Prevention and Preterm of Labour

Prof. Koum Kanal

Content

1. Scientific background and pathophysiology
2. Efficacy in prevention of PTB
3. Prevention in high risk women: recent publications
4. Management and Case study

MENACE OF PRETERM DELIVERY –

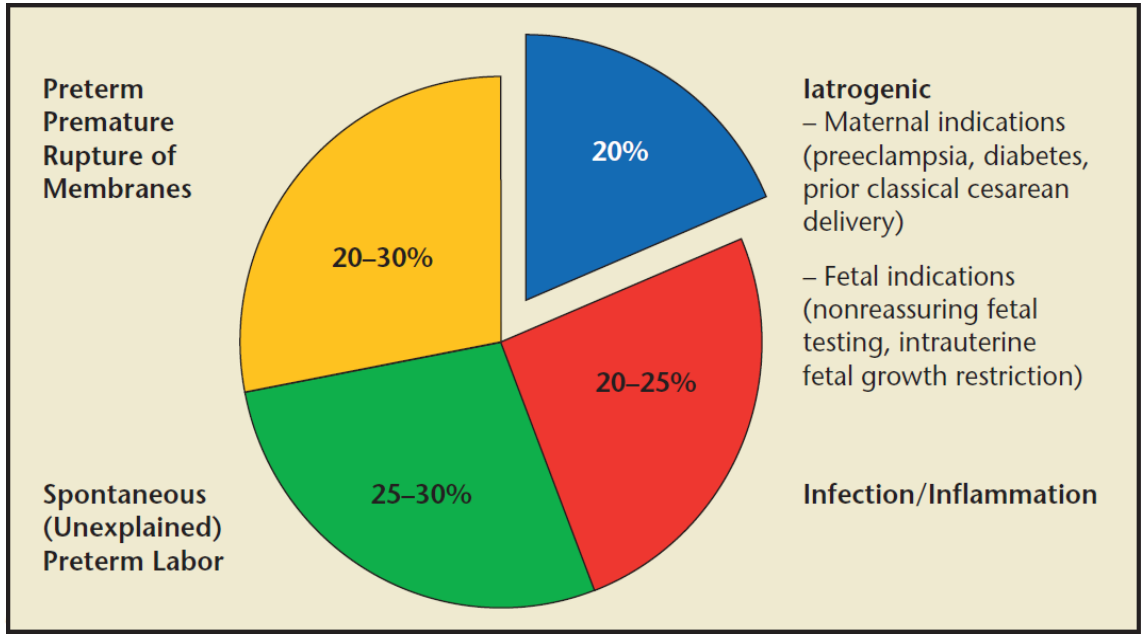
DEFINITIONS

- **Preterm delivery/birth:**
  live birth or stillbirth that takes place after at least 20 but before 37 completed weeks of gestational age[1]

- **Spontaneous preterm birth:**
  preterm births due to spontaneous preterm labour and premature preterm rupture of membranes[2]

- **Preterm labour:**
  regular contractions accompanied by cervical changes at less then 37 weeks of gestation[2]

Obstetric precursors of preterm birth[3]



1. **Zegers-Hochschild F et al.** *Fertil Steril 2009;* **92***: 1520-4*
2. **Goldenberg RL et al.** *Lancet 2008;* **371***: 75-84*
3. **Norwitz ER et al**. *Rev Obstet Gynecol. 2011;***4(2)***:60-72*

MENACE OF PRETERM DELIVERY –

CHALLENGE

– To diagnose patient at risk of preterm labor

– To use scientifically based strategies specifically for the management of this condition

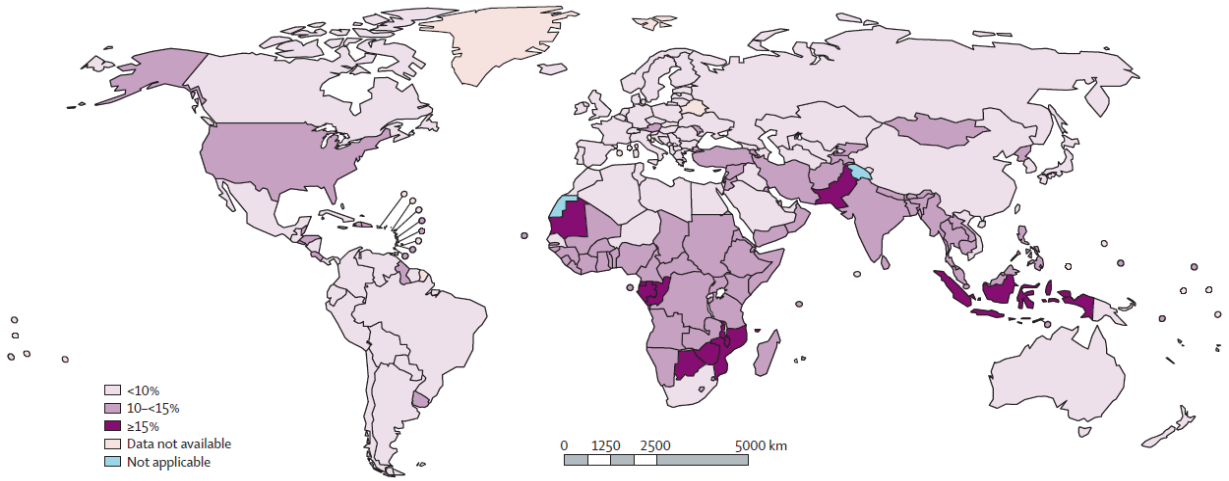
– Prevention rather than treatment

EPIDEMIOLOGY OF PTB

Morbidity/Mortality

Preterm birth is a major determinant of neonatal mortality (70%), neonatal and long term morbidity (>50%) and mortality results in enormous physical, psychological and economic costs (5 - 6 billion $ annually in US). Challis et al. *Obstet Gynecol Survey 2000; **55(10)**: 650-660*

Estimated Preterm birth rate (%) by country/sub region and worldwide in 2010



	Rank for number of preterm births	Number of preterm births (% of global total)	Preterm birth rate (% of livebirths)
India	1	3 519 118 (23·6%)	13·0%
China	2	1 172 259 (7·8%)	7·1%
Nigeria	3	773 597 (5·2%)	12·2%
Pakistan	4	748 142 (5·0%)	15·8%
Indonesia	5	675 744 (4·5%)	15·5%
USA	6	517 443 (3·5%)	12·0%
Bangladesh	7	424 144 (2·8%)	14·0%
Philippines	8	348 871 (2·3%)	14·9%
Democratic Republic of Congo	9	341 421 (2·3%)	11·9%
Brazil	10	279 256 (1·9%)	9·2%
Total	..	8·8 million (59%)	..

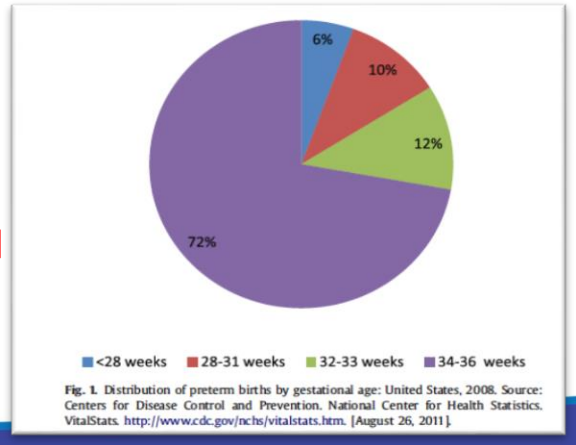


Fig. 1. Distribution of preterm births by gestational age: United States, 2008. Source: Centers for Disease Control and Prevention. National Center for Health Statistics. VitalStats. http://www.cdc.gov/nchs/vitalstats.htm. [August 26, 2011].

Estimated preterm birth rates (%) and total number of livebirths for 2010, by Millennium Development Goal region

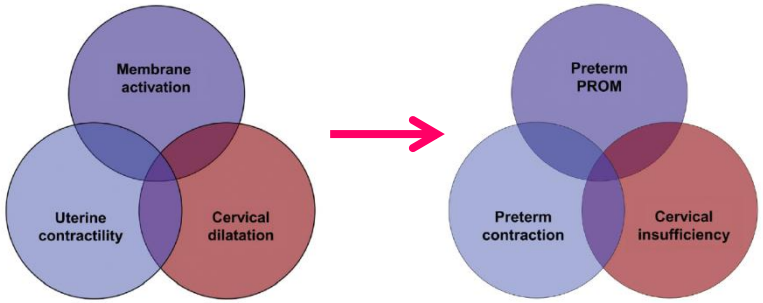
Developed regions	14 300 000	8·6% (8·3–9·4)
Eastern Asia	17 400 000	7·2% (5·4–9·0)
Latin America	10 200 000	8·4% (6·8–11·4)
Northern Africa	3 543 100	7·3% (4·8–10·9)
Oceania	263 200	7·4% (4·5–15·6)
Southeastern Asia	11 000 000	13·6% (9·3–18·6)
Southern Asia	38 700 000	13·3% (10·1–16·8)
Sub-Saharan Africa	32 100 000	12·3% (9·5–15·8)
Western Asia	4 855 300	10·1% (6·9–14·3)
Caribbean	682 800	11·2% (7·8–20·8)
Caucasus and Central Asia	1 643 000	9·2% (6·0–13·0)
Total worldwide	135 000 000	11·1% (9·1–13·4)

