Turkey Maternal Fetal Medicine and Perinatology
Perinatal Medicine 2015
23-25 April 2015, İstanbul - TURKEY

Screening for pre term labor

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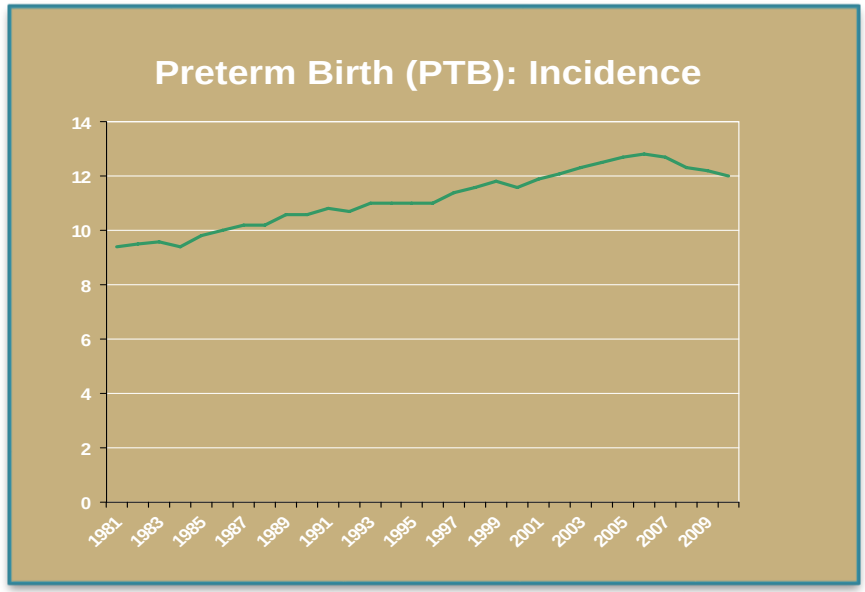
Croatia

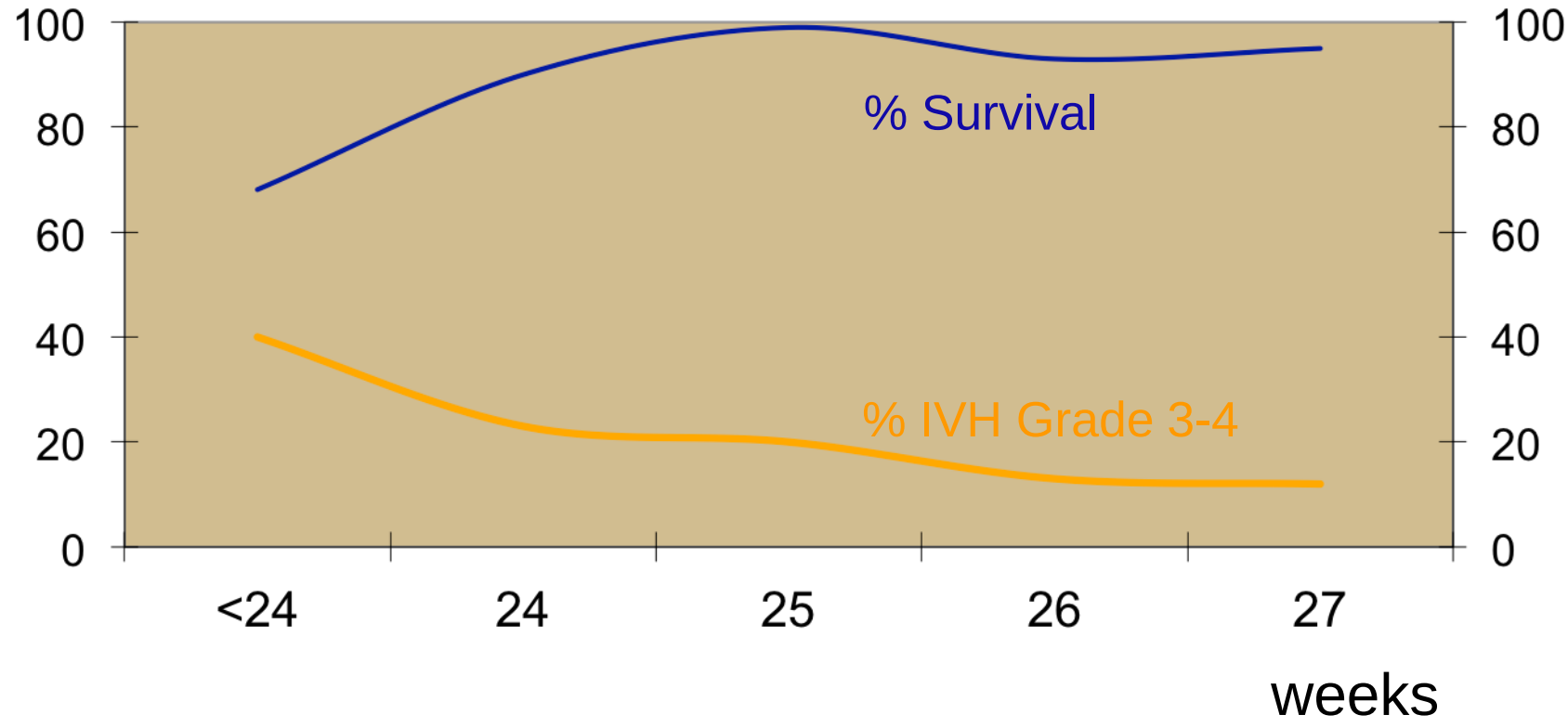
Significance of Preterm Birth (PTB)



