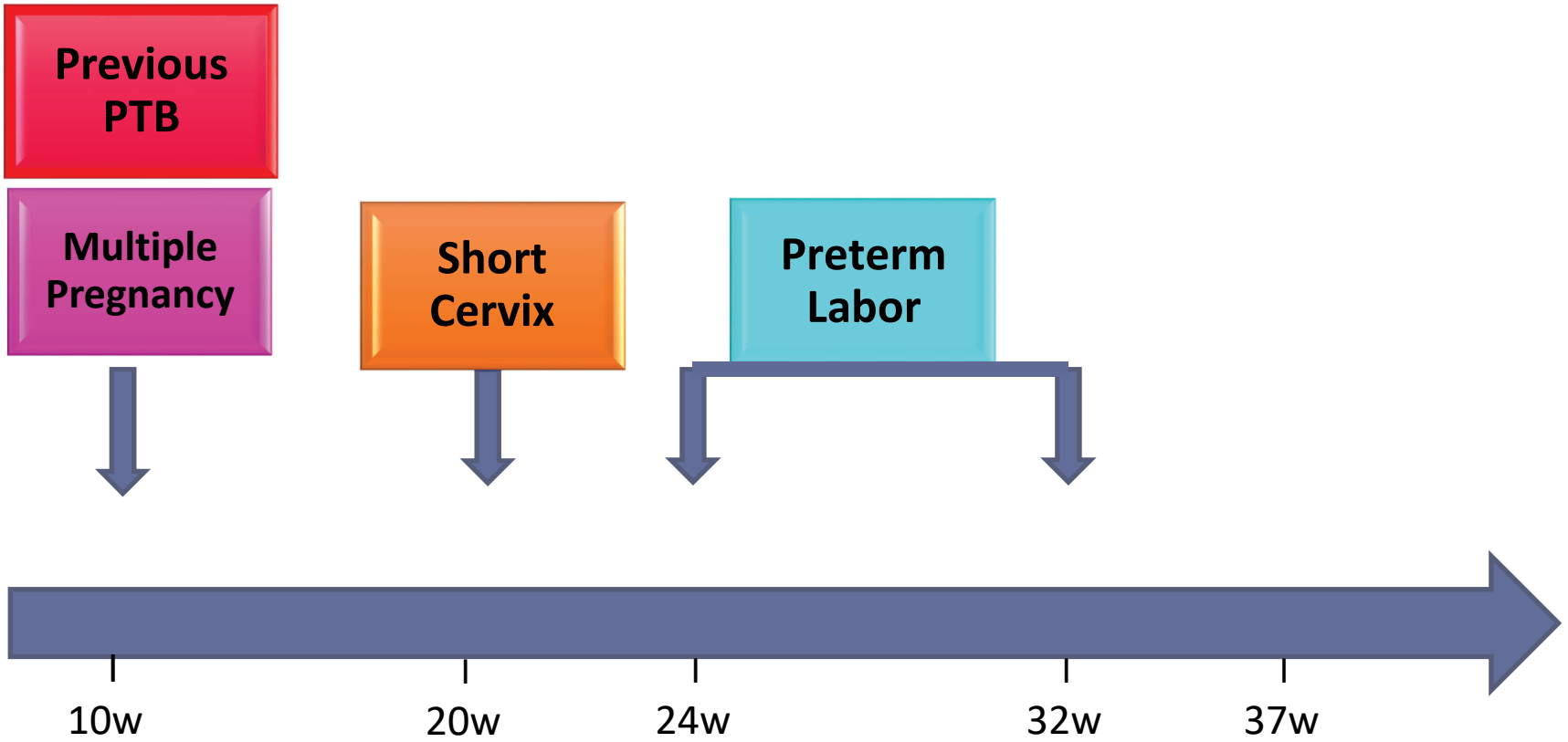


Table 17.4 Selected Effective Interventions for Prevention of PTB

Avoid (as feasible)	• Extremes of age • Interpregnancy interval <6 months • Induced termination of pregnancy without ripening • Multiple gestation • Illegal drugs (e.g., cocaine) • Physical abuse • STIs • Poverty • Poor education • Prepregnancy weight of <50 kg (<120 lb).
Risk	*Intervention*
Smoking	Smoking cessation programs
Short CL ≤ 20 mm (screen every singleton with TVU CL at 18–23-6/7 weeks)[a]	Vaginal progesterone (e.g., 200 mg daily)
Prior spontaneous PTB (SPTB)[b]	17-OH progesterone caproate, moderate (≥3 meals/week) fish intake
Prior SPTB *and* CL <25 mm between 16 and 23 6/7 weeks[b]	Ultrasound-indicated cerclage
Prior ≥3 PTB/STL[b]	History-indicated cerclage
Asymptomatic bacteriuria	Appropriate antibiotics

Risk Factors



Progestogens to prevent PTB in:

Short Cervix

Previous Preterm Birth

Multiple Pregnancy

Preterm Labor

Previous Preterm Birth

sPTB in 1 st pregnancy

→ **sPTB** risk **3.6** (3.2 – 4.0)

sPTB<34 wk in 1 st pregnancy

→ **sPTB<34 wk** risk **13.56** (11.5 – 16.0)

Ananth et al. Am J Obstet Gynecol 2006
Esplin et al. Obstet Gynecol 2008

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Previous PTB

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 12, 2003 VOL. 348 NO. 24

Prevention of Recurrent Preterm Delivery by 17 Alpha-Hydroxyprogesterone Caproate

Paul J. Meis, M.D., Mark Klebanoff, M.D., Elizabeth Thom, Ph.D., Mitchell P. Dombrowski, M.D., Baha Sibai, M.D., Atef H. Moawad, M.D., Catherine Y. Spong, M.D., John C. Hauth, M.D., Menachem Miodovnik, M.D., Michael W. Varner, M.D., Kenneth J. Leveno, M.D., Steve N. Caritis, M.D., Jay D. Iams, M.D., Ronald J. Wapner, M.D., Deborah Conway, M.D., Mary J. O'Sullivan, M.D., Marshall Carpenter, M.D., Brian Mercer, M.D., Susan M. Ramin, M.D., John M. Thorp, M.D., and Alan M. Peaceman, M.D., for the National Institute of Child Health and Human Development Maternal–Fetal Medicine Units Network*

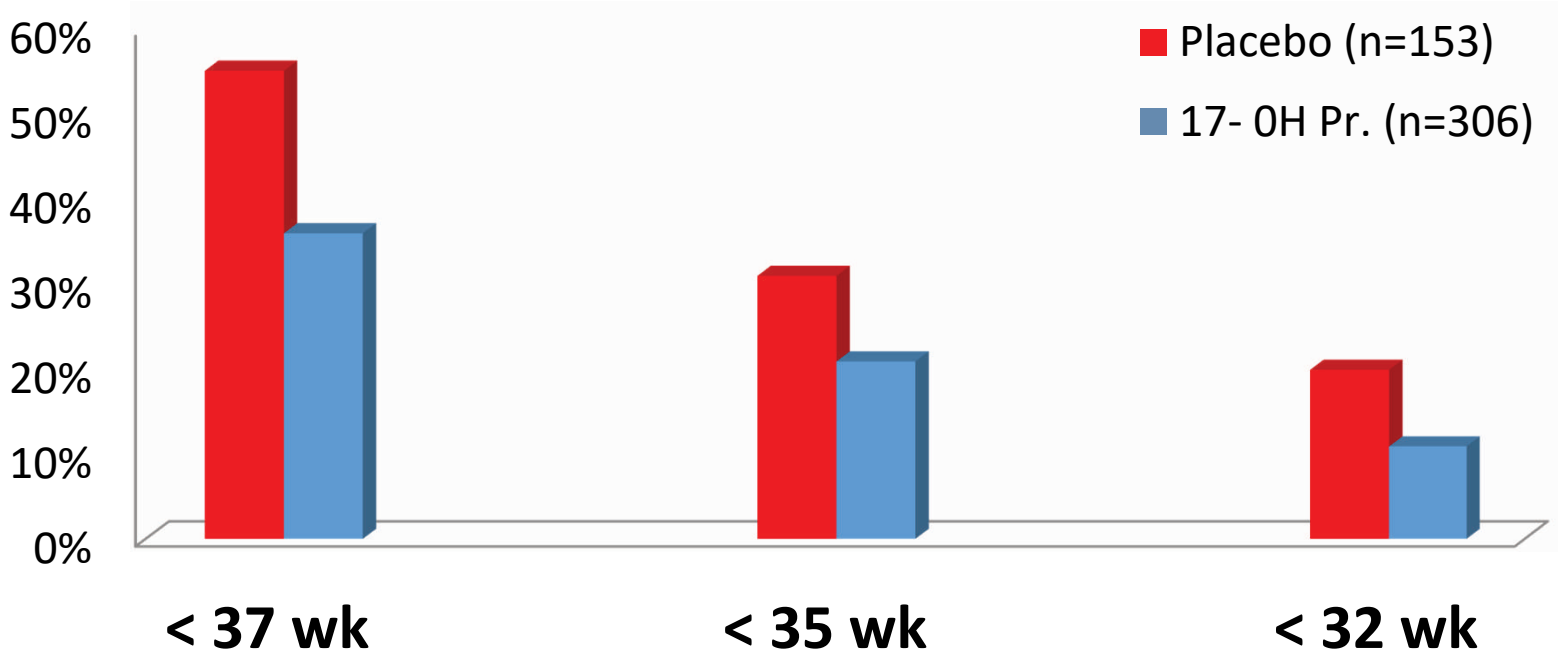
- Double-blind, placebo controlled trial
- 19 participating centers
- History of spontaneous PTB
- Enrollment at 16-20 wks
- 250 mg IM 17P vs. placebo (castor oil)
- Injections weekly until 36 wks or delivery
- Primary outcome: preterm delivery <37 wks

Meis PJ et al. NEJM 2003;348:2379-85

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Previous PTB

17-OH-P in Recurrent PTB



RR = 0.66 (0.54-0.81) 0.67 (0.48-0.93) 0.58 (0.37-0.91)

Meis PJ et al. NEJM 2003;348:2379-85

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Previous PTB

Vaginal progesterone *vs* intramuscular 17α-hydroxyprogesterone caproate for prevention of recurrent spontaneous preterm birth in singleton gestations: systematic review and meta-analysis of randomized controlled trials

3 RCTs, 680 women

Mean GA at randomisation: 16 wks

Low or very low quality by GRADE

Progesterone until 36 wks → 90 mg gel / 200 mg supp. / 100 mg supp.

Vs.

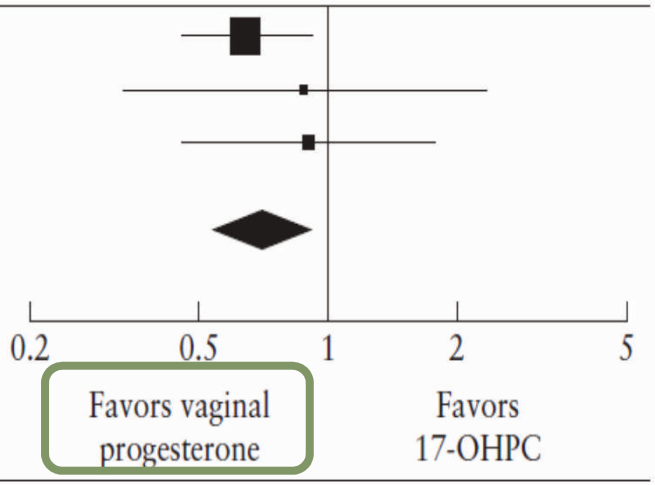
17-OHPC
250 mg weekly

*R*isk of recurrence of sPTB <34 wks

Study or subgroup	Vaginal Events	Vaginal Total	17-OHPC Events	17-OHPC Total	Weight	Risk ratio M–H, random (95% CI)
Maher (2012)[10]	42	253	64	249	72.0%	0.65 (0.46, 0.91)
Bafghi (2015)[12]	5	16	6	17	9.2%	0.89 (0.34, 2.34)
Elimian (2016)[11]	14	79	13	66	18.8%	0.90 (0.46, 1.78)
Total (95% CI)		348		332	100.0%	0.71 (0.53, 0.95)
Total events	61		83			

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.95$, df = 2 ($P = 0.62$); $I^2 = 0\%$

Test for overall effect: $Z = 2.30$ ($P = 0.02$)



Neonatal outcome

Vaginal progesterone was associated with a lower rate of NICU admission compared with 17-OHPC (18.7% vs 23.5%; RR, 0.63, 95% CI, 0.47–0.83)

Saccone et al. Ultrasound Obstet Gynecol 2017; 49: 315–321

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Cerclage for Short Cervix on Ultrasonography in Women With Singleton Gestations and Previous Preterm Birth. A Meta-Analysis

Previous PTB

PTB <35 wk

Study or Subgroup	Cerclage Events	Cerclage Total	No Cerclage Events	No Cerclage Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Rust 2001	13	53	16	49	16.0%	0.75 [0.40, 1.40]
Althuisius 2001	0	14	6	12	6.7%	0.07 [0.00, 1.07]
To 2004	5	21	8	23	7.3%	0.68 [0.27, 1.77]
Berghella 2004	5	14	11	17	9.5%	0.55 [0.25, 1.21]
Owen 2009	48	148	64	153	60.5%	0.78 [0.58, 1.04]
Total (95% CI)		**250**		**254**	**100.0%**	**0.70 [0.55, 0.89]**
Total events	71		105			

Heterogeneity: Chi² = 3.63, df = 4 (P = 0.46); I² = 0%
Test for overall effect: Z = 2.91 (P = 0.004)

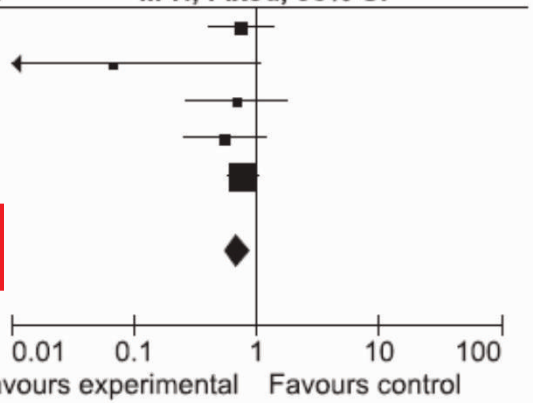


Fig. 3. Forest plot analysis of preterm birth before 35 weeks of gestation.
Berghella. Cerclage for Short Cervical Length. Obstet Gynecol 2011.

