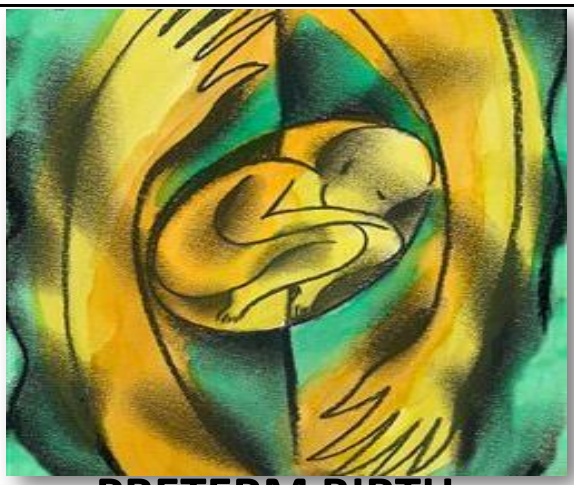

PRETERM BIRTH
PREDICTION & PREVENTION:
THE INTERNATIONAL GUIDELINES

G C DI RENZO, MD PhD FRCOG (hon) FACOG (hon) FICOG (hon)
UNIVERSITY of PERUGIA, ITALY

PREMISES

Benefits of guidelines

- **Limit variations in service delivery among providers, hospitals, and geographical regions, improving the consistency of care**
- **Reduce inappropriate care, either overuse or underuse of services**
- **To make objective the intrinsic desire of healthcare professionals to offer, and of patients to receive, the best care possible**
- **Improve the quality of clinical decisions**
- **Provide authoritative recommendations that reassure practitioners about the appropriateness of their treatment policies (legal implications)**

European Association of Perinatal Medicine
"Study Group on "Preterm birth"

Guidelines for the management of spontaneous preterm labour

G. C. Di Renzo (Italy) L. Cabero Roura (Spain)
F Facchinetti**,** C Houbinont, V Radzinsky, M Wielgos, A Mikhailov,
H Helmer, R Lamont, N Papantoniou, B Jacobsson,
A Shennan, J Stener Jorgensten, GH Visser

J Mat Fet Neon Med 2017

International Federation of Gynecology and Obstetrics
Working Group on Good Practice in Maternal-Fetal Medicine

Chair: G C Di Renzo

Expert members:
E Fonseca, Brasil
E Gratacos, Spain
S Hassan, USA
M Kurtser, Russia
F Malone, Ireland
S Nambiar, Malaysia
M Sierra, Mexico
K Nicolaides, UK
H Yang, China

Expert members ex officio:
C Fuchtner, FIGO
M Hod, EAPM
GH Visser, SM Committee
E Castelazo, CBET Committee
L Cabero, GDM WG
V Berghella, SMFM
Y Ville, ISUOG
M Hanson, DOHaD
PP Mastroiacovo, Clearinghouse
JL Simpson, March of Dimes
D Bloomer, GLOWM

FIGO

www.figo.org

Best Practice Advice

International Journal of Gynecology and Obstetrics xxx (2014) xxx–xxx

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journal homepage: www.elsevier.com/locate/ijgo

FIGO COMMITTEE REPORT

Best practice in maternal–fetal medicine☆

FIGO Working Group on Best Practice in Maternal–Fetal Medicine [1]

Gian Carlo Di Renzo (Chair), S Arulkumaran, E Fonseca, S Hassan, M Kurtzer, M Leis, N Malhotra, P Mastroiacovo, K Nicolaides, M Hod, Y Ville, L Cabero, C Hanson, J Simpson, H Yang

THE ETIOLOGICAL SCENARIO

What Initiates Labor?

- Genetic factors
- Dysfunctional energy metabolism (mother and fetus) – mitochondria, diet
- Inflammatory / Infectious etiologies
- Fetal or maternal signals that initiate labor
- Anatomic changes in uterus, cervix or placenta

Pathological Pathways

infection / inflammation

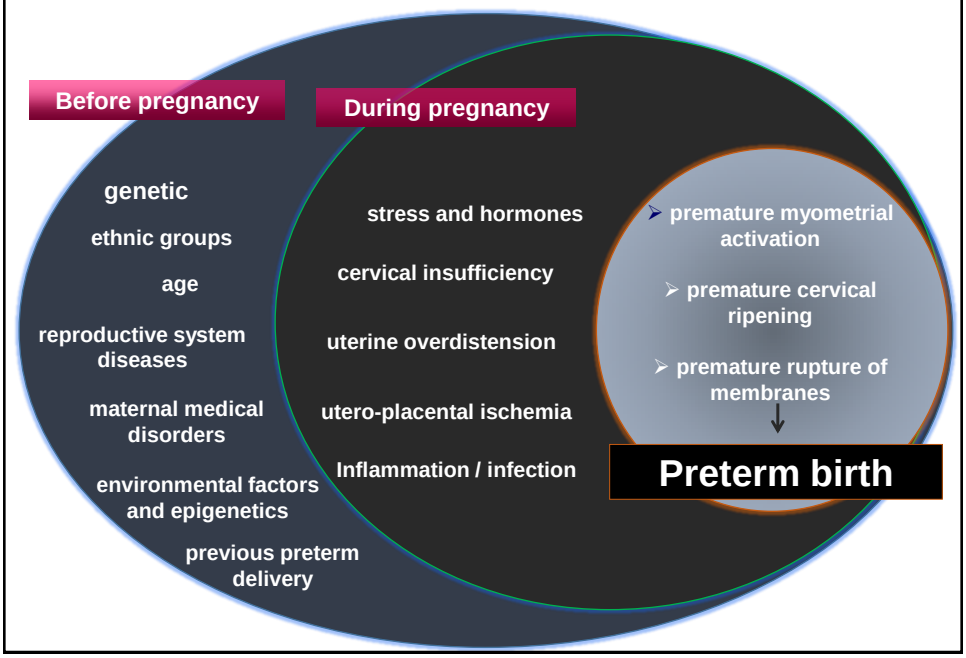
cervical factors

uteroplacental hypoxia /bleeding / thrombosis

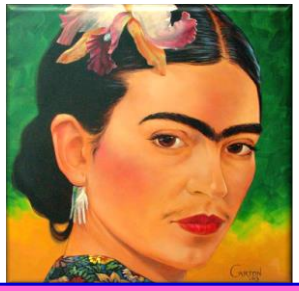
uterine overdistension

mat & fetal endocrine / paracrine activation

Preterm birth: pathogenesis



Preterm birth: reproductive system diseases



Polycystic ovary syndrome

PCOS is associated with a higher risk of developing gestational diabetes, pregnancy-induced hypertension, pre-eclampsia and **preterm birth**

Boomsma et al, Hum Reprod Update 2006

Endometriosis

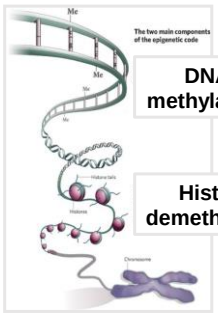
Increased risk of preterm delivery among women with endometriosis

Stephansson O et al., Hum Reprod 2010

Gravid women with adenomyosis were associated with increased risk of both spontaneous preterm delivery and PPROM

Juang CM, BJOG 2007

Preterm birth: epigenetics



DNA methylation

Histone demethylation

Biostructural modifications alter the chromatin without changing the DNA sequence

Alteration of metalloproteinases and other factors involved in PPT

Factors involved in DNA methylation

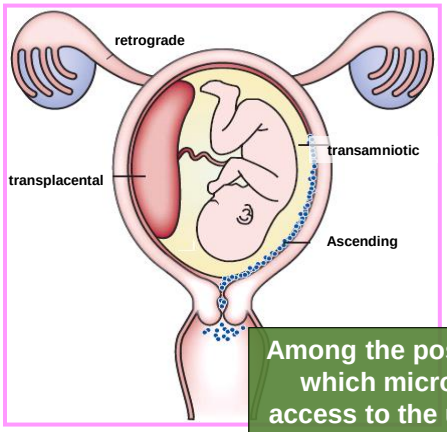
diet

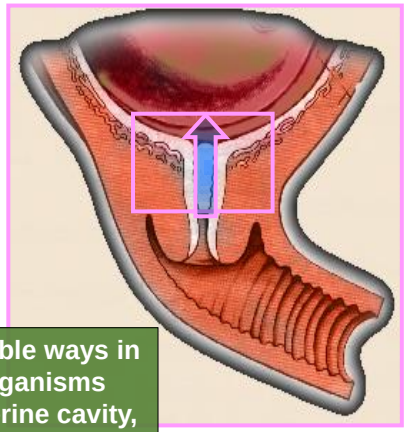
smoke

alchool

Preterm birth: local inflammation/infection

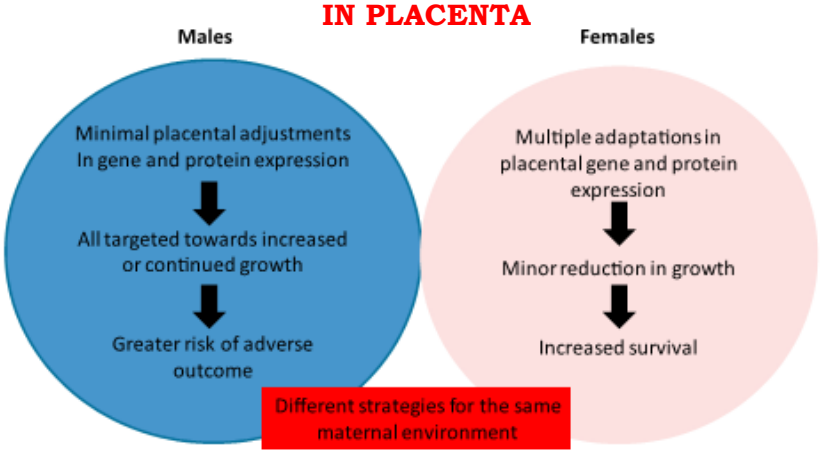
Intrauterine bacterial infection is considered to be the main infectious cause of preterm birth





