Preterm Birth
Prediction and Prevention

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Preterm Delivery

- Major cause of perinatal mortality and morbidity
- Preterm rate for singleton pregnancy in 1995-2011

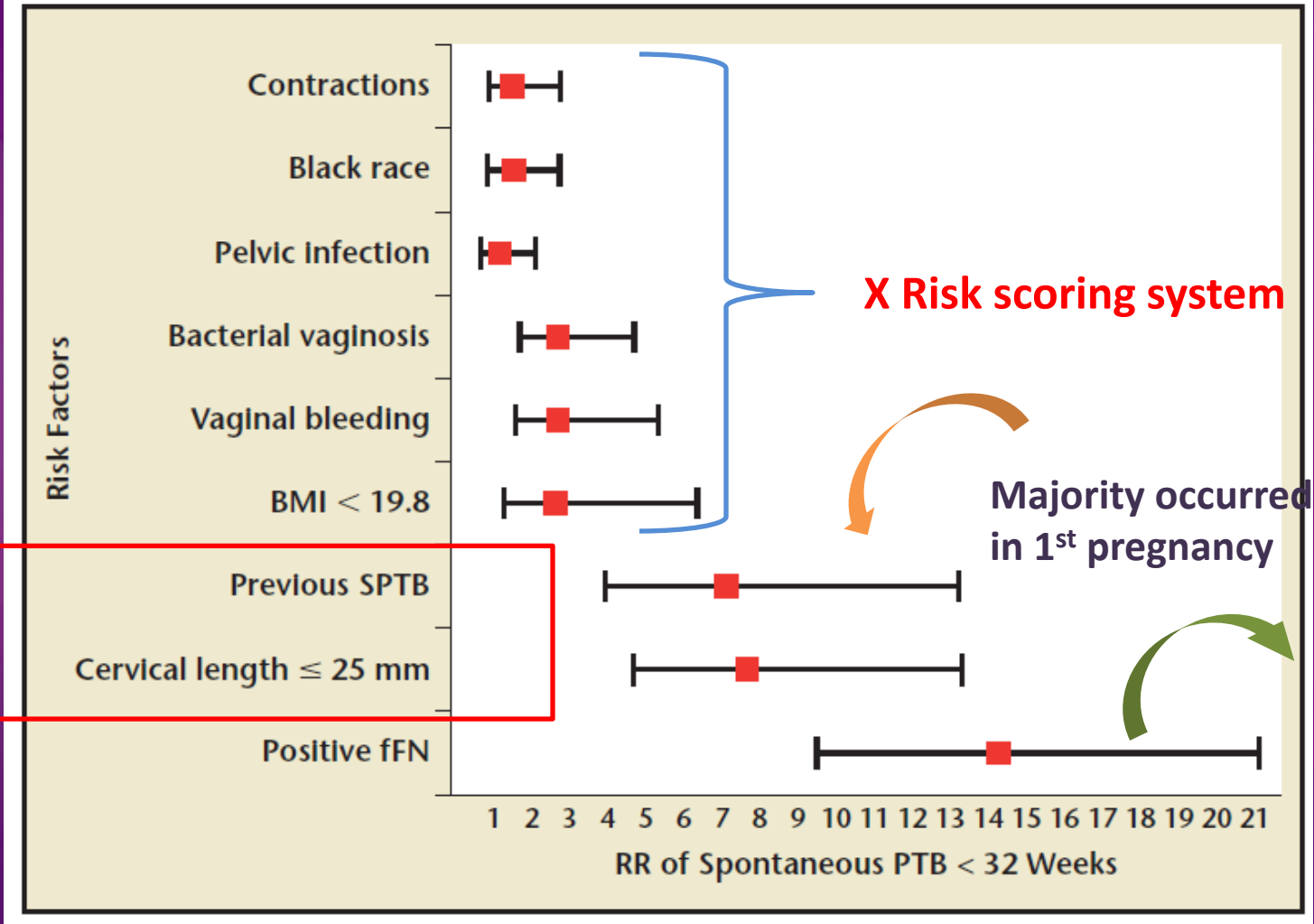
Table 1
Frequency of preterm birth among 103 364 singleton deliveries.

Type	No. (%)
Preterm birth[a]	6722 (6.5)
Early preterm birth[b]	1835 (1.8)
Late preterm birth[c]	4887 (4.7)
Spontaneous preterm birth	4266 (4.1)
Spontaneous preterm birth after PPROM	338 (0.3)
Iatrogenic preterm birth	2456 (2.4)
Iatrogenic preterm birth after PPROM	754 (0.7)

Abbreviation: PPROM, premature rupture of membrane.
[a] Between 24 and 36 weeks, 6 days.
[b] Between 24 and 33 weeks, 6 days.
[c] Between 34 and 36 weeks, 6 days.