Composite neonatal mortality and morbidity

Study or Subgroup	Cerclage Events	Cerclage Total	No Cerclage Events	No Cerclage Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Rust 2001	9	53	9	49	14.9%	0.92 [0.40, 2.14]
Althuisius 2001	0	14	2	12	4.3%	0.17 [0.01, 3.29]
To 2004	0	21	1	23	2.3%	0.36 [0.02, 8.47]
Berghella 2004	4	14	11	17	15.8%	0.44 [0.18, 1.09]
Owen 2009	26	148	40	153	62.7%	0.67 [0.43, 1.04]
Total (95% CI)		**250**		**254**	**100.0%**	**0.64 [0.45, 0.91]**
Total events	39		63			

Heterogeneity: Chi² = 2.32, df = 4 (P = 0.68); I² = 0%
Test for overall effect: Z = 2.46 (P = 0.01)

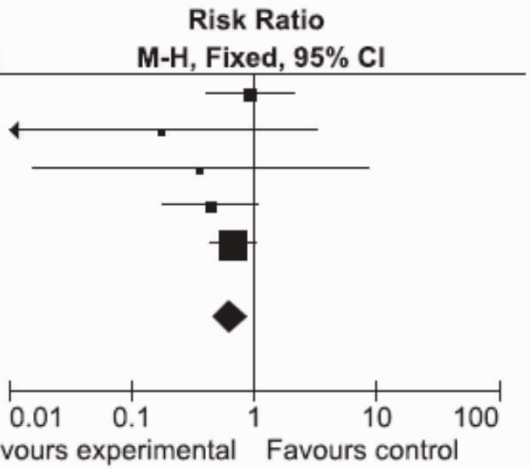


Fig. 4. Forest plot analysis of composite perinatal mortality and morbidity.
Berghella. Cerclage for Short Cervical Length. Obstet Gynecol 2011.

Berghella et al. Obstet Gynecol 2011

Progestogens to prevent PTB in:

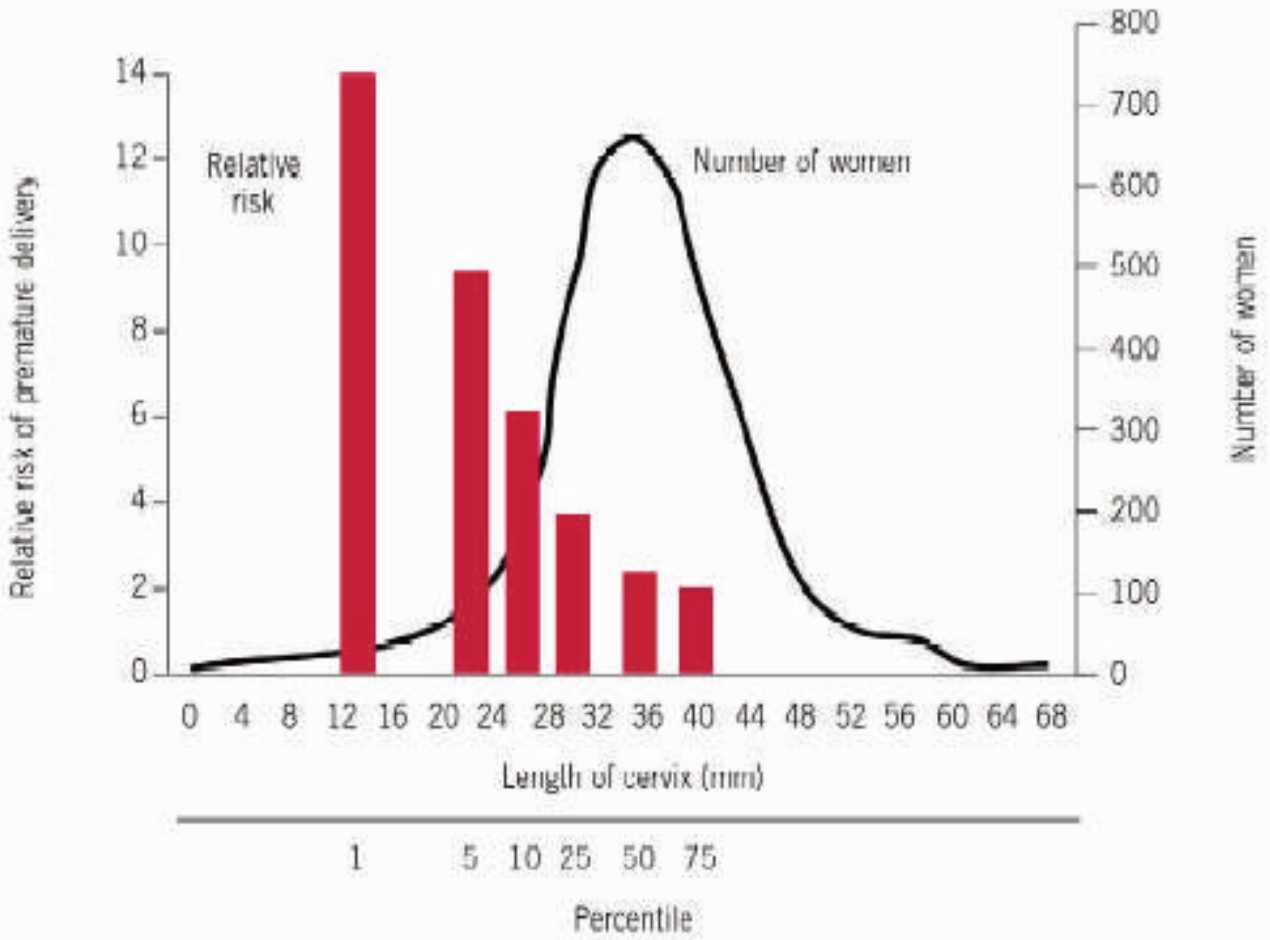
Short Cervix

Previous Preterm Birth

Multiple Pregnancy

Preterm Labor

Short Cervix



24 wk

Figure 2. Distribution of subjects among percentiles for cervical length measured by transvaginal ultrasonography at 24 weeks' gestation *(solid line)* and relative risk of spontaneous preterm delivery before 35 weeks' gestation according to percentiles for cervical length *(bars)*. The risks among women with values at or below the first, fifth, tenth, 25th, 50th, and 75th percentiles for cervical length are compared with the risk among women with values above the 75th percentile. (Modified with permission from Iams JD, Goldenberg RL, Meis PJ, Mercer BM, Moawad A, Das A, et al. The length of the cervix and the risk of spontaneous preterm delivery. N Engl J Med 1996;334:567–72. Copyright © 1996 Massachusetts Medical Society. All rights reserved.)

Iams. Early Detection of Prematurity. Obstet Gynecol 2003.

REPORTS OF MAJOR IMPACT www.AJC

Short Cervix

Vaginal progesterone in women with an asymptomatic sonographic short cervix in the midtrimester decreases preterm delivery and neonatal morbidity: a systematic review and metaanalysis of individual patient data

Roberto Romero, MD; Kypros Nicolaides, MD; Agustin Conde-Agudelo, MD, MPH; Ann Tabor, MD; John M. O'Brien, MD; Elcin Cetingoz, MD; Eduardo Da Fonseca, MD; George W. Creasy, MD; Katharina Klein, MD; Line Rode, MD; Priya Soma-Pillay, MD; Shalini Fusey, MD; Cetin Cam, MD; Zarko Alfirevic, MD; Sonia S. Hassan, MD

- **Primary endpoint :** vP in asymptomatic women with a short cervix at midtrimester (≤25 mm) reduces the rate of preterm birth, and improves neonatal morbidity and mortality?
- **Primary outcome :** PTB <33 wks
- **Secondary outcomes :** preterm birth at <37, <36, <35, <34, <30, and <28 weeks of gestation; RDS; birth weight <1500 g; admission to NICU; and use of mechanical ventilation.

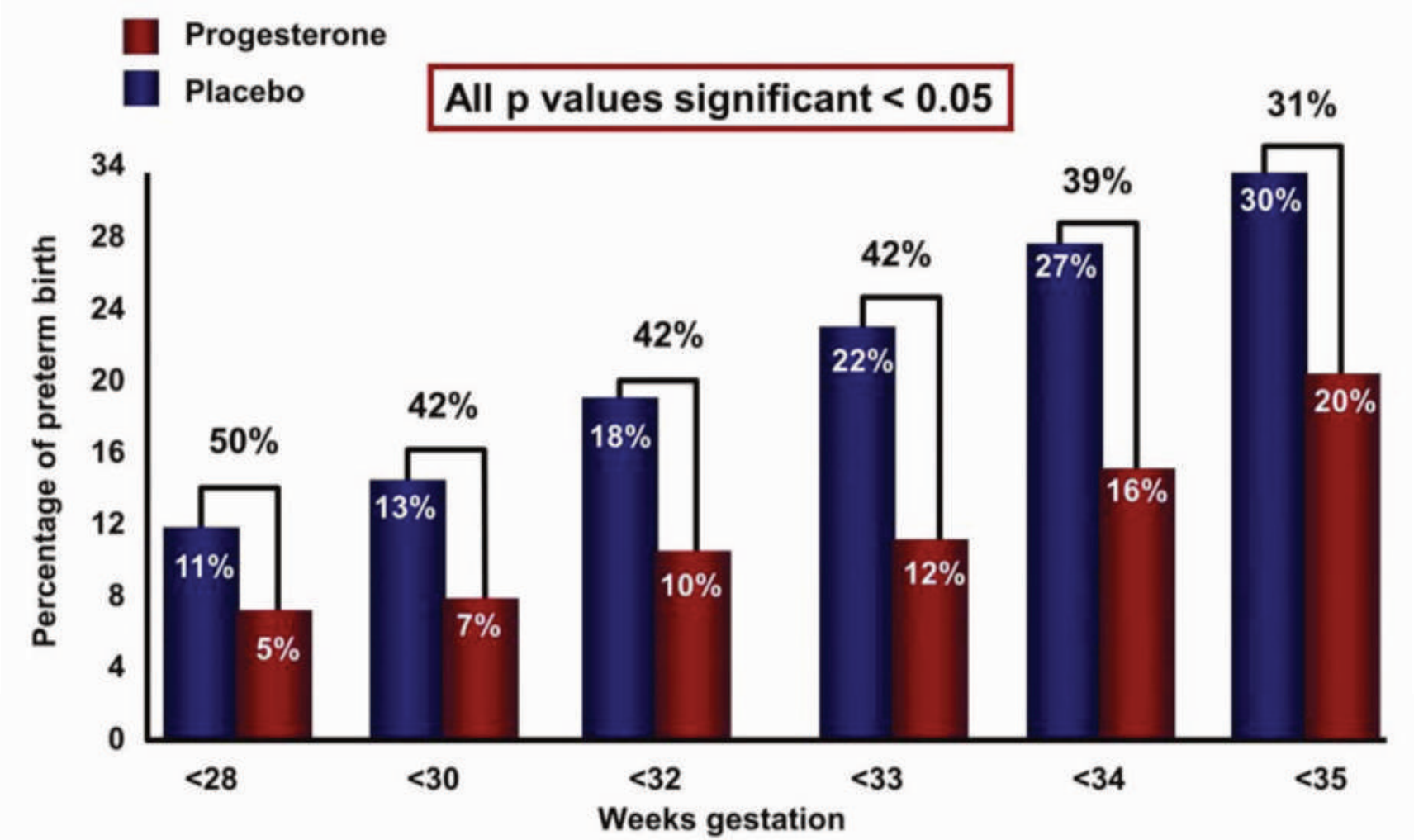
4 high-quality studies :
775 women and 827 infants