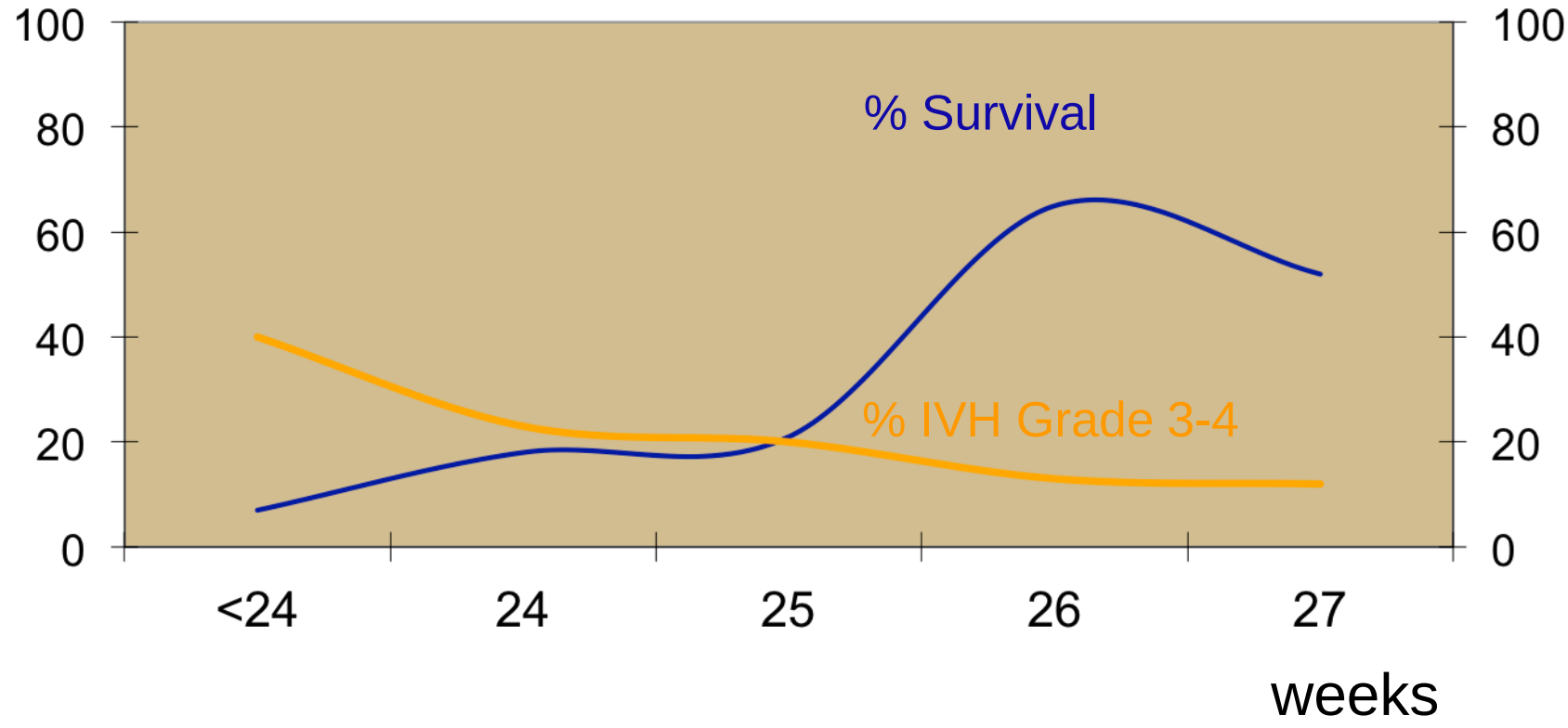
- 11.7 % of births (US, 2011)
- Twice the rate EU
- One sixth of PTDs occur at 24-31 weeks, with highest rate of complications *
- Leading cause of neonatal mortality (early 75%, late 35%), morbidity (70%), and health care expenditures (57% of nursery costs; 10% of all healthcare costs for children)
- 26 bill $/year

* US Nat't Vital Stats Reports 2000 & 2013 and ** CDC 2012

Mortality & morbidity related to PTB (%) Ideal life...



Mortality & morbidity related to PTB (%) Real life....



Rationale for PTL screening

FOR

- <50% with PTL perceive typical symptoms
- 10-20% of uncomplicated patients have similar symptoms
- PTL is diagnosed only after gross structural change of the cervix
- no currently identifiable risk factor

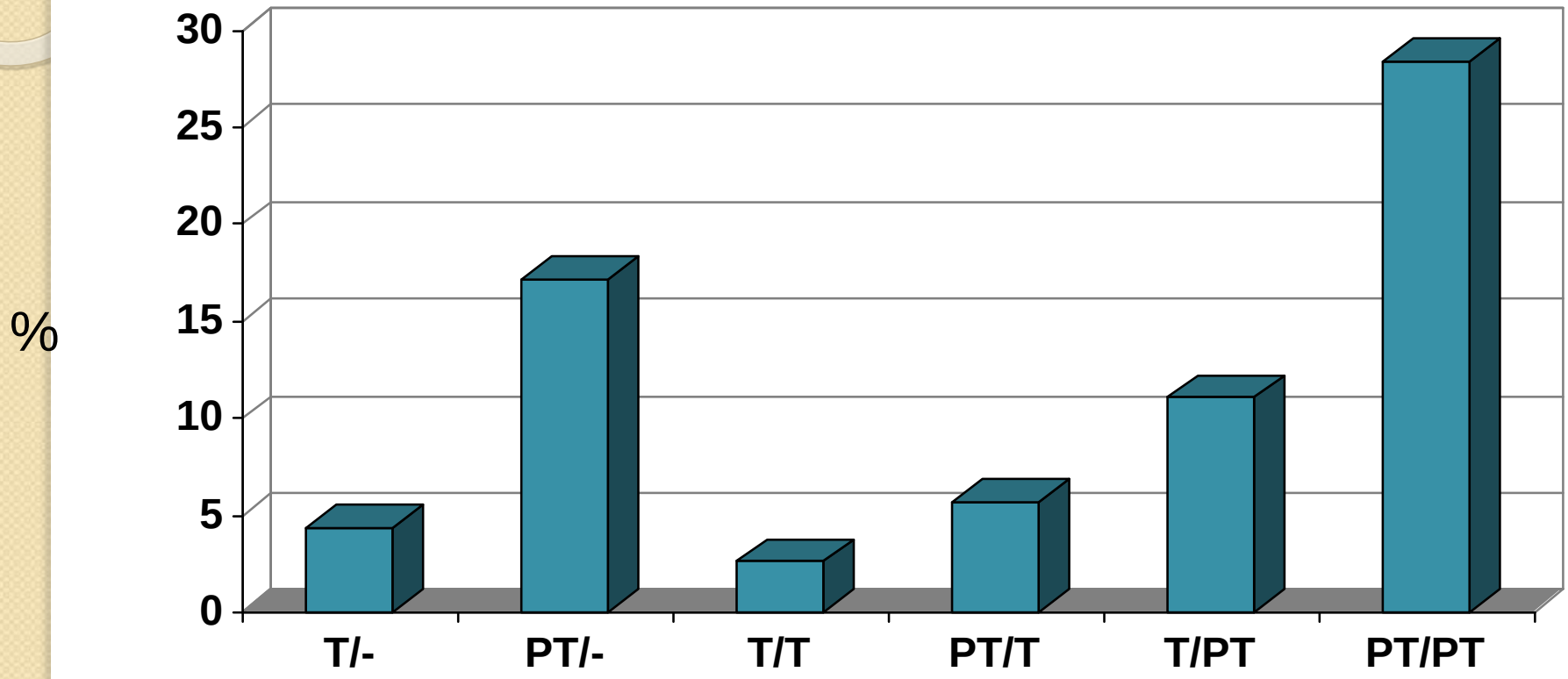
AGAINST

- Inadequate criteria
- No treatment
- Inadequate intervention
- Unsure benefits
- Significant health care cost

Risk factors for PTL/PTB

- Prior PTB (spontaneous PTL) RR 1.5 - 2
- Low socioeconomic status
- Teen and/or age >34
- Prepregnancy low BMI
- Uterine or cervical abnormality
- Maternal smoking
- Pregnency assocaited...