Hui et al
IJGO 2014

Preterm Prediction



Multiple pregnancy
High risk

Absent between 22-37 weeks →more useful after 22 wks

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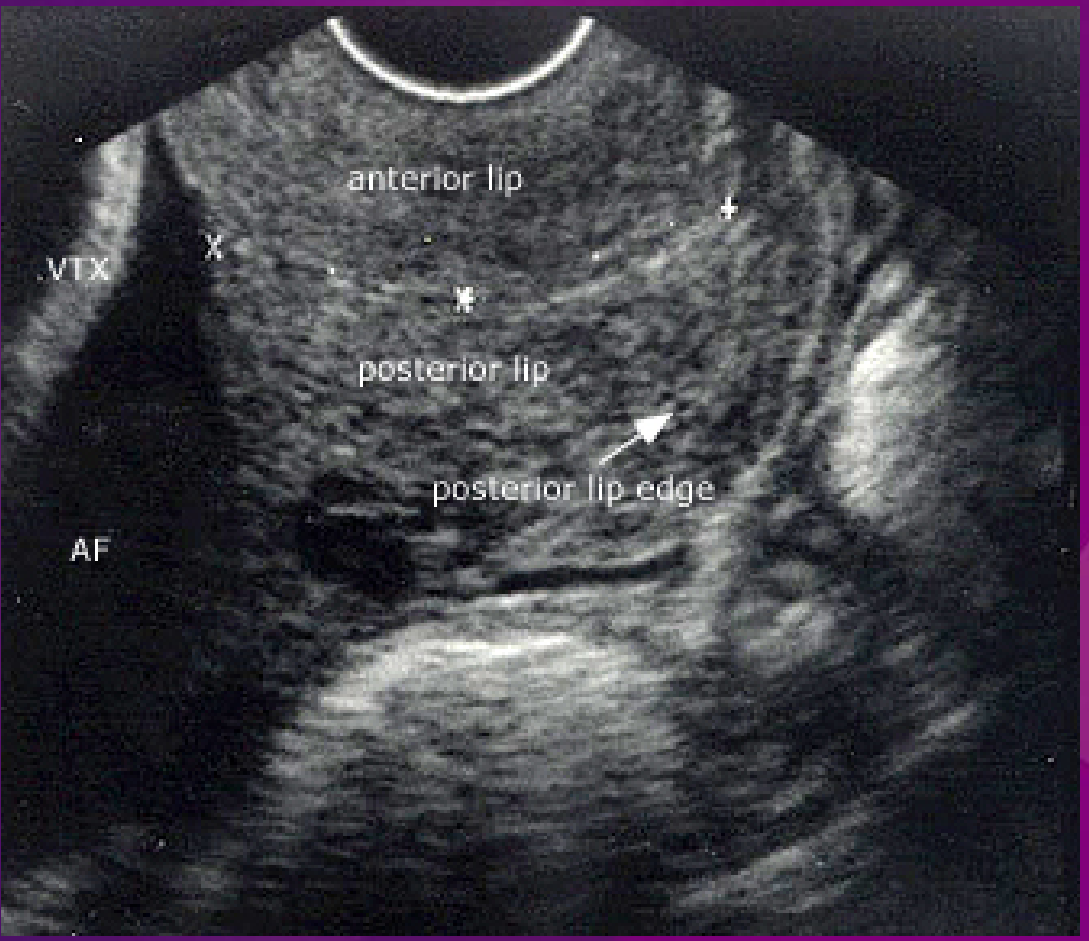
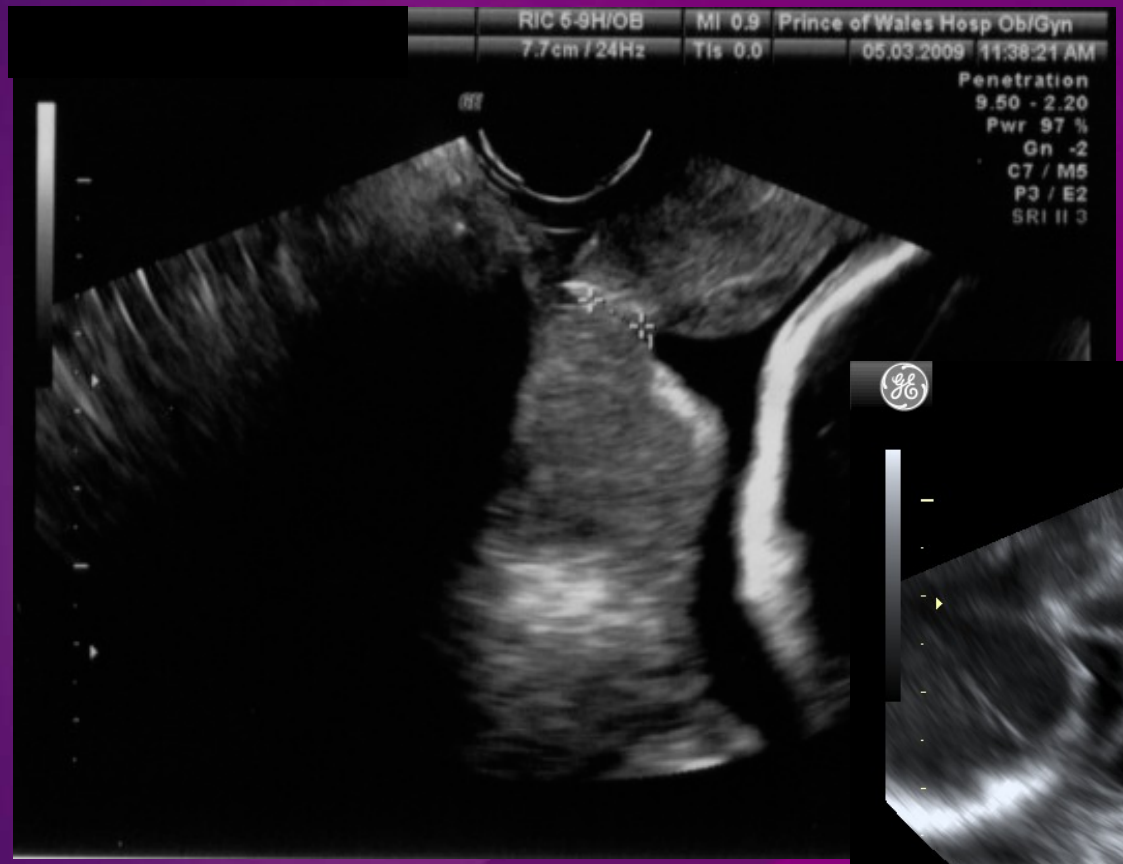
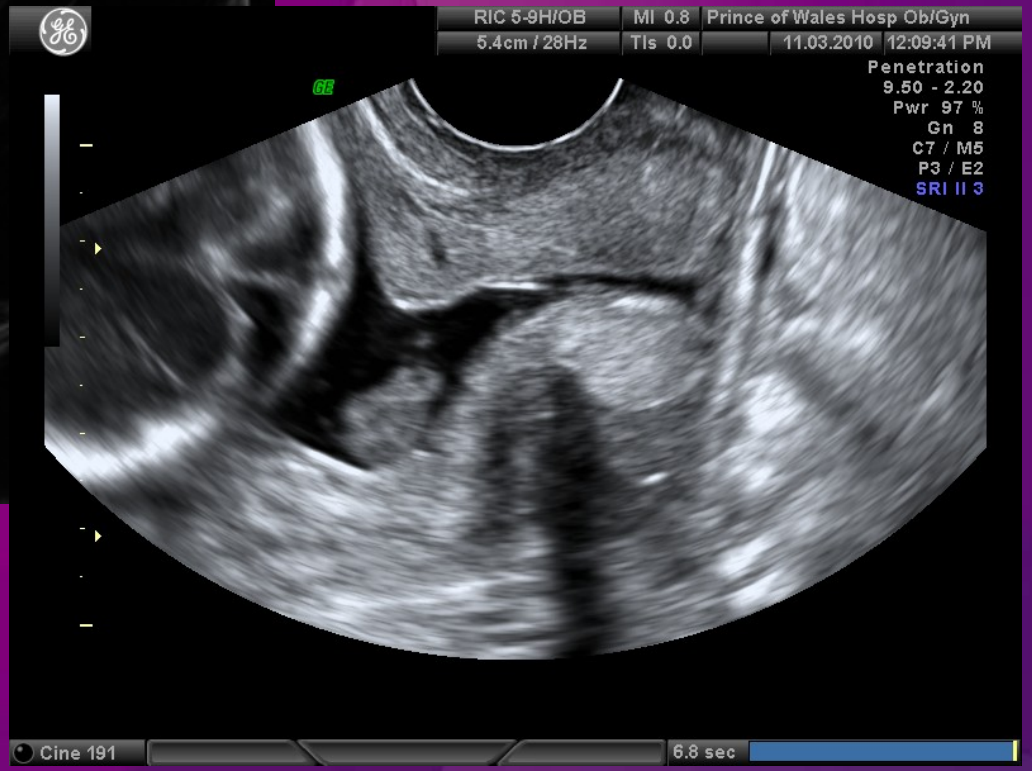
Measurement of Cervical Length



- Transvaginal
- Empty bladder
- Avoid undue pressure
- Identify endocervical mucosa
- Linear measurement
- Shortest measurement

Short Cervix and Sludge





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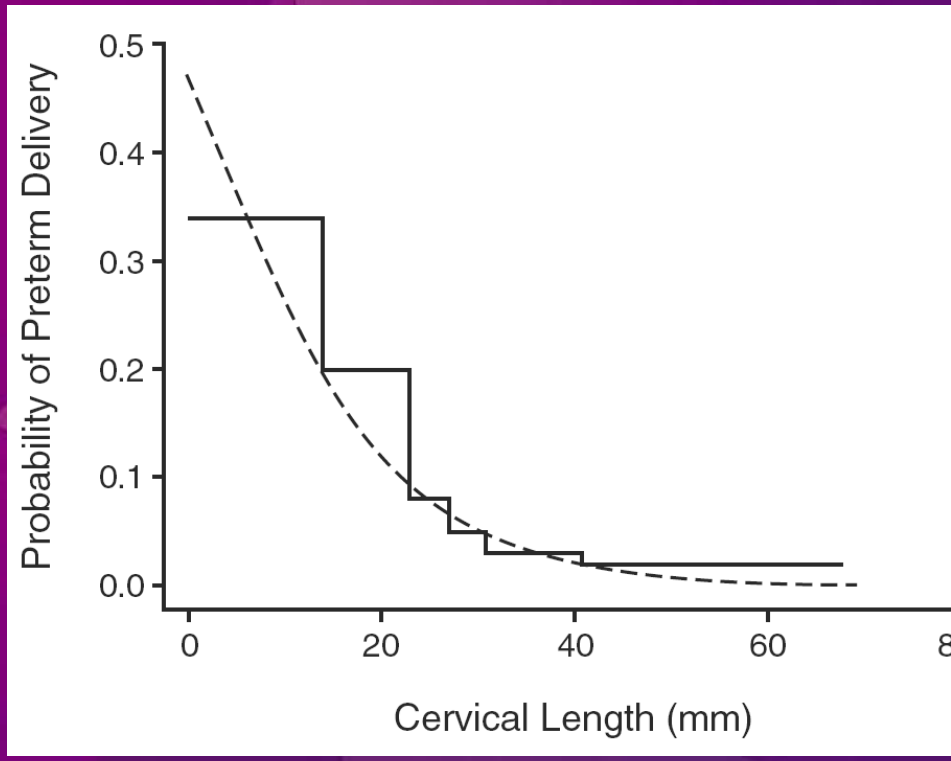
Short Cervix