Romero et al. Am J Obstet Gyn 2012

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Preterm Birth Rates

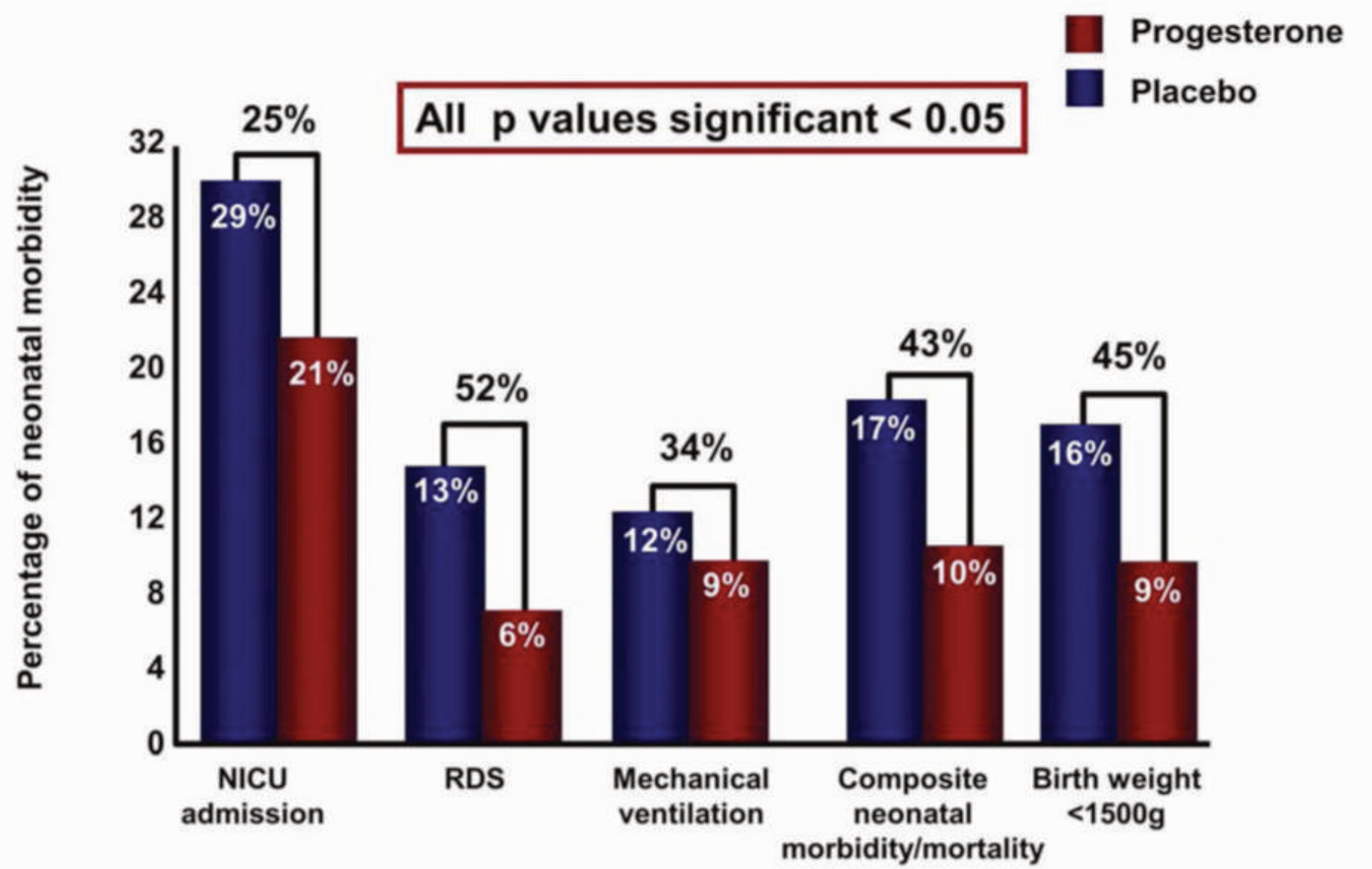
Short Cervix



Romero et al. Am J Obstet Gyn 2014

Neonatal Outcomes

Short Cervix



Romero et al. Am J Obstet Gyn 2014

Vaginal progesterone decreases preterm birth ≤ 34 weeks of gestation in women with a singleton pregnancy and a short cervix: an updated meta-analysis including data from the OPPTIMUM study

Short Cervix

R. ROMERO*†‡§, K. H. NICOLAIDES¶, A. CONDE-AGUDELO*, J. M. O'BRIEN**, E. CETINGOZ††, E. DA FONSECA‡‡, G. W. CREASY§§ and S. S. HASSAN*¶¶

ULTRASOUND in Obstetrics & Gynecology

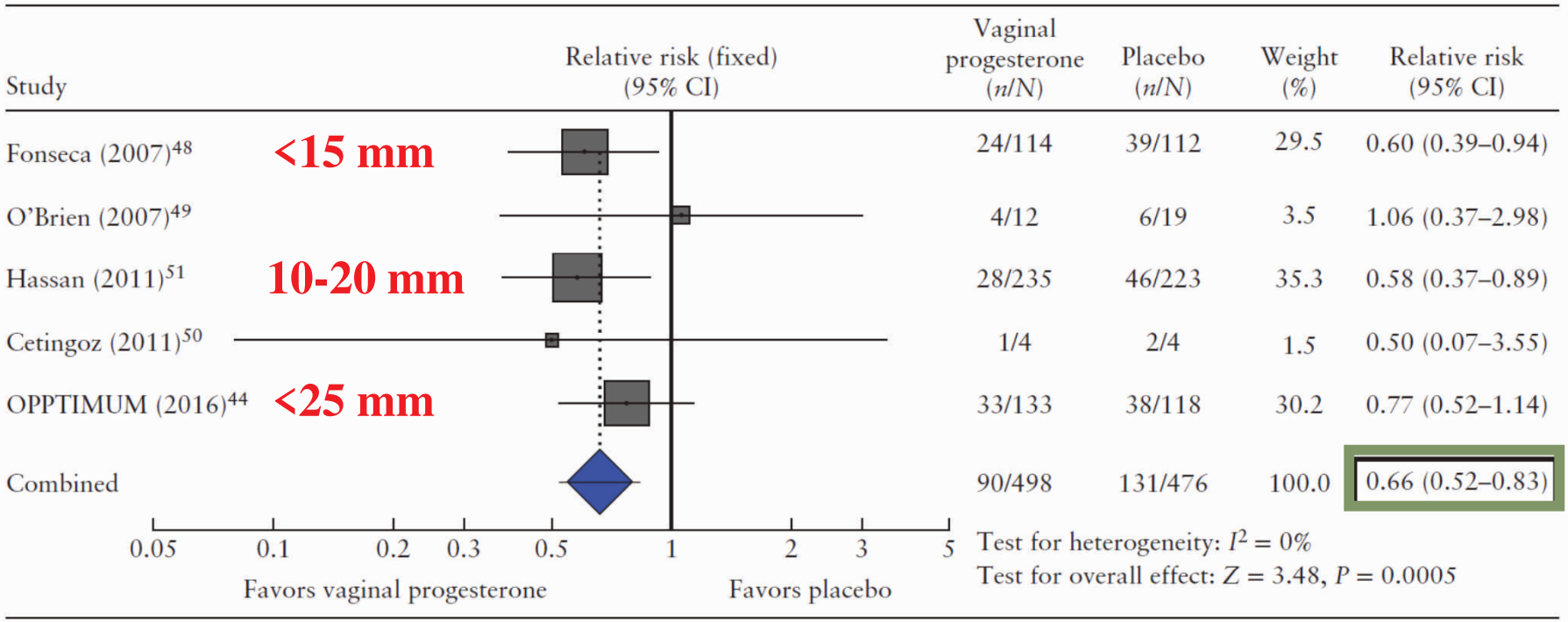


Figure 3 Forest plot of the effect of vaginal progesterone on the risk of preterm birth ≤ 34 weeks of gestation or fetal death.

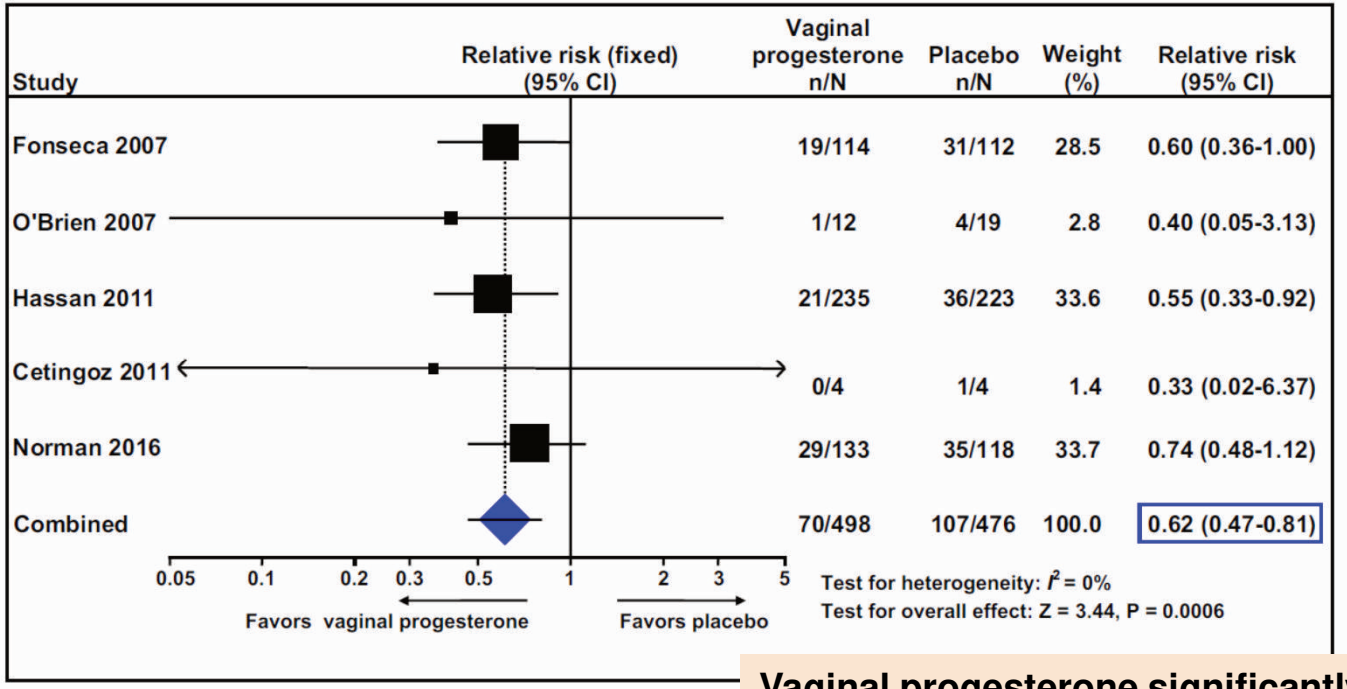
Vaginal progesterone for preventing preterm birth and adverse perinatal outcomes in singleton gestations with a short cervix: a meta-analysis of individual patient data

Roberto Romero, MD, DMedSci; Agustin Conde-Agudelo, MD, MPH, PhD; Eduardo Da Fonseca, MD; John M. O'Brien, MD; Elcin Cetingoz, MD; George W. Creasy, MD; Sonia S. Hassan, MD; Kypros H. Nicolaides, MD

Short Cervix

AJOG American Journal of Obstetrics & Gynecology

FIGURE 3
Effect of vaginal progesterone on preterm birth <33 weeks of gestation



CI, confidence interval.

Romero et al. Vaginal progesterone to prevent preterm birth in singleton gestations with a short cervix.

5 high quality RCTs

974 women (498 vP, 476 placebo)

Vaginal progesterone significantly decreased the risk of

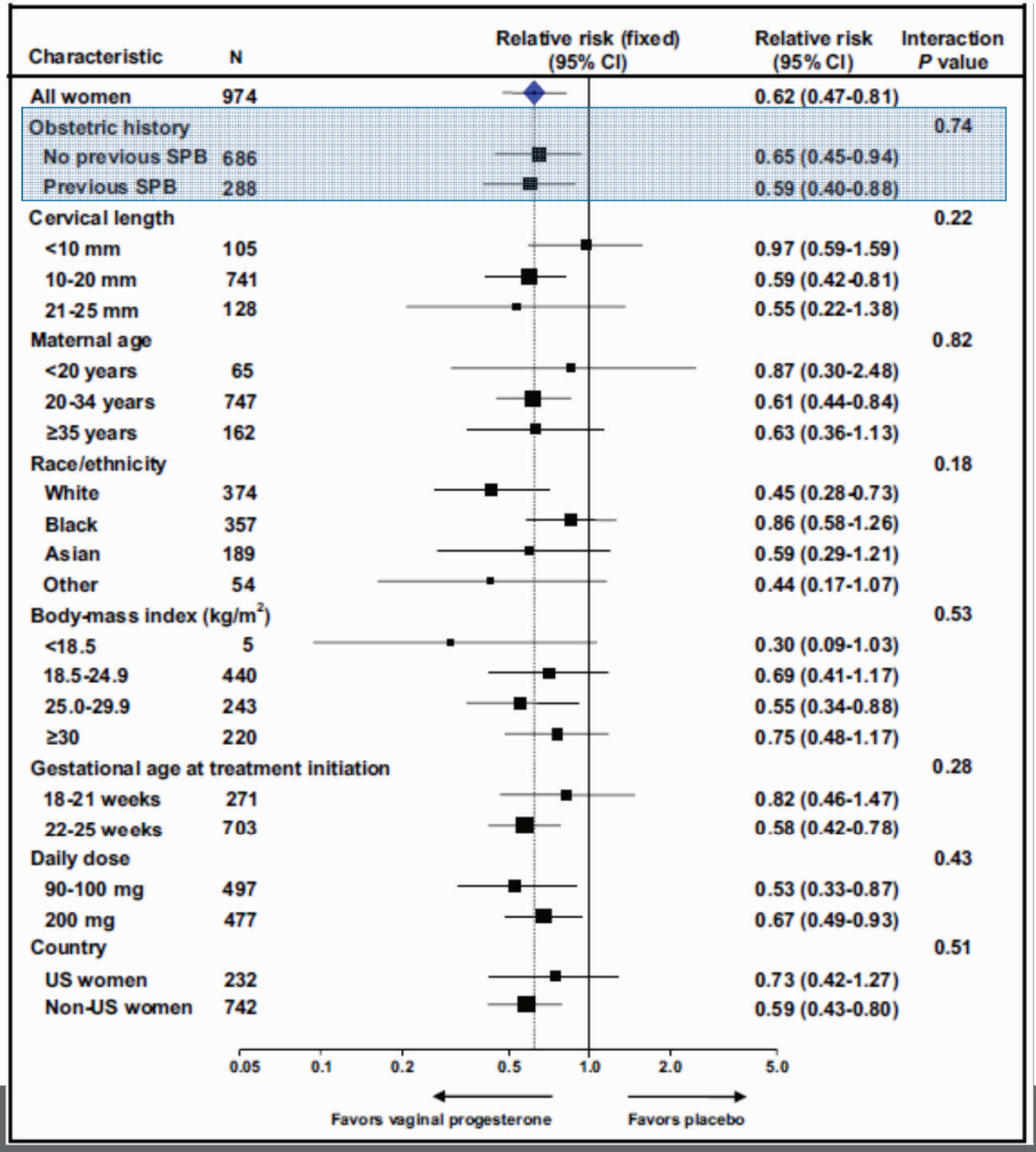
- **preterm birth <36, <35, <34, <32, <30, <28 weeks;**
- **spontaneous preterm birth <33 and <34 weeks;**
- **RDS;**
- **composite neonatal morbidity and mortality;**
- **birthweight <1500 g and <2500 g;**
- **admission to NICU**

Romero et al. Am J Obstet Gyn 2018

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FIGURE 4

Subgroup analyses of the effect of vaginal progesterone on preterm birth <33 weeks of gestation



17 alpha-hydroxyprogesterone caproate to prevent prematurity in nulliparas with cervical length less than 30 mm

AJOG American Journal of Obstetrics & Gynecology

Short Cervix

Multicenter RCT
17-OHP (n=327) and placebo (n=330)

The frequency of **PTB <37 weeks** did not differ between the 17-OHP (n=327) and placebo (n=330) groups (25.1% vs 24.2%; RR 1.03; 95% CI 0.79 –1.35).