Blencowe H et al. *Lancet 2012; **379**: 2162-72*

MENACE OF PRETERM DELIVERY

BACKGROUND

- **Prevalence of preterm births :**
  - 7,2 to 13,6% of live births



Romero R et al. Sem Fet Neonat Med 2014; 19: 15e26

- **Consequences :**
  - Leading cause of neonatal morbidity (>50%) and mortality (70%) in developed countries
  - 60 – 80 % of the deaths of infants without congenital abnormality
  - 1/3 of all health care spending on infants

Goldenberg R et al. *Lancet 2008; **371**: 75-84.*

PRETERM DELIVERY – A PUBLIC HEALTH CONCERN

Clinical interest

Possible consequences of a preterm delivery are numerous and multiple:

- hyaline membrane disease
- **bronchopulmonary dysplasia**
- persistent ductus arteriosus
- **necrotic enterocolitis (NEC)**
- intraventricular bleeding
- apnea
- neurological handicap
- retrolental fibroplasias
- **mortality.**

Medical, psychological and economic burdens of preterm births are very important! (5 - 6 billion $ annually in US)

Bailit et al. *Am J Obstet Gynecol 2007; **196**: 219.e1-7.*
Armstrong J. *Am J Obstet Gynecol 2007; **196**: 194-195*

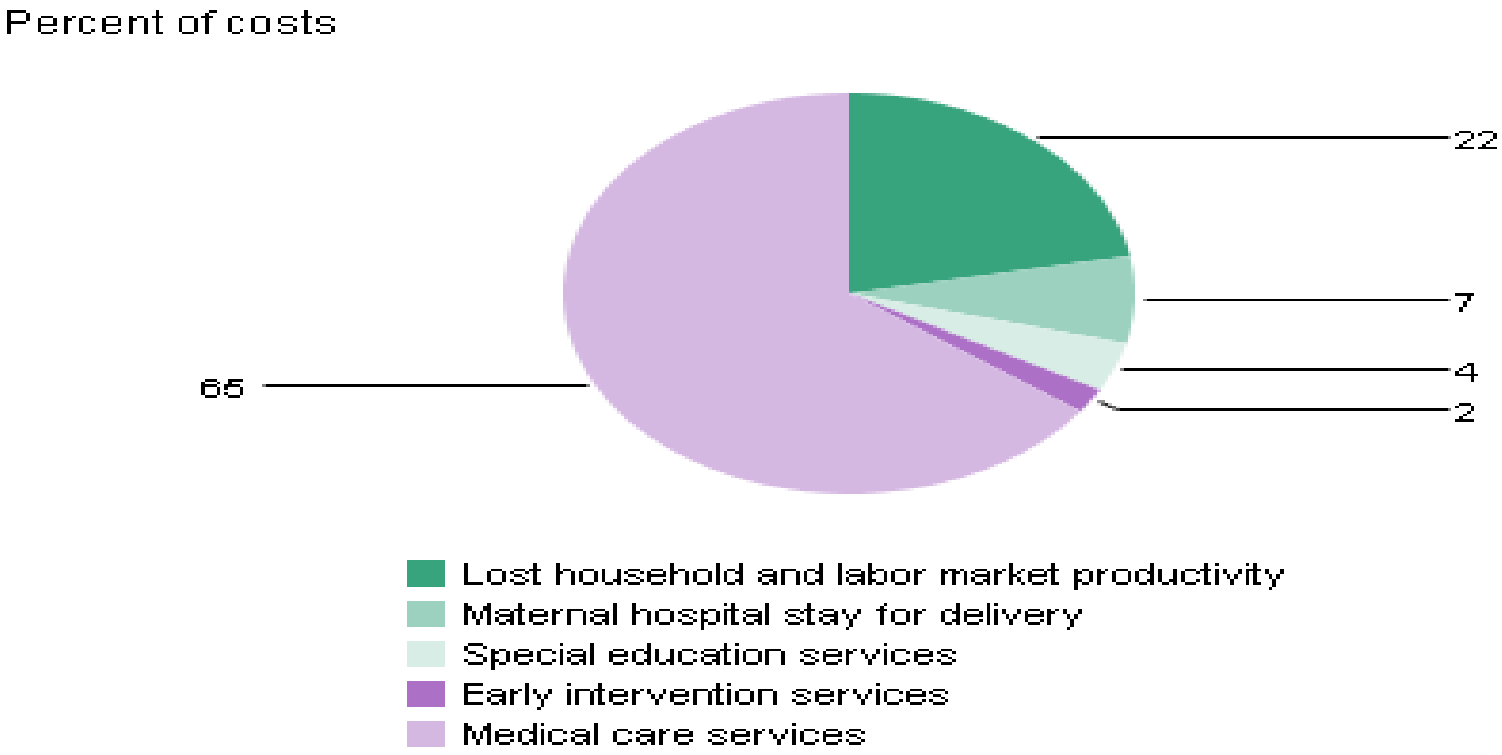
A major Public Health concern…

- $33,200: direct cost of medical care for a preterm infant (US) (85% of this cost being incurred during the first year of life)

- $51,600: Cost per infant
  - when maternal medical care costs ($3,800),
  - early intervention costs ($1,203),
  - special education costs ($2,150), and
  - lost household productivity costs ($11,215) are considered.

Armstrong et al. *N Engl J Med 2011; doi 10.1056/NEJMp1102796.*

Distribution of $26 billion societal economic costs of preterm birth



Source: Institute of Medicine. 2007. Preterm Birth: Causes, Consequences, and Prevention. National Academy Press, Washington, D.C. Published and unpublished analyses.
Retrieved February 16, 2012, from www.marchofdimes.com/peristats.

INSTITUTE OF MEDICINE REPORT (IOM*)

« Babies born before 32 weeks have the greatest risk for death and poor health outcomes, however, infants born between 32 and 36 weeks, which make up the greatest number of preterm births, are still at higher risk for health and developmental problems compared to those infants born full term »

* IOM *Institute Of Medicine, July 2006 Report page 72*

MENACE OF PRETERM DELIVERY –

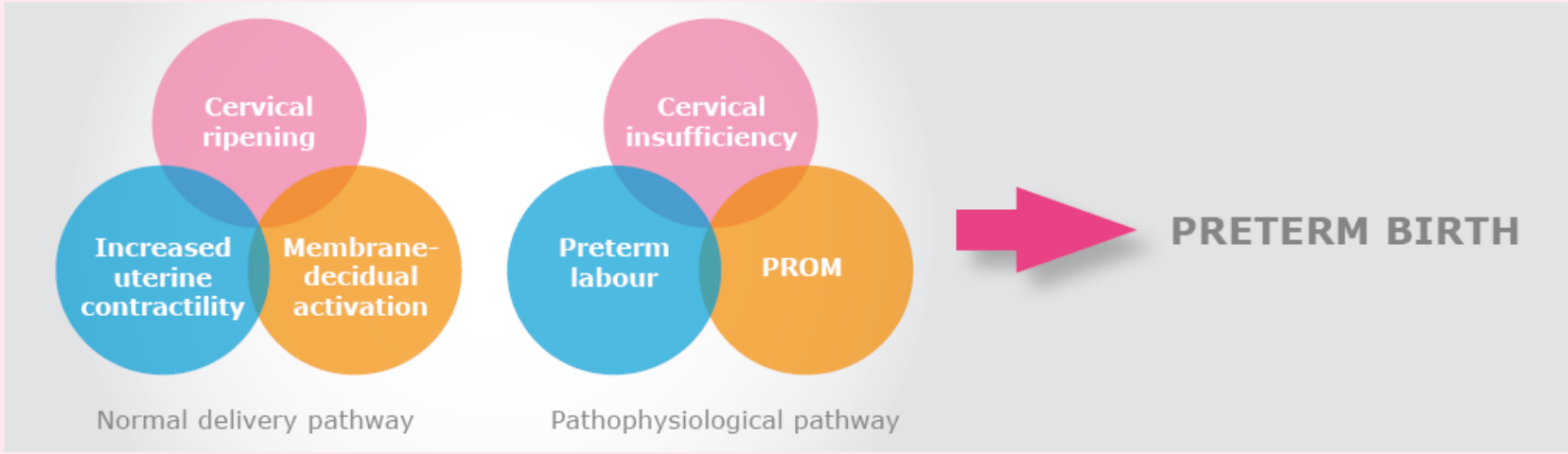
BACKGROUND

Pathophysiology/Etiology[1]

Spontaneous preterm birth is a pathophysiologically heterogeneous syndrome initiated by:

- excessive myometrial and fetal membrane overdistention
- decidual hemorrhage
- precocious fetal endocrine activation
- intrauterine infection or inflammation

Pathway to preterm birth



Adapted from Romero[2]