Short cervix increases the risk of preterm labour

- majority ≤ 25mm (10centile) at 18-24 weeks
- progressive shortening

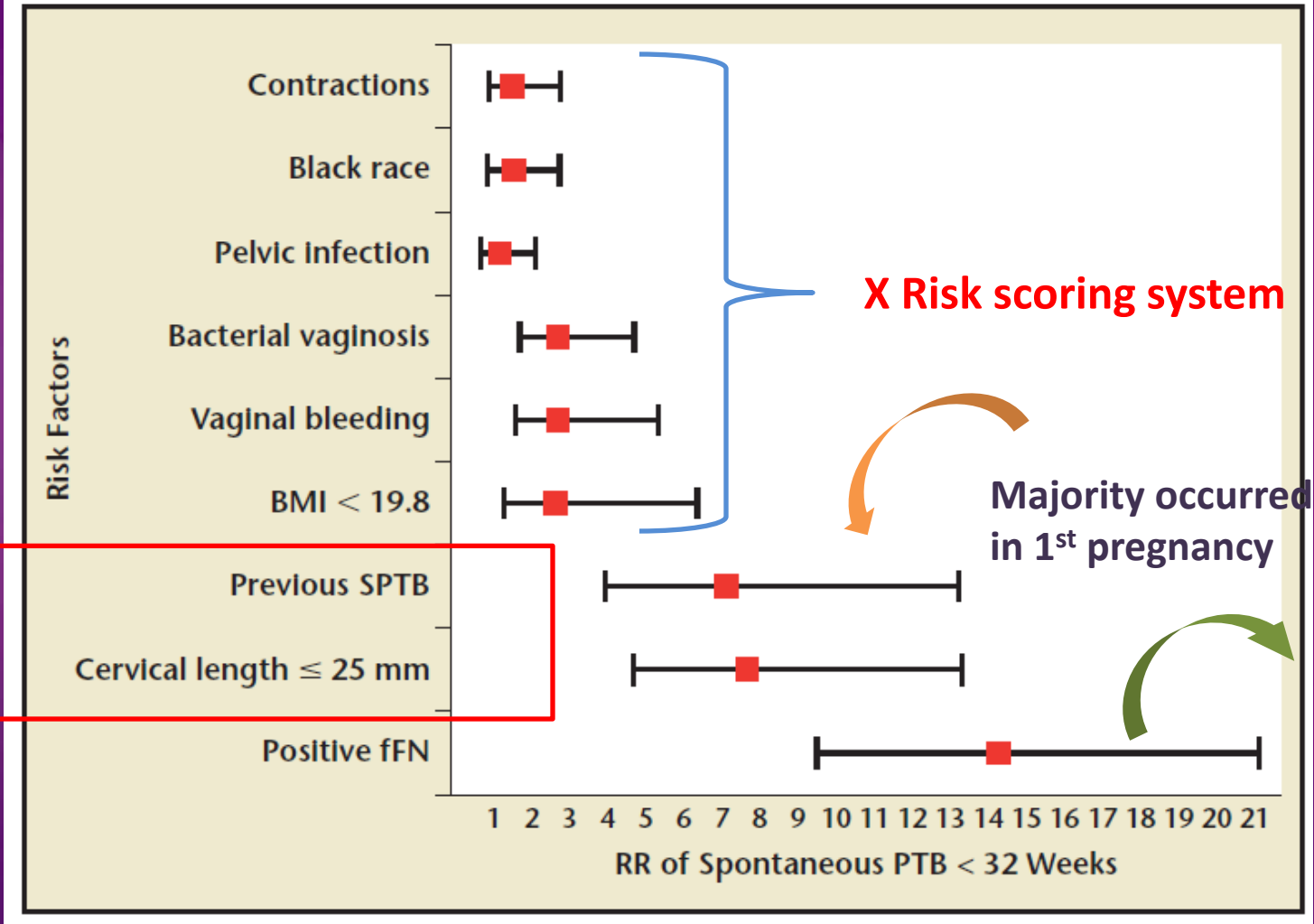
Cervical length (mm)	Prevalence	Risk
1-10	0.6%	44%
11-15	0.5%	23%
16-25	7.1%	3.6%
26-30	16.6%	1.3%
31-35	27.4%	0.8%
36-40	26.9%	0.6%
>40	21.0%	0.4%

↓ Cervical length ↑ Preterm Delivery



Iams et al. NEJM 1996

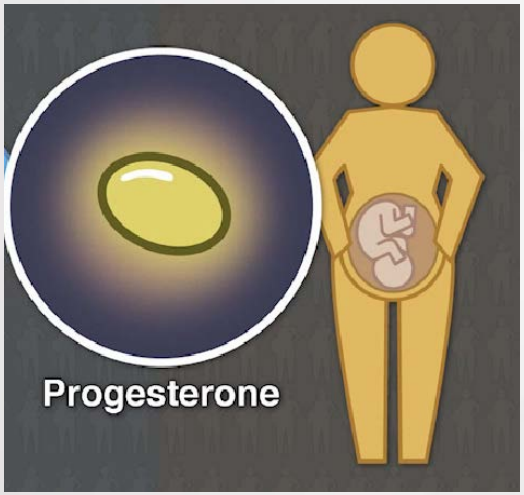
Preterm Prediction



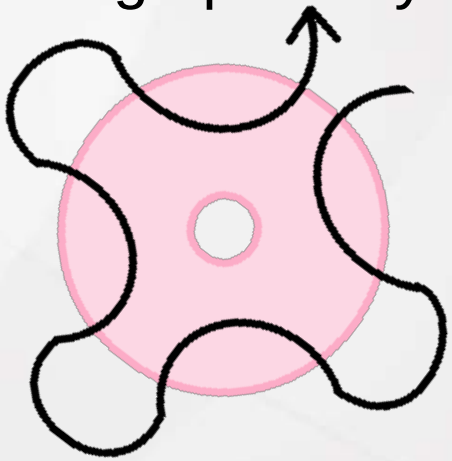
Absent between 22-37 weeks →more useful after 22 wks

Prevention of Preterm labour Management Modalities

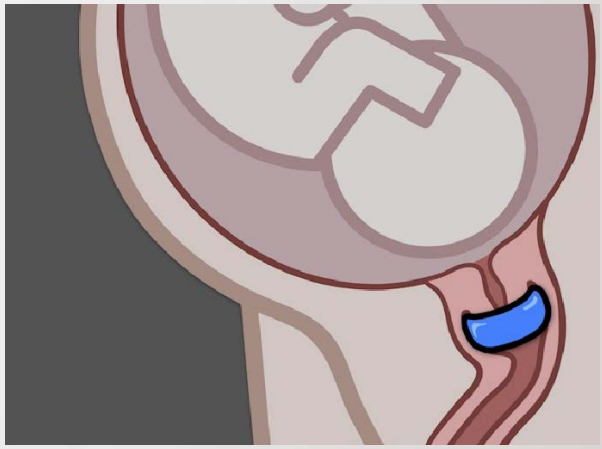
- Minimize risk factors: quit smoking, improve diet
- Treat vaginal infection ?
- Progesterone
- Cervical cerclage/ cerclage pessary



Prophylactic use of progesterone



Cervical cerclage
(previous preterm delivery)



