

Predicting/Preventing

Prematurity:

Knowing who will be too little
before it's too late

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OBJECTIVES

By the end of this presentation the participant will understand:

- Impact and etiology of preterm delivery (PTD)
- Traditional methods of diagnosing and treating preterm labor (PTL) and their shortcomings
- Methods and rationale for predicting prematurity
- The role of ffn and ultrasound of the cervix in predicting the likelihood of spontaneous PTD.

Preterm Labor and Delivery (<37 weeks)

◆ Preterm Labor

- Regular uterine contractions associated with cervical change before 37 weeks

◆ Preterm Delivery

- 11.8 % of all pregnancies result in preterm birth 1999 up from 9.4% in 1981
- 80% Spontaneous
- Single largest cause of perinatal morbidity and mortality

Sequelae of Preterm Birth

◆ Neonatal:

- Respiratory Distress Syndrome (RDS)
- Necrotizing Enterocolitis
- Intraventricular Hemorrhage (IVH)
- Patent Ductus Arteriosus (PDA)

◆ Long-term:

- Cerebral Palsy
- Mental Retardation
- Seizure Disorders
- Blindness and Deafness
- Learning Disabilities

Predicting/Preventing Prematurity

- ◆ Value of Predicting Risk
 - Only if intervention can improve outcome
 - Corticosteroid therapy-NIH
 - Tocolysis for up to 48 hours if truly at risk
 - Transfer to Tertiary Care Center
 - Decreased intervention if low risk

Predicting/Preventing Prematurity

◆ Risk Factors

– Demographics

- ◆ Low socioeconomic status (RR=1.83)
- ◆ Nonwhite race (African American RR=3.3)
- ◆ Maternal age <17 and >35 years (RR 1.47-1.95)
- ◆ Low prepregnancy weight (OR=2.72)

– Prior SPTB (6-8 fold increased risk)

– Vaginal bleeding in more than one trimester

Predicting/Preventing Prematurity

◆ Risk Factors

Job requiring prolonged standing
(> 40 hours per week)

–Smoking

- ◆ Preterm birth
- ◆ Low birth weight
- ◆ Spontaneous abortion

◆ Unable to Reliably Identify Women who will Deliver Preterm

Predicting/Preventing Prematurity

- ◆ Uterine Causes
 - Cervical Insufficiency
 - Uterine Anomalies
 - Uterine Stretch
- ◆ Infectious Causes
 - Association but unknown if etiologic
 - Ureaplasma urealyticum, Mycoplasma hominis, Gardnerella vaginalis, Peptostreptococcus, Bacteroides
- ◆ Cause unknown for most cases

Predicting/Preventing Prematurity

- ◆ Biologic Markers for Predicting PTB
 - Home uterine activity monitoring
 - Salivary Estriol
 - ◆ diurnal variation
 - ◆ suppressed by betamethasone
 - Bacterial Vaginosis
 - Fetal fibronectin
 - ◆ adhesive basement membrane protein
 - ◆ Present in vaginal secretions 16-20 weeks
 - ◆ Strong negative predictor of PTB
 - Cervical Sonography

Predicting/Preventing Prematurity

- ◆ Potential Benefits of Risk Identification
 - More accurately identify women at risk
 - Avoid unnecessary treatment
 - Develop effective ongoing surveillance programs
 - Avoid unnecessary expense

Predicting/Preventing Prematurity

- ◆ Uterine monitoring
 - 13 RCT with conflicting results
 - US Preventative Services Task Force concluded not effective
 - Although FDA approved, NOT recommended
- ◆ Salivary Estriol
 - FPR 23%
 - Investigational only

Predicting/Preventing Prematurity

◆ Bacterial Vaginosis

- Large MFMU RCT showed no difference N=1953 (Carey et al NEJM 2000;342:534-40)
- Insufficient evidence to recommend use

◆ Fetal Fibronectin (fFN)

- Meta-analysis of 27 studies moderate success (Leitich, et al AJOG 1999;180:1169-76)
- NPV 69-92% before 37 weeks, >95% 14 days
- May be useful in high risk groups
 - ◆ Intact membranes
 - ◆ <3cm
 - ◆ 24-34 6/7 weeks
 - ◆ Efficient time frame

Predicting/Preventing Prematurity

- ◆ Transvaginal Sonography (TVUS)
 - ◆ Review of 35 Studies
 - Sensitivities 68-100%
 - ◆ Preterm Predictors Study N=2900+ (Iams, et al NEJM 1996:334:567-72)
 - <40 mm RR=2.8
 - <35 mm RR=3.52
 - <30 mm RR=5.39
 - <26 mm RR=13.88
 - <13 mm RR=24.94
 - ◆ Routine use not recommended

Predicting/Preventing Prematurity

◆ fFN and TVUS

Table 1. Recurrence Risk of Spontaneous Preterm Birth at <35 Weeks of Gestation According to Cervical Length and Fetal Fibronectin in Women with a Prior Preterm Birth

Cervical Length (mm)	Fetal Fibronectin + (%)	Fetal Fibronectin - (%)
25	65	25
26-35	45	14
>35	25	7

Fetal fibronectin and cervical length assessed at 24 weeks of gestation. Cervical length assessed by transvaginal ultrasonography.