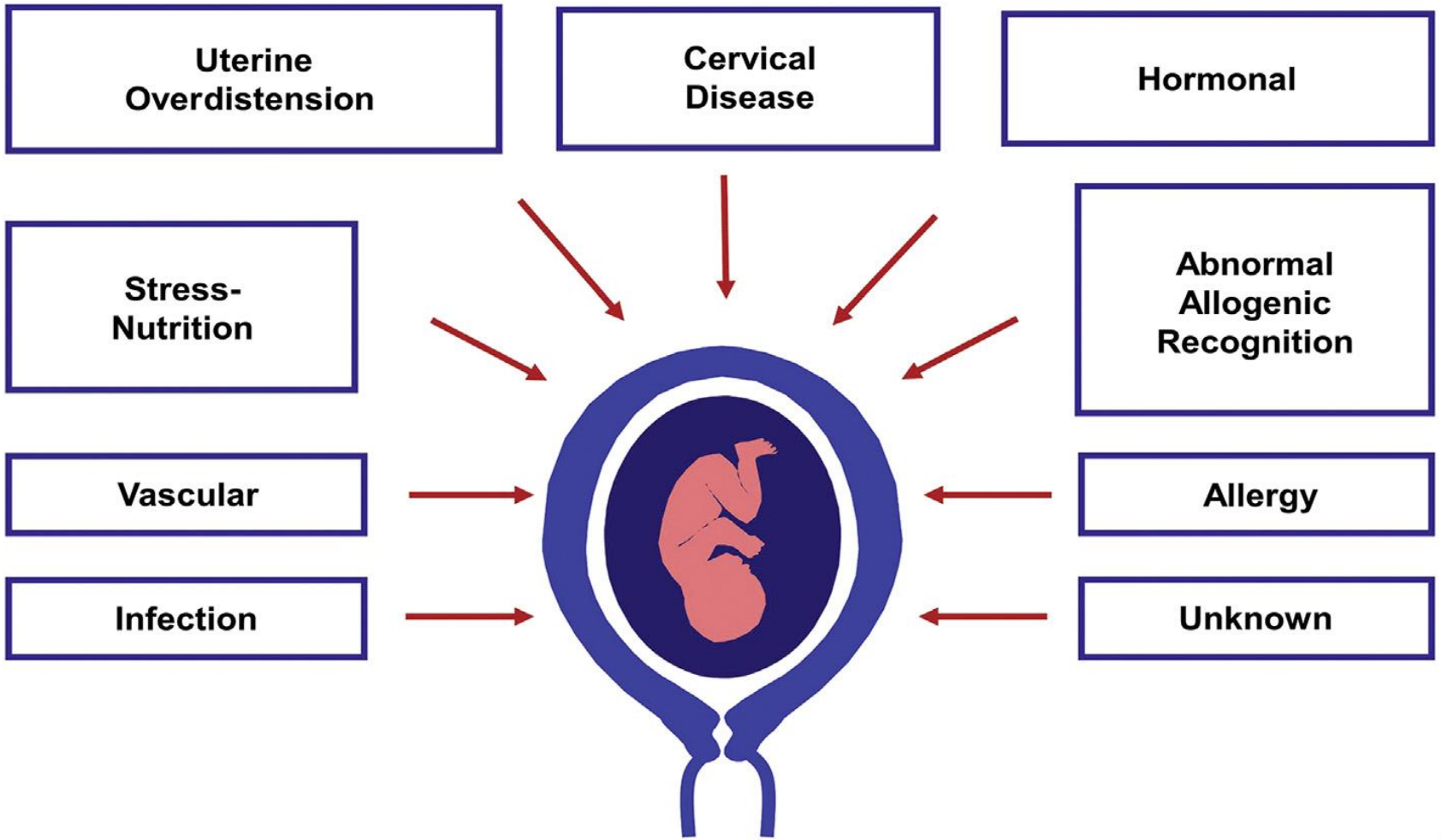
Simhan et al. *N Engl J med 2007:* ***357****: 477-487*
Romero et al. *Ultrasound Obstet Gynecol 2007;* ***30****: 675 - 686*

MENACE OF PRETERM DELIVERY –
BACKGROUND

- 30 – 40% association with underlying infective process
- 40 – 50%: idiopathic !
- other
  - genetic,
  - nutritional,
  - behavioral and other
  - environmental factors

Goldenberg R et al. Lancet 2008; **371**: 75-84.

Pathological processes implicated in the preterm parturition syndrome



Romero R, Espinoza J, Mazor M, Chaiworapongsa T. The preterm parturition syndrome. In: Critchely H, Bennett P, Thornton S, editors. Preterm Birth. London: RCOG Press; 2004..

Risk factors and susceptible women

Risk factors for spontaneous preterm birth

Pregnancy history:

- **previous history of PTD**
- recurrent intra-uterine infections

Present pregnancy characteristics:

- **multiple gestations**
- **intra-uterine infections** (asymptomatic)
- **short cervix**
- vaginal bleeding
- social and psychological stress
- adverse behaviours (tobacco use,…)

Maternal risk factors:

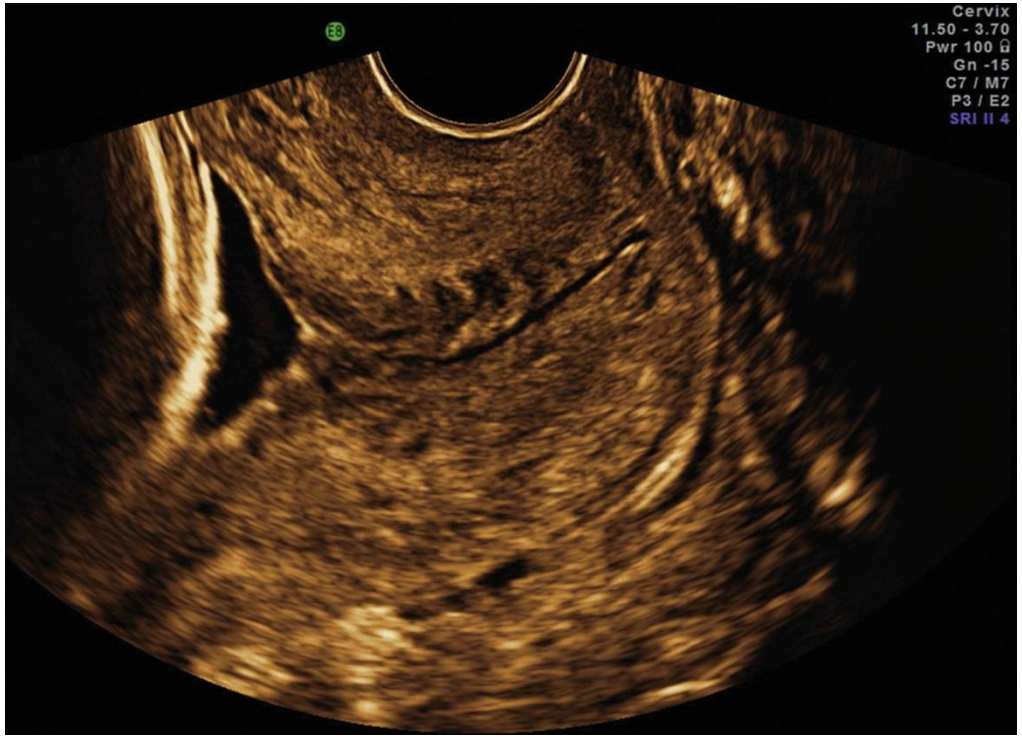
- race
- socio-economic status
- age
- nutritional status (low body mass index, low concentrations of iron, folate, zinc,…)

Biological markers (fetal fibronectin)

Genetic markers (hereditary factors, fetal and maternal genotypes)

Goldenberg et al. *Lancet 2008; **371**: 75 – 84*
Muglia et al. *N Engl J med 2010; **362**: 529 - 535*

Screening Sonographic Cervical Length



Transvaginal ultrasound of the uterine cervix with a normal length

From Romero R et al. Sem Fet Neonat Med 2014; 19: 15e26

- 10th% = 25mm (20 to 30 weeks gestation)
- 80-100% of women who deliver early have cervix <30mm
- 15 mm or less = 50% delivery rate within one week

Challenges in preterm delivery prevention and management

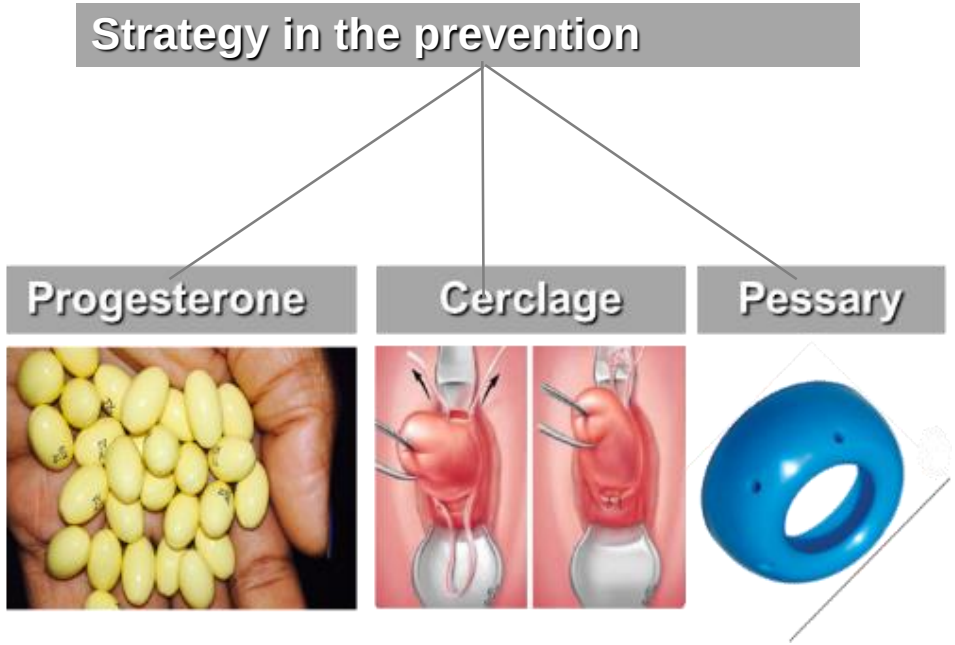
Identification of risk factors

Prior history of preterm birth

Twin pregnancy

Short cervix at scan

TVS-cervical length is the single most powerful predictor for PTD in the index pregnancy.