Cervical pessary

- Preterm labour – steroid and tocolytics

Prevention of Preterm labour Management Modalities

- Minimize risk factors: quit smoking, improve diet
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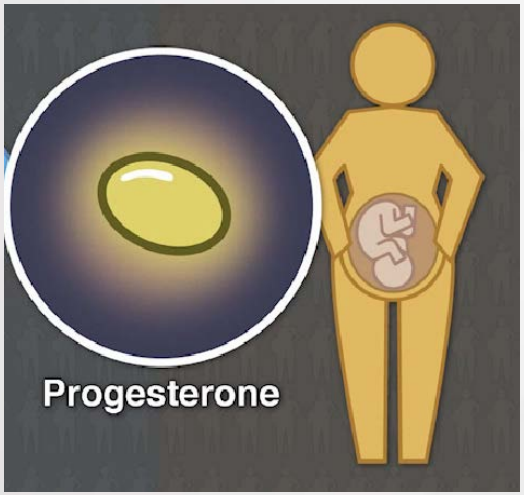
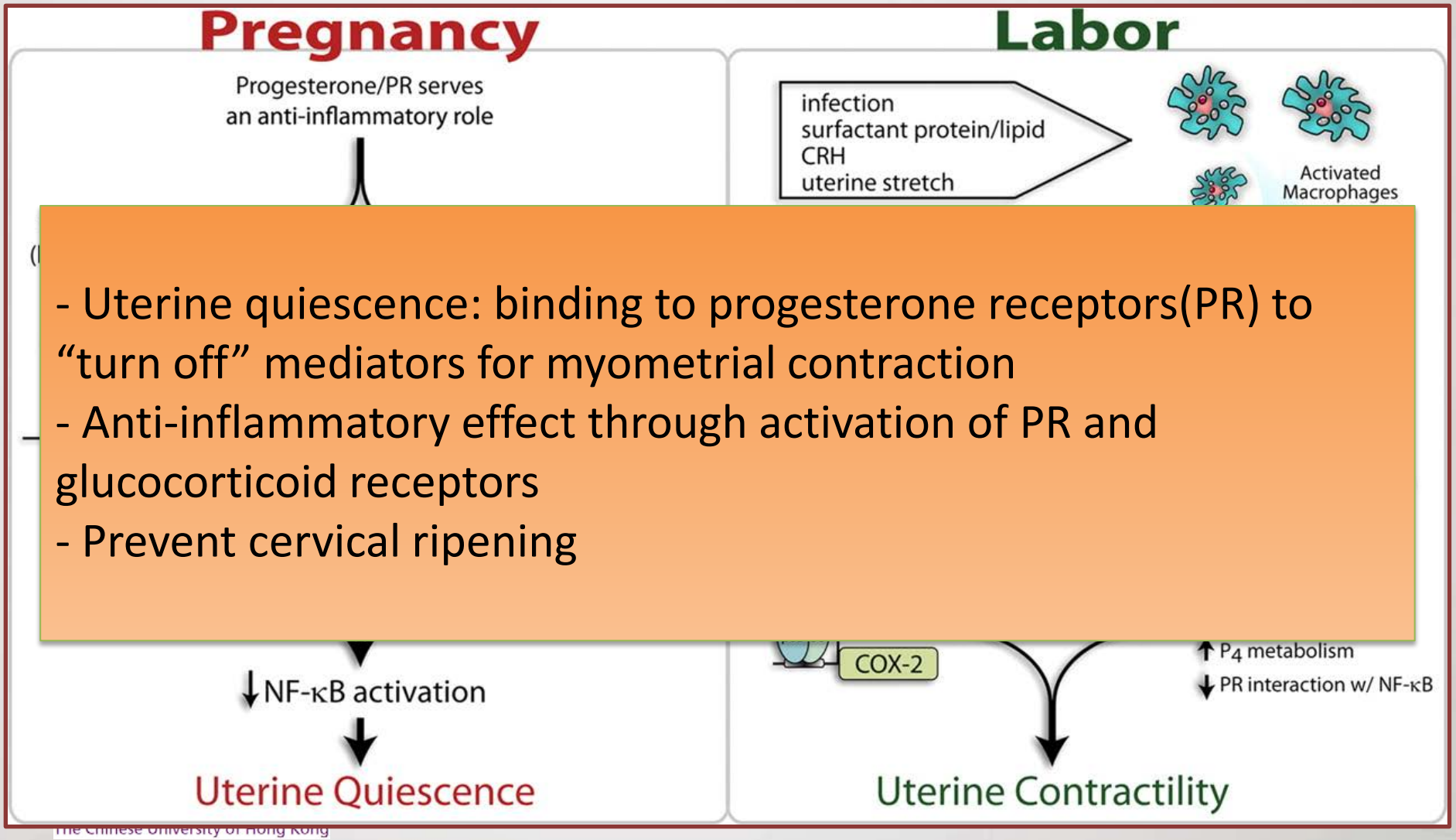
- Cervical cerclage/ cerclage pessary for short cervix



Prophylactic use of progesterone

Progesterone - Mechanism



- Uterine quiescence: binding to progesterone receptors(PR) to "turn off" mediators for myometrial contraction
- Anti-inflammatory effect through activation of PR and glucocorticoid receptors
- Prevent cervical ripening

Prevention of Preterm Labour
Progesterone – prior preterm labour

Proposed Indication	Suggested Management Protocol	Level of evidence (references)
1. Singleton pregnancy PLUS Prior spontaneous preterm	Hydroxyprogesterone caproate 250 mg IM weekly (16-36 weeks) Or Vaginal progesterone suppository 100 -200mg PV daily (24-34 weeks) monitor cervical length.	Level 1 (Supported by RCTs and meta-analysis) 11 trials, n = 1899 women ●Birth <34 weeks (RR 0.31, 95% CI 0.14-0.69) ●Birth <37 weeks (RR 0.55, 95% CI 0.42-0.74) ●Neonatal death (RR 0.45, 95% CI 0.27-0.76) ●Assisted ventilation(RR 0.40,95% CI 0.18-0.90) ●NEC(RR 0.30, 95% CI 0.10-0.89) ●NICU admission (RR 0.24, 95% CI 0.14-0.40)

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Cochrane Library 2013
Cochrane Database of Systematic Reviews

OPPTIMUM

Norman et al. Lancet 2016 Feb

Vaginal progesterone prophylaxis for preterm birth (the OPPTIMUM study): a multicentre, randomised, double-blind trial

Jane Elizabeth Norman, Neil Marlow, Claudia-Martina Messow, Andrew Shennan, Phillip R Bennett, Steven Thornton, Stephen C Robson, Alex McConnachie, Stavros Petrou, Neil J Sebire, Tina Lavender, Sonia Whyte, John Norrie, for the OPPTIMUM study group

- 1228 women
- Inclusion criteria (mixed)
  - previous spontaneous birth at ≤34 weeks
  - cervical length ≤25 mm
  - positive fetal fibronectin test combined with clinical risk factors
- 22-24 weeks till 34 weeks
- Vaginal progesterone did not significantly reduce the:
  - "fetal death or birth before 34 weeks" (adjusted OR 0.86, 95% CI 0.61-1.22)
  - neonatal outcome "death, brain injury, or bronchopulmonary dysplasia" (adjusted OR 0.62, 95% CI 0.38-1.03)

Prevention of Preterm Labour After the OPPTIMUM Progesterone – prior preterm ?

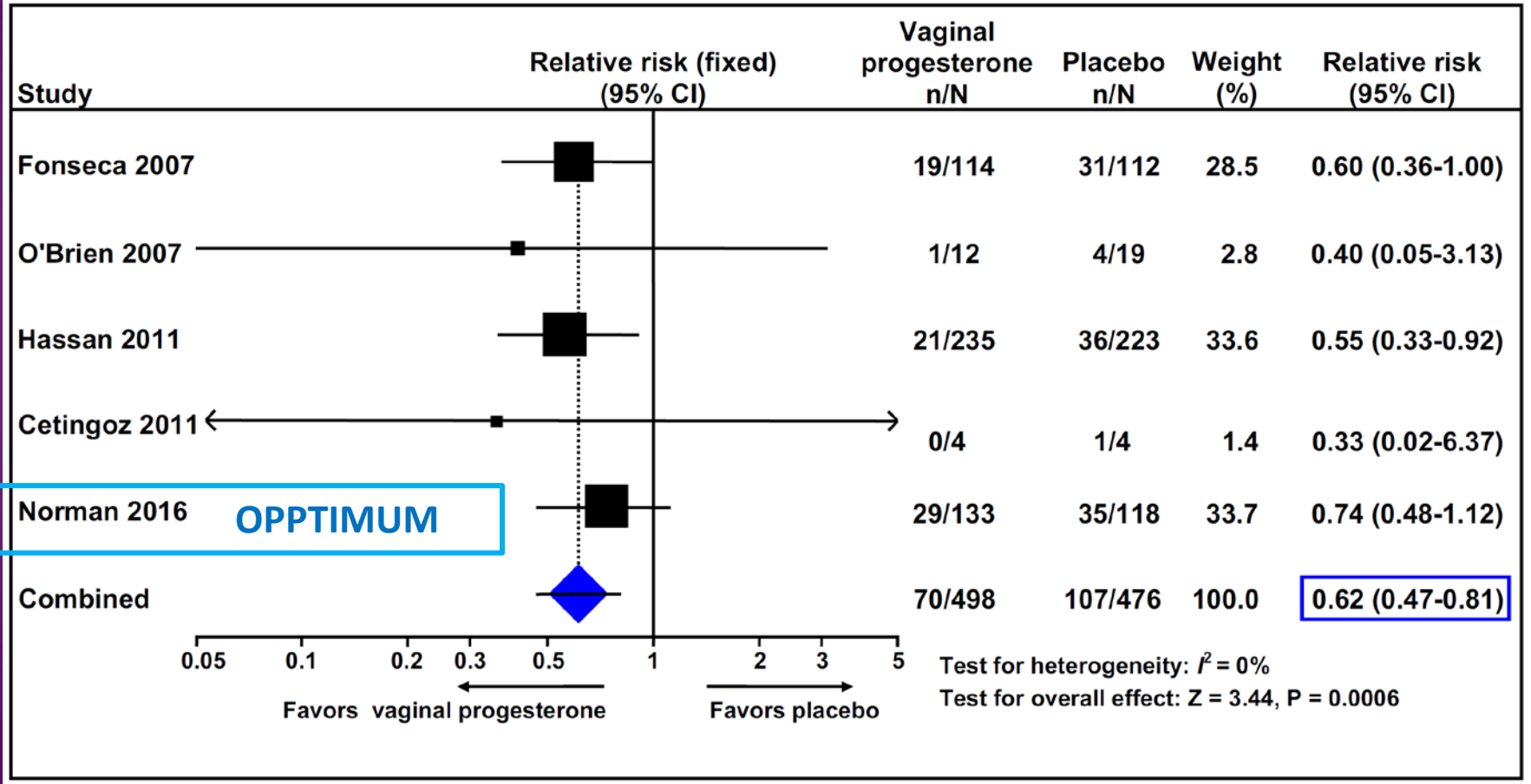
Stewart *et al. Systematic Reviews* (2017) 6:235
DOI 10.1186/s13643-017-0600-x