Risk of subsequent PTB



Bakketeig LS, Hoffman HJ. Harley EE. The tendency to repeat gestational age and the birth weight in successive births. AJOG 1979;135:1086

Rationale for PTL screening

"providing opportunity to identify and treat prematurity related risk factors"

NOT REDUCED PTL INCIDENCE

INTERVENTIONS

- Nutrition (Vit B and C, Ca)

Buppasiri et al, Cochrane, 2011;10:CD007079

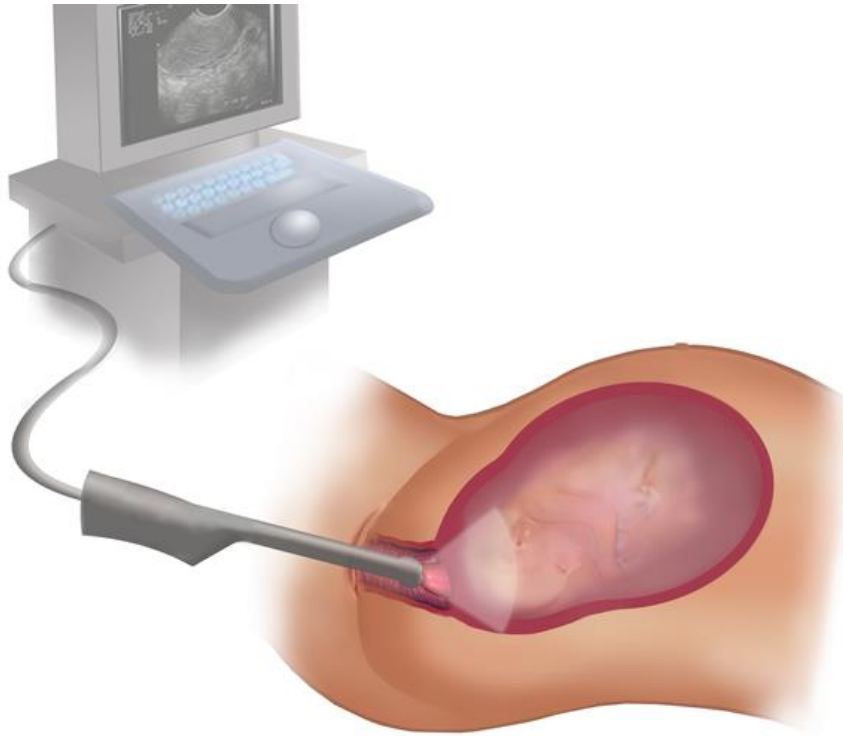
- BV treatment

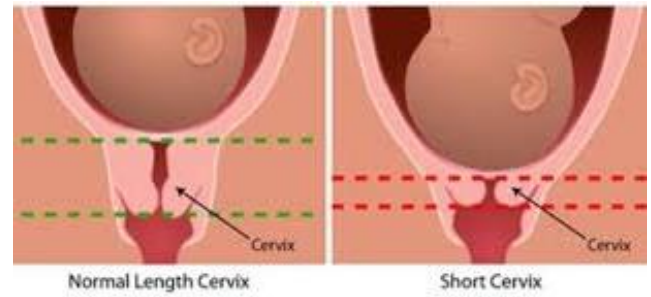
Carey et al, NEJM 2000;342:534

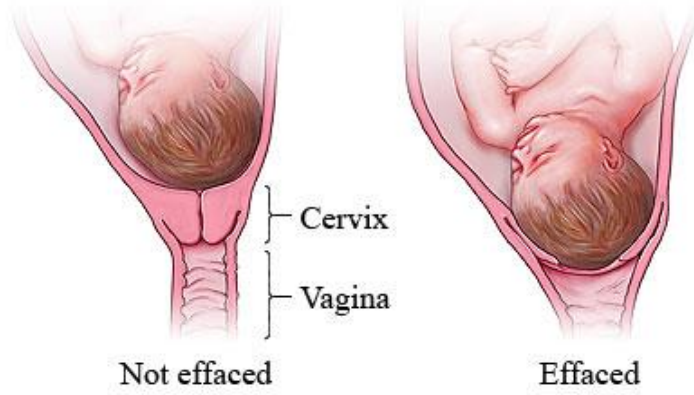
- Peridontal disease treatment

Offenbacher et al, Obstet Gyecol 2009;114:551

Cervical length in pregnancy







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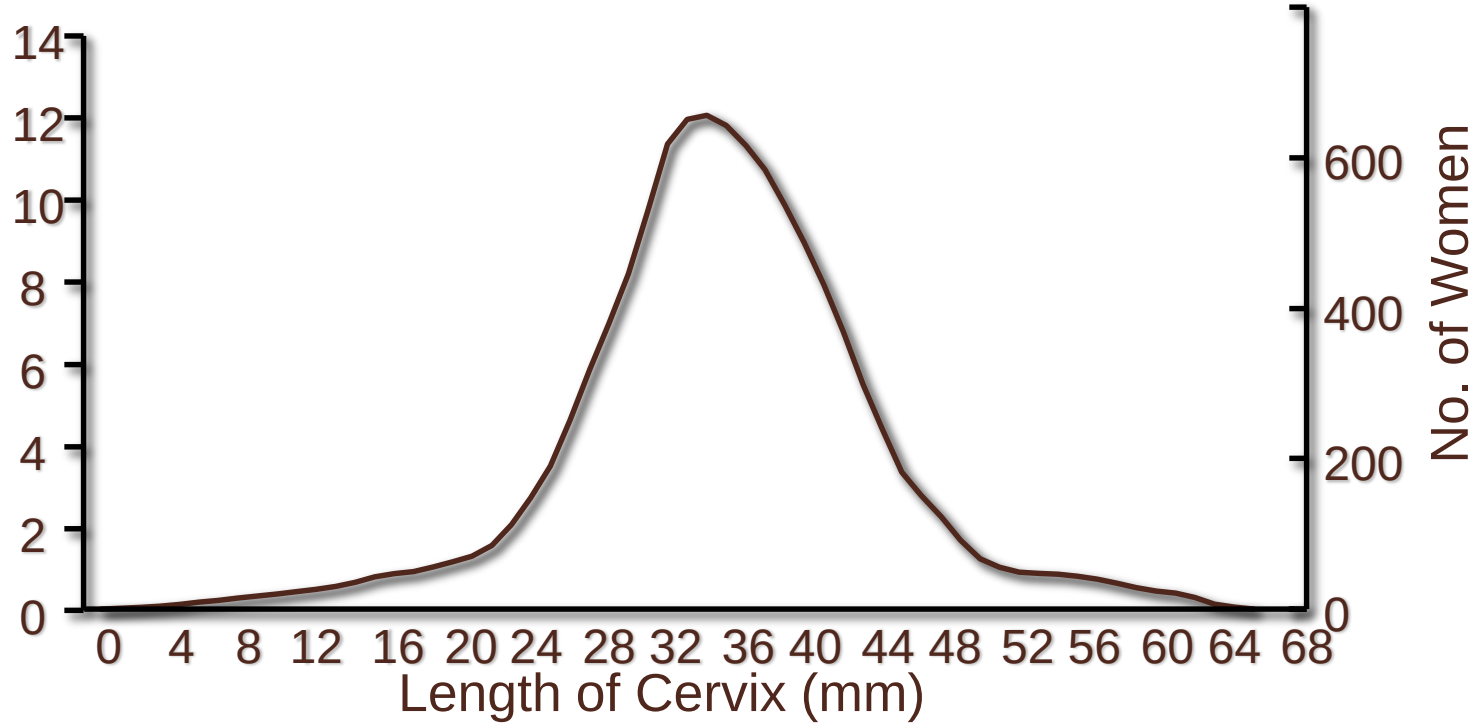
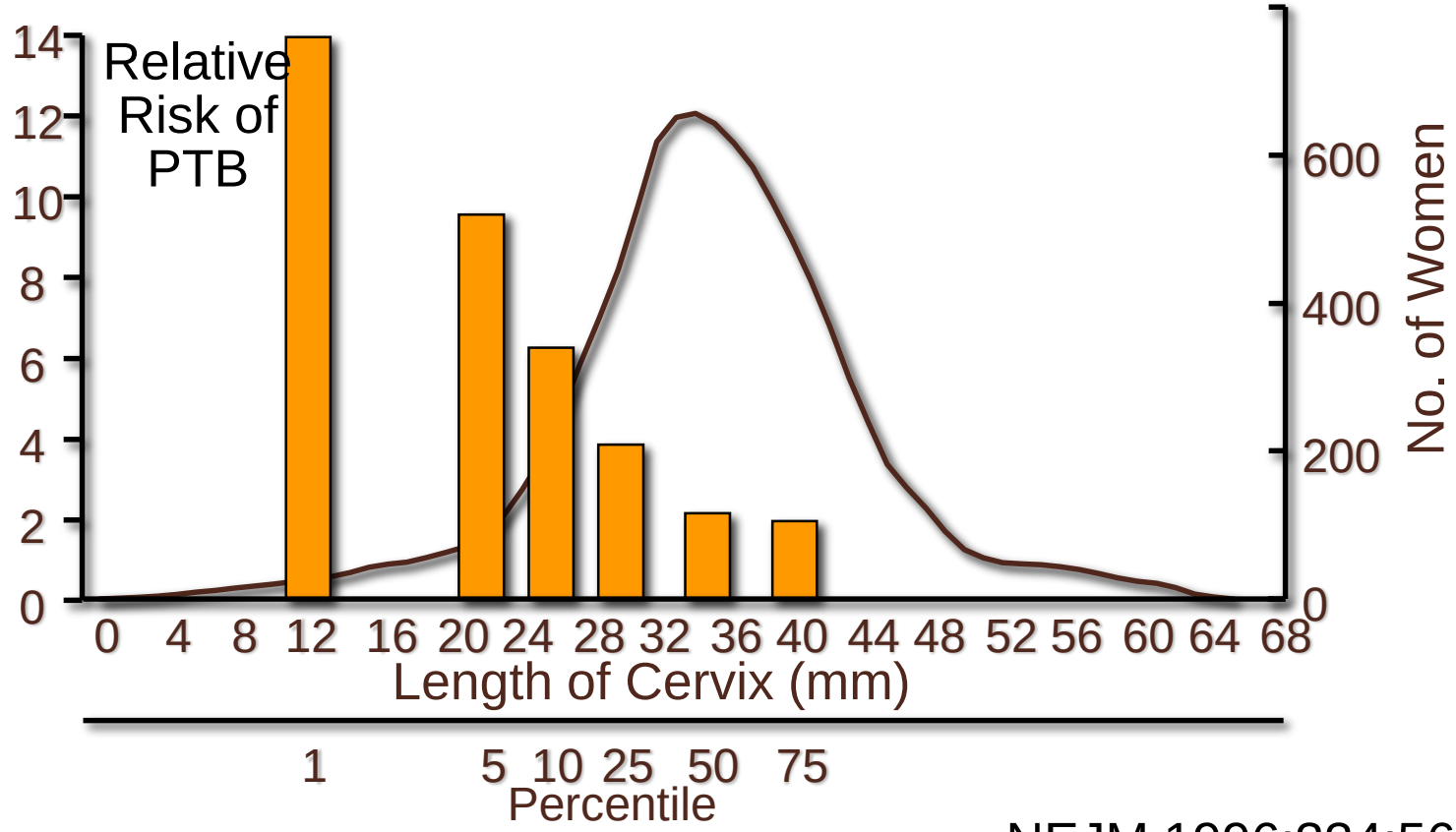
Cervical length in pregnancy



NEJM 1996;334:567

… correlates with PTL



NEJM 1996;334:567

Short CL and high risk ➡ Cerclage

and other...

<25 mm previous PTB (35 weeks)

Cerclage PTB RR 0.7, 95% CI 0.55-0.89

Consequently perinatal mortality and morbidity

Berghella V et al. Cerclage for short cervix on ultrasonography in women with singleton gestatins and previous preterm birth: a meta analysis. Obstet Gynecol 2011;117:663-61.