Among the possible ways in which microorganisms access to the uterine cavity, the most common is the ascending one

MOLECULAR ASPECTS OF GENDER DIFFERENCES IN PLACENTA



Gender differences are observed in the placenta at multiple levels:

- gene expression
- protein expression
- epigenetic modification of DNA
- immune function
- SNPs

PREDICTION = RISK FACTORS + MARKERS

RISK FACTORS

Risk factors: individual socio-economic and behavioural	Association with sPTB	Intervention possible
Black	•	No
Young mother (<15-19 yrs)	•	Yes
Lives alone	•	No
Domestic violence	• •	Yes
Low socioeconomic status	• •	?
Stress, depression, life events	• •	Yes
Hard work	• •	Yes
No or inadequate prenatal care	• •	Yes
Smoking, cocaine	•	Yes
Alcohol, caffeine	•	
Low maternal weight before pregnancy	•	No
Weight gain in pregnancy	•	
Short	•	No

RISK FACTORS

Gynaecological and obstetric history	Association with sPTB	Intervention possible
Preterm delivery or second trimester pregnancy loss	●●●	Yes
Previous cone biopsy	●●	?
Mullerian abnormality	●	No
Parity	●	
Short interval between the two last pregnancies	●	?
Family history (genetic factors)	●	No
Fibroids		
Scarred uterus		

Preterm Birth and Family History

- Data from linked database of birth certificates of two generational cohorts
- Risk of PTD for preterm mothers was higher than those that had been born at term (OR 1.18)
- If **preterm mother** delivered <30 weeks OR increased to 2.38

Gender aspects of preterm birth

National figures from Sweden show that boys are more likely to be delivered prematurely, accounting for 55-60% of all newborns between 23 and 32 gestational weeks. Neonatal deaths in these gestational weeks are also more common among boys. In 1993, the overall 1-year mortality rate (including all gestational weeks) in Sweden was 5.4% for boys and 4.1% for girls. The difference in infant mortality (within 1 year) is most pronounced at extremely early birth (23-24 gestational weeks) being 62% for boys compared with 38% for girls. The release of catecholamines during labour is an important defence mechanism by a hypoxic fetus.

Di Renzo, Gender Med 2007

Employment-related physical activity

- **Tiring postures**
- **Industrial machines**
- **Physical exertion** (prolonged standing, heavy lifting, physically strenuous, long working hours)
- **Mentally unstimulating tasks**
- **Physically unconfortable environment**
- **Work-related psychological stress**

Psychosocial stress – recent evidences

- ♦ unmarried > married
- ♦ uncohabiting > cohabiting
- ♦ unemployed > professional
- ♦ working conditions
  - ♦ factory work
  - ♦ physically demanding work
  - ♦ psychologically demanding work
- ♦ low > high educational level
- ♦ low > high economic status
- ♦ nutritional deficits
- ♦ smoking habits
- ♦ drug abuse
- ♦ ↓ medical care

} **preterm delivery**

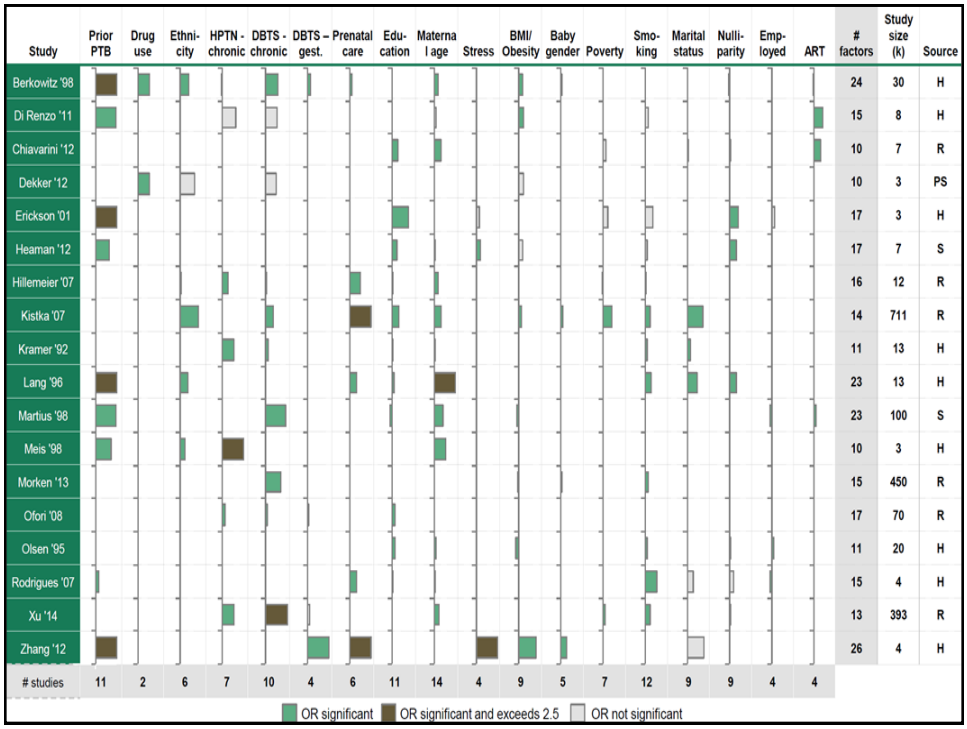
Ancel, Saurel, Di Renzo and the Europop group, Am J Epidemiol 1999

Perinatal outcome of singletons and twins after assisted conception: a systematic review of controlled studies

PRE-TERM < 37 wks

Assist.concept.	Natural	Relat Risk
613/5361 (11.4)	428/7038 (6.1)	2.04 (1.80 to 2.32)

Helmerhorst BMJ 2004



REGRESSION ANALYSIS

	Contrast	Odds Ratio Estimate	Lower 95% Confidence Limit for Odds Ratio	Upper 95% Confidence Limit for Odds Ratio	P-Value
Age (cat.)	2. Age ≥ 35 vs 1. Age < 35	1.234	0.699	2.177	0.4686
BMI	2. BMI > 25 vs 1. BMI ≤ 25	**1.662**	1.033	2.676	**0.0365**
Employment	1.Physical work vs 2.Intellectual work	**1.947**	1.182	3.207	**0.0089**
Diabetes Mellitus	1. Yes vs 2. No	2.286	0.942	5.544	0.0675
Chronic Arterial Hypertension	1. Yes vs 2. No	2.621	0.746	9.206	0.1327
Asthma	1. Yes vs 2. No	1.555	0.367	6.580	0.5489
Endocrinological diseases	1. Yes vs 2. No	1.420	0.594	3.396	0.4307
Congenital/acquired uterine malformations	1. Yes vs 2. No	2.660	0.602	11.745	0.1967
Previous abortion	1. Yes vs 2. No	**1.954**	1.162	3.285	**0.0116**
Previous PTLs	1. Yes vs 2. No	**3.412**	1.342	8.676	**0.0099**
Previous caesarean section	1. Yes vs 2. No	**2.904**	1.066	7.910	**0.0371**
Previous pregnancies <1year before current delivery	1. Yes vs 2. No	0.919	0.398	2.124	0.8440
IVF	1. Yes vs 2. No	2.065	0.263	16.223	0.4906
Cigarette smoking	1. Yes vs 2. No	1.340	0.702	2.557	0.3746
Amniocentesis/Villocentesis	1. Yes vs 2. No	1.006	0.540	1.875	0.9845

RESEARCH ARTICLE

Cross-Country Individual Participant Analysis of 4.1 Million Singleton Births in 5 Countries with Very High Human Development Index Confirms Known Associations but Provides No Biologic Explanation for 2/3 of All Preterm Births

David M. Ferrero[1], Jim Larson[1], Bo Jacobsson[4,13], Gian Carlo Di Renzo[3,10], Jane E. Norman[8], James N. Martin, Jr.[6], Mary D'Alton[7], Ernesto Castelazo[3], Chris P. Howson[2], Verena Sengpiel[4], Matteo Bottai[9], Jonathan A. Mayo[5], Gary M. Shaw[5], Ivan Verdenik[11], Nataša Tul[11], Petr Velebil[12], Sarah Cairns-Smith[1], Hamid Rushwan[3], Sabaratnam Arulkumaran[3], Jennifer L. Howse[2], Joe Leigh Simpson[2]*