Data from: Iams JD, Goldenberg RL, Mercer BM, Moawad A, Thom E, Meis PJ, et al. The Preterm Prediction Study: recurrence risk of spontaneous preterm birth. National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. *Am J Obstet Gynecol* 1998;178:1035-1040

Predicting/Preventing Prematurity

◆ Summary of Recommendations

– Level A

- ◆ No data to support salivary estriol, HUAM or BV screening

– Level B

- ◆ Screening for risk in general population not beneficial
- ◆ TVUS, fFN or combination may be useful, however, clinical utility may rest with NPV
- ◆ fFN may be useful in women with symptoms of PTL (NPV)

Predicting/Preventing Prematurity

- ◆ Potentially Effective Interventions
 - Supplemental Progesterone
 - ◆ Natural-micronized-vaginal for prevention PTD
 - ◆ Synthetic-17 alpha Hydroxyprogesterone Caproate (Makena-FDA approval Feb. 2011, and compounded)
 - \$690/dose vs \$10-20/dose compounded
 - FDA does not plan enforcement against properly compounded products

Predicting/Preventing Prematurity

◆ Potentially Effective Interventions

– Supplemental Progesterone

◆ Dosage

– 17 OHP 250 mg IM weekly

– Natural Progesterone (vaginal)

◆ Crinone or Prochieve 8% (90 mg progesterone gel) daily

◆ Endometrin 100-200 mg (100 mg tablet) daily

◆ Prometrium 100-200 mg capsules daily

Predicting/Preventing Prematurity

◆ Potentially Effective Interventions

– Supplemental Progesterone

◆ Clinical Indications

– H/O SPTB

- ◆ MFMU Trial-17P (Meis et al, NEJM 2003;348:2379)
 - ◆ <37 weeks (36 vs 55% RR=0.66)
 - ◆ <35 weeks (21 vs 31% RR=0.67)
 - ◆ <32 weeks (11 vs 29% RR=0.58)
 - ◆ Lower risk NEC, IVH, supplemental O₂, no virilization of females

Predicting/Preventing Prematurity

◆ Potentially Effective Interventions

– Supplemental Progesterone

◆ Clinical Indications

– H/O SPTB

- ◆ Da Fonseca Trial-100 mg vaginal suppositories N=142 high risk-H/O SPTB, cerclage, uterine malformation (da Fonseca et al, AJOG 2003;188:419)
 - ◆ <37 (14 vs 29%)
 - ◆ <34 (3 vs 19%)
- ◆ O'Brien Trial-progesterone gel N=659 (O'Brien, et al JUOG 2007;30:687)
 - ◆ No difference

Predicting/Preventing Prematurity

◆ Potentially Effective Interventions

– Supplemental Progesterone

◆ Clinical Indications

- Arrested PTL-small studies suggestive of prolongation of pregnancy
- Short Cervix

- ◆ Hassan, et al 2011 JUOG N=458 RCT 10-20 mm 19-24 weeks progesterone gel 8%
 - ◆ <33 weeks (8.9vs16.1% RR=0.55)
 - ◆ <28 weeks (5.1vs10.3% RR=0.50)
 - ◆ <35 weeks (14.5vs23.3% RR=0.62)
 - ◆ Less RDS, NNM, BW<1500g

Predicting/Preventing Prematurity

◆ Potentially Effective Interventions

– Supplemental Progesterone

◆ Clinical Indications

– Short Cervix

- ◆ Secondary analysis of RCT progesterone gel effective in short cervix
- ◆ Fonseca, et al NEJM 2007;357:462
 - ◆ RCT N=250, ≤ 15 mm 20-25 weeks
 - ◆ vaginal progesterone 200 mg vs placebo
 - ◆ < 34 weeks 19.4 vs 34.4% RR=0.54

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Predicting/Preventing Prematurity

◆ Potentially Effective Interventions

– Progesterone No Proven Efficacy

◆ Twins

– RCT 17P N=661 (Rouse, et al, NEJM 2007;357(5):454)

