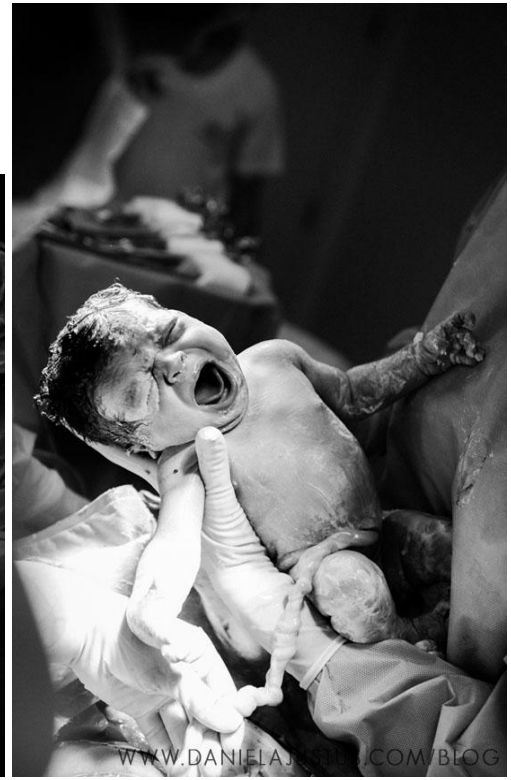
Progesterone, cerclage and pessary

for patient with a short cervical length

Federal University of Paraiba



Eduardo Borges da Fonseca

Professor Ob/Gyn Federal University of Paraiba

President of Perinatology Branch of Brazilian Federation of Obstetricians and Gynecologists

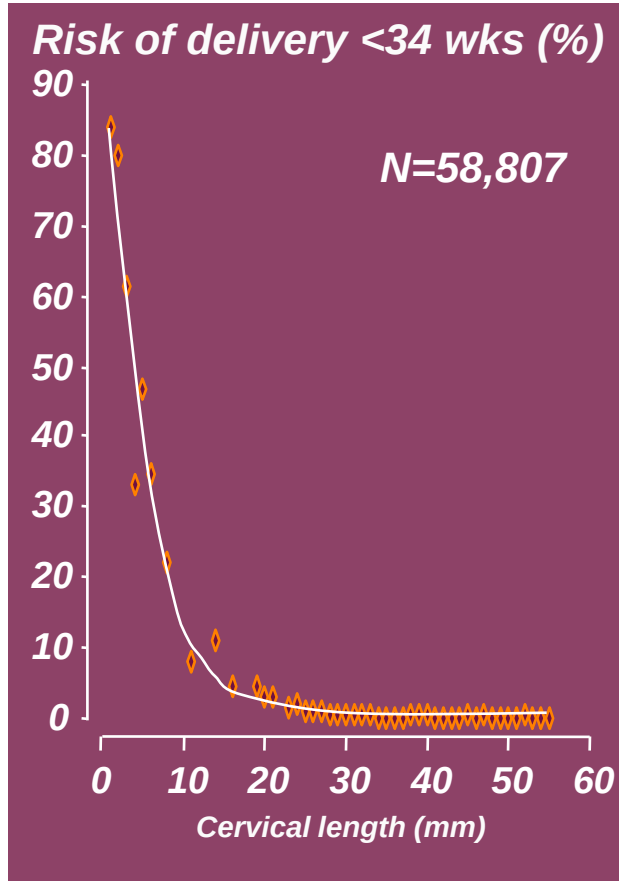
Preterm birth

Screening by cervical length at 22 wks

Take into account

Spontaneous PTD <34 wks ~ 2%

Celik et al. UOG. 2008;31:549-54.

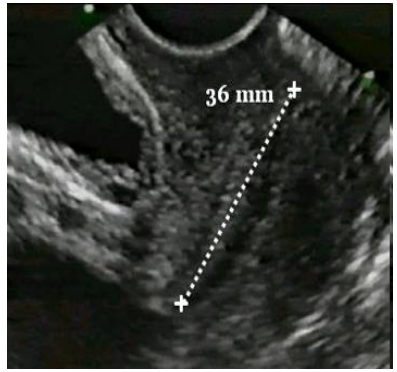


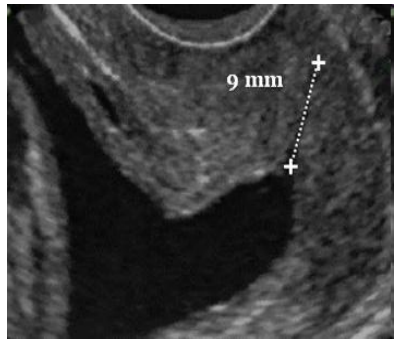
Cervix	Del<34
1-5 mm	70%
6-10 mm	22%
11-15 mm	16%
16-25 mm	4%
26-30 mm	1.3%
31-35 mm	0.8%
36-40 mm	0.6%
40-45 mm	0.4%

vs 2%

Cervical assessment

Identification of risk factor



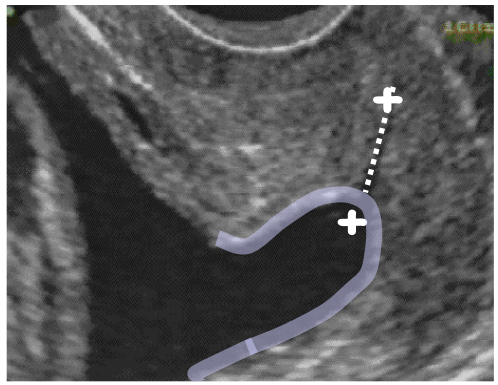


What is a short cervix?