Systematic Reviews

PROTOCOL Open Access

Evaluating progestogens for prevention of preterm birth international collaborative (EPPPIC) individual participant data (IPD) meta-analysis: protocol

Prevention of Preterm Labour
Progesterone – short cervix



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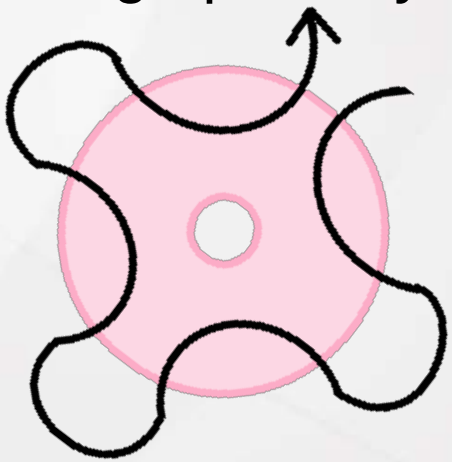
Romero et al. AJOG 2018 Feb

Prevention of Preterm Labour
Progesterone – short cervix

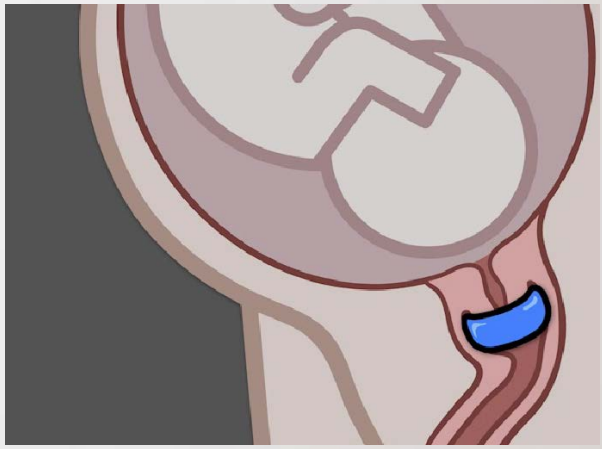
Outcomes	Anticipated absolute effects[a] (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of evidence (GRADE)[b]
	Risk with placebo	Risk with vaginal progesterone			
Neonatal death	Study population		RR 0.44 (0.18–1.07)	974 (5 studies)	⊕⊕⊖⊖ Low[e]
	32 per 1000	14 per 1000 (6–34)			
Perinatal death	Study population		RR 0.66 (0.35–1.22)	974 (5 studies)	⊕⊕⊕⊖ Moderate[d]
	48 per 1000	32 per 1000 (17–59)			
Composite neonatal morbidity/mortality	Study population		RR 0.59 (0.38–0.91)	723 (4 studies)	⊕⊕⊕⊕ High
	137 per 1000	81 per 1000 (52–125)			
Apgar score <7 at 5 min	Study population		RR 0.83 (0.55–1.26)	960 (5 studies)	⊕⊕⊕⊖ Moderate[f]
	92 per 1000	76 per 1000 (50–116)			
Birthweight <1500 g	Study population		RR 0.62 (0.44–0.86)	970 (5 studies)	⊕⊕⊕⊕ High
	163 per 1000	101 per 1000 (72–140)			
Birthweight <2500 g	Study population		RR 0.82 (0.68–0.98)	970 (5 studies)	⊕⊕⊕⊕ High
	355 per 1000	291 per 1000 (242–348)			
Admission to NICU	Study population		RR 0.68 (0.53–0.88)	970 (5 studies)	⊕⊕⊕⊕ High
	247 per 1000	168 per 1000 (131–217)			
Mechanical ventilation	Study population		RR 0.65 (0.41–1.01)	723 (4 studies)	⊕⊕⊕⊖ Moderate[d]
	120 per 1000	78 per 1000 (49–121)			

Prevention of Preterm labour Management Modalities

- Minimize risk factors: quit smoking, improve diet
- Treat vaginal infection ?
- Progesterone
- Cervical cerclage/ cerclage pessary for short cervix



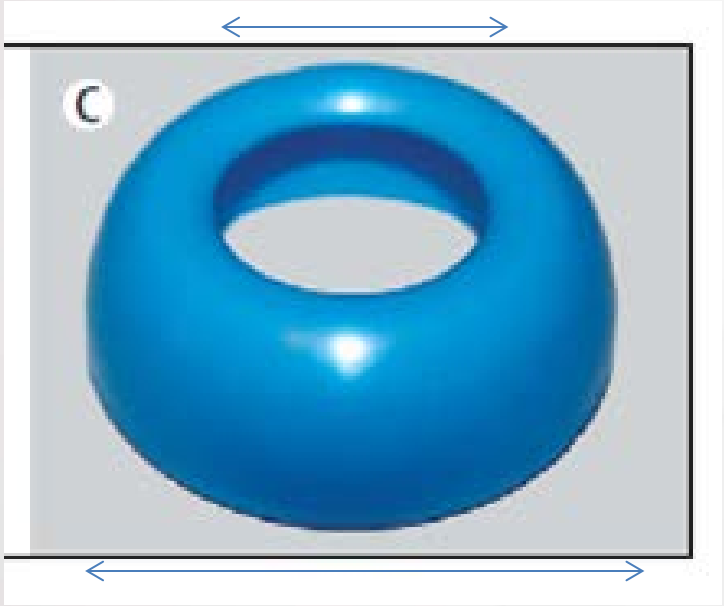
Cervical cerclage
(previous preterm delivery)