◆ 17P injections vs placebo

◆ 16-20 weeks to 35 weeks

◆ IUD or del before 35 weeks 41.5%vs37.3% P=NS

– STOPPIT Trial RCT vaginal progesterone gel vs placebo (Norman, et al, Lancet 2009;373(9680):2034)

◆ 10 weeks from 24 weeks

◆ IUD or del before 34 weeks 24.7%vs19.4% P=NS

◆ No difference in AE

Predicting/Preventing Prematurity

◆ Potentially Effective Interventions

– Progesterone No Proven Efficacy

◆ Twins

– Metanalysis

- ◆ Previous two trials and smaller trial (N=26)
- ◆ Pooled OR 1.36 CI 0.89-1.51

– RCT (Combs, et al, AJOG 2011;204(3):221)

- ◆ N=240, 2:1 ratio 17P vs placebo
- ◆ 16-24 weeks to 34 weeks
- ◆ 35.3 v 35.9 P=NS

◆ Positive FFN

– No information

Predicting/Preventing Prematurity

◆ Potentially Effective Interventions

– Progesterone No Proven Efficacy

◆ Triplets

– RCT (Caritis, et al, OG. 2009;113:285)

- ◆ N=134, 16-24 weeks to 35 weeks
- ◆ Fetal loss or PTB < 35 weeks
- ◆ 17P 250 mg IM vs placebo
- ◆ 83% v 84% P=NS

– RCT (Combs, et al, AJOG. 2010;203:248)

- ◆ N=81, 2:1 ratio, 16-22 weeks to 34 weeks
- ◆ Composite neonatal morbidity
- ◆ 38% v 41% P=NS
- ◆ Mean GA at del 31.9 v 31.8 weeks P=NS
- ◆ 13 midtrimester losses 17P v placebo P=.02

Predicting/Preventing Prematurity

◆ Potentially Effective Interventions

– Progesterone No Proven Efficacy

◆ PROM

– RCT (Briery, et al, AJOG 2011;204:54)

◆ PROM 20-30 weeks

◆ N=69, 17P vs Placebo

◆ Time to delivery, mode of delivery, neonatal morbidity and mortality similar P=NS

◆ Cerclage

– 2^o Analysis (Berghella et al, AJOG 2010;202:351)

◆ Prior SPTB cervix < 25 mm 16-22 6/7 weeks

◆ N=300, 17P vs placebo

◆ Intent to treat, PTB < 35 weeks P=NS in either grp

◆ No cercl grp PTB < 24wks (OR .08), PND (OR .14)

Predicting/Preventing Prematurity

- ◆ Potentially Effective Interventions
 - Inhibition of Acute Preterm Labor
 - ◆ Temporarily abolishes contractions but NOT the underlying stimulus
 - Delay delivery for 48 hours for maximum glucocorticoid effect
 - Time for safe transport of the mother
 - Prolong pregnancy when self-limited condition (pyelonephritis, abdominal surgery)
 - No clear superior tocolytic

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Predicting/Preventing Prematurity

- ◆ Potentially Effective Interventions
 - Diagnosis and treatment of ASB
 - ◆ Meta-analysis of 14 RCT's (Cochrane Rev 2001)
 - Clears ASB (OR 0.07 CI .05-0.1)
 - Reduces Pyelonephritis (OR 0.24 CI 0.19-0.32)
 - Reduces PTD, LBW (OR 0.60 CI 0.45-0.8)
 - ◆ First trimester culture and regular screening if at risk (Hb AS, rec UTI, DM, renal Dz)

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Predicting/Preventing Prematurity

◆ Potentially Effective Interventions

– Smoking Cessation

◆ Dose dependent relationship with PTB

– Abrupton, placenta previa, PROM, IUGR

– May be direct effect on PTL

– Likely cessation will reduce these complications

– Avoid Cocaine

◆ PTL if positive UDS, 60% cocaine

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Predicting/Preventing Prematurity

- ◆ Potentially Effective Interventions
 - Decrease Multiple Gestation from ART
 - ◆ Multiple births 6X PTD rate
 - ◆ Responsible for increased mult gestation
 - ◆ Strategies
 - Firm diagnosis of infertility
 - Limiting # embryos transferred/ART cycle
 - MFR-controversial
 - Cervical Cerclage
 - ◆ H/O multiple painless second trim losses
 - ◆ Short cervix
 - RCT-15 mm N=253 P=NS (To et al, Lancet 2004; 363:1849)

Predicting/Preventing Prematurity

◆ Potentially Effective Interventions

– Reduce Occupational Fatigue

- ◆ Meta-analysis 21 studies N=146,457
(Mozurkewich, OG, 2000;95:623)