NNT 11 PTL/PTD, NNT perinatal death 50 Alfirevic, Florence, ECPM, 2014

Ultrasound screening - options

Universal TV screening 18 – 24

- Need for large number of skilled sonographers, unnecessary examination, follow up
- NNT 11, 375 screened (<25 mm), 1 prevented Romero, ECPM, Floernce, 2014

TA screening followed by TV

- Reproducibility of TA screening is uncertain

Selective TV screening of high risk

- High prevalence and low PPV

Iams JD. Prevention of preterm birth. NEJM 2014;370:254-61

TVS CL measurement for all?

FOR

- Important condition (PTB)
- Technique well-described
- Safe and acceptable
- Reliable (reproducible)
- Recognizable early asymptomatic phase
- Valid (accuracy of prediction)
- 'Early' treatment is effective (Prevention)

AGAINST

- Identification of abnormal cervix does not determine etiology or direct treatment

TVS CL measurement for all?

FOR

Hassan SS. Et al. V
preterm birth in wo
a multicenter, rando

Outcomes	Vaginal Progesterone (%)	Placebo (%)	Risk Reduction (%)	*P*
Any Neonatal Morbidity or Mortality Event	7.7%	13.5%	43%	0.04
Respiratory Distress Syndrome	3.0%	7.6%	61%	0.03
Birthweight < 1500g	6.4%	13.6%	53%	0.01

- 'Early' treatme
effective (Preven

TVS CL measurement for all?