PLOS ONE | DOI:10.1371/journal.pone.0162506 September 13, 2016

FIGO
INTERNATIONAL FEDERATION OF GYNECOLOGY & OBSTETRICS

Preterm Birth Individual Odds Ratio (FIGO)

	Czech Republic	New Zealand	Slovenia	Sweden
Prior Preterm	6.2	5.7	4.6	6.0
Preeclampsia	4.8	3.4	2.8	5.7
Diabetes	3.4		1.9	3.6
Hypertension			2.1	1.7
Age > 40	1.6	1.3	1.6	1.4
Age 35-40	1.4	1.2	1.2	1.2
Nulliparity	1.5	1.4	1.6	2.1
Smoking	1.3	1.5	1.3	1.3
Education, low	1.4		1.2	1.2
Male Sex	1.2	1.2	1.2	1.1

PART 1: IDENTIFICATION OF TRUE PRETERM LABOUR

Since preterm labour is not a disease,
but rather an "event", it may be more appropriate
to replace the term "diagnosis" with the term "identification" in this context

PREMISES

In most countries the identification of preterm labour is based only on clinical subjective data

Excessive:
Hospitalisation
Tocolisis
Corticosteroids

Costs increase

Increase of unuseful and potentially harmful interventions

Prediction of PTB in Symptomatic Women
Biochemical and Biophysical Methods Overview

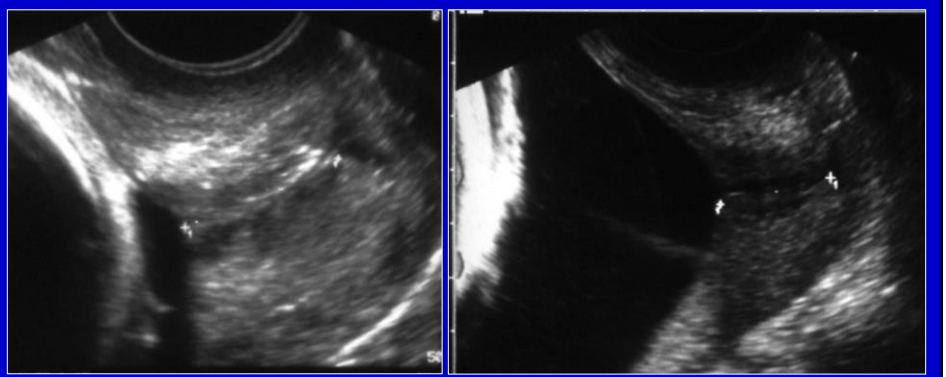
Cervix or vagina
Bacterial vaginosis
IL-6
IL-8
IL1β
fetal fibronectin (fFN) ←
ferritin
α-fetoprotein
Placental alpha microglobulin-1 (PAMG-1) ←
human chorionic gonadotropin
prolactin
C-terminal propeptide of procollagen
pIGFBP-1
Cervical length (TVUS) ←
EMG
Maternal BMI
Previous History

Amniotic fluid
calgranulins
defensins
IL-6
IL-8

Saliva
oestriol

Serum
G-CSF
ferritin
defensins
calgranulins
IGF BP-1 fragment
relaxin
Vitamins and micronutrients
CRP, CD163

Prediction of PTB in Symptomatic Women
Abnormal Cervix / Cervical Shortening

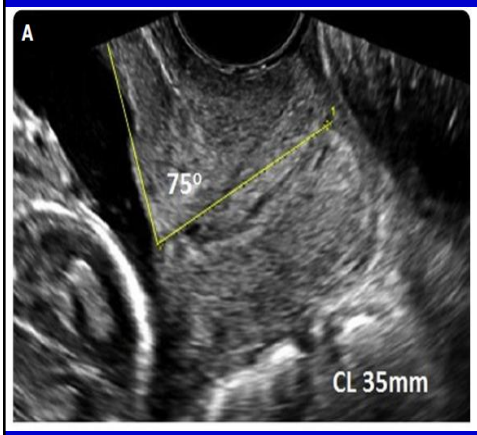


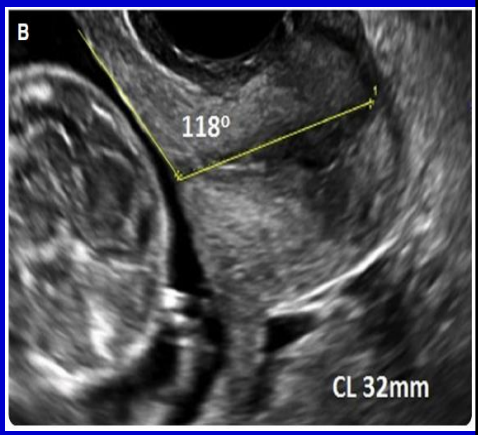
Prediction of PTB in Symptomatic Women
Cervical Shortening

- CL >2.5 cm → **Unlikely true labor**

- CL <1.5 cm → **Likely true labor**

UTERO-CERVICAL ANGLE





ACUTE **OBTUSE**

Uterocervical angle: a novel ultrasound screening tool to predict spontaneous preterm birth

Test characteristics of uterocervical angle and cervical length for prediction of spontaneous preterm birth <34 weeks

Parameters	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Positive likelihood ratio	Negative likelihood ratio
UCA >105 degrees	81% (0.66–0.91)	65% (0.64–0.65)	10% (0.08–0.11)	99% (0.98–0.99)	2.3	0.29
CL ≤25 mm	19% (0.093–0.31)	98% (0.97–0.98)	29% (0.14–0.47)	96% (0.96–0.97)	8.3	0.83
P value	<.001	<.001	<.001	<.001		
UCA >105 degrees *or* CL ≤25 mm	63% (0.47–0.76)	65% (0.64–0.65)	7% (0.057–0.093)	97% (0.96–0.98)	1.8	0.57
UCA >105 degrees *and* CL ≤25 mm	23% (0.13–0.33)	98% (0.98–0.99)	48% (0.27–0.68)	97% (0.96–0.97)	19	0.78

(95% Confidence Interval).

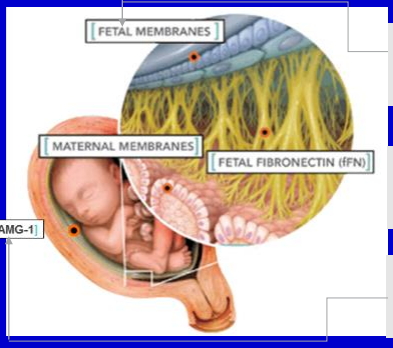
CL, cervical length; *UCA*, uterocervical angle.

Dziadosz et al. Uterocervical angle screen. Am J Obstet Gynecol 2016.

Dziadosz M. AJOG 2016

WHICH BIOMARKER IS MOST USEFUL?

Does the location of the biomarker matter?



Fetal fibronectin (fFN) is a "glue-like" protein that holds the developing baby in the womb.[1]

Phosporylated Insulin Growth Factor Receptor Binding Protein-1 (phIGFBP-1) is is found in high concentrations in the choriodecidual interface.[2]

Placental Alpha Microglobulin-1 (PAMG-1) is a placental protein that is released into the amniotic cavity.[3]

As a result, the release of fFN and phIGFBP-1 into the vaginal cavity can be caused by digital examinations or manipulation of the cervix. Because PAMG-1 is not known to be found in the extracellular matrix, it may not be as easily released due to such manipulations.

Prediction of PTB in Symptomatic Women
Cervical Length (<25 mm) via Transvaginal Ultrasound

	US Cervicometry test (<25mm)
Total patients	96
Patients with preterm birth (≤34 wks)	18
Patients with term birth	78
TP	16/18
FN	2/18
TN	40/78
FP	38/78
Sensitivity (%)	88,9
Specificity (%)	51,3
PPV (%)	29,6
NPV (%)	95,2
Efficiency (%)	58,3

DI RENZO et al. Min Gin 2011

EVALUATION OF QUANTITATIVE fFN TEST IN PREGNANT WOMEN WITH SIGNS AND SYMPTOMS OF PRETERM LABOR

< 34 weeks' gestation

within 14 days from testing

Di Renzo et al JPM, 2016

METHOD

PTB RISK CATEGORIES BASED ON fFN CONCENTRATIONS

Risk categories	fFN concentrations
1 - Low	< 10 ng/ml
2 - Lower Middle	10 - 49 ng/ml
3- Middle	50 - 199 ng/ml
4 - Upper Middle	200 - 499 ng/ml
5 - High	≥ 500 ng/ml

Results of fFN quantification were grouped into 5 categories of PTB risks

RESULTS

DISTRIBUTION OF SPONTANEOUS BIRTH WITHIN fFN PREDEFINED PTB RISK CATEGORIES, BEFORE AND AFTER 34 WEEKS' GESTATION

		1-Low (<10 ng/ml)	2-Lower Middle (10-49 ng/ml)	3-Middle (50-199 ng/ml)	4-Upper Middle (200-499 ng/ml)	5-High (≥ 500 ng/ml)
Patients n		n (%)	n (%)	n (%)	n (%)	n (%)
delivery < 34 weeks' gestation	12	1 (8.3%)	1 (8.3%)	2 (16.7%)	3 (25.0%)	5 (41.7%)
delivery > 34 weeks' gestation	114	47 (41.2%)	31 (27.2%)	24 (21.1%)	11 (9.6%)	1 (0.9%)

- 83.4% of women who delivered before 34 weeks of gestation was within categories 3-Middle, 4–Upper Middle and 5–High (fFN ≥ 50 ng/ml), (P <0.001).
- 68.4% of women who delivered after 34 weeks of gestation was within categories 1-Low, and 2-Lower Middle (fFN ≤ 50 ng/ml), (P <0.001).