Risk factor	CxL
No Risk factor	<20 mm
Prior PTB	<25 mm
Twins	<25 mm
Triplets	<25 mm

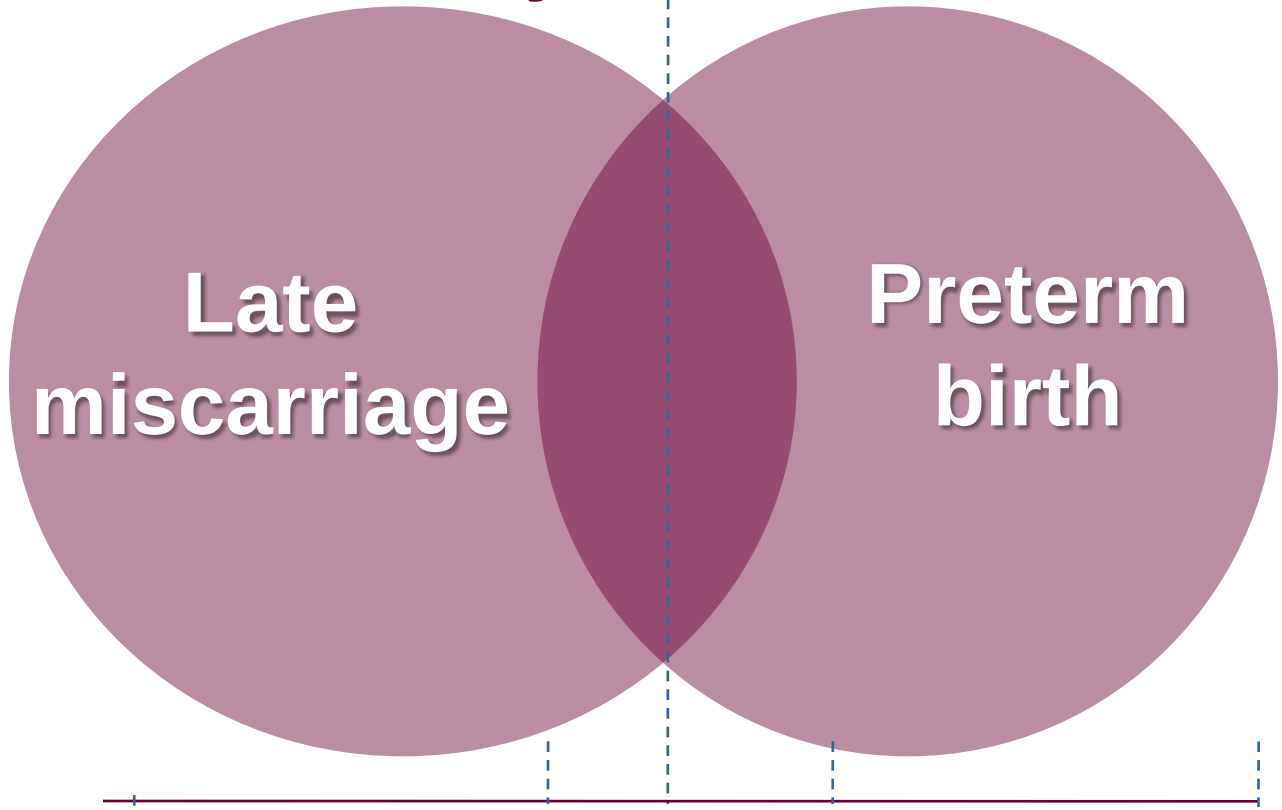
http://www.uptodate.com/contents/second-trimester-evaluation-of-cervical-length-for-prediction-of-spontaneous-preterm-birth?source=search_result&search=screening+for+PTB&selectedTitle=2~150

Short cervix



≤25 mm

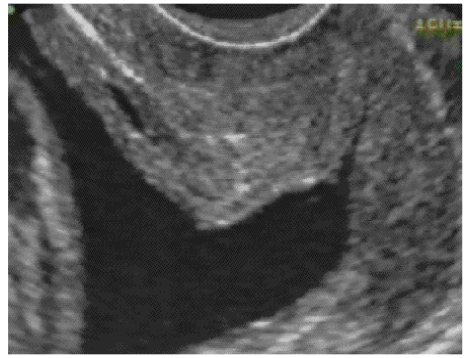
Cervical Insufficiency vs Risk for PTD



Prevention: where are we?

Strategy in the prevention of PTB

Short cervix



<25 mm

Identification of risk factors

- *Nulliparous or NO history of prior PTB*
- *Previous history of preterm birth*
- *Twin pregnancy*

Short cervical lenght

Identification of risk for PTD

Short CLx: micronized progesterone

(200mg/night), 24-34 wks

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

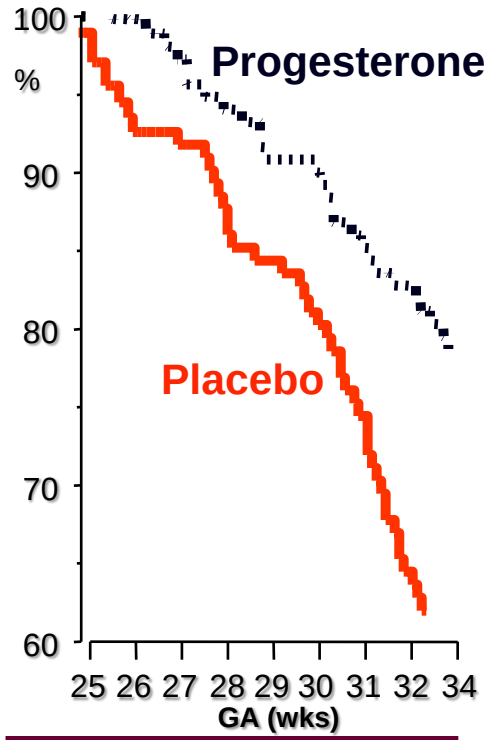
Progesterone and the Risk of Preterm Birth among Women with a Short Cervix

Eduardo B. Fonseca, M.D., Ebru Celik, M.D., Mauro Parra, M.D., Mandeep Singh, M.D., and Kypros H. Nicolaides, M.D., for the Fetal Medicine Foundation Second Trimester Screening Group*

414 short cervix (≤15 mm)

60%

250 randomized



Del < 34 wks
19% vs 34%

Fonseca et al. ***N. Engl. J Med***. 2007; 357:450.