- High cumulative work fatigue score strongest work related risk factor for PTB (OR 1.63 CI 1.33-1.98)

- ◆ European Case control study (Saurel-Cubizolles J Epid Com Health 2004;58:395)

- 42 hours, low job satisfaction, stood > 6 hours

- ◆ No RCT's

- European Regulations-paid mat leave, guaranteed job protection, regulation of hazardous working conditions (only France reduction in PTD)

Predicting/Preventing Prematurity

Working conditions and the risk of adverse pregnancy outcome

Work parameter	Odds ratio for preterm birth	Odds ratio for SGA infant	Confidence interval
Physically demanding work (lifting, load carrying, manual labor, or significant physical exertion)	1.22		1.15, 1.29
		1.37	1.30, 1.44
Prolonged standing (>3 hours/day)	1.26		1.13, 1.40
Shift or night work	1.24		1.06, 1.46
Long working hours	1.03		0.92, 1.16
High cumulative work fatigue score	1.63		1.33, 1.98

SGA: small for gestational age.

Adapted from data in Mozurkewich, EL, Luke, B, Avni, M, Wolf, FM. *Obstet Gynecol* 2000; 95:623.

Predicting/Preventing Prematurity

◆ Potentially Effective Interventions

– Nutritional Intervention

◆ N-3 Fatty Acids (fish oil)

– Meta-analysis

- ◆ 6 RCT's N=2783
- ◆ weighted mean difference in GA 2.55 days CI 1.03-4.07 (3 trials N=1621) (Cochrane Review 2006)
- ◆ Fish oil v placebo (two trials) N=860 PTB<34 weeks (RR 0.69, CI 0.49-0.99), <37 wks NS
- ◆ Fish Oil Trials in Pregnancy (FOTIP) (Olsen, et al BJOG. 2000;107:382)
- ◆ No difference LBW, SGA, preeclampsia
- ◆ Not enough evidence to recommend

Predicting/Preventing Prematurity

◆ Potentially Effective Interventions

– Nutritional Intervention

◆ N-3 Fatty Acids (fish oil)

- RCT (Smuts et al, OG. 2003;101:469)
- N=350 73% African American 24-28 wks
- n-3 LC polyunsaturated FA fortified vs unfortified eggs (133 mg vs 33 mg)
- 6 days longer gestation (p=.009)
- Birth weight, length, HC P=NS

◆ Fish-Observational studies discordant results

- Cardiovascular Risk Reduction Diet in Pregnancy (CARRDIP) N=290 reduced PTB RR 0.1 CI .01-0.77 (Khoury AJOG. 2005;193:1292)
- Prospective Observational Cohort N=2109 P=NS (Oken, et al, AJ Epidem. 2004;160:774)

Predicting/Preventing Prematurity

◆ Potentially Effective Interventions

– Nutritional Intervention

◆ Undernutrition

- Associated with increased risk for PTB
- Protein supplements, vitamins not associated with reduction in PTB
- (Cochrane Rev 2003)
 - ◆ 5 trials to increase calories/protein N=1134 no consistent benefit in outcomes
 - ◆ 13 trials N=4665 balanced energy protein supplement reduced SGA, IUD, NND, **not** PTB
 - ◆ 2 trials N=1076 high protein increased SGA
 - ◆ 3 trials N=966 isocaloric protein increase SGA
 - ◆ 3 trials N=384 energy/protein restriction less weight gain/mean BW, No effect PIH

Predicting/Preventing Prematurity

- ◆ Potentially Effective Interventions
 - Avoid Short Interpregnancy Intervals
 - ◆ Meta-analysis 67 observational studies (Conde-Agudelo JAMA.2006;295:1809)
 - <6 months PT

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Predicting/Preventing Prematurity

◆ Unproven Interventions

– Genital Tract Infection

◆ Chlamydia/GC

- RCT Chlamydia Rx (Martin et al, IDOG.1997;5:10)
- 23-29 weeks Erythromycin v placebo
- 13% vs 15% PTB, 8% vs 11% LBW P=NS

◆ BV, Ureaplasma, GBS

- RCT Meta-analysis (Leitich et al, AJOG.2003;188:752) P=NS
- 10 studies N=3969 PTB (OR 0.83 CI 0.57-1.21)
- Previous SPTB may benefit but Insufficient Evidence