Prevention of Preterm Birth

Women with history of preterm delivery

Women with short cervical length on transvaginal sonography

Prophylactic use of progesterone

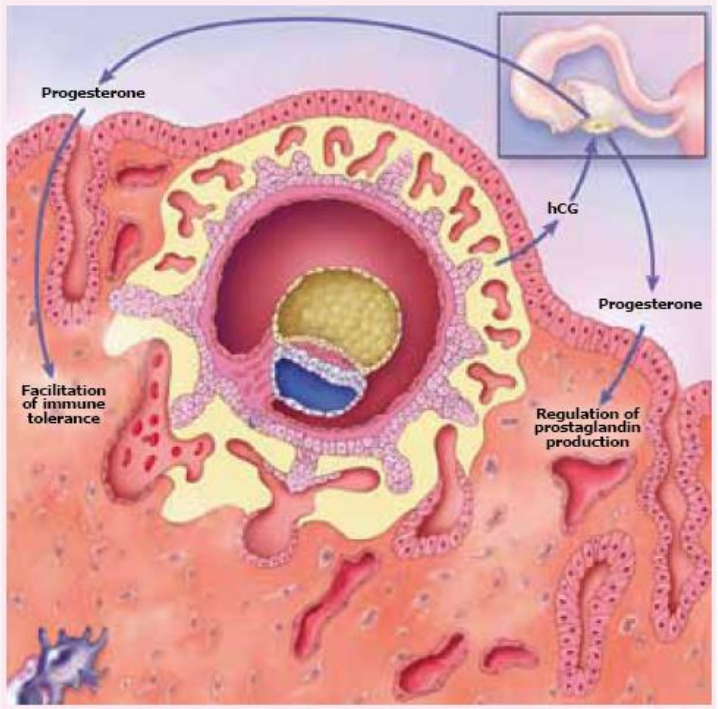
Incidence of preterm delivery significantly reduced

Role of Physiological progesterone

Maintains pregnancy:

- modulates maternal immune responses[3,4]
- reduces uterine contractility[5,6,7]
- improves the utero-placental circulation[8,9]
- suppresses fetal inflammatory response[10]

Maintenance of early pregnancy



Adapted from Norwitz[1]

1. **Norwitz ER et al.** *N Engl J Med 2001;* ***345****: 1400-8*
3. **Druckmann R et al.** *J Steroid Biochem Mol Biol 2005;* ***97****: 389-96*
4. **Szekeres-Bartho J et al.** *Int Immunopharmacol 2001;* ***1****: 1037-48*
5. **Fanchin R et al.** *Hum Reprod 2000;* ***15****: 90-100*
6. **Perusquía M et al.** *Life Sci 2001;* ***68****: 2933-44*
7. **Chanrachakul B et al.** *Am J Obstet Gynecol 2005;* ***192****: 458-63*
8. **Liu J et al.** *Mol Hum Reprod 2007;* ***13****: 869-74*
9. **Czajkowski K et al.** *Fertil Steril 2007;* ***87****: 613-8*
10. **Schwartz N et al.** *Am J Obstet Gynecol 2009;* ***201****: 211-9*

Progesterone and Preterm Delivery: what happening in Russia?

MISTERI trial

Multinational, multicenter, open-label, parallel group trial to evaluate efficacy and safety of micronized progesterone (vaginal capsules) in high risk for preterm delivery women

- Intravaginal progesterone for prevention of preterm delivery in women at risk
  - History of PTD
  - And/or sonographic short cervix in second trimester
- Open label study in two parallel groups
- 220 patients
- 3 countries, more then 20 sites

Progesterone and Preterm Delivery: *MISTERI trial*

Primary Objective

To improve obstetric outcomes by prolonging pregnancy and thereby reduce the rate of preterm birth (birth prior to 34+0 weeks) with prophylactic use of natural progesterone in a dose of 200 mg per day vaginally in weeks 19-34 of gestation in women at high risk for preterm birth compared to the population frequency.

Secondary Objective

To improve neonatal outcomes and correspondingly reduce total neonatal mortality and morbidity compared to the population frequency.

Progesterone and Preterm Delivery: MISTERI trial

Inclusion criteria

Patients at high risk for preterm birth should met at least one of criteria 1–3 and all criteria 4-6

1.Preterm birth or second trimester spontaneous abortion (≥ 16 weeks and < 37 weeks of pregnancy) in medical history
1.Premature rupture of membranes in medical history (≤ 37 weeks of gestation)
2.Sonographic short cervix (>10 and < 25 mm) at weeks 18-0 to 24+0 of pregnancy
3.Pregnancy in all the women must be confirmed by ultrasound at week ≤ 16 so as to make sure that the expected delivery date
4.Signed Patient Information Sheet with Informed Consent Form
5.At least 18 years of age.

Preliminary results: MISTERI trial

- Recruitment completed.
- 110 patient in each group analyzed (N=220)
- Outcomes registered (deliveries) (N=219)
- Efficacy analysis was performed in each subgroup as well as in the general group. A comparison was made with preterm birth population risk, which is at least 25% according to the literature data (Delivery before wk 34+0)

5.9%

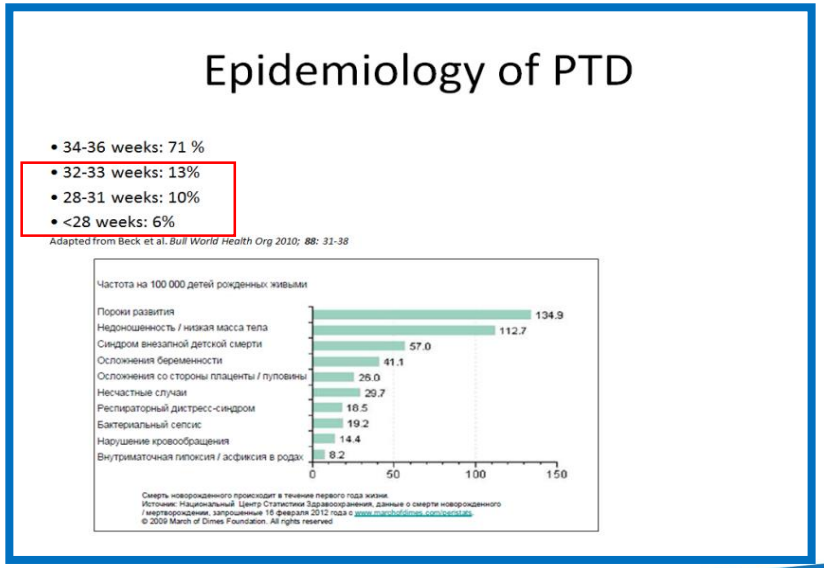
- Delivery before wk 34 - 36

10.5%

- In short cervix arm

3,5%

- <u>No major safety issued reported</u>



Conclusions: MISTERI trial

- **The risk of preterm birth prior to 34 weeks is effectively reduced** by treatment with natural progesterone 200 mg capsules for vaginal use in patients with preterm birth risk factors (cervical shortening and /or medical history of spontaneous preterm birth and/or premature rupture of membranes)

- Natural progesterone 200 mg capsules for vaginal use have **a favourable safety and tolerability profile.**

OPPTIMUM Study

A randomised trial of vaginal progesterone prophylaxis for preterm birth

The OPPTIMUM trial

Prinicipal Investigator: Jane Norman, MD PhD (UK)

Norman et al.
*Lancet 2016. Published **Online February 23**, 2016 http://dx.doi.org/10.1016/S0140-6736(16)00350-0*

In The Lancet 2016

Articles

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

Norman et al.
*Lancet 2016. Published **Online February 23**, 2016 http://dx.doi.org/10.1016/S0140-6736(16)00350-0*

Participation and compliance

- **ITT = 1226 women**
  - **610 pregnancies** *allocated to placebo*
  - **618 pregnancies** *allocated to progesterone*

Data available for women with a cervical length ≤25mm at any time between 18+0 and 24+0 weeks gestation (**N= 251**)

- *Information available showed ≥80%* ***compliance in 68.6% in the placebo group*** *and* **66.3% in the progesterone group**

Comment by Roberto Romero:

"The trial was underpowered to determine the effect of progesterone in the prevention of preterm birth in women with a short cervix".