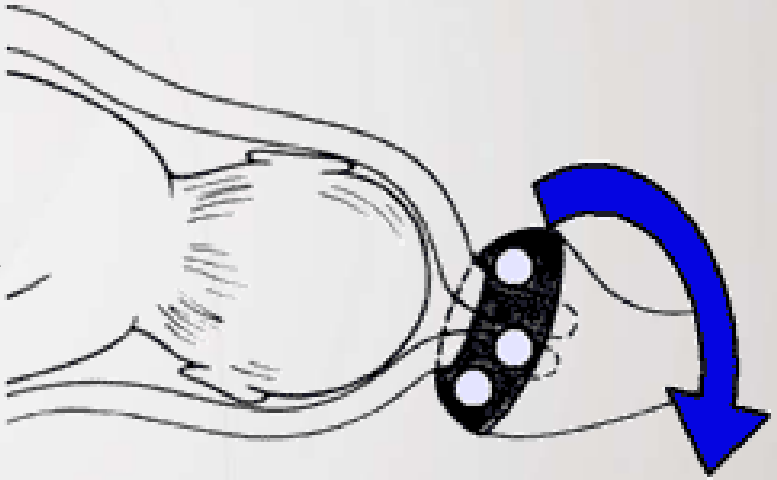
Cervical pessary

Arabin pessary – Size

Proximal internal diameter
32 -35mm



height
17- 30 mm



Distal external diameter
65 - 70 mm

Change the alignment
Redirect the force

Singleton – 3 RCTs

Sample Size	Goya/2012/Spain	Hui/2012/HK	Nicolaides/2016/UK
Inclusion criteria	**Singleton pregnancies Cervical length =<25 mm At 18 to 22 weeks**	**Singleton pregnancies Cervical length <25 mm At 20 to 24 weeks**	**Singleton pregnancies Cervical length =<25mm At 20 to 24 weeks**
	380 women	1120 women	1600 women
Actual	385 women in 5 hospitals	108 women in one centre	746 participants from UK and 189 from other countries

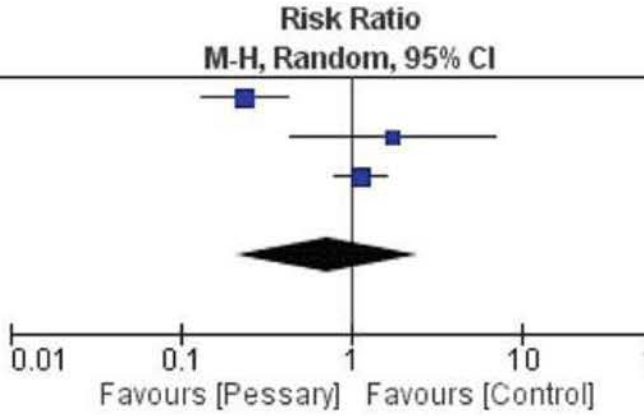
	Goya/2012/Spain		Hui/2012/HK		Nicolaides/2016/UK	
Pregnancy outcome						
	Pessary	Control	Pessary	Control	Pessary	Control
<28 weeks	2%	8%	3.8%	5.5%	5.4%	3.2%
<34 weeks	**6%***	**27%***	9.4%	5.5%	12.9%	11.3%
<37 weeks	**22%***	**59%***	15.1%	18.2%	n/a	n/a
Gestational age at delivery (weeks)	**37.7***	**34.9***	38.1	37.8	38.9	38.7

Prevention of preterm
Cerclage pessary – short cervix

Meta-analysis

Study or Subgroup	Pessary Events	Pessary Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Goya 2012	12	190	51	190	35.8%	0.24 [0.13, 0.43]	2012
Hui 2013	5	53	3	55	26.3%	1.73 [0.43, 6.88]	2013
Nicolaides 2016	60	465	53	467	37.9%	1.14 [0.80, 1.61]	2016
Total (95% CI)		**708**		**712**	**100.0%**	**0.72 [0.21, 2.49]**	
Total events	77		107				

Heterogeneity: $Tau^2 = 1.02$; $Chi^2 = 21.73$, $df = 2$ ($P < 0.0001$)
Test for overall effect: $Z = 0.52$ ($P = 0.61$)



Saccone et al. J Ultrasound Med; 2017

Non-invasive, Simple to insert, Cheap
Safe to mother fetus, Does not increase vaginal infections

Cervical cerclage – types

- **McDonald**
- Shirokar
- Hefnar/Wurm
- **Transabdominal**
- Laparoscopic

- Prophylactic cerclage – History indicated cerclage
- Therapeutic cerclage – Ultrasound indicated cerclage
- Rescue cerclage – Dilated cervix

Prevention of Preterm Labour
Cervical Cerclage

Singleton pregnancy

Delivery <35 wks

Control	Cerclage	RR (CI)
33.9%	24.8%	0.74 (0.57–0.96)

Berghella et al 2005, n=344
(Rust et al 2001, Althuisius et al 2001, Berghella et al 2004, To et al 2004

Preterm births

Control	Cerclage	RR (CI)
		0.80 (0.69–0.95)
10.7%	8.4%	0.78 (0.61-1.00)
10.2%	9.6%	0.95 (0.63-1.43)

Cochrane 2012, 12 trials, n =3328

Cervical Cerclage - main indications

1. History indicated cerclage
2. USG indicated cerclage

= Similar efficacy (↓ 30%)

Berghella et al OG 2011

3. Physical exam indicated cerclage (i.e. rescue cerclage)
   - Meta-analysis, 10 trials, 757 women
   - Compared to control, Cerclage associated with:
   - Increased neonatal survival (71% vs 43%, RR 1.65, 95% CI 1.19-2.28)
   - Prolongation of pregnancy (33.98 days, 95% CI 17.88-50.08)
   - Expectant management 4X risk of delivery between 24-28 weeks

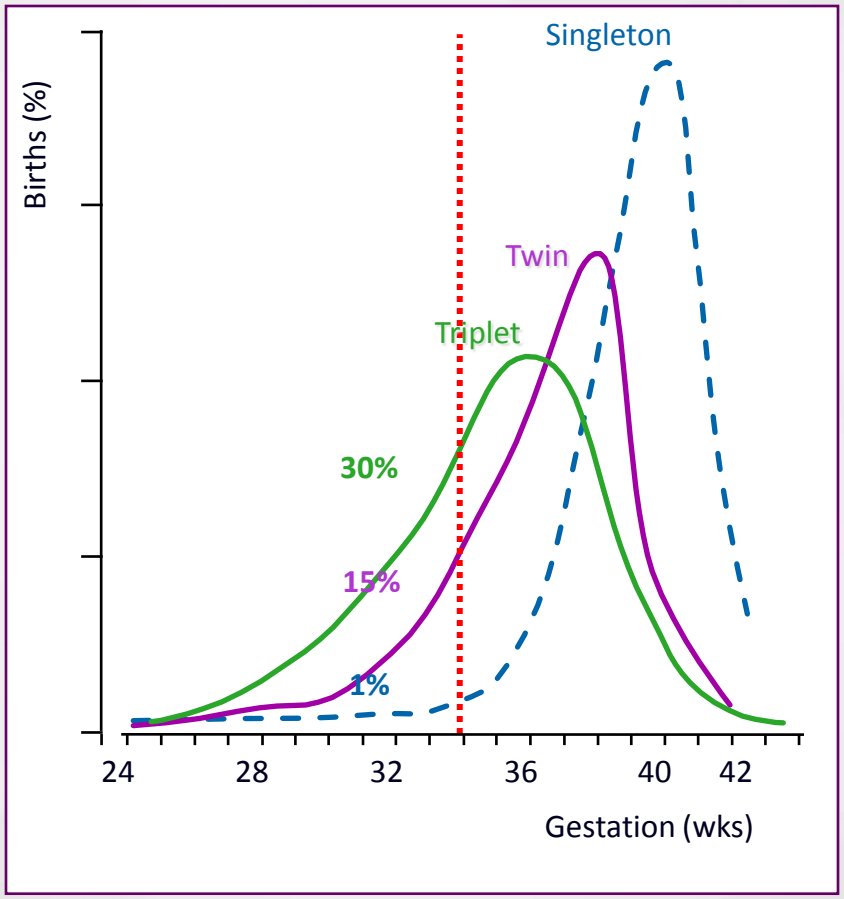
Ehsanipoor et al OG 2015

Prevention of preterm labour Singleton Pregnancy

	Prior preterm birth	Short Cervix
Progesterone	Most RCTs: useful Latest RCT: no significant diff	Useful (vaginal)
Cerclage Pessary	---- (Hx indicated cerclage)	Controversial
Surgical Cerclage	----	Useful

