Advances in the Management of Preterm Labor: Achieving Optimal Practice
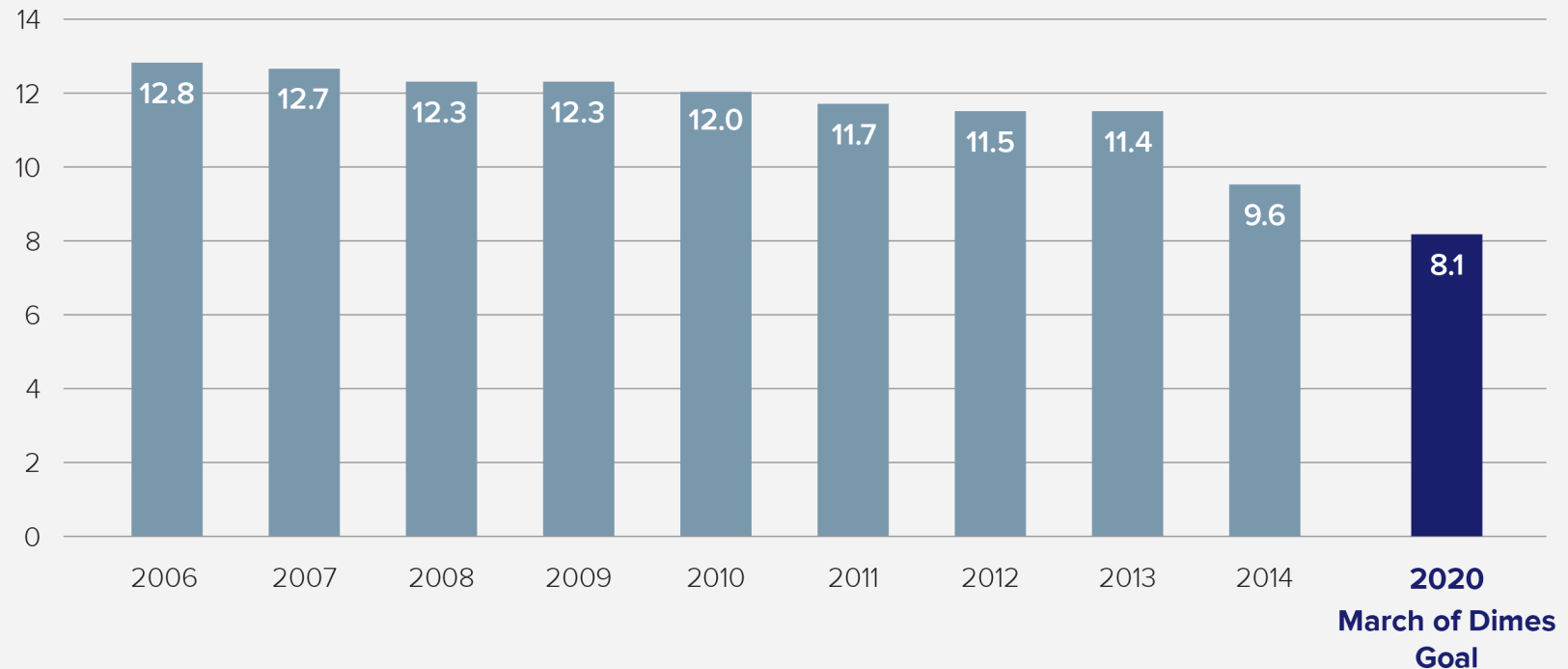
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Learning Objectives

- Understand the risk factors and mechanisms of preterm birth (PTB)