AGAINST

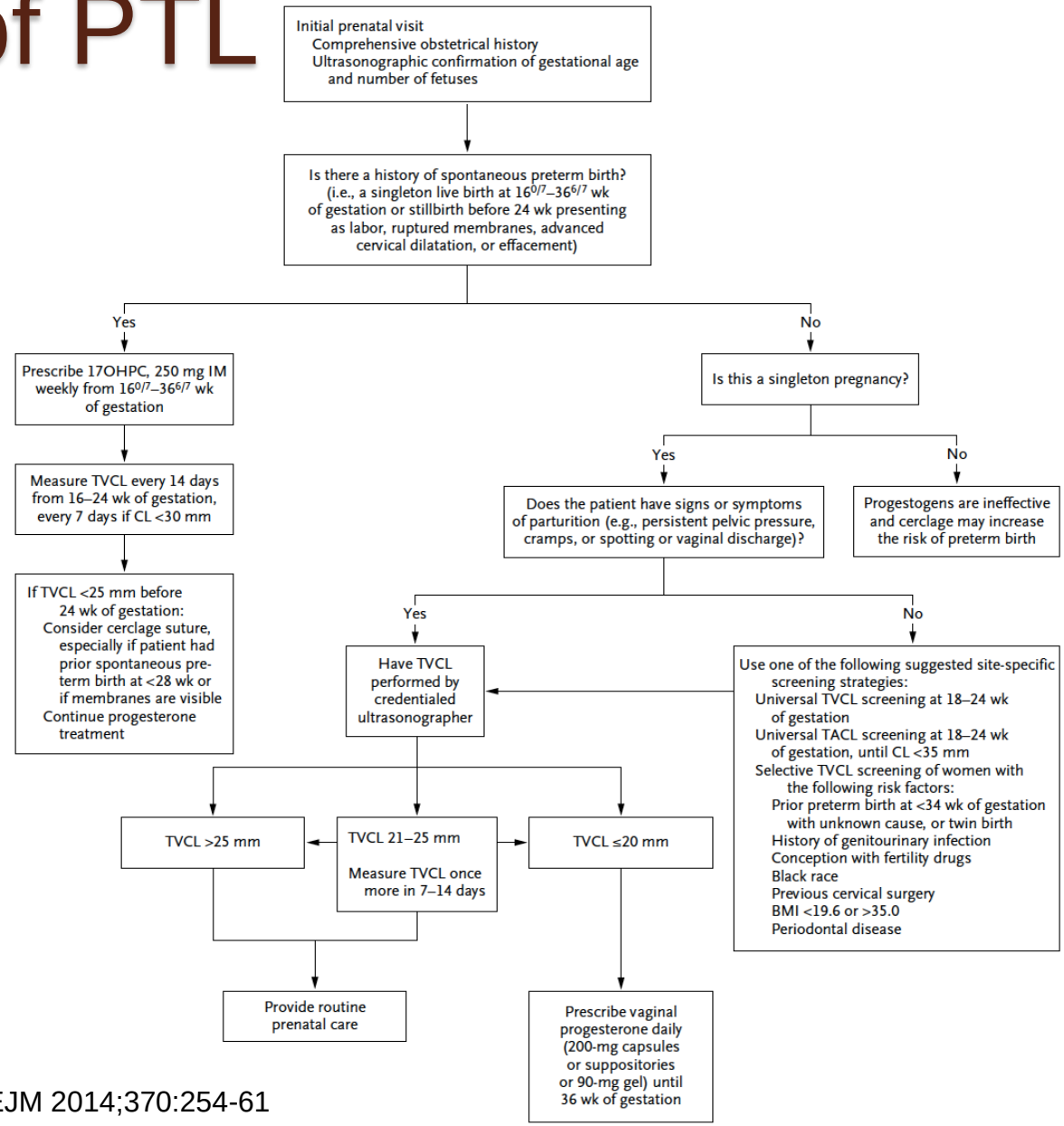
Berghella V, Baxter JK, Hendrix NW. Cervical assesment by ultrasound for preventing preterm delivery. Cochrane Database Syst Rev 2013;CD007235

...insufficient evidence to recommend routine screening of asymptomatic or symptomatic pregnant women with TVU CL.

Non-significant association between knowledge of TVU CL results and a lower incidence of PTB at less than 37 weeks in symptomatic women

Prevention of PTL

Potentialy Treatable Condition



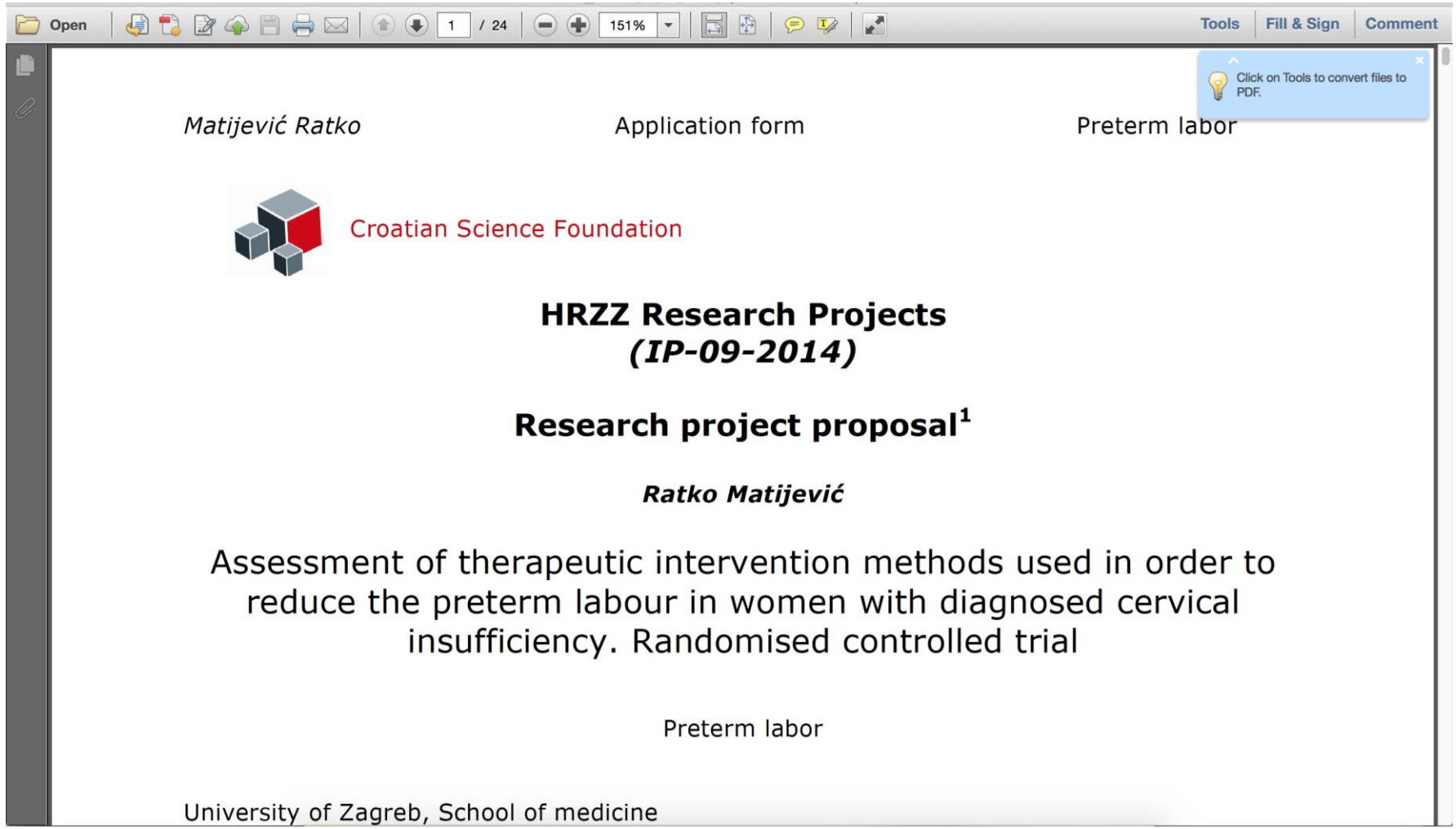
Iams JD. Prevention of preterm birth. NEJM 2014;370:254-61

Alternative options

- Arabin B and Alfirevic Z. Cervical pessaries for prevention of spontaneous preterm birth: past, present and future. Ultrasouns Obstet Gynecol 2013;42:390
- Abdel-Aleem H, Shaaban OM, Abdel-Aleem MA. Cervical pessary for prevention of preterm birth. Cochrane Database Syst Rev 2013;CD007873

... beneficial effect of cervical pessary in reducing preterm birth in women with a short cervix ...