Multiple pregnancies

Multiple pregnancy and Preterm Birth



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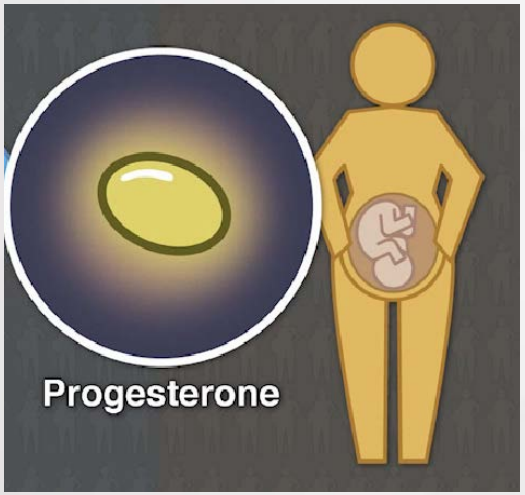
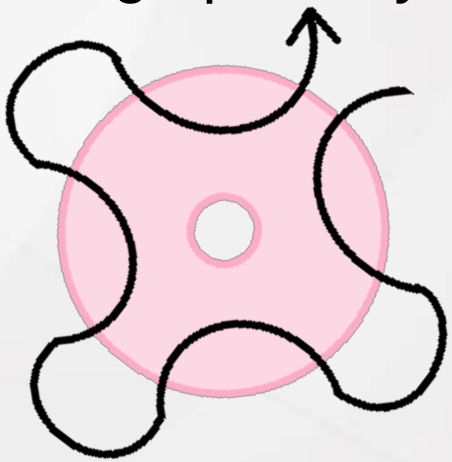
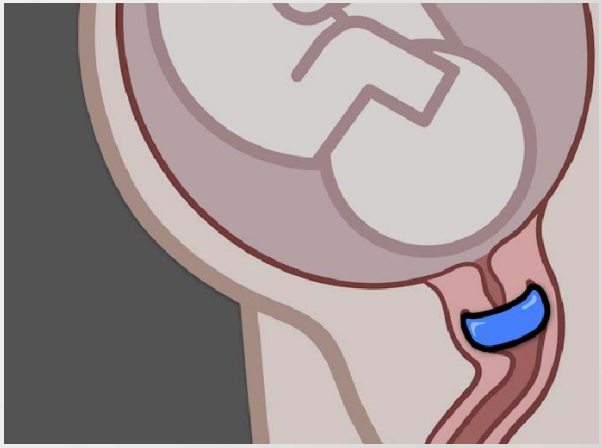


Prophylactic use of progesterone



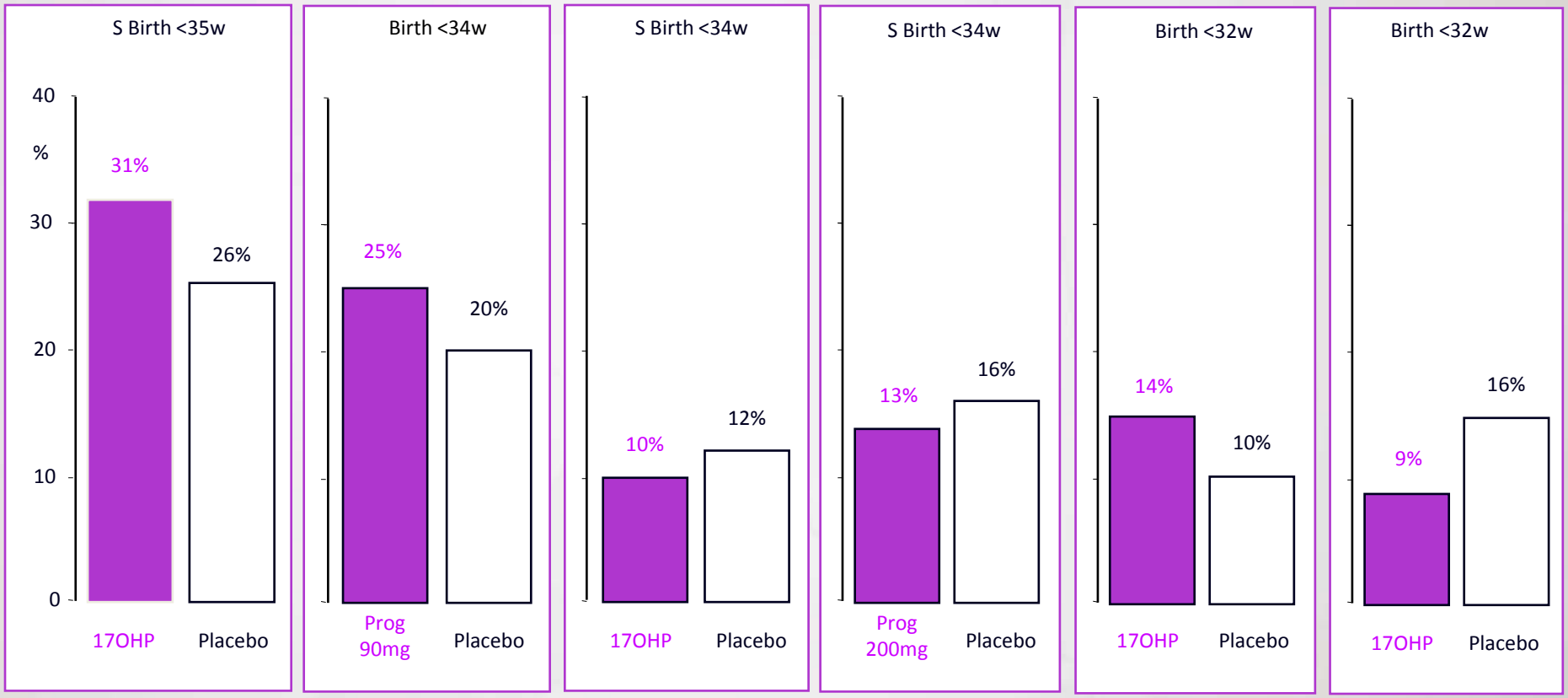
Cervical cerclage (previous preterm delivery)



Cervical pessary

- Preterm labour – steroid and tocolytics

Prevention of preterm labour
Progesterone for Twins (unselected)



Rouse *et al,* 2007 (n=655)

Norman *et al,* 2009 (n=494)

Combs *et al,* 2011 (n=238)

Rode *et al,* 2011 (n=675)

Lim *et al,* 2011 (n=671)

Awwad *et al,* 2014 (n=288)

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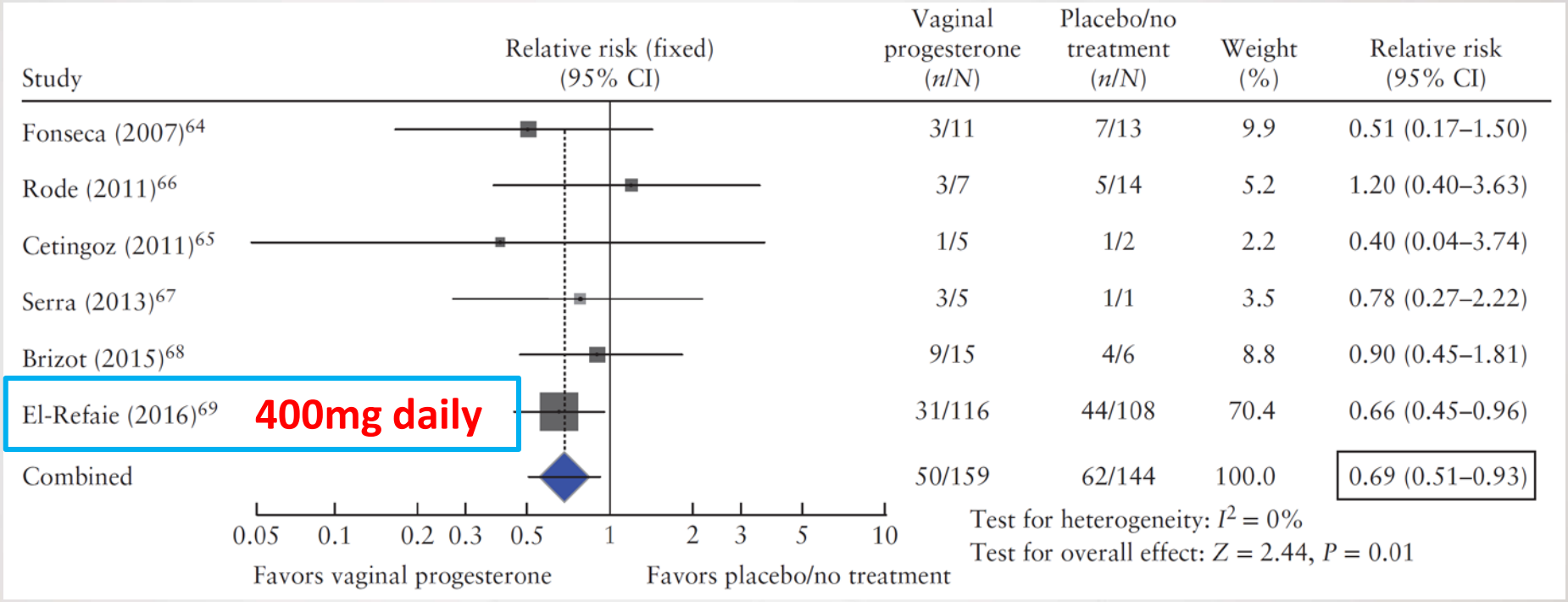
Prevention of preterm labour
Progesterone for Twins + short cervix