- Evaluate clinical efficacy of diagnostic tools

- Discuss management strategies and interventions for PTB for improved outcomes

- Update on literature

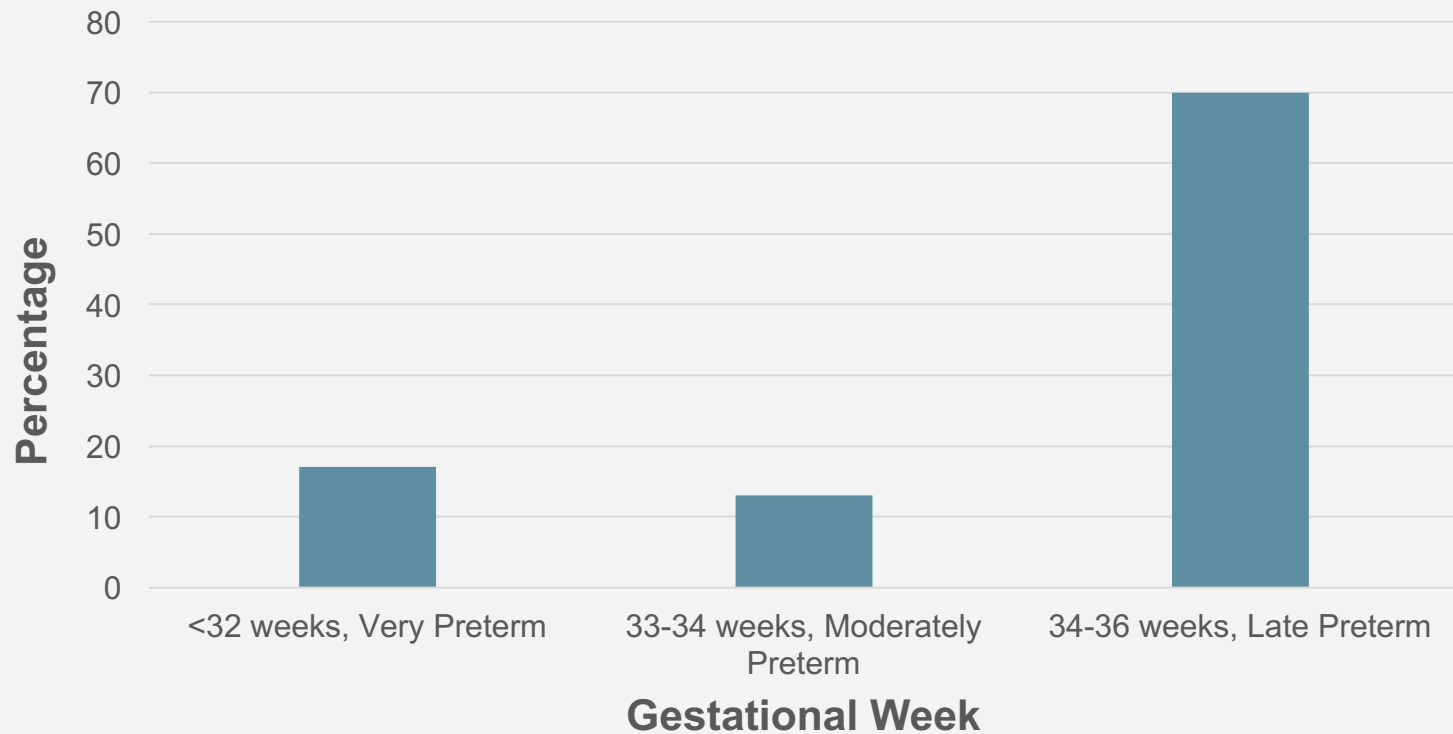# Preterm Birth Is a Major Issue in Obstetrics

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Incidence of Preterm Birth in US, 1 in 10 Infants
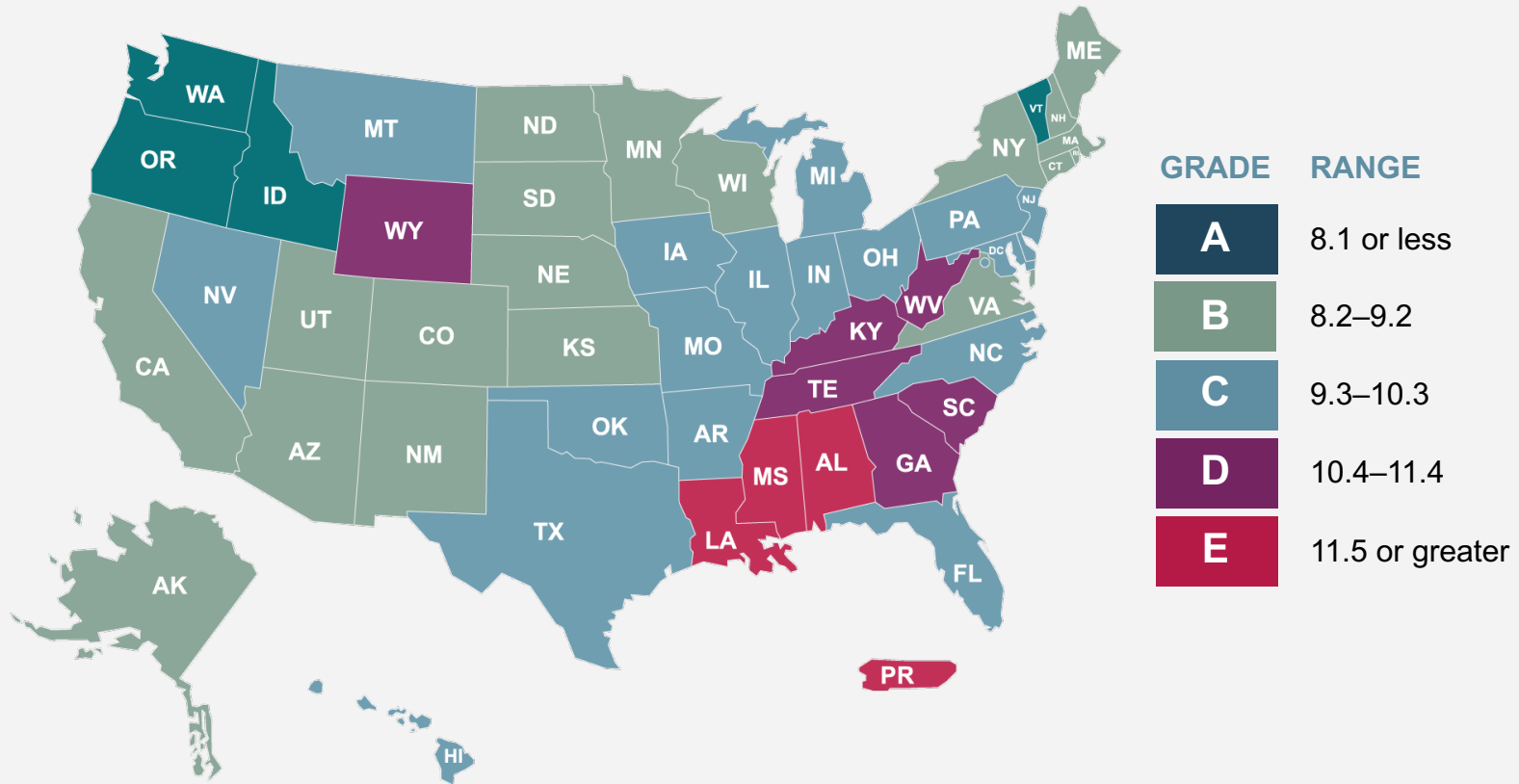
Preterm Births in the US (%)