Di Renzo et al JPM, 2016

RESULTS

PREDICTION OF PTB AT < 34 WEEKS' GESTATION

	1-Low (<10 ng/ml)	2-Lower Middle (10-49 ng/ml)	3-Middle (50-199 ng/ml)	4-Upper Middle (200-499 ng/ml)	5-High (≥ 500 ng/ml)
Negative Predictive Value, %	/	97.9	97.5	96.2	94.2
95% C.I.	/	93.9-102	94.1-100.9	92.6-99.9	90-98.4
Positive Predictive Value, %	9.5	14.1	21.7	40	83.3
95% C.I.	4.4-14.6	6.4-21.8	9.8-33.7	18.5-61.5	53.5-113.2

High NPV > 90%.

PPV increases with increasing fFN concentrations.

Di Renzo et al JPM, 2016

Prediction of PTB in Symptomatic Women
Initial Evaluation of PartoSure (PAMG-1)

- The study population consisted of 101 consecutively recruited pregnant women with singleton pregnancies between 20+0 and 36+6 weeks of gestation with symptoms of preterm labor, clinically intact amniotic membranes, and minimal cervical dilatation (≤3 cm).
- A positive PartoSure test in patients presenting with symptoms of preterm labor, intact membranes, and minimal cervical dilatation (≤3 cm) indicated spontaneous preterm delivery will occur within 7 days with a high degree of accuracy. A negative result indicated that spontaneous preterm delivery within 14 days is highly unlikely.

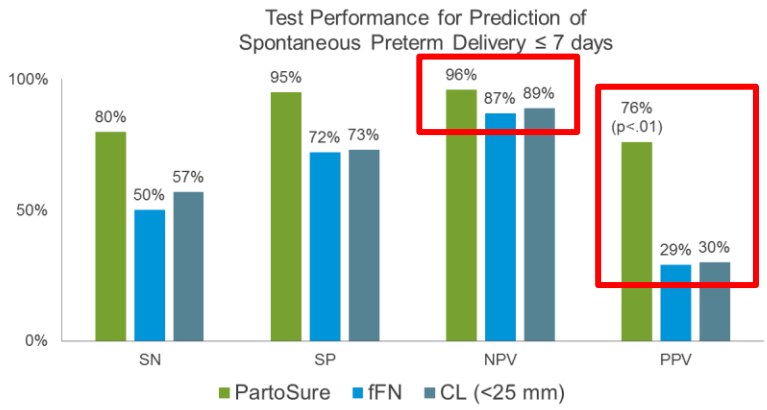
Table 2 PartoSure™ time-to-delivery (TTD) test performance metrics.

TTD (days)	NPV (95% CI)[a]	PPV (95% CI)[a]	SN (95% CI)[a]	SP (95% CI)[a]
≤7	97.4% (91.0%–99.7%)	78.3% (56.3%–92.5%)	90.0% (68.3%–98.8%)	93.8% (86.2%–98.0%)
≤14	93.6% (85.7%–97.9%)	87.0% (66.4%–97.2%)	80.0% (59.3%–93.2%)	96.1% (88.9%–99.2%)

[a]The Clopper-Pearson procedure computed 95% confidence intervals (CI). NPV=negative predictive value, PPV=positive predictive value, SN=sensitivity, SP=specificity.

Nikolova T, Bayev O, Nikolova N, Di Renzo GC. Evaluation of a novel placental alpha microglobulin-1 (PAMG-1) test to predict spontaneous preterm delivery. J Perinat Med. 2014 Jul;42(4):473-7.

PartoSure vs Fetal Fibronectin vs Cervical Length

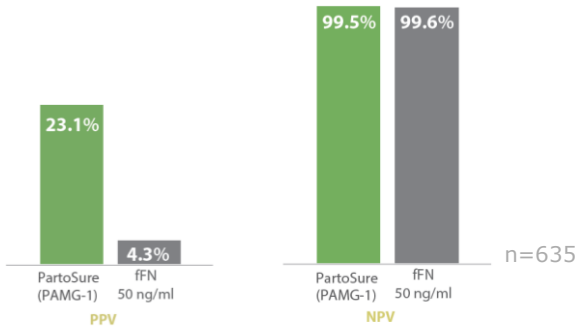


"PartoSure is the single most accurate test when compared to fFN and CL for prediction of imminent spontaneous delivery in patients presenting with signs, symptoms, or complaints suggestive of PTL."

Nikolova T, Bayev O, Nikolova N, Di Renzo GC. Comparison of a novel test for placental alpha microglobulin-1 with fetal fibronectin and cervical length measurement for the prediction of imminent spontaneous preterm delivery in patients with threatened preterm labor. J Perinat Med. 2015 Jan 6. [Epub ahead of print]

LARGE US MULTI-CENTER TRIAL COMPARING PAMG-1 to fFN

Prediction of spontaneous preterm delivery within 7 days among singletons with threatened preterm labor[1] (sub-group analysis)



"In women with symptoms of preterm labor, the PPV for preterm delivery ≤7 or ≤14 days is 2-to-5-fold higher for the PAMG-1 test compared to the fFN test"[1]

1. Wing et al. Society of Reproductive Investigation (2016), (abstract).

PAMG-1 has Superior Performance Across Studies

Prediction of preterm delivery within 7 days in patients with threatened preterm labour

Study	Year	N	PPV (%)	NPV (%)
Nikolova et al.[1]	2014	101	78%	97%
Nikolova et al.[2]	2015	203	76%	96%
Lotfi et al. [3]	2015	150	75%	98%
Heverhagen et al.[4]	2015	64	100%	94%
Bolotskih et al.[5]	2015	49	75%	100%
Van Holsbeke et al.[6]	2015	87	75%	96%
Lou et al.[7]	2016	65	100%	100%

1. Nikolova et al. J Perinat Med. 2014 Jul;42(4):473-7.
2. Nikolova et al. J Perinat Med. 2015 Jul;43(4):395-402.
3. Lotfi et al. J. Perinat. Med. 2015; 43 (S1): 250.
4. Heverhagen et al. J. Perinat. Med. 2015; 43(S1): 240.
5. Bolotskih et al. Scientific and Practical Journal of Obs and Gyn Russian Fed. 2015; 2:94-98.
6. Van Holsbeke et al. Ultrasound in Obstetrics & Gynecology 2016; 48 (S1): 84.
7. Lou et al. BJOG An International Journal of Obstetrics and Gynaecology. 2016; 123(S2): 89.

NEW Prediction of PTB in Symptomatic Women

Stratification of cervical length measurement in the prediction of imminent spontaneous delivery in women symptomatic of preterm labor

	CL < 15 mm	CL 15- 30 mm	CL > 30 mm
% of the total population	6% (3/49)	85% (42/49)	8% (4/49)
PartoSure (PAMG-1) +	100%	2% (1/42)	0
PartoSure (PAMG-1) -	0	98% (41/42)	100%
Delivery within 7 days	67% (2/3)	2% (1/42)	0
PartoSure positive in women, delivered within 7 days	100%	100%	N/A

For patients with 15 mm < CL > 30 mm:

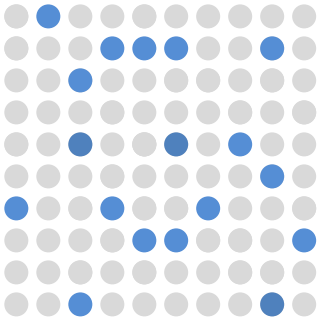
- **100% pts with a (+) PartoSure (PAMG-1) test delivered within 7 days**
- **100% pts with a (-) PartoSure (PAMG-1) test did not deliver within 7 days**

Bolotskikh V.M. 2014

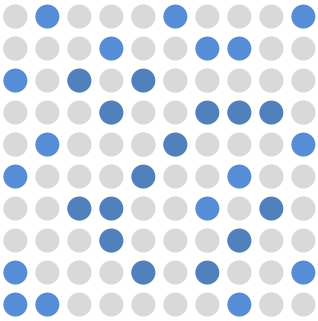
PAMG-1 vs fFN – Reduction in Unnecessary Admissions

For every 100 women presenting with signs and symptoms of preterm labor:

PartoSure produced ~18 Positives



fFN produced ~32 Positives



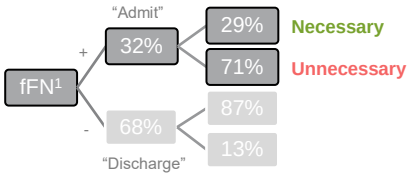
False positive diagnoses (FPR): ~4

False positive diagnoses (FPR): ~23

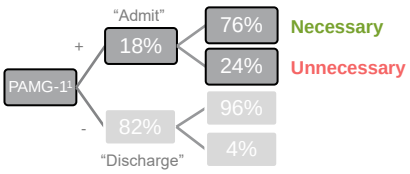
1. Nikolova et al. J Perinat Med. 2015 Jul;43(4):395-402.