No difference in the **composite adverse neonatal outcome** (7.0% vs 9.1%; RR, 0.77; 95% CI 0.46 –1.30).

TABLE 5
Additional subgroup analyses for preterm birth <37 and 34 weeks

Variable	17-OHP (n = 327)	Placebo (n = 330)	RR (95% CI)	*P* value[a]
Preterm birth <37 wk				
Cervical length, mm				.59
<10	5/9 (55.6)	10/16 (62.5)	0.89 (0.44–1.78)	
10-20	19/50 (38.0)	18/40 (45.0)	0.84 (0.52–1.38)	
>20	58/268 (21.6)	52/274 (19.0)	1.14 (0.82–1.59)	
Preterm birth <34 wk				
Cervical length, mm				.82
<15	9/25 (36.0)	13/31(41.9)	0.86 (0.44–1.67)	
≥15	32/302 (10.6)	35/299 (11.7)	0.91 (0.58–1.42)	
Cervical length, mm				.49
<10	5/9 (55.6)	6/16 (37.5)	1.48 (0.63–3.51)	
10-20	11/50 (22.0)	12/40 (30.0)	0.73 (0.36–1.48)	
>20	25/268 (9.3)	30/274 (10.9)	0.85 (0.52–1.41)	

Data are presented as n/N (%).
CI, confidence interval; *RR*, relative risk; *17-OHP*, 17 alpha-hydroxyprogesterone caproate.
[a] *P* value for Breslow-Day interaction term.

Grobman. 17 alpha-hydroxyprogesterone caproate for nulliparas with cervical length <30 mm. Am J Obstet Gynecol 2012.

Grobman et al. Am J Obstet Gynecol 2012

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Short Cervix

Cerclage for Short Cervix on Ultrasound in Singleton Gestations without Prior Spontaneous Preterm Birth: a Systematic Review and Meta-analysis of Trials using individual patient-level data

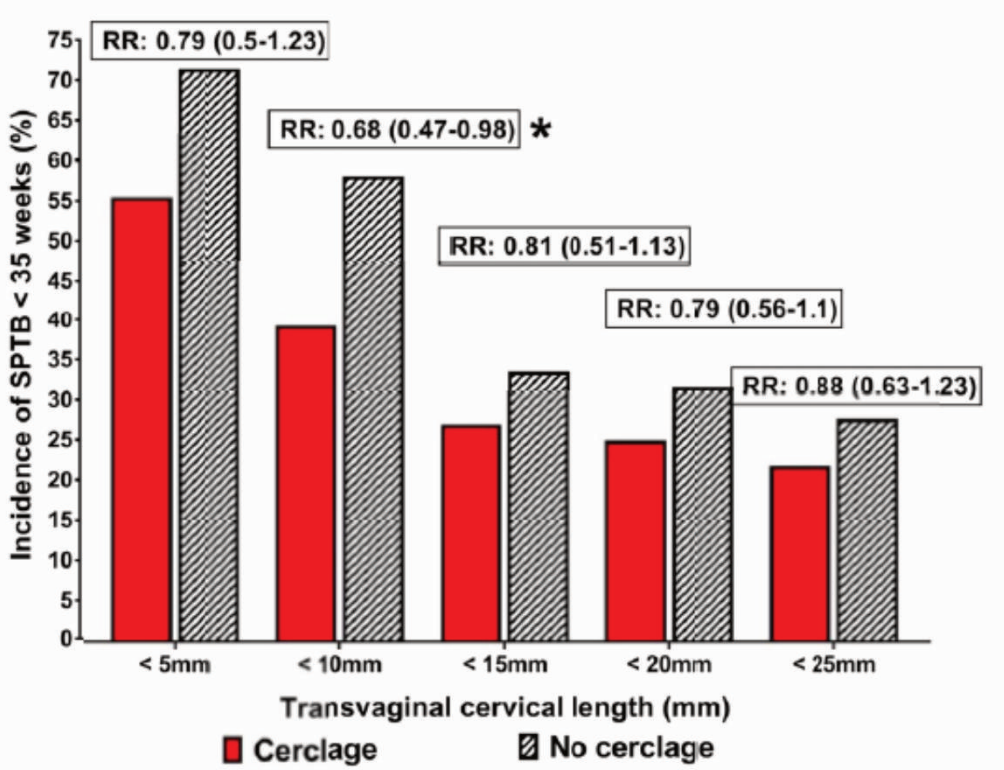
5 RCTs (n=419)

Asymptomatic singletons without prior sPTB and CL < 25 mm

primary outcome was PTB <35 weeks

No differences were found in **PTB <35 (21.9% vs 27.7%; RR 0.88, 95% CI 0.63 to 1.23**)

Cerclage, in singletons without prior spontaneous PTB, seems to be **possible efficacious at lower CLs**



Berghella et al. Ultrasound Obstet Gynecol 2017

Cervical Pessary for Preventing Preterm Birth in Singleton Pregnancies With Short Cervical Length

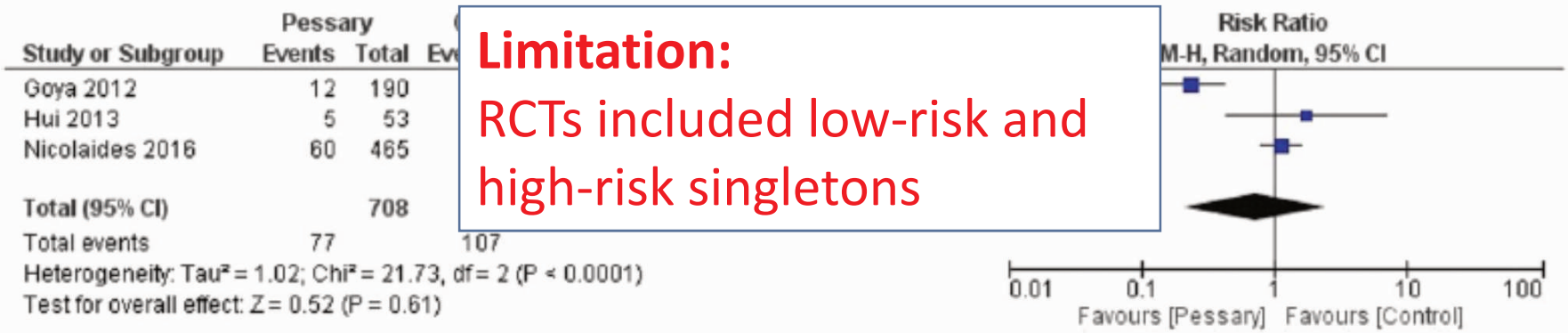
A Systematic Review and Meta-analysis

Short Cervix

3 RCTs (n=1420)
Mean GA at randomization: 22 wks
Pessary removed at 37 wks



Figure 3. Forest plot for the risk of the primary outcome (ie, spontaneous preterm birth <34 weeks). CI, confidence interval; M-H, Mantel-Haenszel; df, degrees of freedom.



Limitation:
RCTs included low-risk and high-risk singletons

In singleton pregnancies with a TVU CL <25mm at 20–24 6/7 weeks, the Arabin pessary does not reduce the rate of spontaneous preterm delivery or improve perinatal outcome.

Saccone et al. J Ultrasound Med. 2017

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Progestogens to prevent PTB in:

Short Cervix

Previous Preterm Birth

Multiple Pregnancy

Preterm Labor

Vaginal progesterone in women with an asymptomatic sonographic short cervix in the midtrimester decreases preterm delivery and neonatal morbidity: a systematic review and metaanalysis of individual patient data

TABLE 3
Effect of vaginal progesterone on preterm birth and perinatal outcomes in singleton and twin gestations

	Singleton pregnancy				Twin pregnancy				
		No. of events/total No.				No. of events/total No.			
Outcome	No. of trials	Vaginal progesterone	Placebo	Pooled RR (95% CI)	No. of trials	Vaginal progesterone	Placebo	Pooled RR (95% CI)	Interaction *P* value
Primary outcome									
Preterm birth <33 wk	4	41/365	72/358	0.56 (0.40–0.80)	3	7/23	13/29	0.70 (0.34–1.44)	.55
Secondary outcomes									
Preterm birth <37									
Preterm birth <35									
Preterm birth <28 wk	4	20/365	39/358	0.51 (0.31–0.85)	3	1/23	4/29	0.44 (0.11–1.85)	.83
Respiratory distress syndrome	4	17/365	37/358	0.47 (0.27–0.81)	3	8/46	15/58	0.48 (0.21–1.09)	.68
Necrotizing enterocolitis	4	5/365	6/358	0.88 (0.29–2.62)	3	0/46	0/58	Not estimable	NA
Intraventricular hemorrhage	4	5/365	7/358	0.68 (0.22–2.13)	3	1/46	2/58	1.00 (0.10–10.11)	.74
Proven neonatal sepsis	4	11/365	14/358	0.80 (0.37–1.74)	3	1/46	6/58	0.33 (0.06–1.67)	.30
Retinopathy of prematurity	4	5/365	3/358	1.51 (0.40–5.69)	3	1/46	0/58	1.42 (0.05–42.22)	.91
Fetal death	4	6/365	7/358	0.82 (0.28–2.40)	3	0/46	0/58	Not estimable	NA
Neonatal death	4	6/365	11/358	0.53 (0.20–1.39)	3	2/46	4/58	0.68 (0.23–2.02)	.69
Perinatal death	4	12/365	18/358	0.64 (0.31–1.31)	3	2/46	4/58	0.68 (0.23–2.02)	.90
Composite neonatal morbidity/ mortality[a]	4	29/365	49/358	0.59 (0.38–0.91)	3	11/46	23/58	0.52(0.29–0.93)	.69
Apgar score <7 at 5 min	4	11/362	23/354	0.48 (0.24–0.95)	3	4/46	4/58	1.03 (0.38–2.81)	.20
Birthweight <1500 g									
Birthweight <2500 g									
Admission to NICU	4	59/365	87/358	0.67 (0.50–0.91)	3	26/46	34/58	0.98 (0.70–1.35)	.12
Mechanical ventilation	4	28/365	43/358	0.65 (0.41–1.01)	3	7/46	8/58	0.68 (0.30–1.56)	.88

CI, confidence interval; *NA*, not applicable; *NICU*, neonatal intensive care unit; *RR*, relative risk.

[a] Occurrence of any of the following events: respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis, proven neonatal sepsis, or neonatal death.

Romero. Vaginal progesterone to prevent preterm birth in women with a short cervix: an IPD metaanalysis. Am J Obstet Gynecol 2012.

non-significant trend towards ↓ in the rate of PTB <33 wks

significant ↓ in composite neonatal morbidity and mortality

Romero R. et al., AJOG 2012

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Multiple Pregnancy

1-0528.13032

Systematic review

2014

Effectiveness of progestogens to improve perinatal outcome in twin pregnancies: an individual participant data meta-analysis

E Schuit,[a,b] S Stock,[c] L Rode,[d] DJ Rouse,[e] AC Lim,[b] JE Norman,[c] AH Nassar,[f] V Serra,[g] CA Combs,[h] C Vayssiere,[i] MM Aboulghar,[j] S Wood,[k] E Çetingöz,[l] CM Briery,[m] EB Fonseca,[n] K Worda,[o] A Tabor,[d] EA Thom,[p] SN Caritis,[q] J Awwad,[f] IM Usta,[f] A Perales,[r] J Meseguer,[s] K Maurel,[t] T Garite,[u] MA Aboulghar,[j] YM Amin,[j] S Ross,[k] C Cam,[l] A Karateke,[l] JC Morrison,[v] EF Magann,[w] KH Nicolaides,[x] NPA Zuithoff,[a] RHH Groenwold,[a] KGM Moons,[a] A Kwee,[y] BWJ Mol,[z] a Global Obstetrics Network (GONet) collaboration

13 included RCTs

- **11** double-blind, vs. placebo
- **1** Open label, 17P vs. no treat.
- **1** Not blind, vs. placebo

3768 women with twin pregnancy ↔ **7536** babies

- **1089** 17-OHPC
- **917** vaginal P

Primary outcome: a composite of adverse perinatal outcome

- **defined differently for 17Pc and vP**
- **based on the availability of different components of perinatal outcome in the studies**

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Multiple Pregnancy

Table 1. Overview of the studies investigating progestogen treatment included in the IPDMA

Type of progestogen	Study	Type of study	*n*	Inclusion criteria	Dosage
17Pc, weekly	Rouse[20]	Placebo-controlled double-blind RCT, multicentre	661	Women carrying twins with a gestational age of 16^{+0}–20^{+3} weeks	250 mg
	Lim[30]	Placebo-controlled double-blind RCT, multicentre	650	Women with a twin pregnancy and a gestational age between 15 and 19 weeks, with chorionicity assessed by ultrasonography	250 mg
	Nassar[31]	Placebo-controlled double-blind RCT, single centre	286	Viable twin pregnancy between 16 and 20 weeks of gestation	250 mg
	Combs[29]	Placebo-controlled double-blind RCT, multicentre	240	Women with a dichorionic diamniotic twin pregnancy at 15–23 weeks of gestation with an ultrasound examination showing no major fetal anomalies	250 mg
	Senat[33]	Open-label RCT, single centre	165	Women carrying twins with cervical length of ≤25 mm between 20 and 32 weeks of gestation	500 mg
	Briery[28]	Placebo-controlled double-blind RCT, single centre	30	Twin pregnancy between 20 and 30 weeks of gestation with intact membranes	250 mg
Vaginal, daily	Rode[32]	Placebo-controlled double-blind RCT, multicentre	677	Women with a live, diamniotic twin pregnancy and with chorionicity assessed by ultrasound before 16 weeks of gestation	200-mg pessaries
	Norman[19]	Placebo-controlled double-blind RCT, multicentre	500	Women carrying twins with gestation and chorionicity established by scan before 20 weeks of gestation	90 mg of gel
	Serra[22]	Placebo-controlled double-blind RCT, multicentre	290	Dichorionic diamniotic twin pregnant women	1× or 2× 200-mg pessaries
	Aboulghar[27]	Placebo-controlled RCT, single centre	92	Nulliparous women who conceived after IVF or ICSI with a dichorionic twin between 18 and 24 weeks of gestation	2× 200-mg suppositories
	Wood[34]	Placebo-controlled double-blind RCT, single centre	81	Women with a multifetal pregnancy between 16^{+0} and 20^{+6} weeks of gestation and ultrasound-confirmed minimum of two live fetuses	90 mg of gel
	Cetingoz[5]	Placebo-controlled double-blind RCT, single centre	67	Women carrying twins	100-mg suppositories
	Fonseca[9]	Placebo-controlled double-blind RCT, multicentre	24	Women carrying twins who were undergoing routine ultrasonography at 20–25 weeks of gestation and had a cervical length of <15 mm	200-mg capsules

ICSI, intracytoplasmatic sperm injection; IVF, *in vitro* fertilisation.