Adapted from: March of Dimes. 2015 Premature Birth Report Card. http://www.marchofdimes.org/materials/premature-birth-report-card-united-states.pdf. Published 2015. Accessed March 8, 2017.

2013 PTB by Gestational Week

PTB=preterm birth.
Adapted from: Child Trends Databank. Preterm Births. http://www.childtrends.org/?indicators=preterm-births. Updated March 2015. Accessed March 8, 2017.

March of Dimes Report Card

US Premature Birth Rate = 9.6%

GRADE	RANGE
A	8.1 or less
B	8.2–9.2
C	9.3–10.3
D	10.4–11.4
E	11.5 or greater

Adapted from: March of Dimes. 2015 Premature Birth Report Card. http://www.marchofdimes.org/materials/premature-birth-report-card-united-states.pdf. Published 2015. Accessed March 8, 2017.

Newborn Survival by Gestational Age

Newborn Survival by Gestational Age
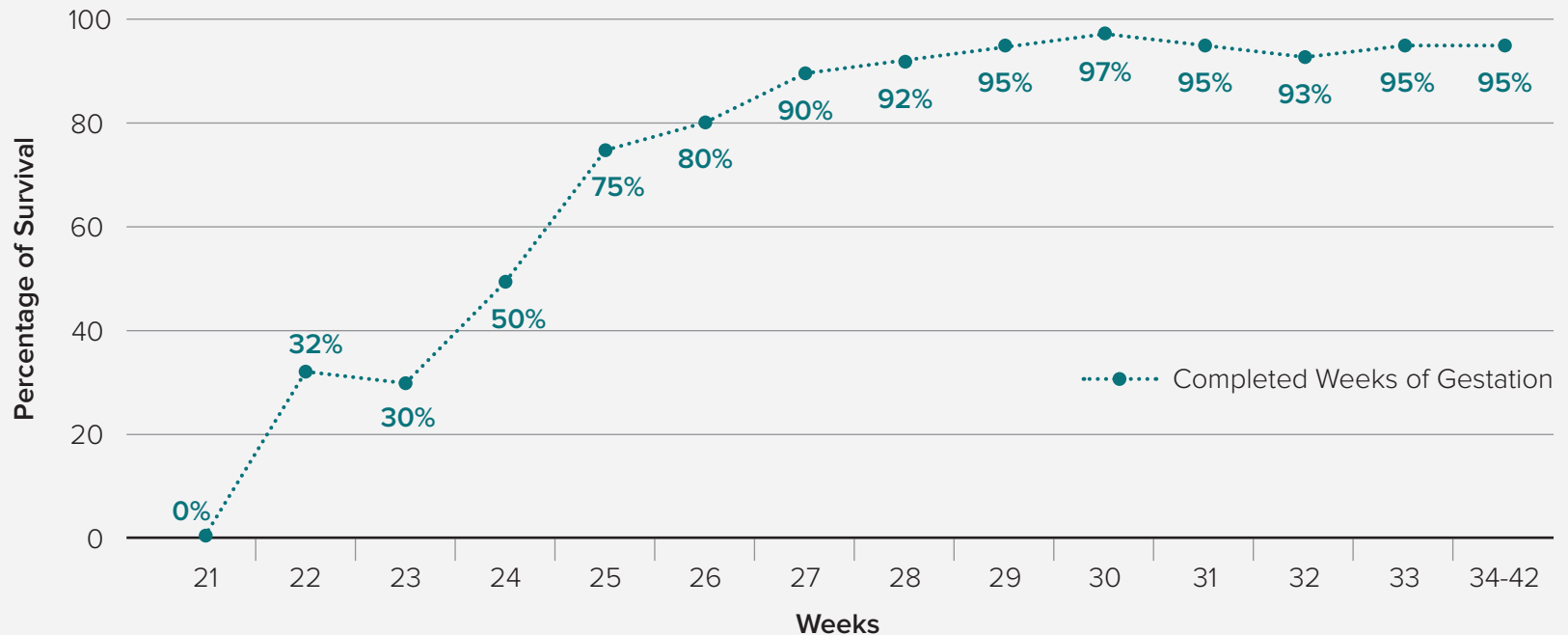
Adapted from: Lemons JA, et al. Very Low Birth Weight Outcomes of the National Institute of Child Health and Human Development Neonatal Research Network, January 1995 Through December 1996. *Pediatrics.* 2001;107(1):E1.