Unnecessary Admissions

Fetal Fibronectin (fFN)



PartoSure™



Key Points

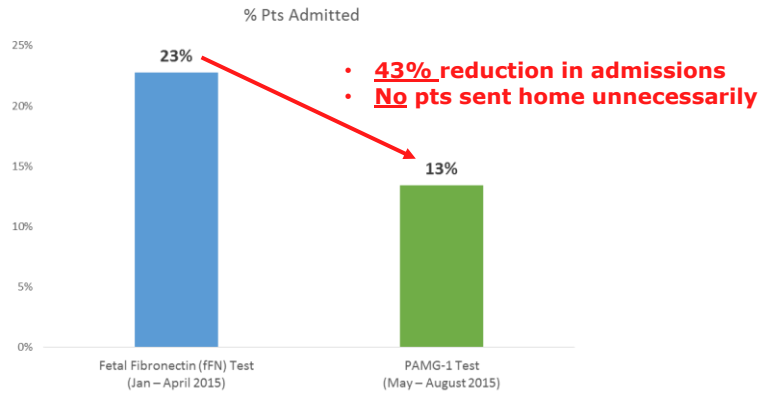
- Average cost of an unnecessary admission estimated at **$20,372 USD** [2]
- PartoSure may reduce unnecessary admissions by up to **80%**[1]

"That the PartoSure test was found to be statistically superior to fFN and CL with respect to SP and PPV (P < 0.01) provides evidence toward being able to significantly enhance current practice to ultimately reduce the unnecessary administration of potentially harmful therapeutics to patients, as well as reduce the economic burden associated with unnecessary hospital admissions."

(1) Di Renzo et al. JPM 2015. (2) Lucovnik et al. AJOG 2013

NEW! Study Data (Medway Hospital, NHS Trust, UK)

A retrospective analysis of fetal-fibronectin (fFN) related admissions vs. PartoSure (PAMG-1) related admissions in a UK birthing center



Test	Dates Audited	# Pts Observed	PPV (%)	Patients Admitted	% Patients Admitted
Fetal Fibronectin (fFN) Test	Jan – April 2015	79	8%	18	23%
PAMG-1 Test	May – August 2015	119	50%	16	13%

Brume D, Harris K, Basu M, & Griffin S. A retrospective cost-benefit analysis: real-world application of the PartoSure test for the prediction of imminent spontaneous delivery in a UK birthing center. Medway Hospital, NHS Trust, UK, 2015. (unpublished)

MAIN POINTS

- **Bearing in mind the excellent NEGATIVE predictive value of such tests (PartoSure/PAMG-1; Ffn is negative and cervical length by ultrasound is > 2.5 cm) we recommend that tocolytic therapy and steroid prophylaxis should be withheld**

- **Bearing in mind the excellent POSITIVE predictive value of PartoSure (PAMG-1) test we recommend that tocolytic therapy and steroid prophylaxis should be administered**

MAIN POINTS

Benefits to the hospital

- Reduces unnecessary admissions and transfer to NICU
- Cost savings to the hospital
- Reduction in administering medical management
- Availability of beds

Benefits to the patient

- Unnecessary medical intervention
- Piece of mind
- Uninterrupted travel plans
- Employment
- Less burden on spouse and family

CONCLUSIONS PART 1

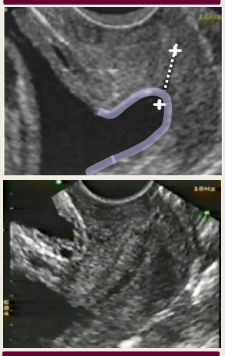
TAKE HOME MESSAGES

- **Proper identification of patients in true preterm labour is essential**
- **Take into consideration new risk factors (age, PMA, fetal sex, psychosocial stress, previous C section etc)**
- **PAMG-1/ quantitative fFn and cervical US measurement are best tests for identifying the true preterm labouring patient or excluding preterm labour**

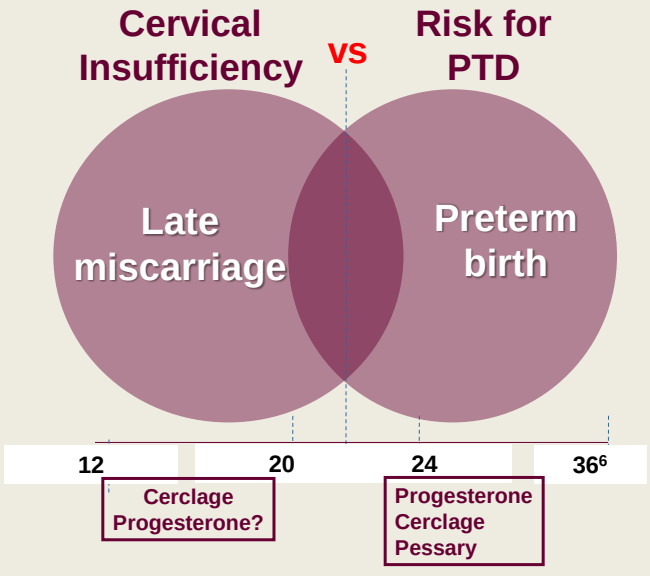
PART 2: PREVENTION

PREVENTION:
IN WHICH CASES?

Short cervix



≤25 mm



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Strategy in the prevention

Identification of risk factors

1-No prior history of PTB
2-Prior history of early PTB
3-Twins in the current pregnancy

Short cervix at scan

WHICH TOOLS?

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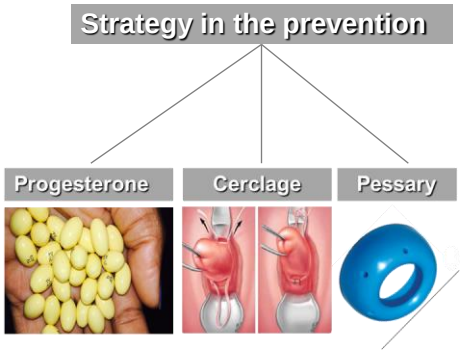


Progesterone: Maintains pregnancy

1 Modulates maternal immune response

Druckmann R, et al. J Steroid Biochem Mol Biol. 2000
Szekeres-Bartho J, et al. Int Immunopharmacol. 2001
Di Renzo GC, et al. Gynec Endocrinol. 2012

2 Suppresses inflammatory response

Schwartz N, et al. Am J Obstet Gynecol. 2009

3 Reduces uterine contractility

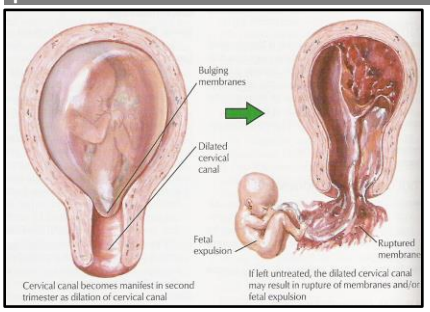
Fanchin R, et al. Hum Reprod. 2000
Perusquía M, et al. Life Sci. 2001
Chanrachakul B, et al. Am J Obstet Gynecol. 2005

4 Improves utero-placental circulation

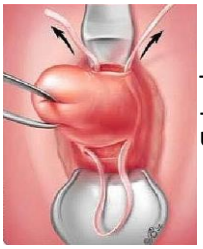
Liu J,et al. Mol Hum Reprod. 2007
Czajkowski K, et al. Fertil Steril. 2007

Cervical Insufficiency

Classically, the term "cervical insufficiency" was used to describe a disorder in which **painless cervical dilation** led to **recurrent second trimester pregnancy losses/ very early preterm birth**.



Treatment Cerclage

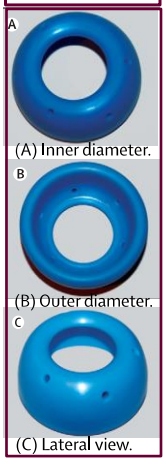


- **History-indicated**
- **US surveillance and US indicated cerclage**

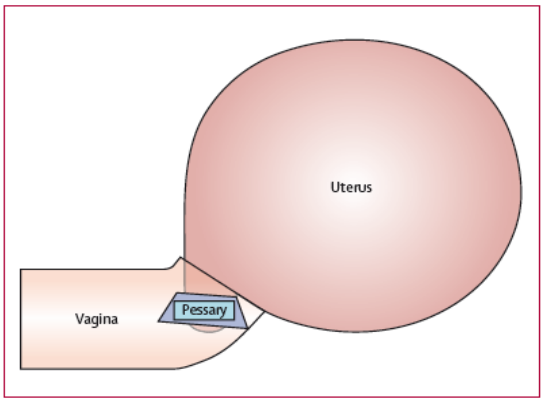
Suhag et al. **Obstet Gynecol**. 2015; 126:962-8.
To et al. **UOG**. 2002;19:475-7.