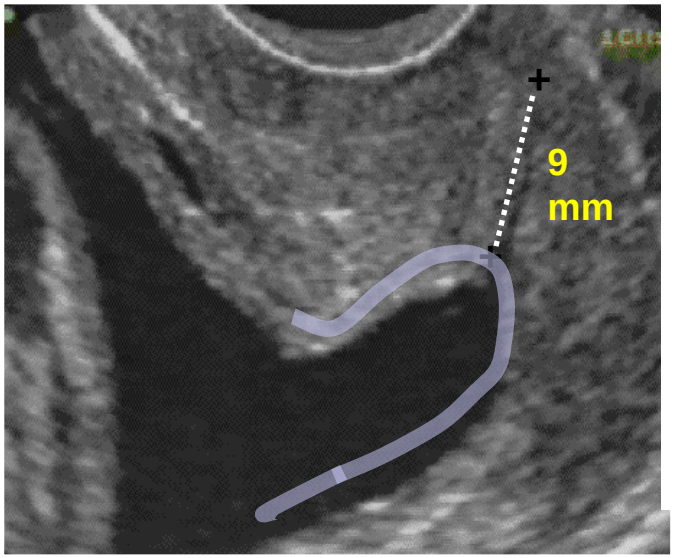
Short cervical lenght

Identification of risk for PTD

Short CLx: micronized progesterone

(200mg/night), 24-34 wks

Asymptomatic



Outcome	Placebo	P4
Delivery before 34 wks		
Spontaneous	34.4%	19.2% *
All	36.0%	20.8% *
Perinatal outcome		
Fetal death	0.7%	0.7%
Neonatal death	5.1%	1.5%
Birth weight <1500g	19.6%	13.2%
Morbidity (IVH, RDS, NEC)	13.8%	8.2%
Therapy (NICU,Ventil)	32.6%	25.0%

Fonseca et al. ***N. Engl. J Med***. 2007; 357:450.

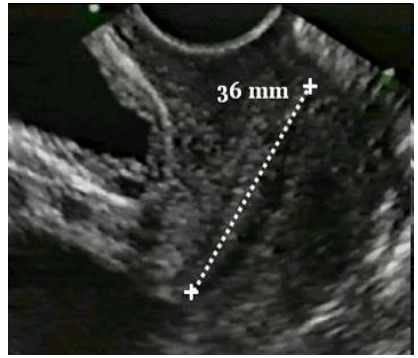
Short cervical lenght

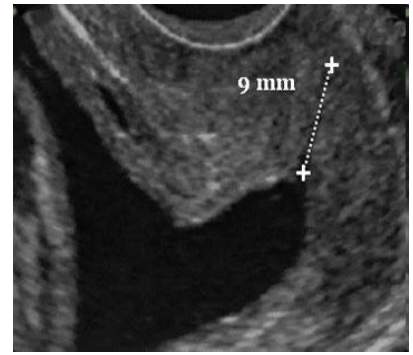
Identification of risk for PTD

Short CLx: gel progesterone

(90mg/day) from 24-36 wks

Sonia Hassan





733 short cervix
(10 – 20 mm)

63%

465 randomized

RESULTS	Placebo (223)	Progesterone (235)
Delivery <33 wks	16.1%	8.9% *
RDS	7.0%	3.6% *
Composite morbidity/mortality	13.5%	7.7% *

Hassan et al. **UOG**. 2011; 38:18-31.

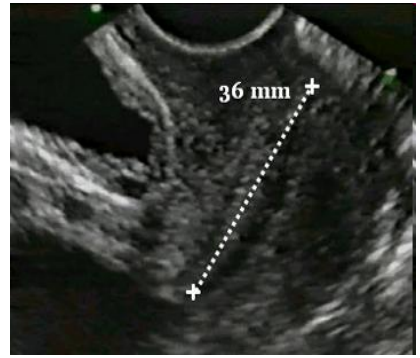
Short cervical lenght

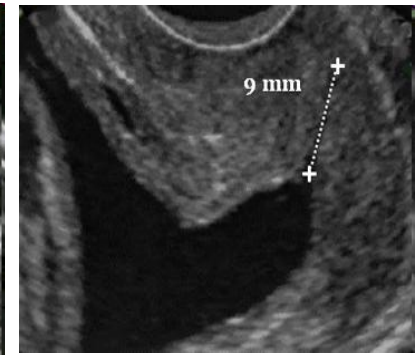
Identification of risk for PTD

Short CLx: gel progesterone

(90mg/day) from 24-36 wks

Sonia Hassan





733 short cervix (10 – 20 mm)

63%

465 randomized

RESULTS	Placebo (223)	Progesterone (235)

- PTD <33sem: 45% reduction
- Decrease neonatal morbidity and mortality

Hassan et al. **UOG**. 2011; 38:18-31.

Prevention of preterm birth

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

American Journal Obsterics & ***Gynecology***. 2012:206:124.