Progesterone *vs.* cerclage vs. pessary



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Matijević Ratko Application form Preterm labor

Croatian Science Foundation

HRZZ Research Projects
(IP-09-2014)

Research project proposal[1]

Ratko Matijević

Assessment of therapeutic intervention methods used in order to reduce the preterm labour in women with diagnosed cervical insufficiency. Randomised controlled trial

Preterm labor

University of Zagreb, School of medicine

Any other options in screening?

Clinical (bimanual) examination

Ultrasound vs. digital examination

RCT: n=282 (144 *vs* 138)

Sensitivity	PPV	
57.1	66.7	TVS
33.3	17.6	DE

CL - 12-fold higher positive LR for PTL in low-risk population (37.4; 95%CI [8.2-170.7] versus 3.2; 95%CI [1.1-9.2]).

General screening not recommended

Matijevic R, Grgic O, Vasilj O. Is sonographic assessment of cervical length better than digital examination in screening for preterm delivery in a low risk population Acta Obstet Gynecol Scand. 2006;85(11):1342-7.

Bacterial vaginosis

PTD OR 1.8 - 2.2

18 studies > 20,000 pregnant women

Miscarriage	OR 9.91 (1.99-49.34)
Endometritis	OR 2.53 (1.26-5.08)

(Hillier 1995, Meis 1995, Hauth 1995)

Leitich H et al. Bacterial vaginosis as a risk factor for preterm delivery: a meta analysis. AJOG 2003;189:139-47

BV vs. CL

BV assessed by vaginal pH	5.0 (95th-percentile threshold)
CL assessed by TVS	26 mm
n=316	
PTL (<37) and EPTL (<34)	

Matijevic R, Grgic O, Kneževic M. Vaginal pH versus cervical lenght in the mid-trimester as secrrenng predictors of preterm labor in low risk population. Int J Gynaecol Obstet 2010;111:41-4

BV vs. CL

BV assessed by vaginal pH	5.0 (95th-percentile threshold)	14 (4.4%)
CL assessed by TVS	26 mm	15 (4.7%)
n=316		
PTL (<37) and EPTL (<34)		7.2% vs. 2.5%

CL was significantly correlated with PTL (likelihood ratio [LR] weighted by prevalence; 2.7; 95% CI, 1.1-6.7) but not with early PTL (LR, 0.8; 95% CI, 0.4-1.8)

BV and CL was a better predictor of PTL (LR, 3.7; 95% CI, 1.3-10.4) and early PTL (LR, 1.7; 95% CI, 1.1-3.1)

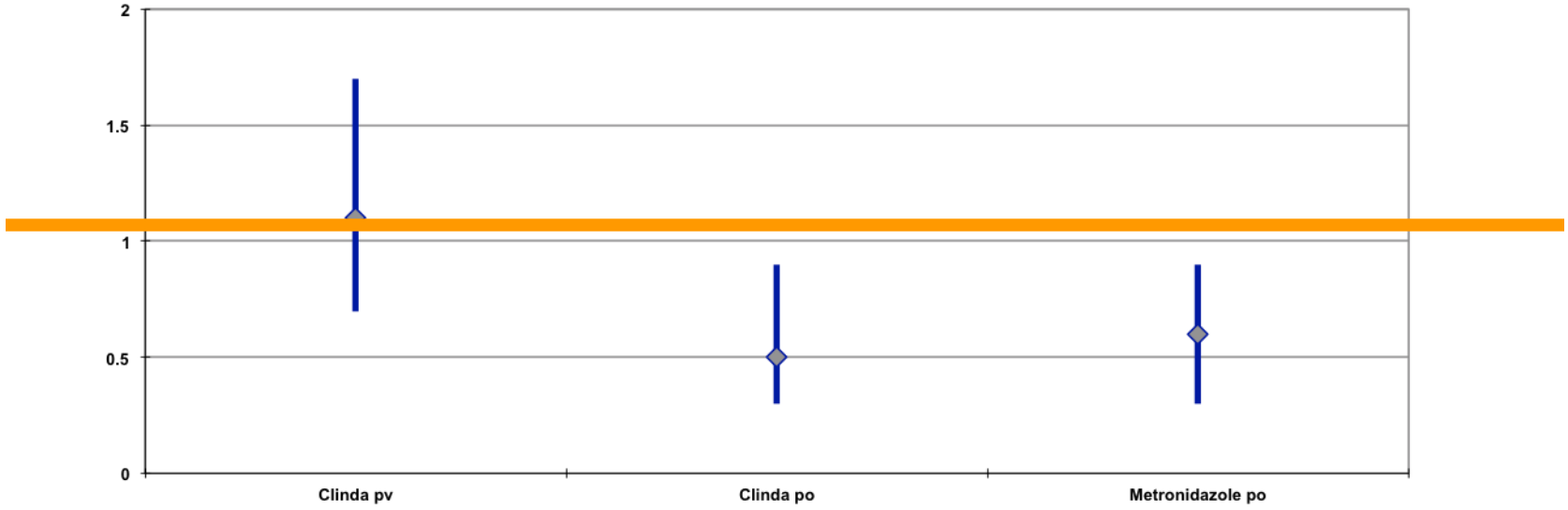
An elevated vaginal pH was a better predictor of early PTL than a shortened CL in this cohort of pregnant women at low risk.

Matijevic R, Grgic O, Kneževic M. Vaginal pH versus cervical lenght in the mid-trimester as secrrenng predictors of preterm labor in low risk population. Int J Gynaecol Obstet 2010;111:41-4

Effect of BV treatment

RR of PTD

Meta-analysis confirms reduction in PTB only in high risk patients (prior PTB)



AJOG 1995;173:1527

300 mg BID
AJOG 1995;173:157

250 mg TDS + 333 mg TDS
NEJM 1995;333:1732

Bacterial vaginosis: summary

- BV increases risk of PTD
- Screen high risk patients
- Systemic treatment for BV (Clinda, Metro,...)
- Other antibiotics (Nifuratel,...)

General screening not recommended

Screening for risks of PTL by means other than history is not beneficial in the general obstetric population