What is the rationale for pessary?

Pessary

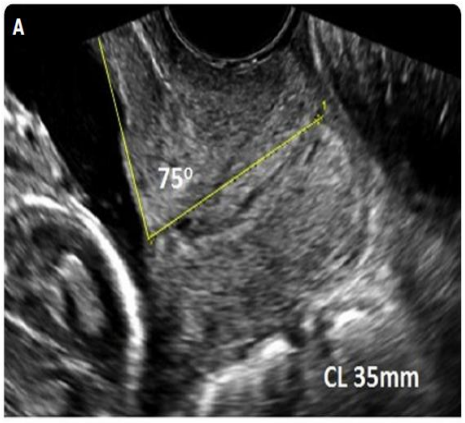


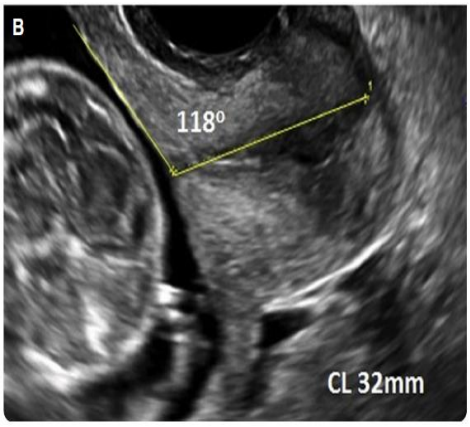
The smaller diameter of the pessary is fitted around the cervix and the larger diameter faces the pelvic floor, thus rotating the cervix to the posterior vaginal wall and correcting the cervical angle.



The effect relies on its mechanical ability to bend the cervix backwards, slightly elongating it and also changing the utero-cervical angle.

UTERO-CERVICAL ANGLE





ACUTE **OBTUSE**

Women with
previous preterm birth

Main results

36 RCTs included **8523 women**
12515 infants

➢ **Progesterone vs placebo for women with a past history of spontaneous PTB**

Perinatal mortality	6 studies	N =1453	RR 0.50	[95% CI 0.33 to 0.75)]
Preterm birth < 34 weeks	5 studies	N = 602	**RR 0.31**	[95% CI 0.14 to 0.69)]
Preterm birth < 37 weeks	10 studies	N =1750	**RR 0.55**	[95% CI 0.42 to 0.74)]
Infant birth weight < 2500 g	4 studies	N = 692	RR 0.58	[95% CI 0.42 to 0.79)]
Use of assisted ventilation	3 studies	N = 633	RR 0.40	[95% CI 0.18 to 0.90)]
Necrotizing enterocolitis	3 studies	N =1170	RR 0.30	[95% CI 0.10 to 0.89)]
Neonatal death	6 studies	N =1453	RR 0.45	[95% CI 0.27 to 0.76)]
Admission to NICU	3 studies	N = 389	RR 0.24	[95% CI 0.14 to 0.40)]
				Statistically significant reduction
	1 study	N= 148	**MD** 4.47**	[95% CI 2.15 to 6.79)].
				Statistically significant increase in pregnancy prolongation weeks

No differential effects in terms of route of administration, time of therapy initiation and dose of progesterone for majority of outcomes examined.

Vaginal progesterone for the prevention of recurrent preterm birth

- **More effective than intramuscular progestogen therapy**
- **Less adverse effects**

Maher MA, Abdelaziz A, Ellaithy M, Bazeed MF. Acta Obstet Gynecol Scand. 2013;92:215-22.

PREVENTION OF PB: PESSARY

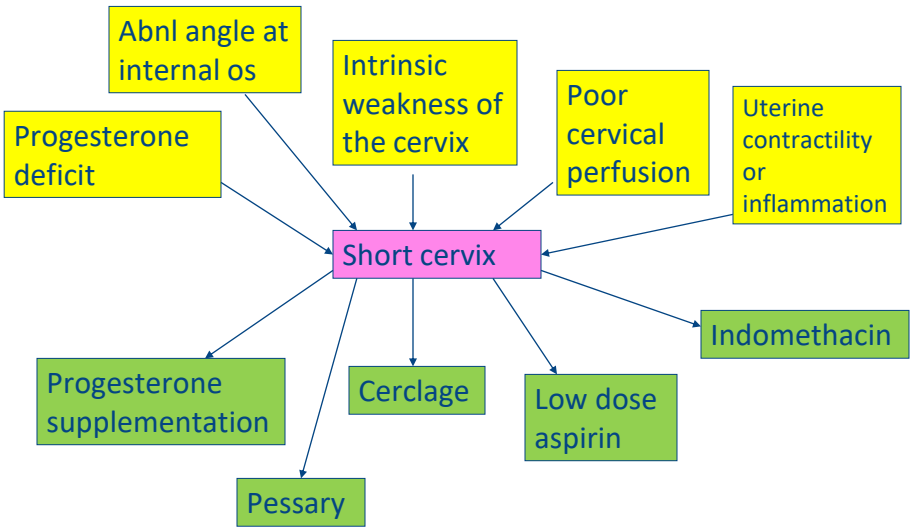
Preterm birth	Singleton pregnancies (n=24)			Twin pregnancies (n=46)		
	Pessary (n=12)	No pessary (n=12)	Significance* (n=23)	Pessary (n=23)	No pessary	Significance*
<28 weeks (n,%)	0	2 (17%)	ns	0	1 (4%)	ns
<32 weeks (n,%)	0	3 (25%)	ns	0	7 (30%)	p<0.001
<36 weeks (n,%)	0	6 (50%)	p<0.001	8 (35%)	12 (52%)	ns
Interval (days,mean/ range) between TVS before treatment or controls and delivery	99 (70–134)	67 (2–130)	p=0.0184	85 (43–129)	67 (21–100)	p=0.001
Gestational age (weeks+days) at delivery (mean/ range)	38 (36+6–41)	33+4 (26–38)	p=0.02	35+6 (33–37+4)	33+2 (24+4–37+2)	p=0.02

*Test: Mann-Whitney

Arabin B. J Perinat Med 2003; 31: 122-133.

Women with a short cervix

Heterogeneity of causative processes for short cervix



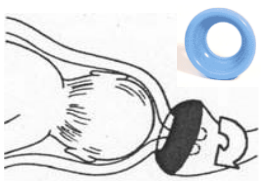
PREVENTION OF PB: PESSARY

REVIEW

- Newcomer, 2000
- Arabin, 2003
- Acharya, 2006
- Dharan, 2009
- Trojnar, 2010
- Cochrane, 2010

TRIAL

- PECEP Trial



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Challenges in preterm birth prevention and management

Pessary: short cervix

Articles

Cervical pessary in pregnant women with a short cervix (PECEP): an open-label randomised controlled trial (N=385)

385 pregnant with a cervix ≤ 25 mm were randomly assigned to pessary (n=192) or expectant management (n=193). The primary outcome was spontaneous PTD <34 wks.

Pessary group (*n* = 190)	Expectant group (n = 190)
Sp birth < 34 wks	
6.3%	26.8%

Pessary prevent PTB in a population screened for CxL assessment at the midtrimester scan.

Goya *et al*, **Lancet**. 2012; 379:1790.

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Challenges in preterm birth prevention and management

Pessary: short cervix

The Fetal Medicine Foundation

Cervix ≤25 mm at 20-24 wks (N=935)

Pessary group (*n* = 466)	Expectant group (*n* = 469)
Sp birth < 34 wks	
Total 52 (11.2%)	Total 49 (10.5%)

	FMF	Goya
Maternal age in yrs, median	29.8	29.9
BMI in Kg/m², median	23.8	24.7
Non White, %	34.1	42.9
Smoking, %	13.8	19.7
Nullip, %	51.5	50.0
Parous with previous birth <34w, %	12.7	10.8
Cervical length in mm, median	20.0	19.0
Cervical length ≤5 mm, %	3.3	2.6

In singleton pregnancies with a short cervical length, insertion of cervical pessary at 20-24 wks:

Does not reduce the rate of preterm birth

Does not reduce perinatal death or neonatal morbidity

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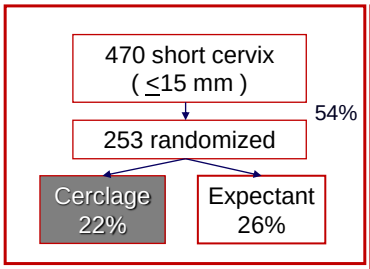
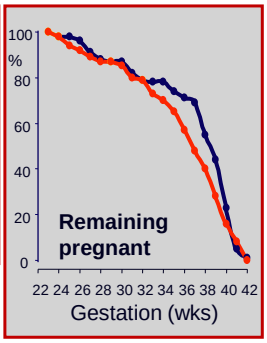
Cerclage for short cervix

Cervical cerclage for prevention of preterm delivery in women with short cervix: randomised controlled trial





The insertion of a Shirodkar suture in women with a short cervix DOES NOT REDUCE the risk of early preterm delivery.