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

Prevention of preterm birth

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

Progesterone in women with an asymptomatic short CxL at 22 wks (N=775)

Outcome	No. of trials	No. of events/total no.		Pooled RR (95% CI)	I^2 (%)	NNT (95% CI)
		Vaginal progesterone	Placebo			
Preterm birth <37 wk	5	144/388	165/387	0.89 (0.75–1.06)	0	–
Preterm birth <36 wk	5	108/388	136/387	0.82 (0.67–1.00)	0	–
Preterm birth <35 wk	5	79/388	118/387	0.69 (0.55–0.88)	0	11 (7–27)
Preterm birth <34 wk	5	62/388	105/387	0.61 (0.47–0.81)	0	9 (7–19)
Preterm birth <30 wk	5	29/388	51/387	0.58 (0.38–0.89)	0	18 (12–69)
Preterm birth <28 wk	5	21/388	43/387	0.50 (0.30–0.81)	0	18 (13–47)
Spontaneous preterm birth <33 wk	5	39/388	71/387	0.57 (0.40–0.81)	0	13 (9–29)
Spontaneous preterm birth <34 wk	5	51/388	87/387	0.62 (0.46–0.84)	0	12 (8–28)

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. ***American Journal Obsterics*** & ***Gynecology***. 2012:206:124.

Prevention of preterm birth

Vaginal progesterone in women with an asymptomatic short cervix at 22 weeks (N=775)

Outcome	No. of trials	No. of events/total no.		Pooled RR (95% CI)	I^2 (%)	NNT (95% CI)
		Vaginal progesterone	Placebo			
Respiratory distress syndrome	5	25/411	52/416	0.48 (0.30–0.76)	0	15 (11–33)
Intraventricular hemorrhage	5	6/411	9/416	0.74 (0.27–2.05)	0	–
Neonatal death	5	8/411	15/416	0.55 (0.26–1.19)	43	–
Admission to NICU	5	85/411	121/416	0.75 (0.59–0.94)	0	14 (8–57)
Mechanical ventilation	5	35/411	51/416	0.66 (0.44–0.98)	0	24 (15–408)
Congenital anomaly	7	30/1967	34/1954	0.89 (0.55–1.44)	0	–
Any maternal adverse event	3	86/624	80/595	1.04 (0.79–1.38)	0	–

Vaginal progesterone administration to asymptomatic women with a sonographic short cervix reduces the risk of preterm birth and neonatal morbidity and mortality.

Making progress: evidence for micronized progesterone Where are we?

Intervention	To prevent:	RR (95% CI)	NNT (95% CI)
Magnesium sulfate	Eclampsia	0.41 (0.29-0.58)	100 (50-100)
Magnesium sulfate	Cerebral palsy	0.69 (0.55-0.88)	52 (31-154)
Antenatal corticosteroids	RDS	0.66 (0.59-0.73)	11 (9-14)
	Neonatal death	0.69 (0.58-0.81)	22 (16-36)

NNT: Number Needed to Treat

Making progress: evidence for micronized progesterone Where are we?

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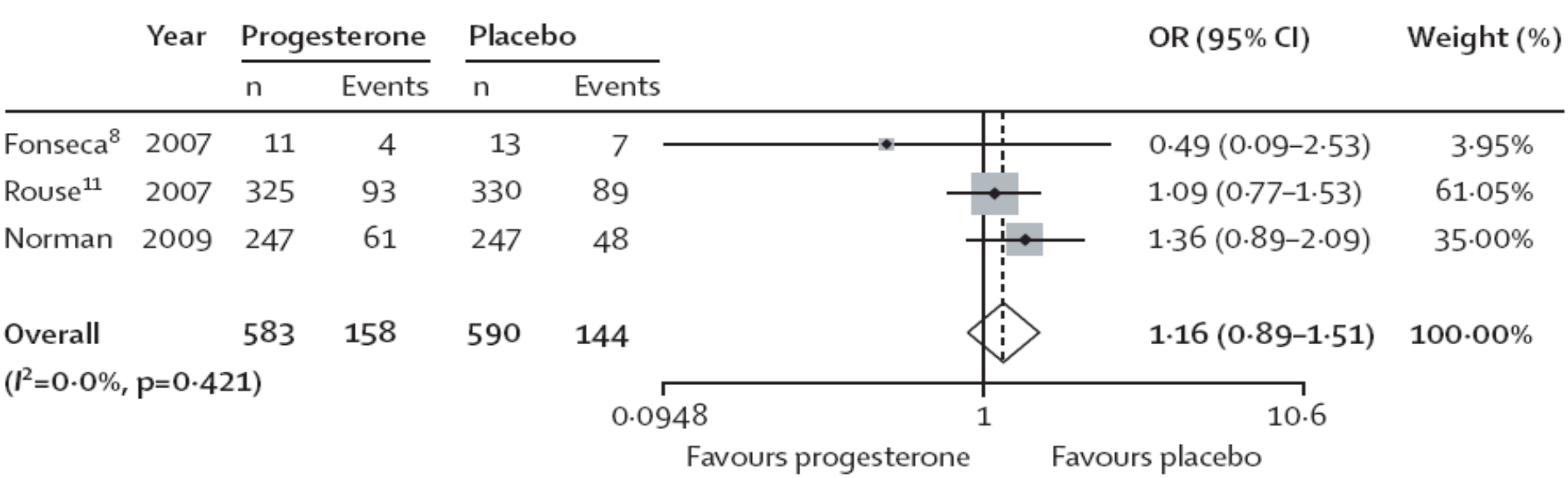
Magnesium sulfate	Eclampsia	0.41 (0.29-0.58)	100 (50-100)
Magnesium sulfate	Cerebral palsy	0.69 (0.55-0.88)	52 (31-154)
Antenatal corticosteroids	RDS	0.66 (0.59-0.73)	11 (9-14)
	Neonatal death	0.69 (0.58-0.81)	22 (16-36)
Vaginal progesterone in short cervix	Preterm birth <33 weeks	0.55 (0.33-0.92)	14 (8-87)
	RDS	0.39 (0.17-0.92)	22 (12-186)