Primary outcomes

Opptimum Trial

	Placebo group	Progesterone group	Unadjusted odds ratio (95% CI) or difference in means (95% CI)	p value (unadjusted)	Adjusted odds ratio (95% CI)* or difference in means (95% CI)	p value (adjusted*)
Fetal death or delivery <34 weeks of gestation	108/597 (18%)	96/600 (16%)	0·86 (0·64 to 1·17)	0·34	0·86 (0·61 to 1·22)	0·67
Neonatal morbidity or death	60/587 (10%)	39/589 (7%)	0·62 (0·41 to 0·94)	0·02	0·62 (0·38 to 1·03)	0·072
Cognitive composite score at 2 years†‡	97·7 (17·5)	97·3 (17·9)	−0·48 (−2·77 to 1·81)§	0·68	−0·48 (−2·77 to 1·81)§	0·68
Components of the obstetric outcome						
Fetal death	7/597 (1%)	8/600 (1%)	1·14 (0·41 to 3·17)	0·8	..	..
Liveborn delivery before 34 weeks	101/590 (17%)	88/592 (15%)	0·85 (0·62 to 1·15)	0·29	..	..
Components of the neonatal outcome						
Neonatal death	6/597 (1%)	1/600 (<1%)	0·17 (0·06 to 0·49)	0·0009¶	..	..
Bronchopulmonary dysplasia‖	18/574 (3%)	17/580 (3%)	0·94 (0·49 to 1·78)	0·84	..	..
Brain injury on ultrasound scan**	34/574 (6%)	18/584 (3%)	0·50 (0·31 to 0·84)	0·008	..	..

*

* p unadjusted = 0.02 (statistically significant)

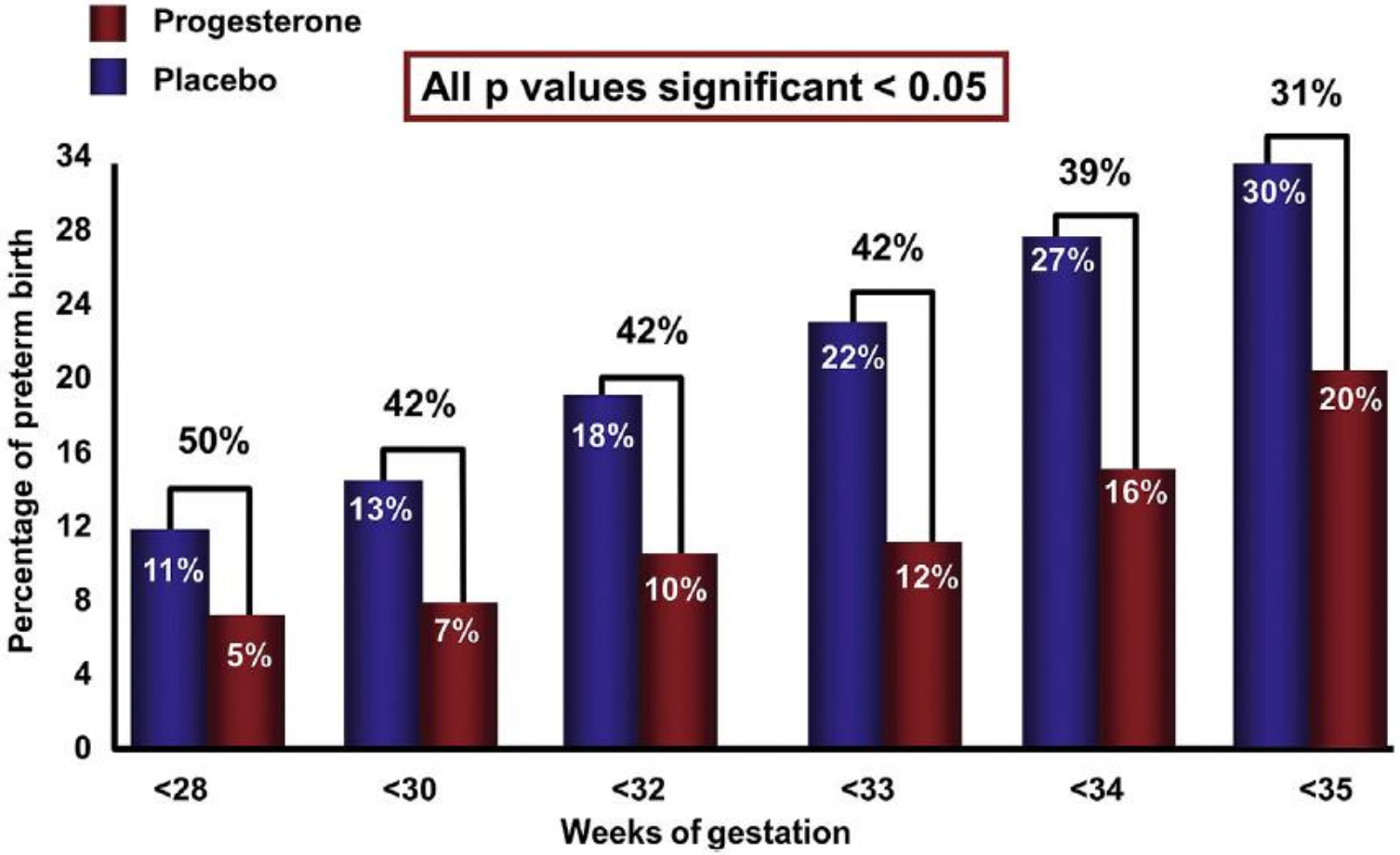
¶ p unadjusted for previous pregnancy of at least 14 weeks because of small sample size.

Neonatal morbidity or death:

- **Five time less neonatal death** in progesterone group **(0.2%)** vs **1%** deaths in placebo group (***P=0.0009***)
- **Two time less brain injury** in progesterone group **(3 %)** vs **6%** in placebo (***P=0.008***)

PREIS SCHOOL
Permanent International and European School in Perinatal, Neonatal and Reproductive Medicine

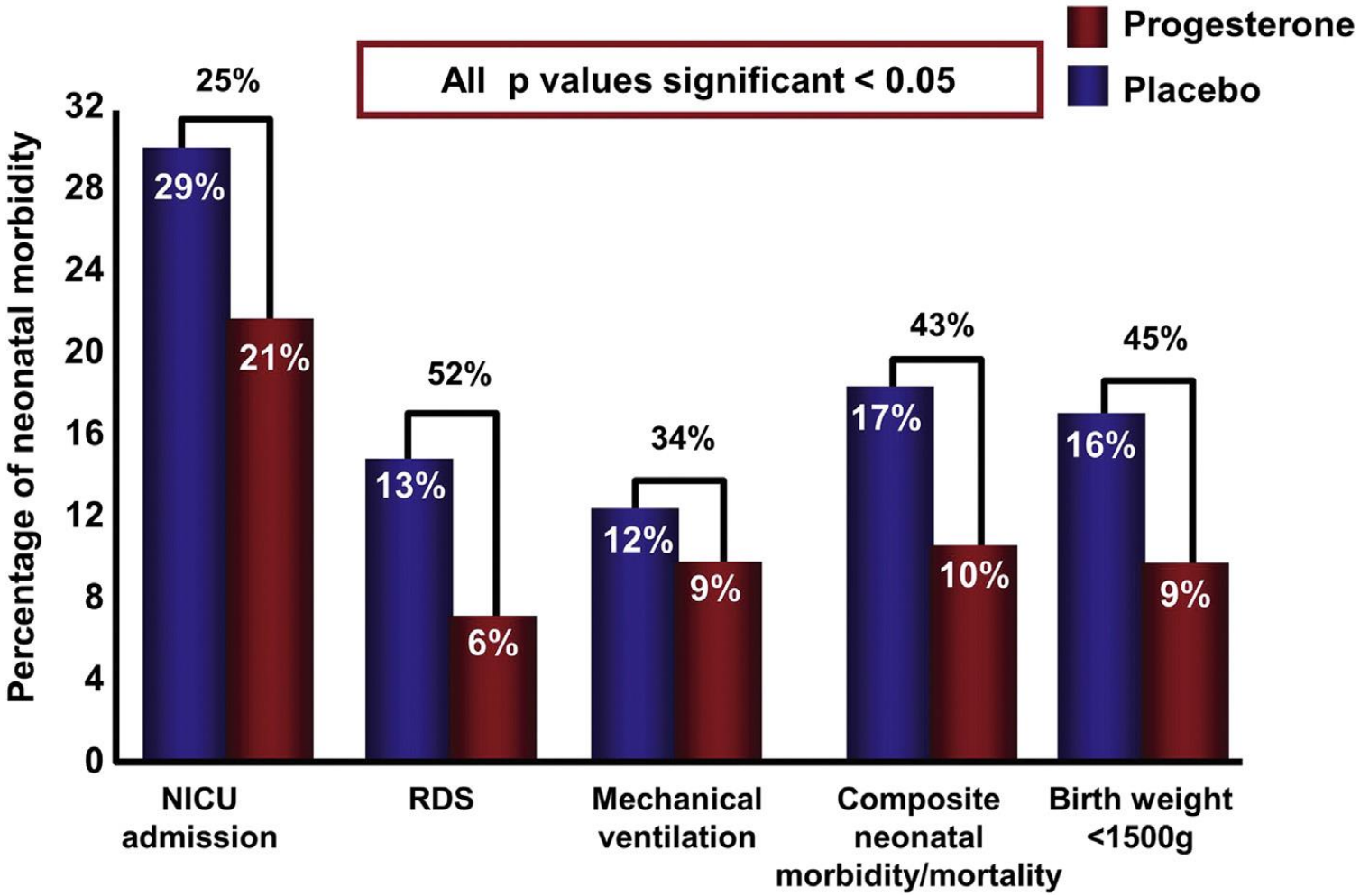
Effect of Vaginal Progesterone on the Rate of Preterm Birth



Patients with a short cervix allocated to receive vaginal progesterone (vs placebo) had a significantly lower risk in the rate of preterm birth <28, <33, and <35 weeks of gestation