ACOG Practice Bulletin # 31, 10/01

Fibronectins

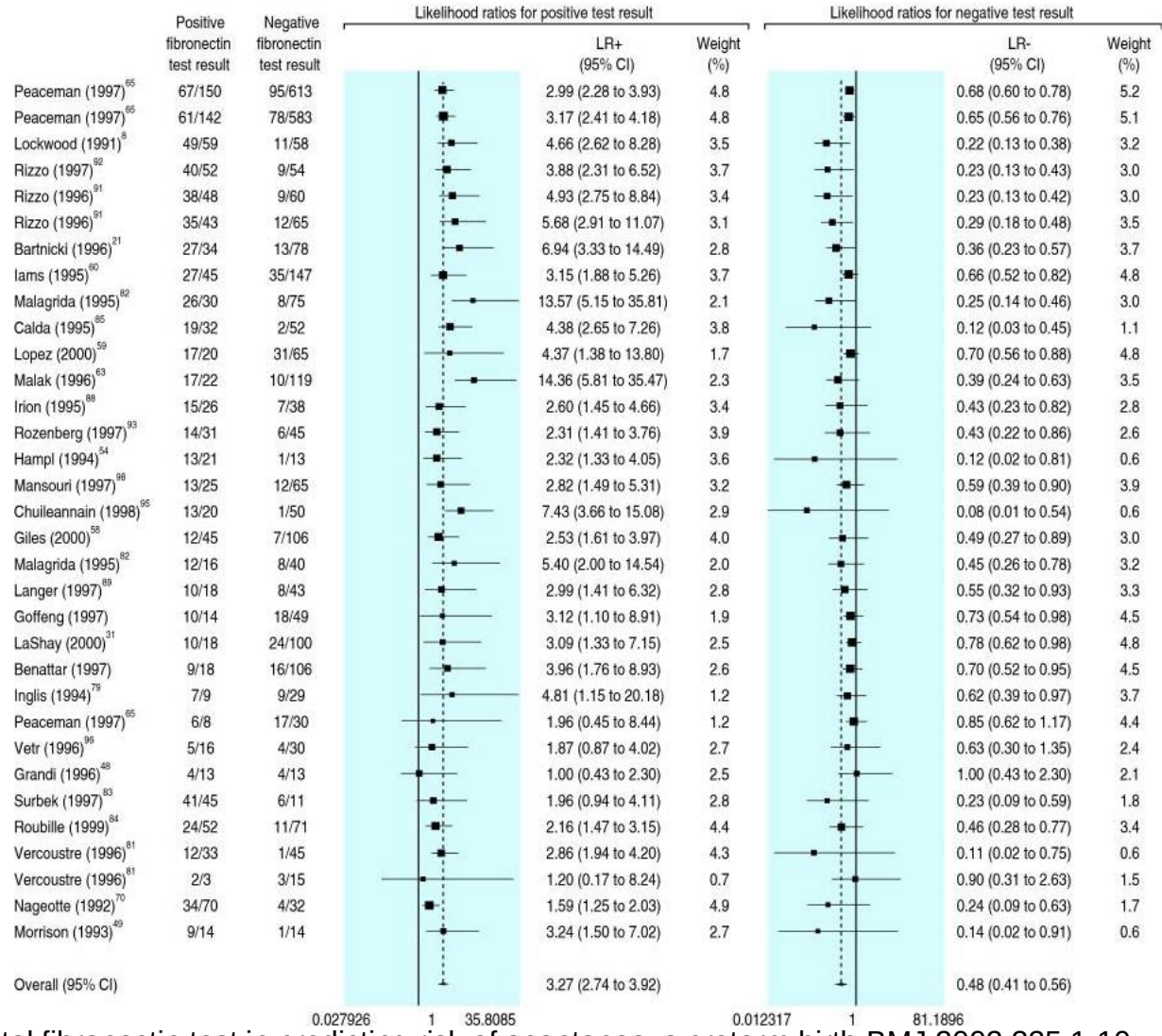
- glycoproteins in plasma and ECM

- fFN in ECM of decidua basalis and cytotrophoblasts
- fFN rarely present in cervical/vaginal secretion of women without PTL/PROM (3%)
- fFN common in cervical/vaginal secretion of women with PTL (50%) or PROM (94%)

- HYPOTHESIS: mechanical or inflammatory damage to placenta or membranes releases fFN into cervical/vaginal secretions

fFN as a predictor of PTB

Meta-analysis; 13 studies; n=22,390



Honest H et al. Accuracy of cervicovaginal fetal fibronectin test in predicting risk of spontaneous preterm birth BMJ 2002;325:1-10

Fibronectin: summary

- fFN is fairly sensitive marker for PTD in high risk patients (55-97%)
- High short term NPV (71-100%) may identify women not needing tocolysis

- General screening not recommended
- No intervention

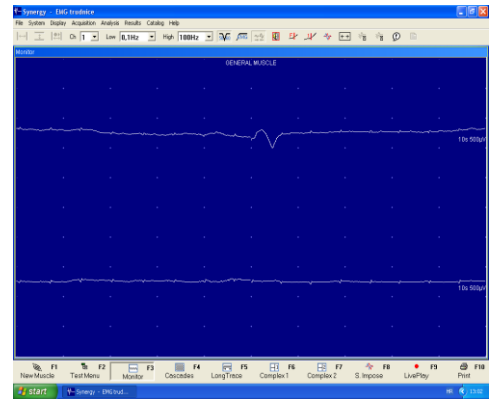
Electromyography (uterine electrical activity measurement)

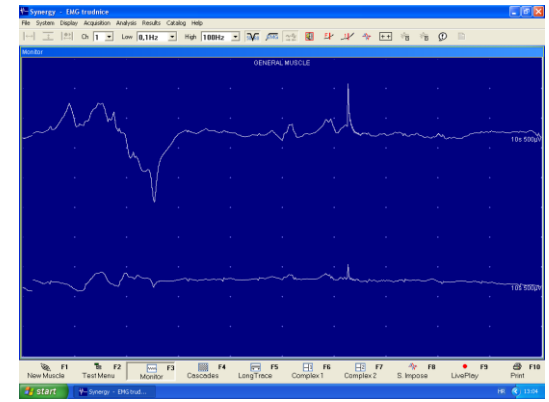
Uterine electrical activity – result of the depolarization and repolarization of thousands of myometrial smooth muscle cells

- causes action potentials (AP)

- by spreading unchanged, trough gap junctions, result in electrical activity

- organized uterine electrical activity precedes uterine contractions and the associated cervical shortening





Grgic O, Matijevic R. Uterine electrical activity and cervical shorthening in the midtrimester of pregnency. Int J Gynecol Obstet 2008;102:246-8

Electromyography *vs.* (and with) CL

n=308

CL ≤25 mm (≤5th centile)

EMG ≥20 action potentials in 20 min (≥95th centile)

Outcome measures: prediction of PTD and early PTD (≤34 weeks).

Grgic O, Matijevic R, Kuna K. Raised electrical uterine activity and shortened cervical length could predict preterm delivery in a low risk population. Arch Gynecol Obstet 2012;285:31-5

Electromyography *vs.* (and with) CL

n=308

CL ≤25 mm (≤5th centile)

EMG ≥20 action potentials in 20 min (≥95th centile)

Outcome measures: prediction of PTD and early PTD (≤34 weeks).