To et al 2004

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Progesterone is given prophylactically to prevent preterm birth among women

- Meis et al, 2003. *N Engl J Med*
- Da Fonseca et al, 2003. *Am J Obstet Gynecol*
- Fonseca et al, 2007. *N Engl J Med*
- O'brien et al, 2007. *Ultrasound Obstet Gynecol*
- DeFranco et al, 2007. *Ultrasound Obstet Gynecol*
- Rai et al, 2009. *Int J Gynecol Obstet*
- Mahji et al, 2009. *J Obstet Gynecol*
- Cetingoz et al, 2009. *Arch Gynecol Obstet*
- Hassan et al, 2011. *Ultrasound Obstet Gynecol*
- Rode et al, 2011. *Ultrasound Obstet Gynecol*
- Maher MA et al, 2013. *Acta Obstet Gynecol Scand*
- Norman J et al, *2016. The Lancet*

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Progesterone for short cervix

Micronized P4
(200mg/night),
24-34 wks

Cervix ≤15 mm at 20-24 wks (N=250)

Sp birth < 33 wks

Total 22/125 (17.6%)	Total 38/125 (30.4%)

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

Cervix 10-20 mm at 20-24 wks (N=458)

Sp birth < 33 wks

Total 21/235 (8.9%)	Total 36/223 (16.1%)

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

P4 Gel
(90mg/night),
24-36 wks

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

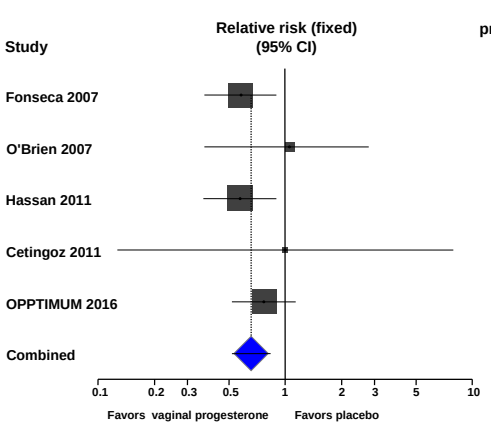
Short cervical length

Vaginal progesterone in women with an aymptomatic short cervix in the midtrimester ultrasound decrease PTD (N=775)

Outcome	No. of trials	No. of events/total no. Vaginal progesterone	Placebo	Pooled RR (95% CI)	I^2 (%)	NNT (95% CI)
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	–

…and this reduction has been translated to improvement of morbidity and mortality in these babies

METANALYSIS: SHORT CERVIX & VAGINAL NATURAL PROGESTERONE



Study	Vaginal progesterone n/N	Placebo n/N	Weight (%)	Relative risk (95% CI)
Fonseca 2007	23/114	39/112	30.4	0.58 (0.37-0.90)
O'Brien 2007	4/12	6/19	3.6	1.06 (0.37-2.98)
Hassan 2011	26/235	43/223	34.1	0.57 (0.37-0.90)
Cetingoz 2011	1/4	1/4	0.8	1.00 (0.09-11.03)
OPPTIMUM 2016	33/133	38/118	31.1	0.77 (0.52-1.14)
Combined	87/498	127/476	100.0	0.66 (0.52-0.83)

Test for heterogeneity: $I^2 = 0\%$
Test for overall effect: Z = 3.44, P = 0.0006

OBSTETRICS WORLD PREMATURITY DAY

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

William A. Grobman, MD, MBA; Elizabeth A. Thom, PhD; Catherine Y. Spong, MD; Jay D. Iams, MD; George R. Saade, MD; Brian M. Mercer, MD; Alan T. N. Tita, MD; Dwight J. Rouse, MD; Yoram Sorokin, MD; Ronald J. Wapner, MD; Kenneth J. Leveno, MD; Sean Blackwell, MD; M. Sean Esplin, MD; Jorge E. Tolosa, MD, MSCE; John M. Thorp Jr, MD; Steve N. Caritis, MD; J. Peter Van Dorsten, MD; for the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Maternal-Fetal Medicine Units (MFMU) Network

CONCLUSION: Weekly IM 17-OHPc does not reduce the frequency of PTB in nulliparous women with a short cervix < 30 mm

Grobman WA et al. Am J Obstet Gynecol. 2012 Nov;207(5):390.e1-8

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Strategy in the prevention

In singleton pregnancies with a short cervical length:

- **Progesterone reduce the rate of PTB.**
- **Progesterone reduce perinatal death and neonatal morbidity.**

~~**• Cerclage DOES NOT reduce the rate of PTB**~~

THE COCHRANE COLLABORATION®

- **Pessary: the review including only one RCT concluded there is a NEED for more RCT in different settings.**

Abdel-Aleem H. et al. ***Cochrane Database Syst Rev***. 2013; 5:CD007873. doi: 10.1002/14651858.CD007873.pub3.

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Prior PTB and short cervix

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 progesterone can reduce the risk of PTB in a specific group of women at very high risk, those with all 3 of the following:

- **Current singleton pregnancy *plus***
- **Prior spontaneous PTB (**<34 weeks**) *plus***
- **Short cervix** (<25 mm) ≤24 wks in the current pregnancy.

Untreated, such women have A risk of recurrent **PTB**:

<28 wks: 15-20%.
<32 wks: 25-30%.

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Prior PTB and short cervix

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

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

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

Conde-Agudelo, eta al. AJOG. 2013 Jan;208: 1-42.

Women with twin pregnancy

Twins and short cervix

THE COCHRANE COLLABORATION®

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

5 RCT; N:128 pregnant women with multiple gestation (twins 122, triplets 6)

Aim: To assess whether the use of a cervical cerclage in multiple gestations, improves obstetrical and perinatal outcomes.

Rafael T, Berghella V, Alfirevic Z. *Cochrane* 2014

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

THE COCHRANE COLLABORATION®

5 RCT; N:128 pregnant women with multiple gestation (twins 122, triplets 6)

Aim: To assess whether the use of a cervical cerclage in multiple gestations, improves obstetrical and perinatal outcomes.

AUTHORS' CONCLUSIONS: 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 T, Berghella V, Alfirevic Z. *Cochrane* 2014

Twins and 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

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,[r] IM Usta,[r] 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 RCT
- 3,768 women
- 7,536 babies

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.

Strategy in the prevention

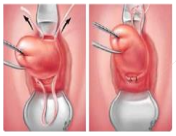
In twin pregnancies with a short cervical length:

Progesterone

- Vaginal progesterone may be effective in the reduction of adverse perinatal outcome.
- RCT is needed to confirm this hypothesis.

Schuit et al. **BJOG**. 2015; 122:27-37.

Cerclage



- **Does not** reduce the rate of PTB in unselected twin cohorts.
- **Should not** be used in the prevention of PTB in twin pregnancy.

Rafael T, Berghella V, Alfirevic Z. ***Cochrane*** 2014

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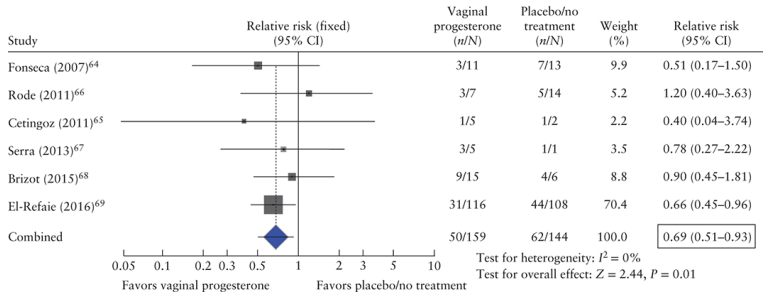
Effect of vaginal progesterone
on preterm birth in twin gestation



CONCLUSION: Administration of vaginal P4 to asymptomatic women with a twin gestation and a sonographic short cervix in the mid-trimester reduces the risk of preterm birth occurring at < 30 to < 35 gestational weeks, neonatal mortality and some measures of neonatal morbidity, without any demonstrable deleterious effects on childhood neurodevelopment.