Predicting/Preventing Prematurity

◆ Unproven Interventions

– Genital Tract Infection

◆ Trichomonas

- RCT N=617 (Klebanoff et al NEJM.2001;345:487)
- 16-23 weeks and 24-29 weeks, two 2 g doses metronidazole vs placebo
- PTB<37 19% v 10.7% RR 1.8 CI 1.2-2.7, P=.004

◆ Positive Gram Stain of Vaginal Smear

- RCT N=4429 (Kiss, et al, BMJ. 2004;329:371)
- PTB<37 weeks 3% vs 5.3% P=.0001
- results need confirmed before rec. treatment

Predicting/Preventing Prematurity

◆ Unproven Interventions

– Periodontal Disease

- ◆ Meta-analysis 7 RCT's (Polyzos et al, AJOG.2009;200:225)

- Treatment with scaling and/or root planing
- PTB OR 0.55 CI 0.35-0.86, P=.008

- ◆ Maternal Oral Therapy to Reduce Obstetric Risk (MOTOR)

- RCT N=1806 Early Second Trimester
- Immediate vs Delayed treatment
- PTB<37 13.1% vs 11.5% P=.316

Predicting/Preventing Prematurity

◆ Unproven Interventions

– Uterine Activity Monitoring

- ◆ Multiple RCTs show no efficacy and increased visits to labor and delivery

– Bedrest and Hospitalization

- ◆ No evidence for decreasing risk of PTD
- ◆ RCT N=101 Home vs hospitalization after arrested PTL (Yost, et al, OG.2005;106:14)
- ◆ 71% vs 72% ≥ 36 weeks P=NS

– Abstinence

- ◆ Not a risk for PTB

Predicting/Preventing Prematurity

◆ Unproven Interventions

– Prophylactic Tocolytic Drugs

◆ Beta Mimetics

– One RCT found Isoxuprine vs placebo (Cochrane Review 2008)

– No difference in PTB < 37 weeks, PNM, PTL

– Antibiotics

◆ RCT's

– Positive fFN N=715 Metronidazole/Azithromycin vs placebo (Andrews, et al, OG.2003;101:847)

◆ No difference PTB <37, <35 or <32 weeks

Predicting/Preventing Prematurity

◆ Unproven Interventions

– Antibiotics

◆ RCT's

- Mostly HIV positive (Africa) N=2661 Met/Azith 20-24 wks, Met/amp in labor vs placebo (Goldenberg, et al AJOG.2006;194:650)
 - ◆ No reduction in PTB
- N=241, After PTD Azithromycin/Metronidazole vs placebo (Andrews, et al, AJOG.2006;194:617)
 - ◆ Interconceptional q 4 months
 - ◆ No difference in PTB < 37, < 35, < 32, SAB
 - ◆ Antibiotic group nonsignificant increase in GA at delivery and decrease in BW

Predicting/Preventing Prematurity

◆ Unproven Interventions

– Antibiotics

- ◆ Meta-Analysis 17 RCT's (Silmcox et al, ANZJOG.2007;47:368)

- PTB RR 1.03 CI 0.86-1.24 P=NS

– Enhanced PNC

- ◆ MOD Multicenter Prematurity Prevention Trial N=2395 (AJOG. 1993;169:352)

- PTB < 37 16.1% vs 15.4% P=NS

– Social Support

– Thyroid Hormone

Predicting/Preventing Prematurity

◆ Summary

- Risk factors may increase risk but most PTD's occur in those without risk factors
- Usually unable to prevent PTB
 - ◆ Can optimize with corticosteroids/transport
- Progesterone Supplementation
 - ◆ Previous SPTB (Grade 1B)
 - ◆ Shortened cervix (Grade 1B)
 - ◆ Not useful in multiples or PROM
- Treating ASB reduces PTB, LBW (Grade 1A)
- Smoking Cessation
- Prevent Multiple Gestation
- Treatment of Asx Trichomonas does not reduce and may even increase risk PTB

Predicting/Preventing Prematurity

◆ Summary

- Periodontal Disease increases risk PTB but insufficient evidence for treatment to reduce risk of PTB
- HUAM, self-palpation, bedrest, abstinence, prophylactic tocolytics or ABX, enhanced PNC and social support have not been shown to reduce PTB
- Interpregnancy interval > 6 months may reduce risk of PTB
- Cervical Cerclage, reduction in occupational stress/exertion, nutritional intervention may benefit selected women

OBJECTIVES

By the end of this presentation the participant will understand:

- Impact and etiology of preterm delivery (PTD)
- Traditional methods of diagnosing and treating preterm labor (PTL) and their shortcomings
- Methods and rationale for predicting prematurity
- The role of ffn and ultrasound of the cervix in predicting the likelihood of spontaneous PTD.
- Current trends in treating PTL.