7.4% **2.9%**

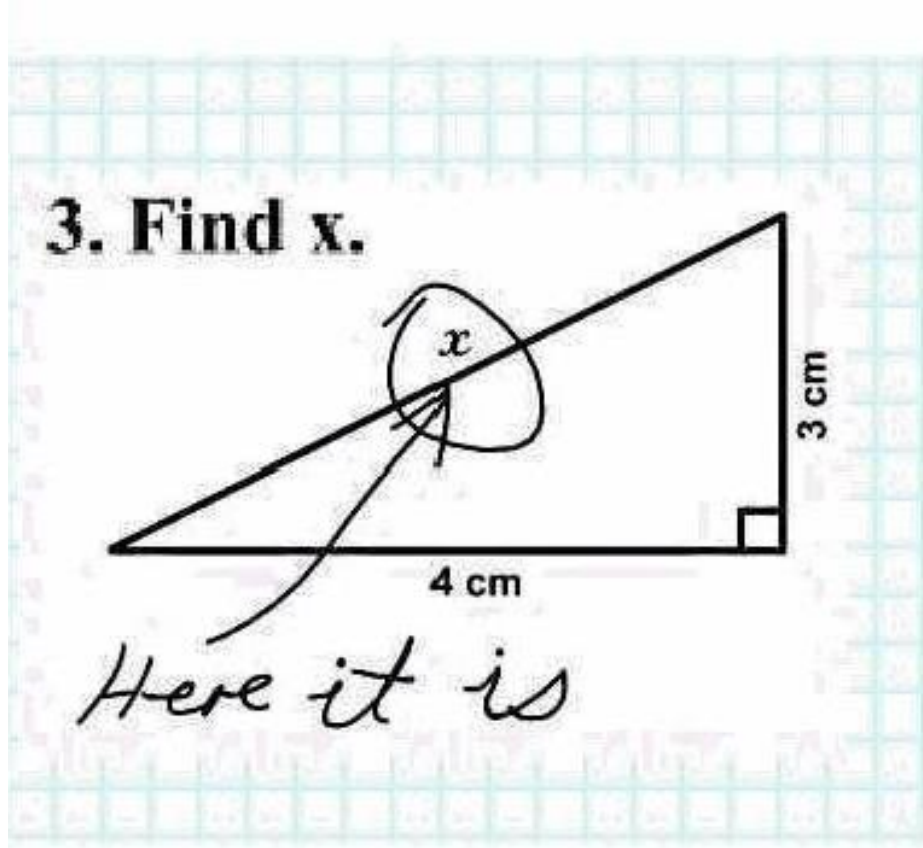
LR wp	PTD	EPTD
CL	1.9, 95% CI 1.0-3.5	0.4, 95% CI 0.2-0.8
EMG	9.5, 95% CI 2.5-35.7	0.6, 95% CI 0.3-1.7
BOTH		**4,95% CI 1.3-14.3**

Grgic O, Matijevic R, Kuna K. Raised electrical uterine activity and shortened cervical length could predict preterm delivery in a low risk population. Arch Gynecol Obstet 2012;285:31-5

Electromyography

- Problem:

- General screening
  not recommended



"Do not do a test which will not change your clinical management"

May be...

The Genetics of Preterm Birth: True Labor or False Labor?

News | May 21, 2014 | Pregnancy and Birth , Prenatal Genetic Testing By Sarah Bruyn Jones

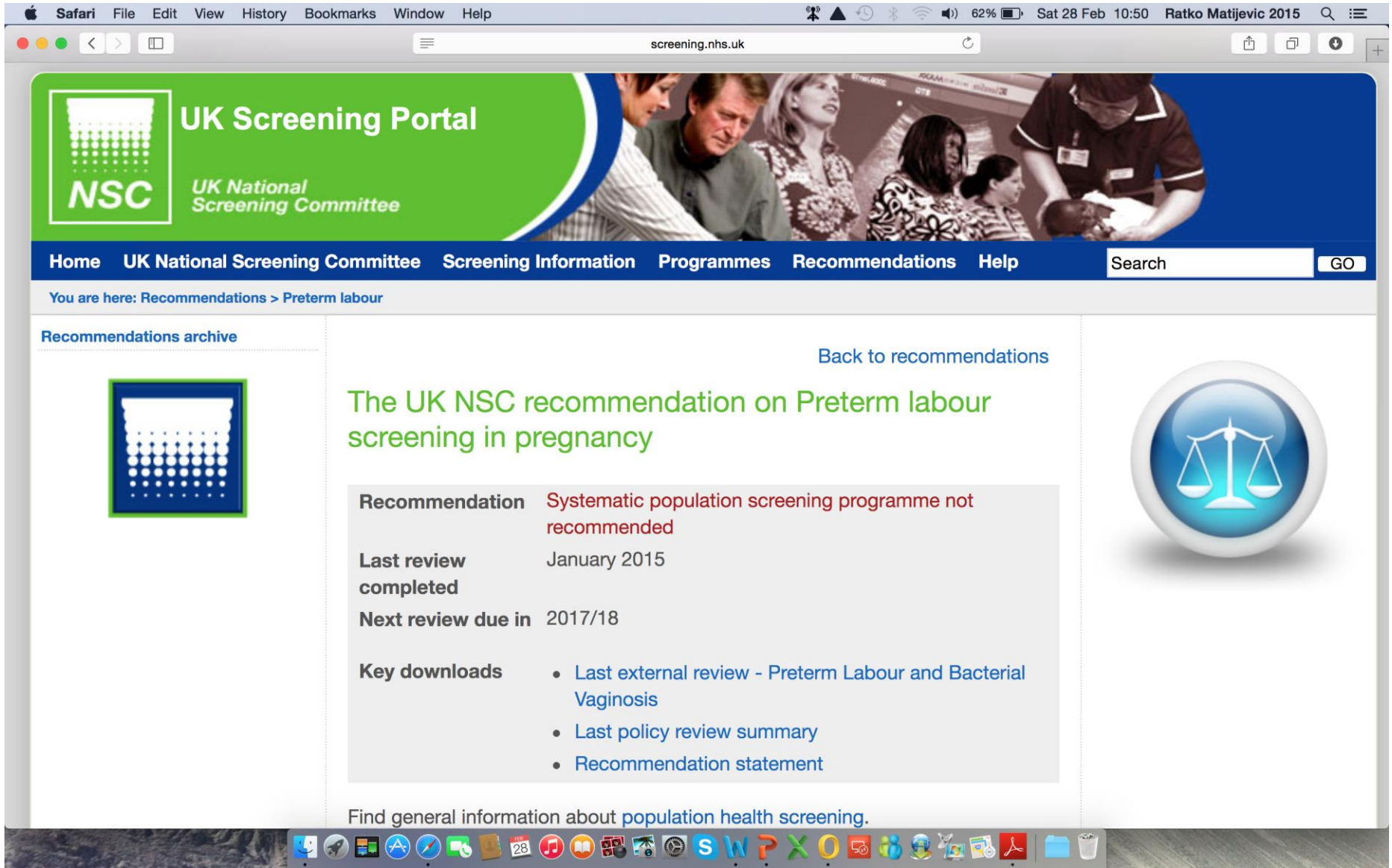
... the predictive efficacy of the nine gene signature coupled with clinical blood data outperformed the fetal fibronectin test ...

PTB prediction and prevention: Conclusions

- Most routine screening (BV, fFN, EMG) *not* indicated for *low risk* patients
- Possible ultrasound screening for all (US)

- Consider progesterone supplementation for women at high risk for PTB (whatabout all...?)

Finally...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Recommendations archive
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The UK NSC recommendation on Preterm labour screening in pregnancy
Recommendation
Systematic population screening programme not recommended
Last review completed
January 2015
Next review due in
2017/18
Key downloads
Last external review - Preterm Labour and Bacterial Vaginosis
Last policy review summary
Recommendation statement
Find general information about population health screening.

Why not (UK)

- The measurement of cervical length in asymptomatic women is not reliable enough for use as a screening tool. There are unanswered questions over the timing of the test and there is no standardised 'normal' measurement of cervical length in order to establish what an 'abnormal' measurement is.

- Not known when the test should be offered or whether it is reliable in identifying which pregnancies are at risk and which are not. Screening would identify many women as at risk when they are not, leading to unnecessary preventative treatment.

- There is not enough evidence to be sure that vaginal progesterone (a hormone treatment) is an effective treatment for preventing preterm labour or that it reduces the most severe outcomes (death or disability) for the baby.

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