NNT: Number Needed to Treat

Old evidence: ***twin pregnancy***

Meta-analysis of the effect of progesterone in the prevention of preterm delivery <34 wsks (N=1,173)

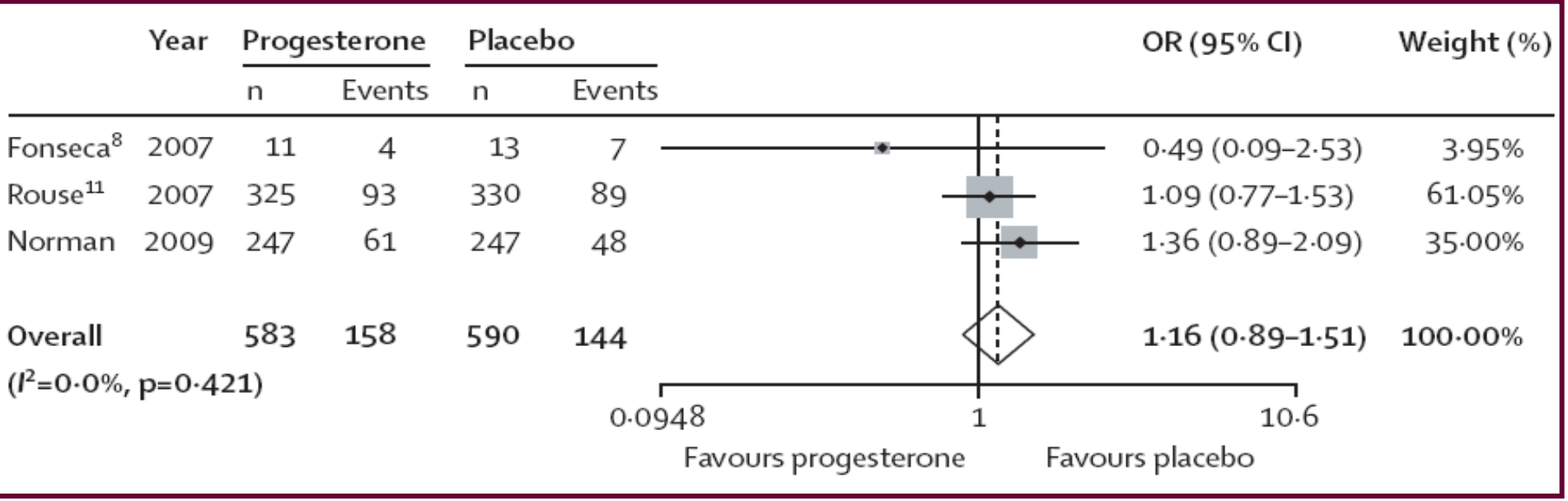


- **Square** shows the **OR** for each study and the horizontal line depicts the 95% CIs.
- **Vertical line**, at the odds ratio of unity, corresponds to the line of no effect
- **Open diamond** indicates the final odds ratio with 95% CI overall

Norman et al. ***TheLancet***. 2009; 373: 2034-40.

Old evidence: ***twin pregnancy***

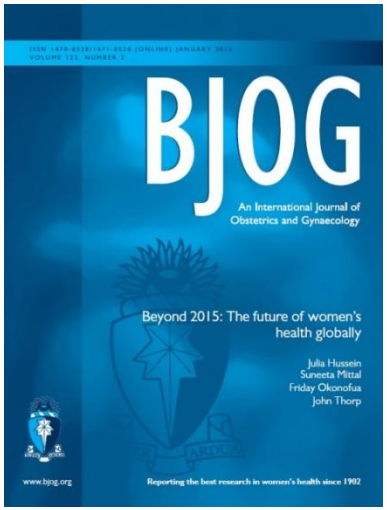
Meta-analysis of the effect of progesterone in the prevention of preterm delivery <34 wsks (N=1,173)



Meta-analysis confirmed: progesterone does not prevent early preterm birth in women with twin pregnancy (pooled OR 1.16, 95% CI 0.89-1.51).-

Norman et al. ***TheLancet***. 2009; 373: 2034-40.

Near future:
twin pregnancy plus short cervix



DOI: 10.1111/1471-0528.13032
www.bjog.org

Systematic review

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

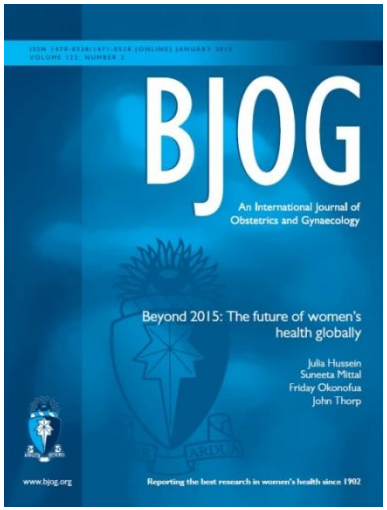
- 13 RCT
- 3,768 women
- 7,536 babies

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

- Neither 17Pc nor vaginal P4 reduced the incidence of adverse perinatal outcome.
- **In subgroup of women with a short cervix** ≤25 mm, **vaginal progesterone reduced** adverse perinatal outcome (15/56 vs 22/60; RR 0.57; 95% CI 0.47-0.70).

BJOG. 2015; 122:27-37.