Romero et al., 2017: META ANALYSIS

Progesterone reduces the risks of preterm birth in twin pregnancies with short cervical length

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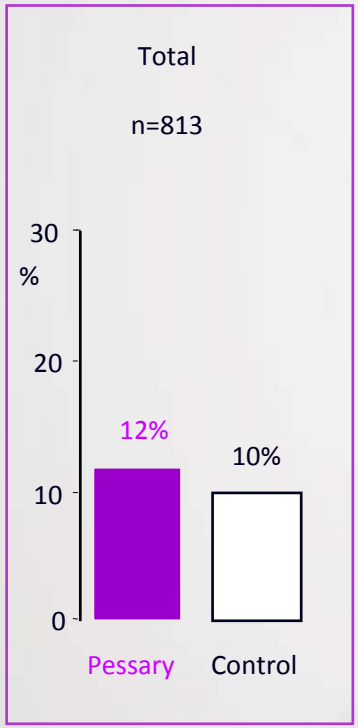
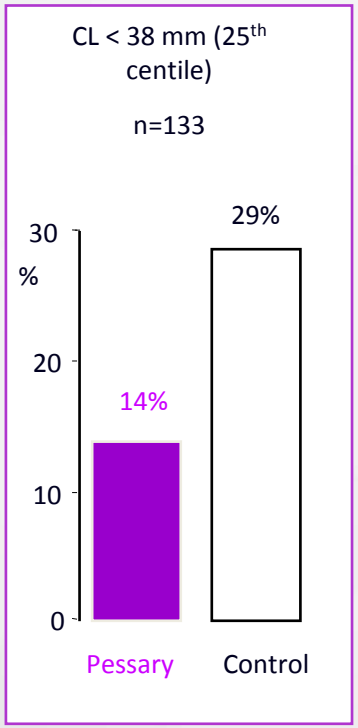
Prevention of preterm labour
Cerclage Pessary for Twins

Delivery < 32 w

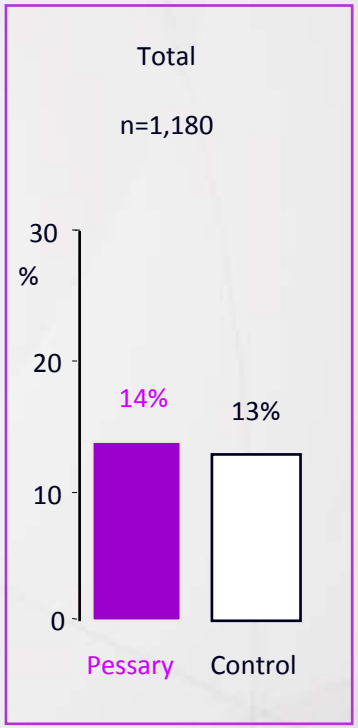


Median CL= 44 mm

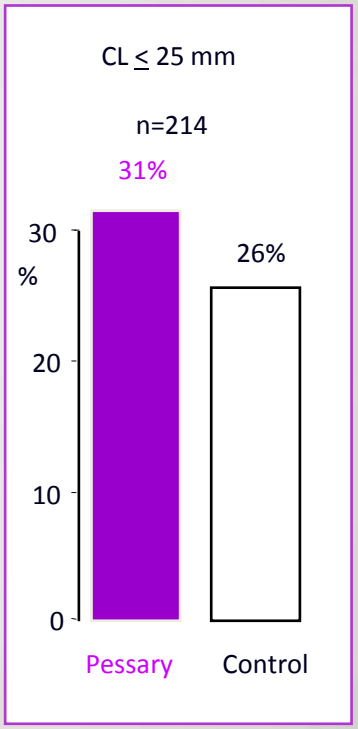


Liem et al, 2013

Delivery < 34 w



Median CL= 32 mm



Nicolaides et al, 2015

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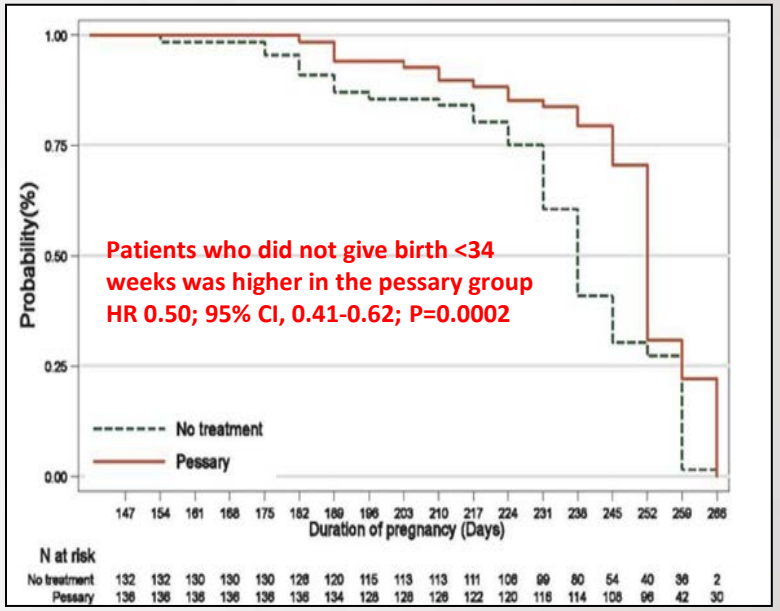
Prevention of preterm labour
Pessary for Twins + Short cervix

- Prospective, open-label, multicentre RCT
- 5 hospitals in Spain
- Cx ≤25 cm at 18-22w (n=154, 6.7%)
- Randomisation 1:1
  - Pessary group (n=68)
  - Expectant group (n=66)
- Outcomes
  - Primary: spontaneous preterm birth <34 weeks
  - Secondary: birthweight, IUFD, neonatal death, neonatal morbidity



Outcomes	No treatment	Pessary	P value	RR (CI 95%)
Spontaneous delivery <34w	26/66 (39.4%)	11/68 (16.2%)	0.003	0.41 (0.22-0.76)
GA at delivery	33.1	35.3	0.01	
Birthweight <2500g	62/130 (47.7%)	47/136 (34.6%)	0.01	0.72 (0.54-0.97)
Composite neonatal outcomes	12/130 (9.1%)	8/136 (5.9%)	NS	0.64 (0.27-1.50)

Prevention of preterm labour
Cervical cerclage for short cervix

Outcome	Cerclage	Control	RR (95% CI)	aOR (95% CI)
Delivery <35 w	18/24 (75%)	9/25 (36%)	1.63 (0.88 – 3.02)	1.44 (0.66 – 7.11)
Delivery <34 w	15/25 (60%)	6/25 (24%)	2.19 (0.72 – 6.63)	1.17 (0.23 – 3.79)
Delivery <32 w	11/25 (44%)	4/25 (16%)	2.48 (0.96 – 6.37)	1.77 (0.88 – 3.39)

Saccone et al., 2015: META ANALYSIS

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Cerclage does not prevent preterm birth in twin pregnancies with short cervical length

Prevention of preterm labour
Twin Pregnancy

	Unselected	Short Cx
Cerclage	-	Not useful
Progesterone	Not useful	Likely useful
Pessary	Not useful	May be

Assisted reproductive technology accounted for 77% of multiple pregnancies in PWH
Single embryo transfer should be advocated

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Thank You

Preterm Birth
Prediction and Prevention

Dr. LAW, Lai Wa
Consultant
Department of O&G
Prince of Wales Hospital

THANK YOU

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