Romero R et al. *J Perinat Med 2013;***41***:27e44.*

The Effect of Vaginal Progesterone on neonatal outcomes



Infants whose mothers (with a short cervix) received vaginal progesterone (vs placebo) had a significantly lower risk of respiratory distress syndrome, composite neonatal morbidity and mortality, birthweight <1500 g, admission to the neonatal intensive care unit, and requirement for mechanical ventilation

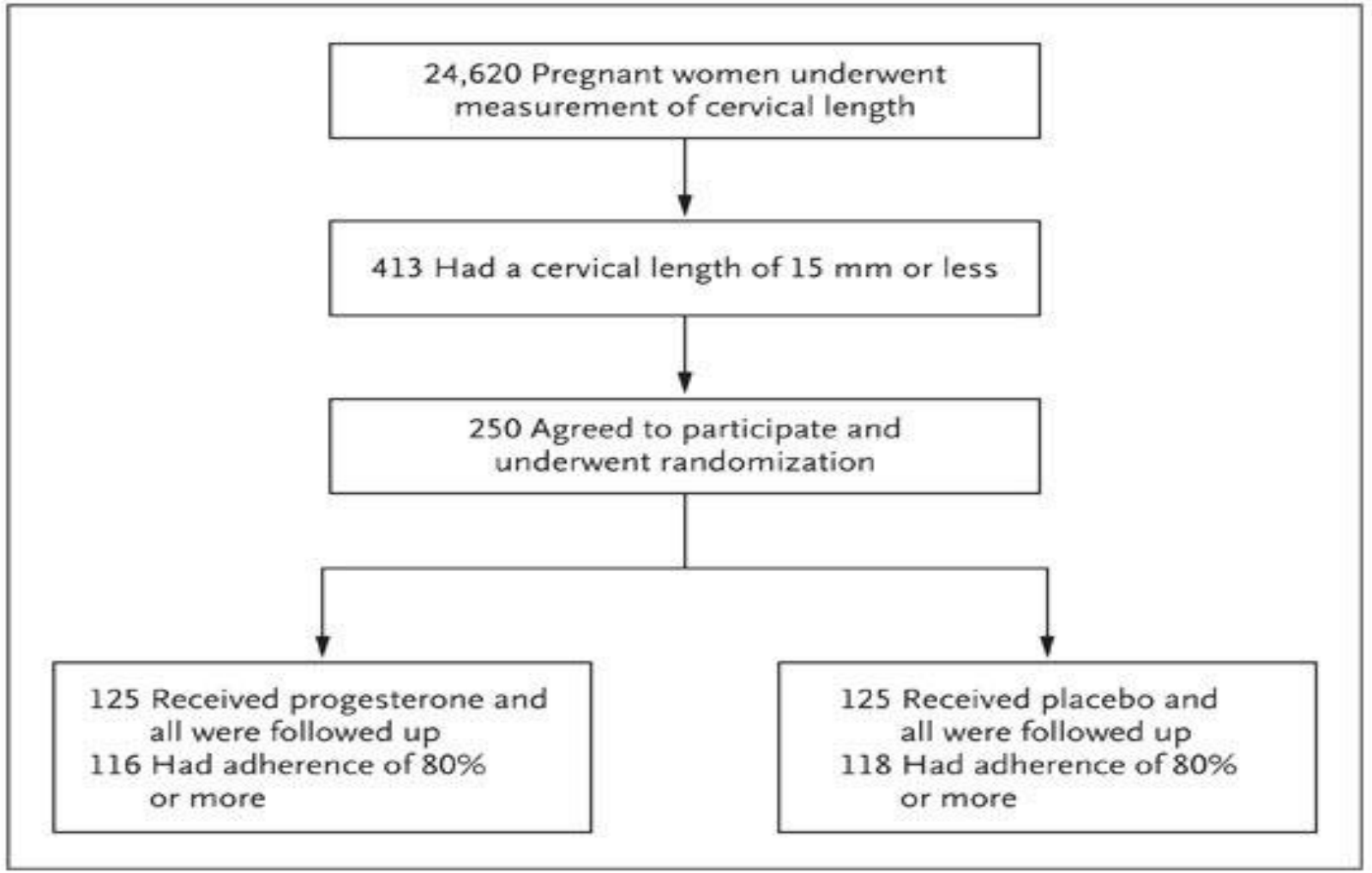
Romero R et al. *J Perinat Med 2013;***41***:27e44.*

Study Overview Short Cervix Patient

- Asymptomatic women who have a short cervix at midgestation are at increased risk for spontaneous early preterm delivery
- In this randomized trial, women with a short cervix (15 mm or less in length) assigned to treatment with vaginal progesterone* had a significantly lower rate of spontaneous delivery before 34 weeks of gestation than did women assigned to placebo
- In contrast to another trial published in this issue of the Journal, which showed no reduction in the risk of preterm birth among women with twins treated with 17 alpha-hydroxyprogesterone caproate, this study indicates the efficacy of vaginal progesterone in reducing this risk among women with a short cervix

*** Vaginal micronised progesterone 200 mg/d from 24 to 33 weeks 6 days of gestation every night before going to sleep**

Patient Enrolment



Fonseca EB et al. N Engl J Med 2007;357:462-469

Characteristics of the Study Participants

Table 1. Characteristics of the Study Participants.

Characteristic	Progesterone Group (N=125)	Placebo Group (N=125)	P Value
Age — yr			0.91
Median	29	29	
Interquartile range	24–34	24–34	
Obstetrical history — no. (%)			0.33
Nulliparous	71 (56.8)	69 (55.2)	
Parous with no previous preterm births	39 (31.2)	33 (26.4)	
Parous with ≥1 previous preterm birth	15 (12.0)	23 (18.4)	
Race — no. (%)*			0.61
White	46 (36.8)	49 (39.2)	
Black	68 (54.4)	69 (55.2)	
Other	11 (8.8)	7 (5.6)	
Body-mass index†			0.11
Median	23.8	25.4	
Interquartile range	21.6–27.7	22.3–28.4	
Cigarette smoking during pregnancy — no. (%)	6 (4.8)	10 (8.0)	0.44
Single vs. multiple gestations — no. (%)			0.89
Singleton	114 (91.2)	112 (89.6)	
Twin (dichorionic)	8 (6.4)	9 (7.2)	
Twin (monochorionic, diamniotic)	3 (2.4)	4 (3.2)	
Days of gestation at randomization			0.78
Median	165	164	
Interquartile range	159–168	160–169	
Cervical length at randomization — mm			0.74
Median	11.0	12.0	
Interquartile range	9–14	9–14	
Adherence rate <80% — no. (%)	9 (7.2)	7 (5.6)	0.80

* Race was self-reported.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.

Outcomes According to Study Group

Table 2. Outcomes According to Study Group.*

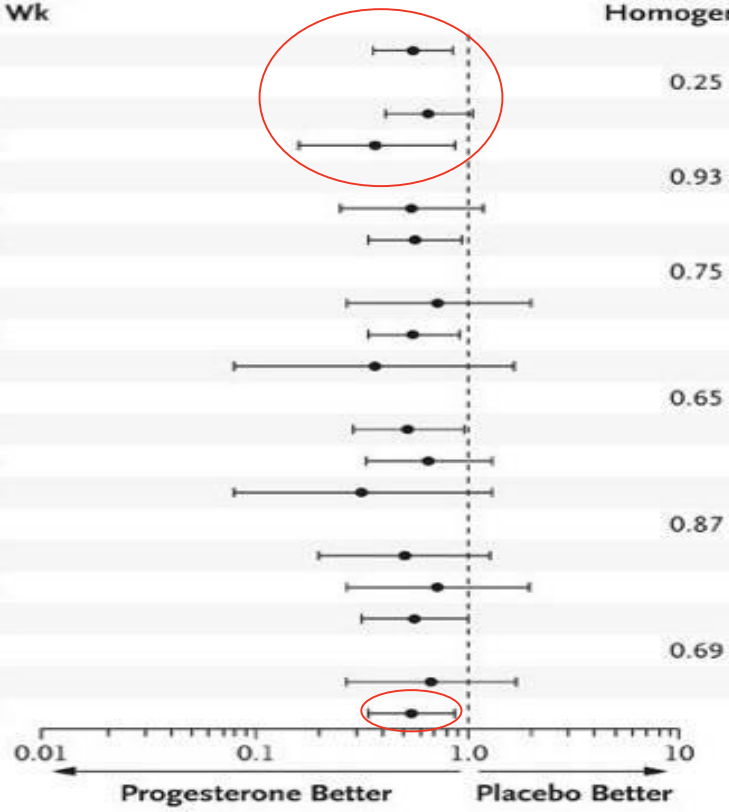
Outcome	Progesterone Group†	Placebo Group‡	Relative Risk (95% CI)	P Value	Adjusted Relative Risk (95% CI)	P Value
	no. (%)					
Maternal						
Spontaneous delivery at <34 wk	24 (19.2)	43 (34.4)	0.56 (0.36–0.86)	0.007	0.56 (0.32–0.91)	0.02
Any delivery at <34 wk	26 (20.8)	45 (36.0)	0.58 (0.38–0.87)	0.008	0.60 (0.35–0.94)	0.02
Perinatal						
Fetal death	1 (0.7)	1 (0.7)		0.98		
Neonatal death	2 (1.5)	7 (5.1)	0.29 (0.06–1.42)	0.13	0.34 (0.06–1.81)	0.22
Birth weight <2500 g	56 (41.2)	59 (42.8)	0.96 (0.69–1.26)	0.81	0.97 (0.68–1.29)	0.85
Birth weight <1500 g	18 (13.2)	27 (19.6)	0.68 (0.36–1.21)	0.20	0.74 (0.36–1.37)	0.35
Composite adverse outcomes	11 (8.1)	19 (13.8)	0.59 (0.26–1.25)	0.17	0.57 (0.23–1.31)	0.19
Intraventricular hemorrhage§	1 (0.7)	2 (1.4)	0.51 (0.05–5.30)	0.58	0.33 (0.01–8.84)	0.52
Respiratory distress syndrome	11 (8.1)	19 (13.8)	0.59 (0.26–1.25)	0.17	0.57 (0.23–1.31)	0.19
Retinopathy of prematurity	2 (1.5)	0				
Necrotizing entercolitis	0	1 (0.7)				
Composite therapy	34 (25.0)	45 (32.6)	0.77 (0.48–1.15)	0.21	0.75 (0.44–1.16)	0.20
Neonatal intensive care	33 (24.3)	42 (30.4)	0.80 (0.49–1.21)	0.30	0.80 (0.47–1.24)	0.34
Ventilation	16 (11.8)	25 (18.1)	0.65 (0.33–1.21)	0.18	0.64 (0.30–1.25)	0.20
Phototherapy	16 (11.8)	14 (10.1)	1.16 (0.56–2.25)	0.68	1.09 (0.50–2.19)	0.82
Treatment for sepsis	3 (2.2)	11 (8.0)	0.28 (0.07–1.01)	0.05	0.29 (0.07–1.10)	0.07
Blood transfusion	4 (2.9)	5 (3.6)	0.81 (0.22–2.86)	0.75	0.79 (0.19–3.10)	0.74