Near future:
twin pregnancy plus short cervix



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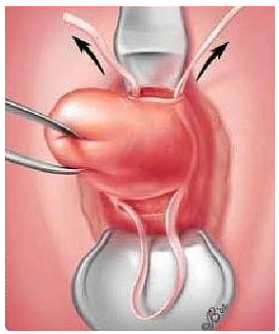
Authors' conclusions Vaginal progesterone may be effective in the reduction of adverse perinatal outcome in women with a cervical length of ≤25 mm; however, further research is warranted to confirm this finding.

BJOG. 2015; 122:27-37.

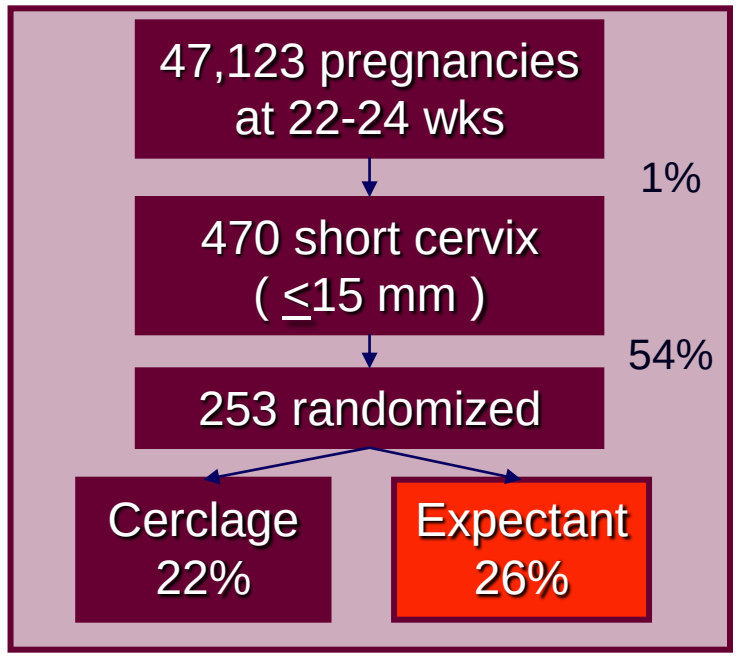
Old evidence:

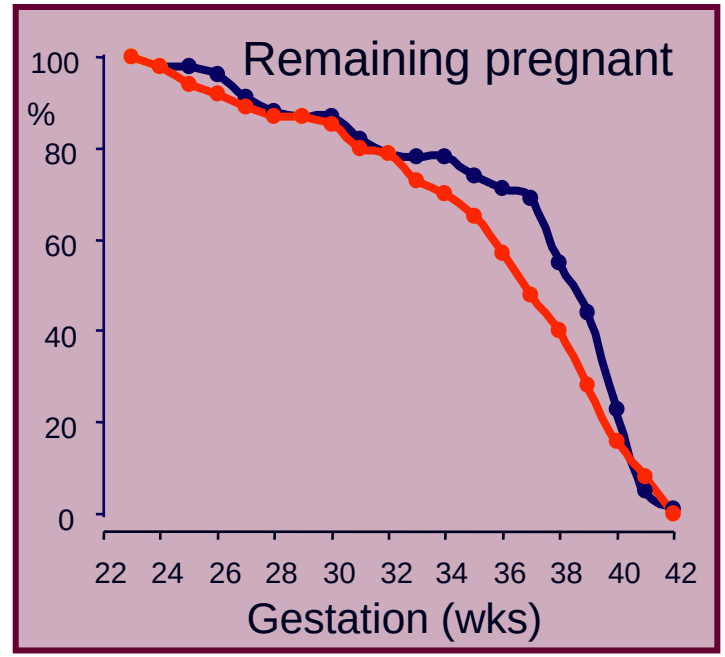
Cerclage: short cervical length

Cervical cerclage for prevention of preterm delivery in women with short cervix: RCT.



Meekai To





The insertion of a Shirodkar suture in women with a short cervix DOES NOT reduce the risk of early PTD.

To et al 2004

New evidence:
Prior PTB plus short cervical length

Vaginal progesterone or cerclage to prevent recurrent PTB in women with a short cervical length less than 25mm?

Recent evidence shows that targeted use of either cerclage or vaginal micronized progesterone can reduce the risk of PTB in a specific group of women at very high risk, those with all 3 of the following:

- A current **singleton** pregnancy.
- A **history** of spontaneous **PTB (**<34 weeks**)** in a prior pregnancy.
- A **short cervix** (<25 mm) before 24 weeks in the current pregnancy.

Untreated, such women have a 15-20% risk of recurrent PTB <28 weeks, a 25-30% risk of PTB <32 Weeks.

New evidence:
Prior PTB plus short cervical length

Vaginal progesterone or cerclage to prevent recurrent PTB in women with a short cervical length less than 25mm?

- A current **singleton** pregnancy.
- A **history** of spontaneous **PTB (**<34 weeks**)** in a prior pregnancy.
- A **short cervix** (<25 mm) before 24 weeks in the current pregnancy.

Cerclage

- **Recurrent PTB <35 wks, RR 0.70**
- **Composite neonatal morbidity, RR 0.60**
- **Perinatal mortality, RR 0.65**

Micronized progesterone

- **Recurrent PTB <34 wks, RR 0.67**
- **Composite neonatal morbidity, RR 0.59**
- **Perinatal mortality, RR 0.64**

Berghella et a. Cerclage for short cervix on ultrasonography in women with singleton gestation and previous preterm birth. A meta-analysis. **Obstet Gynecol** 2011;117:663-71.

Romero et al. 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. **Am J Obstet Gynecol** 2012;206:124.e1-19.