Schuit E. et al., BJOG 2014

Effectiveness of progestogens to improve perinatal outcome in twin pregnancies: an individual participant data meta-analysis

17P

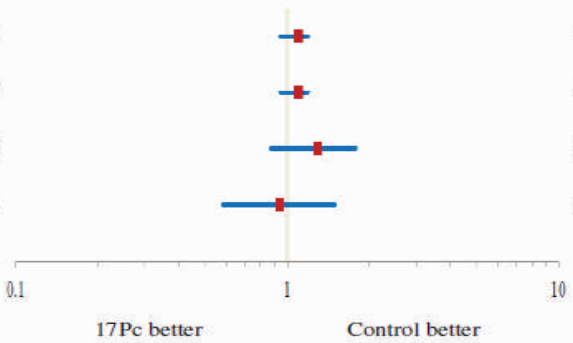
Multiple pregnancy

Neonatal Outcome

	17Pc N=2178	Control N=1888	RR (95% CI)*	P value	I^2 (95% CI) [%]	Available from how many studies	Available for (%)
Adverse neonatal outcome - n (%) ¶	423 (20)	318 (17)	1.2 (0.87-1.5)	0.24	64 (14-85)	6/6	4003 (98)
Perinatal death – n (%)	78 (4)	78 (4)	0.80 (0.33-1.9)	0.54	70 (31-87)	6/6	4032 (99)
RDS – n (%)	330 (15)	233 (13)	1.2 (0.93-1.6)	0.12	50 (0-80)	6/6	3965 (98)
BPD – n (%)	45 (2)	31 (2)	1.3 (0.88-1.9)	0.14	0 (0-61)	6/6	3963 (97)
IVH – n (%)	23 (1)	12 (1)	1.7 (0.73-3.8)	0.17	0 (0-66)	6/6	3957 (97)
PVL – n (%)	7 (0)	7 (1)	1.3 (0. 91-1.8)	0.11	0 (0-72)	4/6	2609 (64)
NEC – n (%)	16 (1)	11 (1)	1.2 (0.79-2.0)	0.26	0 (0-19)	6/6	3974 (98)
Sepsis – n (%)	47 (2)	38 (2)	1.0 (0.35-2.9)	0.98	64 (13-85)	6/6	3970 (98)
ROP – n (%)	7 (1)	10 (1)	0.98 (0.08-12.6)	0.98	11 (0-86)	4/6	2149 (53)

Maternal Outcome

	17Pc N=1089	Control N=944	RR (95% CI)*	P value	I^2 (95% CI)	Available from how many studies	Available for (%)
IUFD or delivery							
< 37 weeks	726 (67)	587 (63)	1.1 (0.94-1.2)	0.40	0 (0-69)	6/6	2021 (99%)
< 35 weeks	396 (36)	312 (33)	1.1 (0.94-1.2)	0.27	47 (0-78)	6/6	2021 (99%)
< 32 weeks	163 (15)	115 (12)	1.3 (0.87-1.8)	0.22	59 (0-83)	6/6	2021 (99%)
< 28 weeks	60 (6)	50 (5)	0.94 (0.58-1.5)	0.81	0 (0-73)	6/6	2021 (99%)



Effectiveness of progestogens to improve perinatal outcome in twin pregnancies: an individual participant data meta-analysis

17P

Multiple pregnancy

Subgroup analyses in 17Pc treatment

↑ Adverse perinatal outcome in women with Cervical Length > 25 mm:

- **At randomisation**:

  14/78 17-OHPC vs. 8/88; **RR 2.1**; 95% CI 1.9-2.2

- **Before 24 wk**:

  82/518 17-OHPC vs. 60/512; **RR 1.4**; 95% CI 1.26-1.5

Schuit E. et al., BJOG 2014

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Effectiveness of progestogens to improve perinatal outcome in twin pregnancies: an individual participant data meta-analysis

Vaginal P

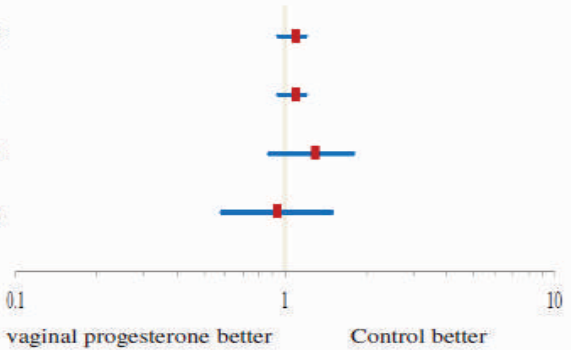
Multiple pregnancy

Neonatal Outcome

	Vaginal progesterone N=1834	Control N=1636	RR (95% CI)*	P value	I^2 (95% CI)	Available from how many studies	Available for (%)
Adverse neonatal outcome - n (%) ¶	219 (13)	201 (13)	0.96 (0.83-1.1)	0.50	0 (0-65)	7/7	3249 (94)
Perinatal death – n (%)	41 (2)	36 (2)	0.97 (0.65-1.4)	0.84	0 (0-44)	7/7	3460 (100)
RDS – n (%)	184 (10)	165 (10)	0.96 (0.81-1.1)	0.58	0 (0-43)	7/7	3423 (99)
BPD – n (%)	16 (1)	13 (1)	0.65 (0.08-5.1)	0.55	29 (0-74)	4/7	1837 (53)
IVH – n (%)	19 (2)	17 (1)	1.1 (0.57-2.0)	0.82	0 (0-65)	6/7	3237 (93)
PVL – n (%)	1 (0)	1 (0)	NA	NA	NA	3/7	1680 (48)
NEC – n (%)	8 (0)	8 (1)	0.90 (0.28-2.9)	0.83	0 (0-56)	6/7	3237 (93)
Sepsis – n (%)	46 (3)	32 (2)	1.3 (0.71-2.2)	0.29	0 (0-69)	4/7	3032 (87)
ROP – n (%)	13 (1)	10 (1)	1.2 (0.57-2.5)	0.54	0 (0-88)	5/7	3080 (89)

Maternal Outcome

	Vaginal progesterone N=917	Control N=818	RR (95% CI)*	P value	I^2 (95% CI)	Available from how many studies	Available for (%)
IUFD or delivery							
< 37 weeks	485 (53)	446 (55)	0.97 (0.85-1.1)	0.66	18 (0-61)	7/7	1714 (99)
< 35 weeks	232 (26)	225 (28)	0.94 (0.80-1.1)	0.41	0 (0-40)	7/7	1714 (99)
< 32 weeks	81 (9)	80 (10)	0.88 (0.62-1.3)	0.49	24 (0-67)	7/7	1714 (99)
< 28 weeks	30 (3)	21 (3)	1.3 (0.73-2.2)	0.40	0 (0-61)	7/7	1714 (99)



Effectiveness of progestogens to improve perinatal outcome in twin pregnancies: an individual participant data meta-analysis

Vaginal P

Multiple pregnancy

Subgroup analyses in vP treatment

BENEFIT on adverse perinatal outcome in women with Cervical Length ≤ 25 mm:

- **At randomisation**:

  15/56 vaginal P vs. 22/60; **RR 0.57**; 95% CI 0.47-0.70

- **Before 24 wk**: 14/52 vaginal P vs. 21/56; **RR 0.56**; 95% CI 0.42-0.75

Schuit E. et al., BJOG 2014

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Vaginal progesterone decreases preterm birth and neonatal morbidity and mortality in women with a twin gestation and a short cervix: an updated meta-analysis of individual patient data

Multiple pregnancy

ULTRASOUND in Obstetrics & Gynecology

6 RCTs (303 women, 606 fetuses)

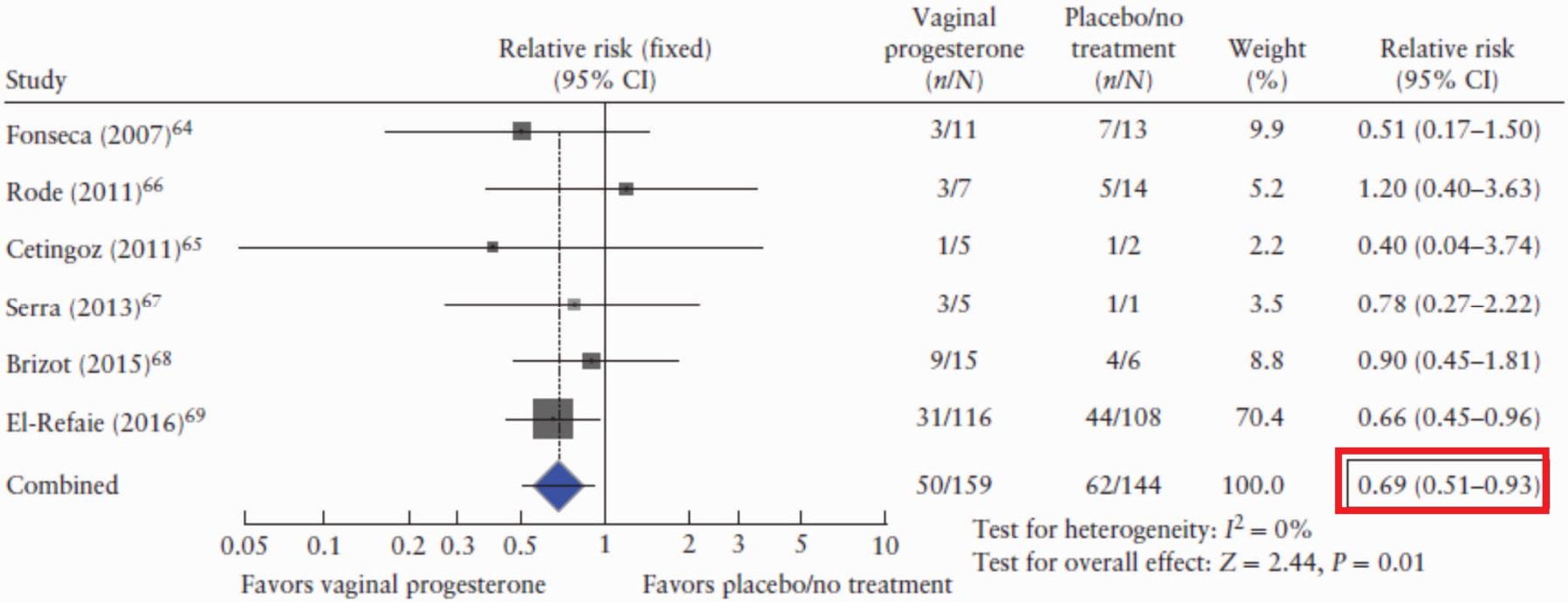


Figure 3 Forest plot of the effect of vaginal progesterone on the risk of preterm birth < 33 weeks' gestation. CI, confidence interval.

Significant decrease in the risk of preterm birth <35, <34, <32 and<30 weeks, neonatal death, respiratory distress syndrome, composite neonatal morbidity and mortality, use of mechanical ventilation, and birth weight<1500 g.

Romero et al. Ultrasound Obstet Gynecol 2017

UNIMORE

Multiple pregnancy

Cervical stitch (cerclage) for preventing preterm birth in multiple pregnancy (Review)

5 trials (n=128)

History-indicated and US-indicated cerclage

No significant differences in **primary outcome**:

- Perinatal death
- Neonatal morbidity

No signficant differences in **secondary outcomes**:

- PTB <34 wk
- PTB <35 wk
- Low birth weight <2500g
- Very low birth weight <1500g
- RDS

Authors' conclusions

This review is based on limited data from five small studies of average to above average quality. For multiple gestations, there is no evidence that cerclage is an effective intervention for preventing preterm births and reducing perinatal deaths or neonatal morbidity.

Rafael TJ et al. 2014

UNIMORE

Cervical pessary for preventing preterm birth in twin pregnancies with short cervical length: a systematic review and meta-analysis.