* For perinatal outcomes, the relative risks, 95% confidence intervals, and P values were estimated by logistic regression clustered on maternal identifiers to account for nonindependence between twin pairs. Relative risks were adjusted for maternal age, body-mass index, smoking status, race, history of preterm birth, and cervical length at the time of randomization.
† There were 125 pregnancies and 136 infants in the progesterone group.
‡ There were 125 pregnancies and 138 infants in the placebo group.
§ Intraventricular hemorrhage was grade 2 in all infants.

Fonseca EB et al. *N Engl J Med 2007;**357**:462-469*

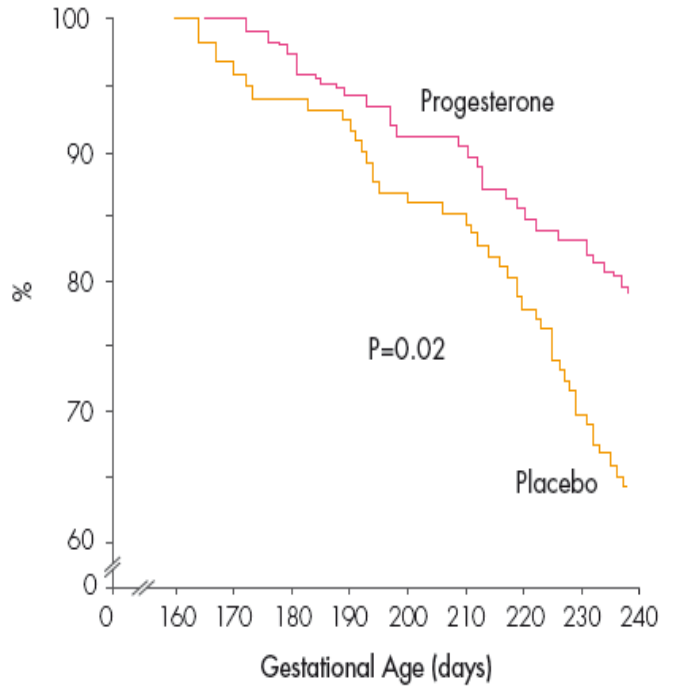
Relative Risk of Spontaneous Birth before 34 Weeks Associated with Progesterone Use in Relation to Maternal Characteristics at the Time of Randomization

Maternal Characteristic	Total No. of Patients	No. Delivering Spontaneously at <34 Wk	P Value for Homogeneity
All patients	250	67	
Cervical length			0.25
<12 mm	125	44	
12–15 mm	125	23	
Age			0.93
≥35 yr	46	18	
<35 yr	204	49	
Body-mass index			0.75
≥30.0	37	12	
20.0–29.9	187	49	
<20.0	26	6	
Race			0.65
White	95	33	
Black	137	28	
Other	18	6	
Obstetrical history			0.87
Parous with ≥1 previous preterm birth	38	16	
Parous with no previous preterm birth	72	13	
Nulliparous	140	38	
No. of gestations			0.69
Twin	24	11	
Singleton	226	56	



Fonseca EB et al. *N Engl J Med 2007;**357**:462-469*

Kaplan-Meier Plot of the Probability of Continued Pregnancy without Delivery among Patients Receiving Vaginal Progesterone as Compared with Placebo



No. at Risk for Spontaneous Birth

Progesterone	125	125	122	118	114	112	107	103	99
Placebo	125	121	119	115	109	105	98	87	80

In women with a short cervix, (< 15 mm) treatment with progesterone* reduces significantly the rate of spontaneous early preterm delivery

Delivery <34 wks:	**24 (19%)**	**43 (34%)**
Perinatal death:	**3 (2.4%)**	**7 (5.6%)**

*** Vaginal micronised progesterone 200 mg/d from 24 to 33 weeks 6 days of gestation every night before going to sleep**

Fonseca EB et al. *N Engl J Med 2007;**357**:462-469*

Conclusion

In women with a short cervix, treatment with progesterone* reduces the rate of spontaneous early preterm delivery

(ClinicalTrials.gov number, NTC00422526)

The drug and placebo were purchased from the companies, which provided no financial support and had no involvement in study design, data collection, data handling, data analysis, study interpretation, the drafting of the manuscript, or the decision to publish

* Vaginal micronised progesterone 200 mg/d from 24 to 33 weeks 6 days of gestation every night before going to sleep

New FIGO COMMITTEE REPORT

FIGO recommendations regarding the use of transvaginal sonographic cervical length and vaginal progesterone use for the prevention of preterm birth.

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.

FIGO Working Group on Best Practice in Maternal–Fetal Medicine.
Int J Gynecol Obstet 2015; **128**: *80–82*

European Guidelines

The Journal of Maternal-Fetal and Neonatal Medicine, May 2011; 24(5): 659–667
© 2011 Informa UK, Ltd.
ISSN 1476-7058 print/ISSN 1476-4954 online
DOI: 10.3109/14767058.2011.553694

informa
healthcare

GUIDELINES

Guidelines for the management of spontaneous preterm labor: identification of spontaneous preterm labor, diagnosis of preterm premature rupture of membranes, and preventive tools for preterm birth

GIAN CARLO DI RENZO[1], LLUIS CABERO ROURA[2], FABIO FACCHINETTI[3], EUROPEAN ASSOCIATION OF PERINATAL MEDICINE-STUDY GROUP ON "PRETERM BIRTH"

Main points

1. **In asymptomatic women presenting with prior history of PTB, the early prophylaxis with either P4 micronized** or 17 OHP-C **demonstrated to be efficacious in preventing recurrence** [83,98,102,105–108]. In the above reported conditions, we advice to implement prophylaxis (**200 mg vaginal P4** or 250 mg/weekly i.m. 17 OHP-C) since early second trimester, in such condition.
2. In single pregnant, nulliparous women where a silent cervical shortening (15 mm) could be detected with transvaginal ultrasound both **micronized P4** and 17 OHP-C have proven to be able to reduce PTB, in respect with placebo [6,89,109]. Two good quality studies performed in few subjects support this intervention which, however, requires further confirmation before being recommended in the clinical practice.
3. **In single pregnant, nulliparous women successfully treated for a preterm labor episode microionized P4 reduced the rate of PTB in respect with no intervention/ placebo** [90,110]. The use of progestogens (400 mg/daily vaginal micronized P4 or 375 mg/ twice a week i.m. 17 OHP-C) as a maintenance tocolysis, however, requires further studies before being recommended for the tertiary prophylaxis of PTB.
4. In multiple pregnancies, either twins or triplets, neither micronized P4 nor 17 OHP-C is able to prevent PTB [111–114]. Data are consistent and number of women studied enough to advice not to use progestogens in such condition [115].
5. **Maternal safety of either micronised P4** or 17 OHP-C **administration has been reported in different trials [97].** Neonatal safety has been evaluated in only one trial where mothers have been treated with 17 OHP-C [116]. No effects of general health status, external genitalia, and psychomotor development have been reported at follow-up. However, there is concern about the increase in fetal death in mid-trimester and the higher incidence of gestational diabetes linked to 17-OHP-C. Since the paucity of data, ongoing trials are encouraged to include neonates follow-up in their design. Moreover, in view of the widespread use of progestogens in pregnant women, physicians should be aware of these facts for proper informed recommendation about the use of 17-OHP-C and post-marketing surveillance has to be advised. Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

Di Renzo GC et al. J Matern Fetal Neonatal Med 2011; Early Online: 1–9. © 2011 Informa UK, Ltd. DOI: 10.3109/14767058.2011.553694

1. In asymptomatic women presenting **with prior history of PTB**, the early prophylaxis with P4 micronized …demonstrated to be efficacious in preventing recurrence. (prophylaxis **200 mg vaginal P4** since early 2nd trim)
2. **In single pregnant**, **nulliparous women** where **a silent cervical shortening** (15 mm) could be detected with transvaginal ultrasound micronized P4 …have proven to be able to reduce PTB, in respect with placebo
3. In nulliparous women in single pregnant successfully treated for a PTL as maintenance tocolysis, reduced rate in PTD. (**400 mg vaginal P4**) Further studies required
4. Maternal safety of micronized progesterone has been reported in several trials.