Choice of cerclage or micronized vaginal progesterone

Which treatment is better for these very high-risk women?


AJOG American Journal of Obstetrics & Gynecology

The Gray Journal www.AJOG.org Founded 1889

FEBRUARY 2012 ■ Volume 206, Number 2

EDITORIALS

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See related article, page 104

99 Making sense of preterm birth
William A. Grobman
See related articles, pages 108, 113, and 119

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C. Andrew Combs
See related article, page 124

EXPERT REVIEW

104 Achievement of the 30-minute standard in obstetrics—can it be done?
Michael P. Nageotte; Beverly Vander Wal

ON THE COVER

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FEBRUARY 2012 American Journal of Obstetrics & Gynecology 3A

Vaginal progesterone vs cervical cerclage for the prevention of preterm birth in women with a sonographic short cervix, previous preterm birth, and singleton gestation: a systematic review and indirect comparison metaanalysis

Agustin CONDE-AGUDELO, Roberto ROMERO, Kypros NICOLAIDES, Tinnakorn CHAIWORAPONGSA, John M. O'BRIEN, Elcin CETINGOZ, Eduardo DA FONSECA, George CREASY, Priya SOMA-PILLAY, Shalini FUSEY, Cetin CAM, Zarko ALFIREVIC & Sonia S. HASSAN.

	Cerclage	Progesterone
Delivery <35 wks	↓ 33%	↓ 41%
Composite morbidity	↓ 40%	↓ 70%
Perinatal mortality	↓ 35%	↓ 27%

There was NO statistical difference between Progesterone e Cerclage

Am J Obstet Gynecol. 2013 Jan;208: 1-42.

Choice of cerclage or micronized vaginal progesterone

Which treatment is better for these very high-risk women?


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	Cerclage	Progesterone
Delivery <35 wks	↓ 33%	↓ 41%

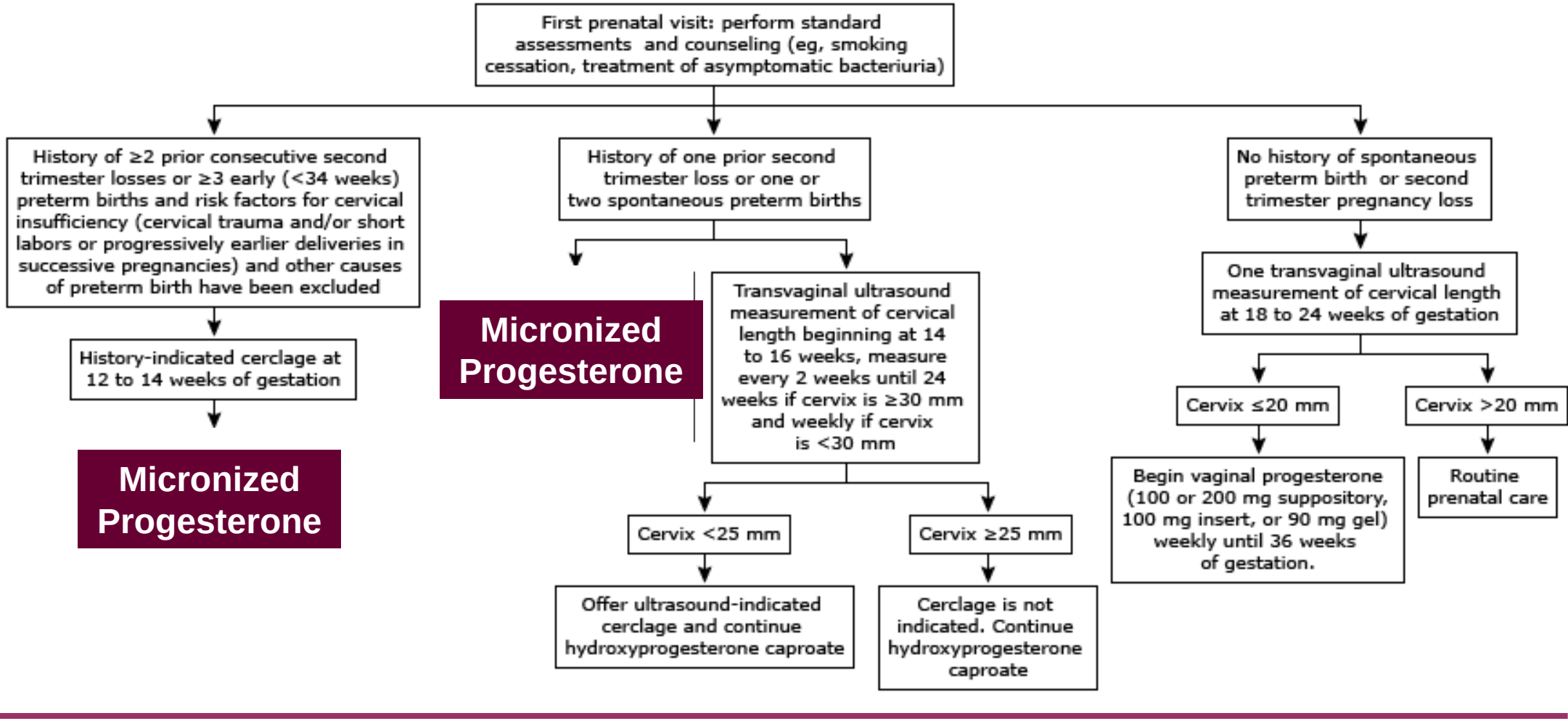
Based on state-of-the-art methodology for indirect comparisons, either vaginal progesterone or cerclage are equally efficacious in the prevention of preterm birth in women with a sonographic short cervix in the midtrimester, singleton gestation, and previous preterm birth.