Romero R et al. *Ultrasound Obstet Gynecol 2017;* **49(3)***: 303-14*

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Twins and short cervix

OBSTETRICS

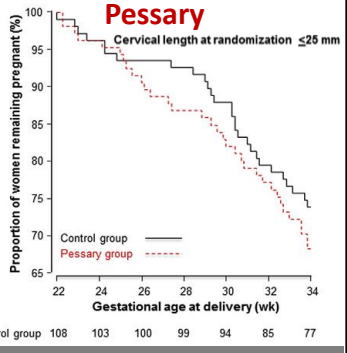
Cervical pessary placement for prevention of preterm birth in unselected twin pregnancies: a randomized controlled trial

Pessary group (*n* = 588)	Expectant group (*n* = 589)
Sp birth < 34 wks	
Total 80 (13.6%)	Total 76 (12.9%)

Cervix ≤25 mm at 20-24 wks (N=214)

Pessary group	Expectant group
Sp birth < 34 wks	
Total 33/106 (31.1%)	Total 28/108 (25.9%)

Nicolaides et al. **AJOG**. 2015; dx.doi.org/10.1016/j.ajog.2015.08.051



In patients with twin pregnancy, pessary DOES NOT reduce the rate of PTB

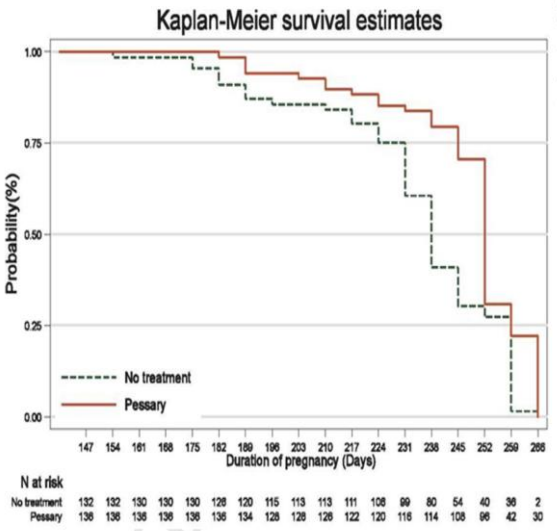
Reports of Major Impact ajog.org

Cervical pessary to prevent preterm birth in women with twin gestation and sonographic short cervix: a multicenter randomized controlled trial (PECEP-Twins)

Maria Goya, MD, PhD; Maria de la Calle, MD; Laia Pratcorona, MD; Carme Merced, MD; Carlota Rodó, MD; Begoña Muñoz, MD, PhD; Miquel Juan, MD; Ariadna Serrano, MD; Elisa Llurba, MD, PhD; Teresa Higueras, MD, PhD; Elena Carreras, MD, PhD; Luis Cabero, MD, PhD, on behalf of the PECEP-Twins Trial Group

Am J Obstet Gynecol 2016

FIGURE 2



print & web 4C/FPO

Kaplan-Meier plot of probability of continued pregnancy without delivery among patients receiving cervical pessary compared with expectant management group.

Goya et al. RCT of cervical pessary in twin gestations with short cervix. Am J Obstet Gynecol 2015.

Conclusions and implications

- **Cervical pessary could have potential value as a treatment for high risk SPB patient, could be beneficial in pregnant women with a short cervix carrying twins regardless of their obstetric history, and may reduce the risk of SPB in nulliparous women.**
- **The pessary is an affordable, safe, and a reliable alternative for preventing SPB in a population of appropriately selected at-risk twin pregnancies previously screened by CL assessment at the mid-trimester scan.**

CONCLUSIONS PART 2

Strategy in the prevention

FIGO COMMITTEE REPORT

Best practice in maternal–fetal medicine☆

FIGO Working Group on Best Practice in Maternal–Fetal Medicine [1]

FIGO recommendations regarding the use of TVS CxL and vaginal progesterone for the prevention of PTB

Population	All pregnant women with a singleton gestation.
Recommendation	Tranvaginal sonographic cervical length measurement at 19–23 6/7 weeks for all pregnant patients. Vaginal progesterone administered to women with a cervical length ≤25 mm. **200 mg vaginal soft capsules or 90 mg vaginal gel of micronized progesterone can be used for treatment.**
Time using progesterone	Treatment should begin at the time of the diagnosis of a short cervix until 36 6/7 weeks, labor, or rupture of membranes.
Risk assessment	Transvaginal sonographic cervical length on all patients regardless of obstetrical history.
Other recommendation	When a transvaginal ultrasound is not available other devices may be used as a screening tool to measure objectively and reliably the cervical length.

International Journal of Gynecology and Obstetrics xxx (2014) xxx–xxx

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European Association of Perinatal Medicine

"Study Group on "Preterm birth"

Guidelines for the management of spontaneous preterm labour

G. C. Di Renzo (Italy)

L. Cabero Roura (Spain)

F Facchinetti, C Houbinont, V Radzinsky, M Wielgos, A Mikhailov, H Helmer, R Lamont, N Papantoniou, B Jacobsson, A Shennan, J Stener Jorgensten, GH Visser

J Mat Fet Neon Med 2016

Comparison of Strategies used for Screening in Medicine

Test	Number needed to screen
Pap Smear for Cervical Cancer[1]	1140
Mammography more than 50 years[1]	543
Mammography between 40 and 49 years[1]	3125
Prostate-specific Antigen for Prostate Cancer[2]	1254
Ultrasound cervical length to prevent one case of PTB < 33 weeks (<25 mm)[3]	357
Ultrasound cervical length to prevent one case of neonatal morbidity/mortality (<25 mm)[3]	218

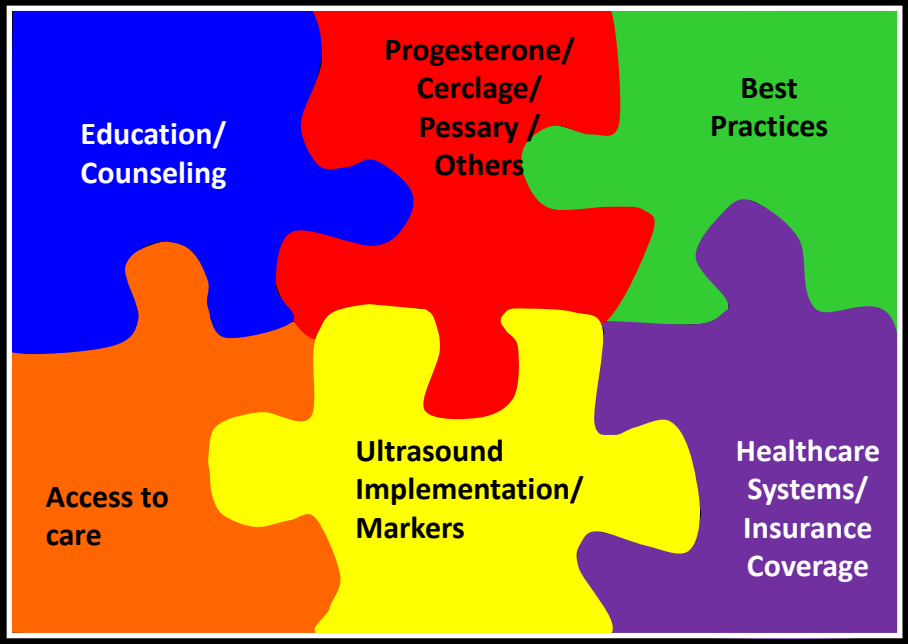
Romero R, Conde A, Number needed to screen

1. *Gates TJ, et al. Am Fam Physician 2001;63:513-22*
2. *Loeb S, et al. J Clin Oncol 29:464-467*
3. *Romero R, Conde-Agudelo A, unpublished.*

Comparison with other Interventions in Perinatal Medicine/Obstetrics

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)
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



Preterm Birth Risk Factors Odds Ratios

18 reports on 20 factors

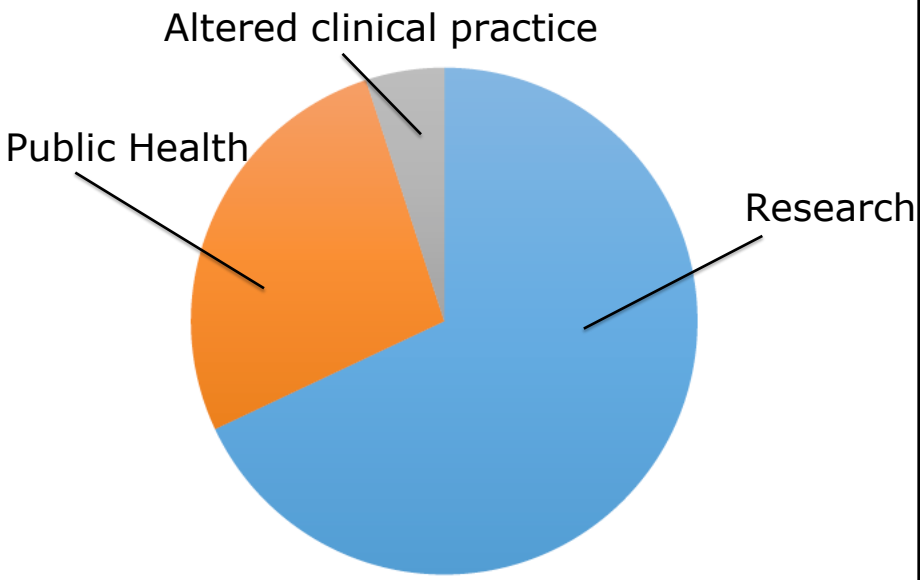
- Prior PTB
- Hypertension / Preeclampsia
- Diabetes

High Individual Risk
Lower Population Prevalence

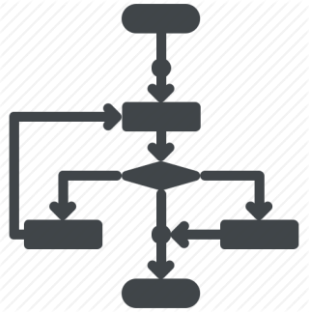
- Maternal Age
- BMI
- Prenatal Care
- Education/Poverty
- Fetal male sex

Low Individual Risk
Higher Population Prevalence

Intervention areas



It is easier to find a guideline in a drawer and a protocol/algorithm in the wall !

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gracias
thank you
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tack
どうも
tak
obrigado
Баярлалаа
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choukrane
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