Multiple pregnancy

3 trials (n=481)
Primary outcome PTB <34 wk
Short CL at 16-24 wks

Study or Subgroup	Pessary Events	Pessary Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Nicolaides 2016	33	106	28	108	52.1%	1.20 [0.78, 1.84]	2016
Goya 2016	12	68	27	66	47.9%	0.43 [0.24, 0.78]	2016
Total (95% CI)		**174**		**174**	**100.0%**	**0.73 [0.27, 2.01]**	
Total events	45		55				

Heterogeneity: $Tau^2 = 0.46$; $Chi^2 = 7.64$, df = 1 (P = 0.006); $I^2 = 87\%$
Test for overall effect: Z = 0.60 (P = 0.55)

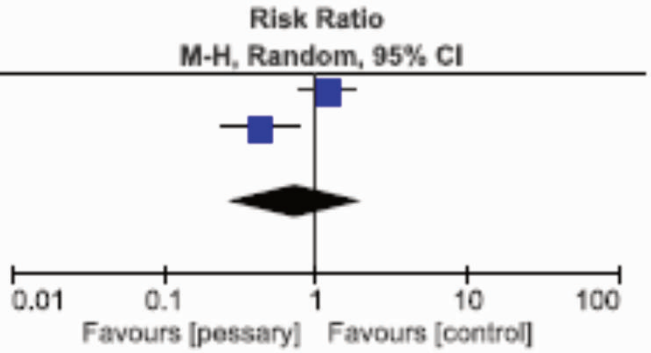


Figure 2. Risk of preterm birth <34 weeks of gestation in twin pregnancies with a cervical length <25 mm.[37]

Mean gestational age at delivery and the mean latency were similar in the pessary group compared to the control group.
No benefits were noticed in neonatal outcomes

Saccone et al. J Matern Fetal Neonatal Med. 2017

Progestogens to prevent PTB in:

Short Cervix

Previous Preterm Birth

Multiple Pregnancy

Preterm Labor

Preterm Labor

17-alpha-hydroxyprogesterone caproate for maintenance tocolysis: a systematic review and metaanalysis of randomized trials

Gabriele Saccone, MD; Anju Suhag, MD; Vincenzo Berghella, MD

5 TRIALS:
212 17-P and 214 ctr

- **Singleton**
- **Arrested PTL**
- **Exclusion criteria:** PPROM and maintenance tocolysis with vaginal progesterone
- **Primary outcome: PTB <37 wks**
- **Secondary outcomes:** PTB <34 weeks, latency, sPTB <37 weeks, <34 weeks, birthweight, neonatal death, NICU, RDS, BPD, IVH, NEC, and neonatal sepsis.

Saccone et al. Am J Obstet Gynecol 2015

Preterm Labor-17P

TABLE 1
Descriptive data for each trial

Variable	Facchinetti et al,[28] 2007	Rozenberg et al,[29] 2012	Regmi et al,[30] 2012	Lotfalizadeh et al,[27] 2013	Briery et al,[31] 2014	Total
Study location	Italy	France	Nepal	Iran	United States	—
No. of patients, n (intervention vs control)	60 (30 vs 30)	188 (94 vs 94)	60 (29 vs 31)	73 (37 vs 36)	45 (22 vs 23)	426 (212 vs 214)
Dose, mg	341	500	250	250	250	—
Frequency of 17P treatment	Twice weekly	Twice weekly	Weekly	Weekly	Weekly	—
Control	No treatment	No treatment	No treatment	No treatment	Placebo	—
Primary tocolytic agent	Atosiban	Nifedipine, nicardipine, or salbutamol	Nifedipine	Magnesium sulfate or nifedipine	Magnesium sulfate, calcium channel blockers, or antiprostaglandin drugs	—
Range GA at randomization, wk	From 25^{+0} to 33^{+6}	From 24^{+0} to 31^{+6}	From 28^{+0} to 34^{+6}	From 26^{+0} to 36^{+0}	From 20^{+0} to 30^{+6}	—
Mean GA at randomization, wk	30 vs 30	28 vs 28[a]	33 vs 33	34 vs 33	29 vs 27	Mean difference 0.50 wk (95% CI, 0.24–1.25)[a]
Study primary outcomes	CL shortening at discharge, and at day 7 and 21 of discharge	Latency period	Latency period and rate of recurrent PTL within 48 h	Rate of recurrent PTL	Preterm delivery <37 wk	—

Data are presented as 17P vs placebo.

Saccone et al. Am J Obstet Gynecol 2015

Preterm Labor-17P

TABLE 2
Primary and secondary outcomes

Variable	Facchinetti et al,[28] 2007	Rozenberg et al,[29] 2012	Regmi et al,[30] 2012	Lotfalizadeh et al,[27] 2013	Briery et al,[31] 2014	Total	RR (95% CI)
No. of patients	60 (30 vs 30)	188 (94 vs 94)	60 (29 vs 31)	73 (37 vs 36)	45 (22 vs 23)	426 (212 vs 214)	–
PTB <37 wk	5/30 vs 17/30	37/94 vs 36/94	N/A	N/A	19/22 vs 22/33	61/146 (42%) vs 75/147 (51%)	0.78 (0.50–1.22)
PTB <34 wk	N/A	15/94 vs 19/94	N/A	N/A	14/22 vs 21/23	29/116 (25%) vs 40/117 (34%)	0.60 (0.28–1.12)
Recurrent PTL	N/A	N/A	11/29 vs 20/31	N/A	N/A	11/29 (38%) vs 20/31 (65%)	0.59 (0.34–1.00)
Mean GA delivery, wk	N/A	38 vs 38[a]	37 vs 34	N/A	32 vs 30	–	Mean difference 2.28 wk (95% CI, 1.46–3.10)[a,b]
Mean latency, d	N/A	61 vs 63[a]	25 vs 16	N/A	23 vs 16	–	Mean difference 8.36 d (95% CI, 3.20–13.51)[a,b]
Mean birthweight, g	3103 vs 2809	2930 vs 2850[a]	2903 vs 2781	N/A	1693 vs 1536	–	Mean difference 224.30 g (70.87–377.74)[a,b]
Neonatal death	N/A	0/94 vs 0/94	N/A	N/A	0/22 vs 3/23	0/116 (0%) vs 3/117 (3%)	0.15 (0.01–2.73)
Admission in NICU	N/A	24/94 vs 16/94	3/29 vs 2/31	8/37 vs 14/36	N/A	35/160 (22%) vs 32/161 (20%)	1.09 (0.71–1.66)
RDS	N/A	14/94 vs 12/94	3/29 vs 2/31	N/A	7/22 vs 10/23	24/145 (16%) vs 24/148 (16%)	1.02 (0.62–1.69)
BPD	N/A	2/94 vs 1/94	N/A	N/A	N/A	2/94 (2%) vs 1/94 (1%)	2.02 (0.18–22.68)
IVH	N/A	N/A	N/A	N/A	0/22 vs 6/23	0/22 (0%) vs 6/23 (26%)	0.08 (0.11–1.35)
NEC	N/A	1/94 vs 1/94	N/A	N/A	0/22 vs 3/23	1/116 (1%) vs 4/117 (3%)	0.34 (0.05–2.13)
Sepsis	N/A	N/A	2/29 vs 2/31	N/A	1/22 vs 7/23	3/51 (6%) vs 9/54 (17%)	0.35 (0.10–1.25)

Data are presented as number 17-alpha-hydroxyprogesterone caproate vs number placebo.

Preterm Labor

Saccone et al. Am J Obstet Gynecol 2015 Conclusions

17P maintenance tocolysis is associated with:

- a similar rate of PTB <37 weeks and PTB <34 weeks
- significantly later gestational age at delivery
- longer latency
- higher birthweight
- Other secondary outcomes including incidences of recurrent PTL, neonatal death, NICU, RDS, BPD, IVH, NEC, and sepsis were similar in both groups

17P maintenance tocolysis cannot be currently recommended for clinical use, but further research is necessary

OBSTETRICS

Vaginal progesterone for maintenance tocolysis: a systematic review and metaanalysis of randomized trials

Anju Suhag, MD; Gabriele Saccone, MD; Vincenzo Berghella, MD

5 TRIALS:
223 vP and 218 CTR

- **Singleton**
- **Arrested PTL**
- **Exclusion criteria** :PPROM and maintenance tocolysis with 17OH-P
- **Primary outcome: PTB <37 wks**
- **Secondary outcomes:** PTB <34 weeks, latency, spontaneous PTB <37 weeks, <34 weeks, birthweight, neonatal death, NICU, RDS, BPD, IVH, NEC, and neonatal sepsis

Suhag et al. Am J Obstet Gynecol 2015

Preterm Labor-17P

TABLE 1
Descriptive data for each trial

Variable	Borna and Sahabi,[23] 2008	Sharami et al,[24] 2010	Arikan et al,[25] 2011	Lotfalizadeh et al,[27] 2013	Areia et al,[26] 2013	Total
Study location	Iran	Iran	Turkey	Iran	Portugal	—
No. of patients —progesterone vs control	70 (37 vs 33)	163 (80 vs 83)	83 (43 vs 40)	73 (37 vs 36)	52 (26 vs 26)	441 (223 vs 218)
Daily dose, mg	400	200	200	400	200	—
Control	No treatment	Placebo	No treatment	No treatment	Placebo	—
Primary tocolytic agent	Magnesium sulfate	Magnesium sulfate	Ritodrine	Magnesium sulfate or nifedipine	Atosiban	—
GA at randomization, wk[a]	24^0–34^6	28^0–36^6	24^0–34^6	26^0–36^6	24^0–34^6	—
Mean GA at randomization, wk	31/32	33/34	32/32	34/33	28/29	Mean difference −0.37 d (95% CI, −1.17 to 0.44)
Definition of PTL	At least 6 contractions in 30 min accompanied by cervical changes	At least 6 contractions in 30 min accompanied by cervical changes	At least 6 contractions in 30 min accompanied by cervical changes	At least 4 contractions per 20 min accompanied by 2-cm dilatation	At least 4 contractions per 20 min accompanied by cervical length <25 mm	
Prior PTB —progesterone vs control, n/N (%)	5/37 (13.5%) vs 4/33 (12.1%)	1/80 (1.3%) vs 3/83 (3.6%)	4/43 (9.3%) vs 3/40 (7.5%)	N/R	9/26 (34.6%) vs 9/26 (34.6%)	28/186 (15.0%) vs 19/182 (10.4%) $P = .19$
Study primary outcomes	Latency period, recurrent PTL	Latency period, PTB <37 wk, PTB <34 wk	Latency period, GA at delivery, PTB <37 wk	Rate of recurrent PTL	Latency period	—

Suhag et al. Am J Obstet Gynecol 2015

Preterm Labor-17P

TABLE 2
Primary and secondary outcomes

Variable	Borna and Sahabi,[23] 2008	Sharami et al,[24] 2010	Arikan et al,[25] 2011	Lotfalizadeh et al,[27] 2013	Areia et al,[26] 2013	Total	RR (95% CI)
No. of patients	70 (37 vs 33)	163 (80 vs 83)	83 (43 vs 40)	73 (37 vs 36)	52 (26 vs 26)	441 (223/218)	–
PTB <37 wk[a]	N/A	33/80 (41%) vs 45/83 (54%)	20/43 (47%) vs 28/40 (70%)	N/A	9/26 (35%) vs 13/26 (50%)	62/149 (42%) vs 86/149 (58%)	0.71 (0.57–0.90)[b]
PTB <34 wk[a]	N/A	8/80 (10%) vs 9/83 (11%)	N/A	N/A	3/26 (12%) vs 6/26 (23%)	11/106 (10%) vs 15/109 (14%)	0.75 (0.36–1.57)
Recurrent PTL[a]	13/37 (35%) vs 19/33 (58%)	N/A	N/A	N/A	2/26 (8%) vs 8/26 (31%)	15/63 (24%) vs 27/59 (46%)	0.51 (0.31–0.84)[b]
Mean GA delivery, wk	37 vs 35	37 vs 36	36 vs 35	N/A	38 vs 37	–	Mean difference 1.29 wk (0.43–2.15)[b]
Mean latency, d	36 vs 24	24 vs 17	32 vs 21	N/A	63 vs 39	–	Mean difference 13.80 d (3.97–23.63)[b]
Mean birthweight, g	3101 vs 2609	2997 vs 3025	2983 vs 2585	N/A	2547 vs 2628	–	Mean difference 194 g (−100.01 to 488.32)
Neonatal death[a]	N/A	1/80 (1%) vs 6/83 (7%)	0/43 vs 1/40 (3%)	N/A	2/26 (8%) vs 2/26 (8%)	3/149 (2%) vs 9/149 (6%)	0.43 (0.12–1.54)
Admission in NICU[a]	9/37 (24%) vs 13/33 (39%)	3/80 (4%) vs 2/83 (2%)	3/43 (7%) vs 3/40 (8%)	10/37 (27%) vs 14/36 (39%)	5/26 (19%) vs 7/26 (27%)	30/223 (13%) vs 39/218 (18%)	0.72 (0.47–1.08)
RDS[a]	4/37 (11%) vs 12/33 (36%)	7/80 (9%) vs 10/83 (12%)	1/43 (2%) vs 1/40 (3%)	N/A	2/26 (8%) vs 2/26 (8%)	14/186 (8%) vs 25/182 (14%)	0.54 (0.30–1.00)
IVH[a]	0/37 vs 0/33	N/A	0/43 vs 0/40	N/A	0/26 vs 0/26	0/106 (0%) vs 0/99 (0%)	N/E
NEC[a]	0/37 vs 0/33	N/A	0/43 vs 0/40	N/A	0/26 vs 0/26	0/106 (0%) vs 0/99 (0%)	N/E
Sepsis[a]	2/37 (5%) vs 6/33 (18%)	0/80 vs 3/83 (4%)	2/43 (5%) vs 2/40 (5%)	N/A	0/26 vs 1/26 (4%)	4/186 (2%) vs 11/156 (7%)	0.34 (0.12–0.98)[b]

Suhag et al. Am J Obstet Gynecol 2015 Conclusions

Preterm Labor

Maintenance tocolysis with vP is associated with:

- **29% prevention of PTB compared to controls**
- **delivery >1 week later**
- **longer latency from randomization to delivery**
- **Lower incidence of recurrent PTL (49%)**
- **Lower rate of neonatal sepsis (66%)**

HOWEVER, given the lack of blinding in some trials and the generally **poor quality of the trials**, we do not suggest a change in clinical care of women with arrested PTL