The selection of the optimal treatment may depend upon adverse events, cost and patient/clinician preferences.

Am J Obstet Gynecol. 2013 Jan;208: 1-42.

Choice of cerclage or micronized vaginal progesterone

Strategy for reducing the risk of spontaneous PTB



Preterm birth prevention

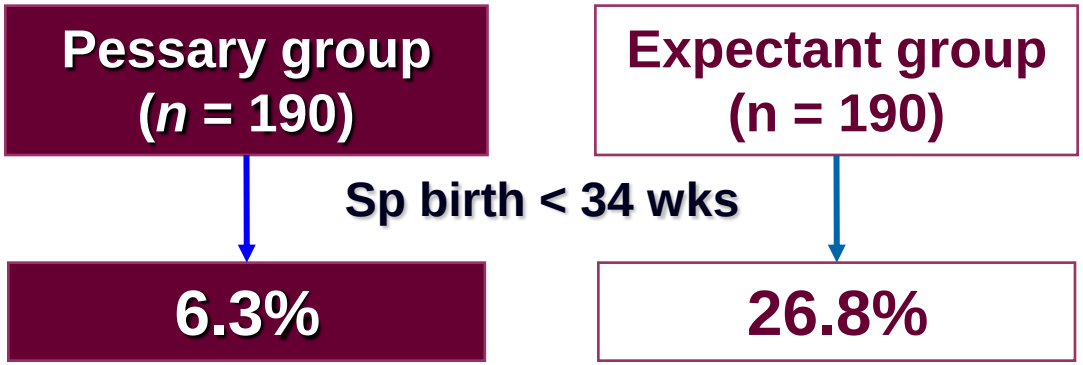
Pessary for short CxL at 18-24w

Cervical pessary in pregnant women with a short cervix (PECEP): a multicentre randomised controlled trial

Maria Goya, Laia Pratcorona, Carme Merced, Carlota Rodó, Leonor Valle, Azahar Romero, Miquel Juan, Alberto Rodríguez, Begoña Muñoz, Belén Santacruz, Juan Carlos Bello-Muñoz, Elisa Llurba, Teresa Higueras, Elena Carreras, Luis Cabero*, on behalf of the Pesario Cervical para Evitar Prematuridad (PECEP) Trial Group*

Methods The Pesario Cervical para Evitar Prematuridad (PECEP) trial was undertaken in five hospitals in Spain. Pregnant women (aged 18–43 years) with a cervical length of 25 mm or less were randomly assigned according to a computer-generated allocation sequence by use of central telephone in a 1:1 ratio to the cervical pessary or expectant management (without a cervical pessary) group. Because of the nature of the intervention, this study was not masked. The primary outcome was spontaneous delivery before 34 weeks of gestation. Analysis was by intention to treat. This study is registered with ClinicalTrials.gov, number NCT00706264.

Cervical pessary use could prevent PTB in a population of appropriately selected at risk women previously screened for CxL assessment at the midtrimester scan.

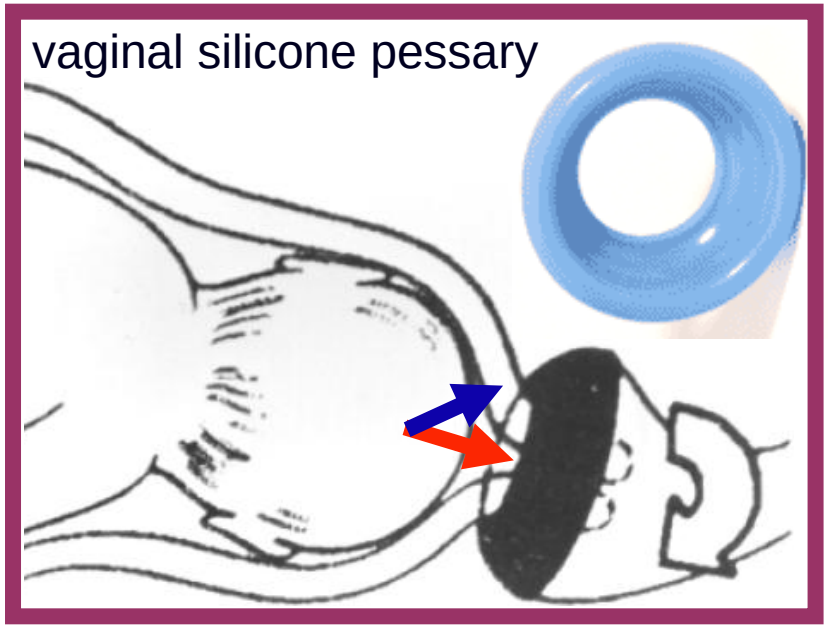


Goya *et al*, 2012

The Fetal Medicine Foundation

Preterm birth prevention

Pessary for short CxL at 18-24w



FMF study

Randomized study: Pessary vs expectant

Cervical length ≤25 mm at 20-24 wks (n=935)

Pessary group (*n* = 466)	Expectant group (*n* = 469)
Total 60 (12.9%)	Total 53 (11.3%)
Spontaneous 52 (11.2%)	Spontaneous 49 (10.5%)

Birth < 34 wks

Progesterone, cerclage and pessary

for patient with a short cervical length

Take home messages

Singleton pregnancy, short cervix, no prior PTB	**Progesterone reduces the rates of both PTB and neonatal morbidity**
	Cerclage has been shown NOT to reduce risk for PTB
	Pessary appears to have reduced risk for PTB but the results are conflicting
Twins, no prior PTB, short cervix	**Progesterone might reduce neonatal morbidity**
	Cerclage & Pessary is not recommended as it increases the rate of PTB

Thank you!