North American & Canadian Guidelines

ACOG COMMITTEE OPINION

Number 419 • October 2008 *(Replaces No. 291, November 2003)*

Use of Progesterone to Reduce Preterm Birth

SOGC TECHNICAL UPDATE

No. 202, January 2008

The Use of Progesterone for Prevention of Preterm Birth

This technical update has been reviewed by the Maternal Fetal Medicine Committee and approved by the Executive of the Society of Obstetricians and Gynaecologists of Canada.

PRINCIPAL AUTHORS

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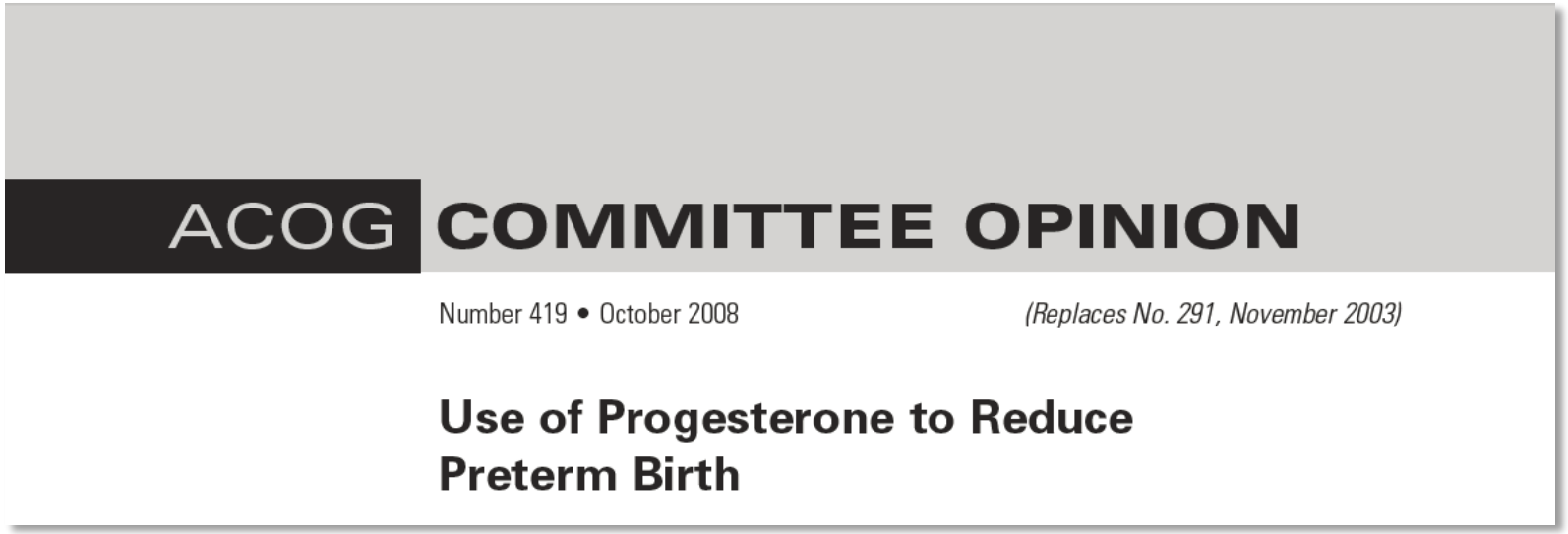
represents an abstraction of the evidence rather than a methodological review. The level of evidence and quality of recommendations are described using the criteria and classifications of the Canadian Task Force on Preventive Health Care (Table 1).

Values: This update is the consensus of the Maternal Fetal Medicine Committee of the Society of Obstetricians and Gynaecologists of Canada (SOGC).

Benefits, Harms, and Costs: Counselling the patient at increased

North America: ACOG Guidelines



ACOG COMMITTEE OPINION

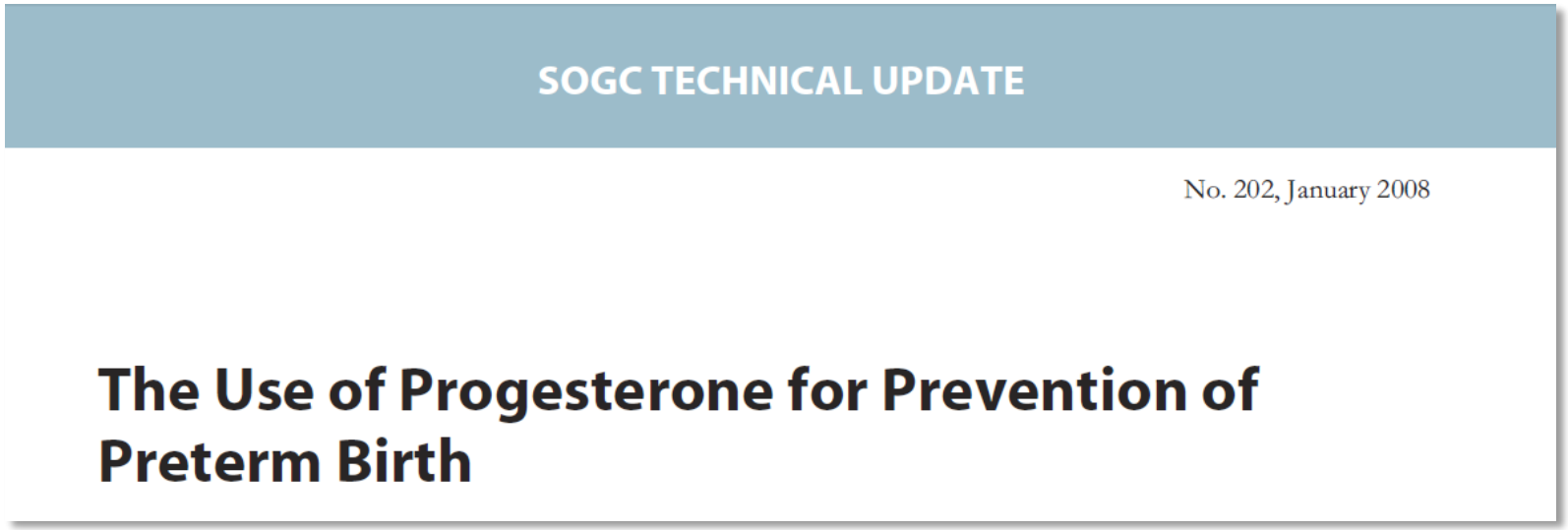
Number 419 • October 2008 *(Replaces No. 291, November 2003)*

Use of Progesterone to Reduce Preterm Birth

Offer progesterone for pregnancy prolongation to women with history of previous spontaneous birth <37 weeks.

Society for Maternal Fetal Medicine Publications Committee. *Obstet Gynecol 2008;***112(4)***:963-965.*

Canada: SOGC Guidelines


SOGC TECHNICAL UPDATE

No. 202, January 2008

The Use of Progesterone for Prevention of Preterm Birth

A previous preterm labor **and/or short cervix (< 15 mm at 22-26 weeks' gestation)** on transvaginal ultrasound could be used as an indication for progesterone therapy.

Farine D, et al. *J Obstet Gynaecol Can 2008;**30**:67-71.*

CLINICAL PRACTICE

Caren G. Solomon, M.D., M.P.H., *Editor*

Prevention of Preterm Parturition

Jay D. Iams, M.D.

KEY CLINICAL POINTS

PREVENTION OF PRETERM PARTURITION

- Despite advances in neonatal care, preterm birth remains a leading cause of infant death in the United States, especially among blacks.
- Systemic changes in reproductive health care to reduce the incidence of multifetal pregnancies and scheduled births before 39 weeks of gestation that lack a medical indication have been temporally associated with decreased preterm birth rates.
- Strategies to identify and treat medical risk factors in early pregnancy (e.g., genitourinary infection and poor nutrition) have not been effective in reducing preterm birth rates.
- Previous preterm birth and a short cervix (≤20 mm, as measured by transvaginal ultrasonography) are major risk factors for preterm birth.
- The use of progesterone supplementation in women with a previous preterm birth, a short cervix, or both was shown in randomized trials to reduce the frequency of preterm birth and is recommended for women with these risk factors.
- Cervical cerclage reduces the risk of recurrent preterm birth among women with a short cervix.

Iams J. *N Engl J Med 2014;* **370***; 254-261*

TAKE HOME MESSAGE

- The **role of progesterone** in the **physiopathology of pregnant women** is **crucial** from conception until delivery.

- There is **strong biological plausibility** to support exogenous progesterone for the management of prevention of preterm birth in women at risk with a short cervix and/or a history of preterm delivery.

- The **optimal** dose, **route of administration** and **duration** remains to be determined in **symptomatic women** and in **pregnancy maintenance after tocolysis.**

- **Neonatal effects, health infant** and cost-effectiveness with vaginal micronized progesterone are now available with a level 1 of evidence.

Thanks For Attention!