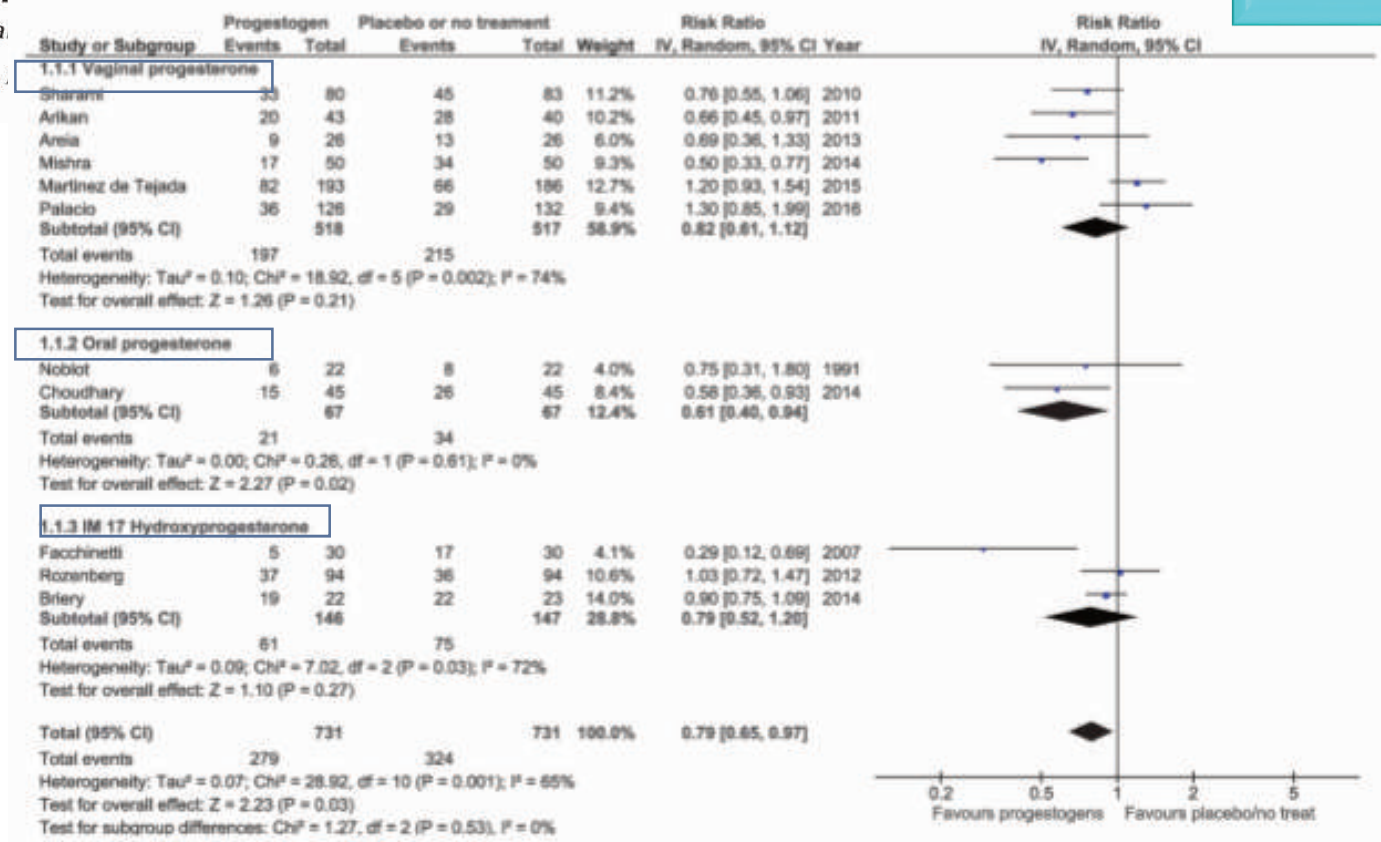
Prematurity: *Review*

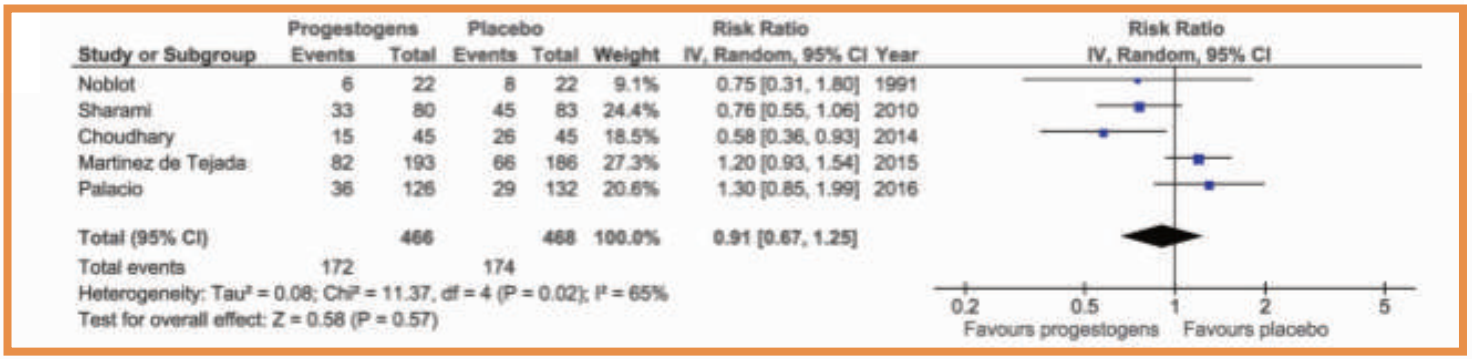
Progestogens as Maintenance Treatment in Arrested Preterm Labor

A Systematic Review and Meta-a

Montse Palacio, MD, PhD, Stefania Ronzoni, MD, PhD, and Kellie E. Murphy, MD, MSc

Preterm Labor





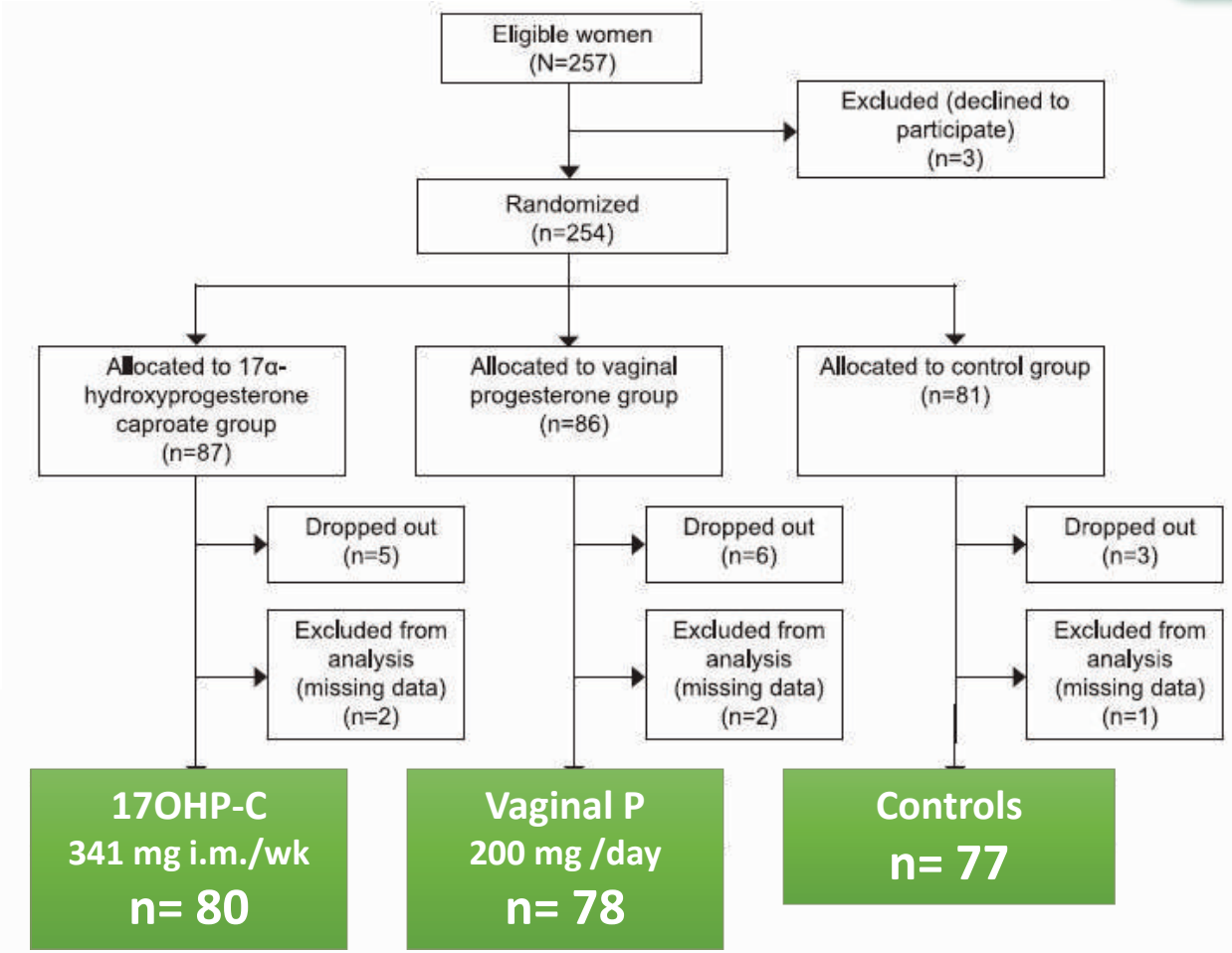
Palacio et al. Obstet Gynecol 2016

UNIMORE

Original Research

Progestogens for Maintenance Tocolysis in Women With a Short Cervix

A Randomized Controlled Trial



Facchinetti et al. Obstet Gynecol 2017

Original Research

Progestogens for Maintenance Tocolysis in Women With a Short Cervix

A Randomized Controlled Trial



	17OHP-C	P	Control	17OHP-C versus Control		P versus Control	
	N=80	N=78	N=77	Measures of association 97.5% CI	*p*-value	Measures of association 97.5% CI	*p*-value
Primary outcome							
Preterm delivery < 37 weeks, n/N (%)	**18/80 (22.5)**	**30/78 (38.5)**	**17/77 (22.1)**	**RR=1.02 (0.52 - 1.99)**	**0.949**	**RR=1.74 (0.98 - 3.10)**	**0.027**
Secondary outcomes							
Maternal outcomes							
Hospitalised before delivery, n/N (%)	10/80 (12.5)	10/78 (12.8)	14/77 (18.2)	RR=0.69 (0.29 - 1.62)	0.323	RR=0.71 (0.30 - 1.66)	0.356
GA at delivery, Mean ± SD	37.7 ± 2.5	36.8 ± 3.4	37.7 ± 2.5	MD=-0.05 (-0.95 - 0.85)	0.894	MD=-0.92 (-2.00 - 0.16)	0.055
Preterm delivery < 35 weeks, n/N (%)	**7/80 (8.8)**	**18/78 (23.1)**	**7/77 (9.1)**	**RR=0.96 (0.31 - 3.02)**	**0.940**	**RR=2.54 (1.00 - 6.44)**	**0.018**
Preterm delivery < 32 weeks, n/N (%)	1/80 (1.3)	4/78 (5.1)	3/77 (3.9)	RR=0.32 (0.02 - 4.16)	0.293	RR=1.32 (0.25 - 7.02)	0.712
Neonatal outcomes							
Birth-weight Kg, Mean ± SD						.15 (-0.35 - 0.51)	0.142
Birth -weight<2500 g, n/N (%)						.29 (0.69 - 2.39)	0.426
Birth -weight<1500 g, n/N (%)						ot estimable	-
LGA >90° centile, n/N (%)						.83 (0.36 - 1.89)	0.611
SGA ≤10° centile, n/N (%)						.42 (0.07 - 2.66)	0.276
NICU admission, n/N (%)						.60 (0.63 - 4.10)	0.253
NICU stay days, Median (IQR⁺)						-	0.663 §
Need of oxygen supply in NICU, n/N (%)	1/80 (1.25)	6/78 (7.7)	4/77 (5.2)	RR=0.24 (0.02 - 2.87)	0.159	RR=1.48 (0.36 - 6.01)	0.527
Composite morbidity, n/N (%)	6/80 (7.5)	9/78 (11.5)	7/77 (9.1)	RR=0.83 (0.25 - 2.72)	0.718	RR=1.27 (0.44 - 3.71)	0.617
Congenital anomalies, n/N (%)	0/80 (0)	2/78 (2.6)	3/77 (3.9)	-	-	RR=0.66 (0.09 - 4.93)	0.639

The use of progestogens for maintenance tocolysis in women with a short cervix did not reduce the rate of preterm birth.

Facchinetti et al. Obstet Gynecol 2017

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WOMEN'S HEALTH CARE PHYSICIANS

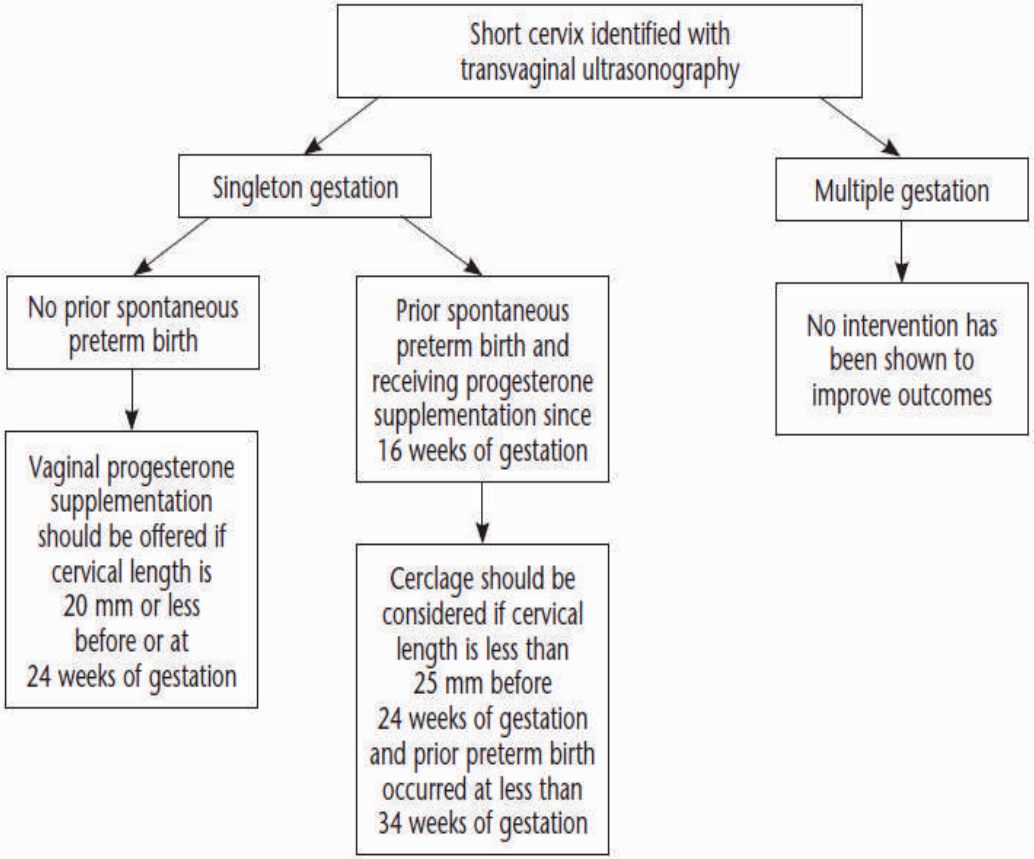
PRACTICE BULLETIN

CLINICAL MANAGEMENT GUIDELINES FOR OBSTETRICIAN—GYNECOLOGISTS

NUMBER 130, OCTOBER 2012

(Replaces Practice Bulletin Number 31, October 2001 and Committee Opinion No. 419, October 2008)

Prediction and Prevention of Preterm Birth



Summary of Recommendations and Conclusions

Recommendations based on good and consistent scientific evidence (Level A):

- A woman with a singleton gestation and a prior spontaneous preterm singleton birth should be offered progesterone supplementation starting at 16–24 weeks of gestation, regardless of transvaginal ultrasound cervical length, to reduce the risk of recurrent spontaneous preterm birth.
- Vaginal progesterone is recommended as a management option to reduce the risk of preterm birth in asymptomatic women with a singleton gestation without a prior preterm birth with an incidentally identified very short cervical length less than or equal to 20 mm before or at 24 weeks of gestation.
- Tests, such as fetal fibronectin screening, bacterial vaginosis testing, and home uterine activity monitoring, are not recommended as screening strategies.
- Progesterone treatment does not reduce the incidence of preterm birth in women with twin or triplet gestations and, therefore, is not recommended as an intervention to prevent preterm birth in women with multiple gestations.

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Linee Guida a confronto

	SMFM 2012	ACOG 2012 (reaffirmed in 2018)	NICE 2015	EAPM 2017
Gravidanza singola, no pregresso PTB, raccorciamento cervicale	Progesterone vaginale se CL≤20mm (EG ≤24 sett.)	Progesterone vaginale se CL≤20mm (EG ≤24 sett.)	Progesterone vaginale se CL<25mm (tra 16-24 sett.)	Progesterone vaginale se CL<25mm (tra 16-24 sett.)
Gravidanza singola, pregresso PTB	17P dalla 16° sett.	Progesterone dalla 16° sett.	Progesterone vaginale dalla 16° sett. (anche in caso di pregresso aborto tardivo)	17P o P vaginale dall'inizio del II trim. (anche in caso di pregresso aborto tardivo)
Gravidanza singola, pregresso PTB, raccorciamento cervicale	Considerare cerchiaggio se CL<25mm (EG ≤24 sett.) + 17P	Considerare cerchiaggio se CL<25mm (EG ≤24 sett.) + progesterone	Considerare cerchiaggio se CL<25mm (con storia di pPROM o trauma cervicale)	Considerare cerchiaggio se CL<25mm (EG ≤24 sett.) + progesterone
Gravidanza gemellare	No progesterone No cerchiaggio	No progesterone No cerchiaggio	No progesterone No cerchiaggio (NICE 2011)	Progesterone vaginale se CL<25mm No cerchiaggio

PRETERM BIRTH: RISK FACTORS

- **Obstetric-gynecological history**: prior spontaneous PTB; prior ≥ 2 D&Es; prior cone biopsy; uterine anomalies; DES exposure; myomata; extremes of
- interpregnancy interval;
- ART
- Maternal lifestyle (smoking, drug abuse, STIs, etc.)
- Maternal pre-pregnancy weight <50 kg or low BMI;
- poor nutritional status
- Maternal age (<19 years old; >35 years old)
- Race (especially Afro-American)
- Low Education
- Certain medical conditions (e.g. DM, HTN)
- Low socioeconomic status
- Limited prenatal care
- Vaginal bleeding (especially during second trimester)
- Stress (mostly related to above risks)

Universal cervical length screening in singleton gestations without a previous preterm birth: ten reasons why it should be implemented

Adeeb Khalifeh, MD; Vincenzo Berghella, MD

AJOG American Journal of Obstetrics & Gynecology

TABLE

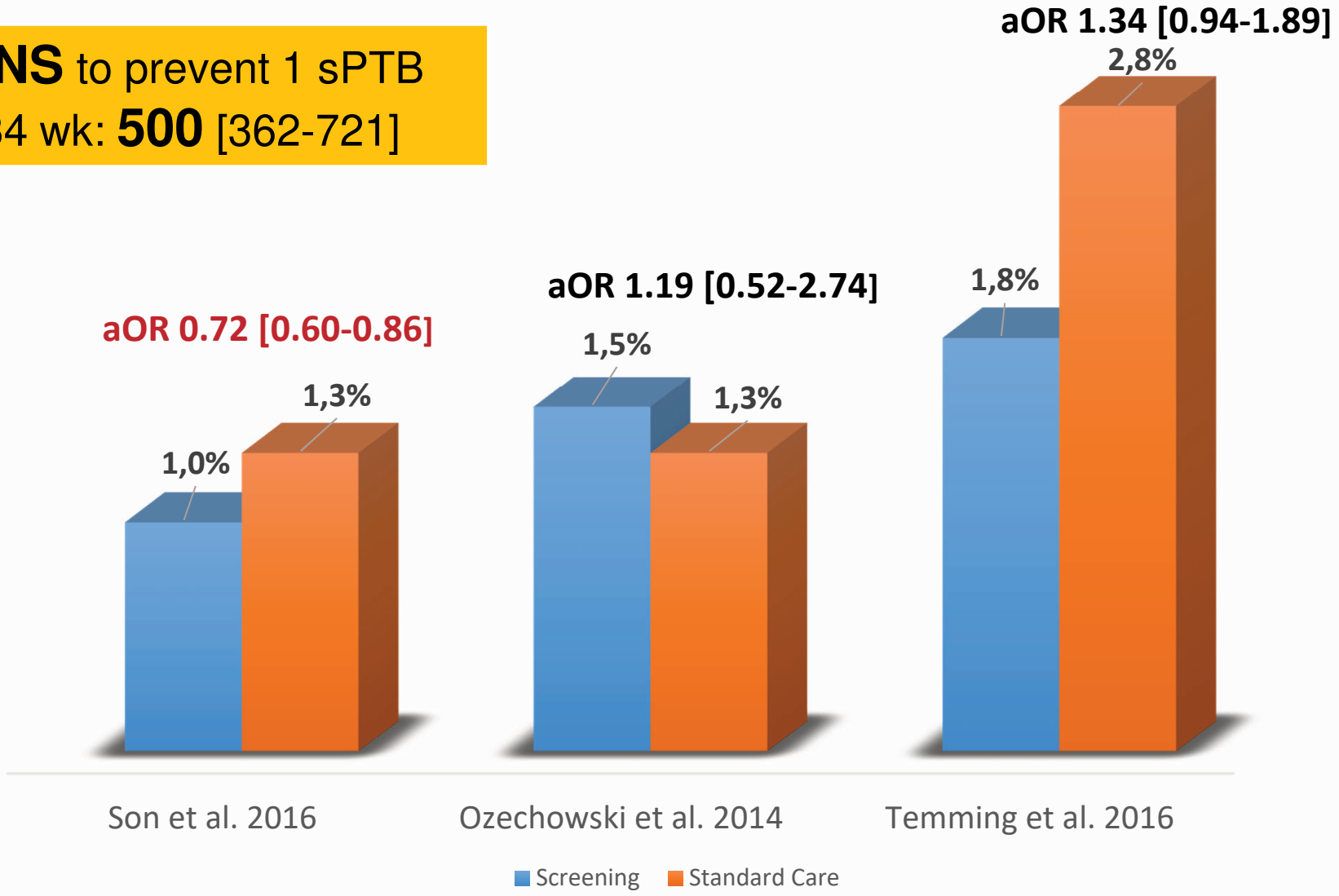
Wilson and Jungner's classic screening criteria (1968)[1]

Criteria	Universal transvaginal ultrasound cervical length screening
1. The condition sought should be an important health problem.	Preterm birth is associated with 1 million neonatal deaths worldwide.
2. There should be an accepted treatment for patients with recognized disease.	Vaginal progesterone is a proven treatment for preterm birth prevention in singleton gestations with a short cervix.
3. Facilities for diagnosis and treatment should be available.	All pregnant women are offered ultrasound at 18-24 weeks of gestation and can be offered transvaginal ultrasound cervical length.
4. There should be a recognizable latent or early symptomatic stage.	A short transvaginal ultrasound cervical length is an early predictor of preterm birth.
5. There should be a suitable test or examination.	Transvaginal ultrasound is a validated reliable test for cervical length measurement.
6. The test should be acceptable to the population.	Transvaginal ultrasound cervical length is acceptable by more than approximately 75% of women with singleton gestations and no previous spontaneous preterm birth.
7. The natural history of the condition, including development from latent to declared disease, should be understood adequately.	Transvaginal ultrasound cervical length shortening precedes, by weeks or months, digitally detected cervical changes, symptomatic uterine contractions, and eventual preterm birth.
8. There should be an agreed policy on whom to treat as patients	Transvaginal ultrasound cervical length $\leq$20 mm at $<$24 weeks of gestation is the currently accepted indication for treatment in singleton gestations without previous preterm birth.
9. The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be balanced economically in relation to possible expenditure on medical care as a whole.	Several studies have confirmed the cost-effectiveness of universal transvaginal ultrasound cervical length screening.
10. Case-finding should be a continuing process and not a "once and for all" project.	Preterm birth prevention is a continuous process; preterm birth is not an infection for which a vaccine can be devised, and the disease eradicated.

Khalifeh. Universal CL screening for the prediction and prevention of PTB. Am J Obstet Gynecol 2016.

Universal cervical length screening & vaginal P
(sPTB < 34 wk)

NNS to prevent 1 sPTB <34 wk: **500** [362-721]



Decrease in the incidence of threatened preterm labor after implementation of transvaginal ultrasound cervical length universal screening



- retrospective cohort study
- singleton gestations without prior SPTB presenting to obstetric triage for threatened PTL between 23 0/7 and 33 6/7 week

Before screening

After screening

Table 2. Primary and secondary outcomes.

	2011 $N = 1550$[a]	2014 $N = 1751$[a]	p value
Threatened PTL	172 (11.1%)	118 (6.7%)	<.001
Admitted for PTL	35 (2.3%)	24 (1.4%)	.04
LOS	4.4 ± 3.7	4.6 ± 4.2	.15

PTL: preterm labor; PTB: preterm birth; LOS: length of stay.
[a]Only singleton gestations without prior spontaneous preterm birth (PTB).

Conclusion: The introduction of a universal TVU CL screening program in women with singleton gestations without a history of SPTB is associated with a reduction in the frequency of threatened PTL and admission for PTL.

Navathe et al. J Matern Fetal Neonatal Med 2018

TVU CL cut-offs and prevalence in singleton pregnancies

Study	n	cut-off (mm)	prevalence (%)	population
Kuusela 2015	2122	≤30	3.40	mixed population
Kuusela 2015	2122	≤25	0.50	mixed population
Goya 2012	11875	≤25	6	mixed population
Orchewski 2014	1569	≤25	1.10	mixed population
Fonseca 2007	24620	≤15	1.70	mixed population
Hassan 2011	32091	10-20	2.30	mixed population
Grobman 2012	15435	<30	10.30	nulliparous
van der Ven 2015	5710	≤30	2.20	nulliparous
Facco 2013	1237	≤20	4.90	nulliparous
Facco 2013	1237	≤15	2.10	nulliparous
van der Ven 2015	6233	≤30	1.40	multiparous no prior PTB
Facco 2013	1284	≤20	2.20	multiparous no prior PTB
Facco 2013	1284	≤15	0.90	multiparous no prior PTB

A sensitivity analysis reported that universal TVU CL screening is unlikely to be cost-effective when the prevalence of TVU CL ≤20 mm falls below **0.31%**

Pedretti et al. Aust N Z Obstet Gynecol 2017

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CONCLUSIONI

- I **Progestageni sono efficaci nella prevenzione della ricorrenza** (donne con storia di sPTB o aborto tardivo). Da considerare il **cerchiaggio se vi è un raccorciamento cervicale**.
- Il **P vaginale** è efficace **in donne asintomatiche con cervice corta (<25 mm)**
- Anche nelle **gemellari**, l'uso di **P vaginale** sembra efficace, nei casi di **raccorciamento cervicale**.
- In seguito ad episodio di PTL non è indicato l'uso di progestageni come tocolosi di mantenimento.
- E' giunto il tempo di **testare l'efficienza dello Screen & Treat** per attuare finalmente un intervento di prevenzione.

Grazie per l’attenzione…