Complications of PTB

Early Consequences	Long-Term Consequences

Early Consequences

- Mortality:
  - 16-fold higher risk for infants born at 28–30 weeks compared with term infant

- Morbidity:
  - Respiratory, gastrointestinal, immunological and CNS complications
  - Significant economic and emotional costs

Long-Term Consequences

- Neurodevelopmental disabilities.

- Altered pulmonary function.

- Metabolic and cardiovascular risk.

- Decreased long-term survival and reproductive capabilities.

CNS=central nervous system; PTB=preterm birth.
Behrman RE, et al, eds. Preterm Birth: Causes, Consequences and Prevention. Institute of Medicine (US) Committee on Understanding Premature Birth and Assuring Healthy Outcomes. Washington, DC: National Academies Press; 2007.

The High Cost of PTB

The estimated annual societal economic cost of preterm birth in the US was $26.2 billion, or more than $51,000 per premature infant.

Average first-year medical cost, in 2005 dollars
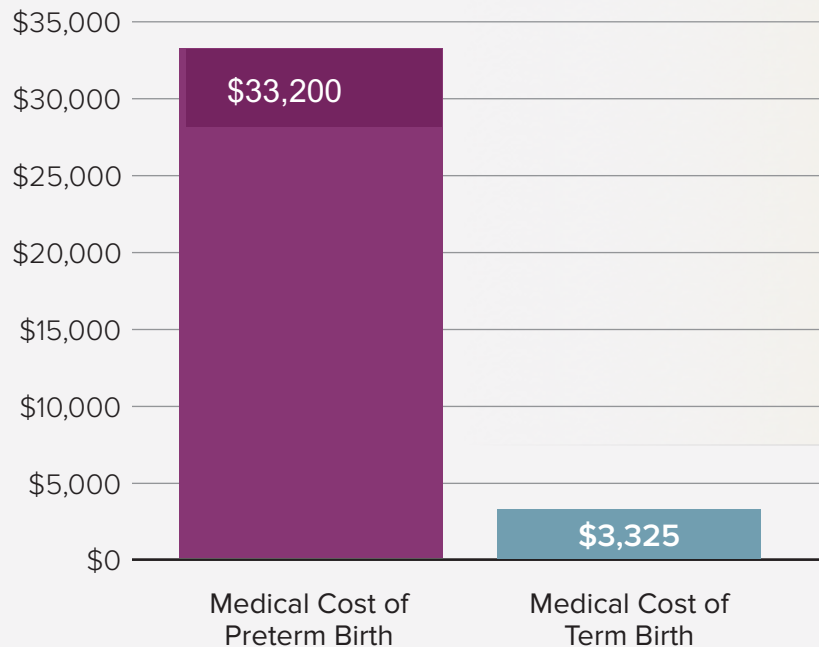
	These 2005 costs show that the medical cost of a preterm birth is **10 times** the cost of an uncomplicated term birth.

Chart:
- Medical Cost of Preterm Birth: $33,200
- Medical Cost of Term Birth: $3,325

Behrman RE, et al, eds. Preterm Birth: Causes, Consequences and Prevention. Institute of Medicine (US) Committee on Understanding Premature Birth and Assuring Healthy Outcomes. Washington, DC: National Academies Press; 2007.

Preterm Birth as a Syndrome

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PTL as a Syndrome Associated With Multiple Mechanisms of Disease

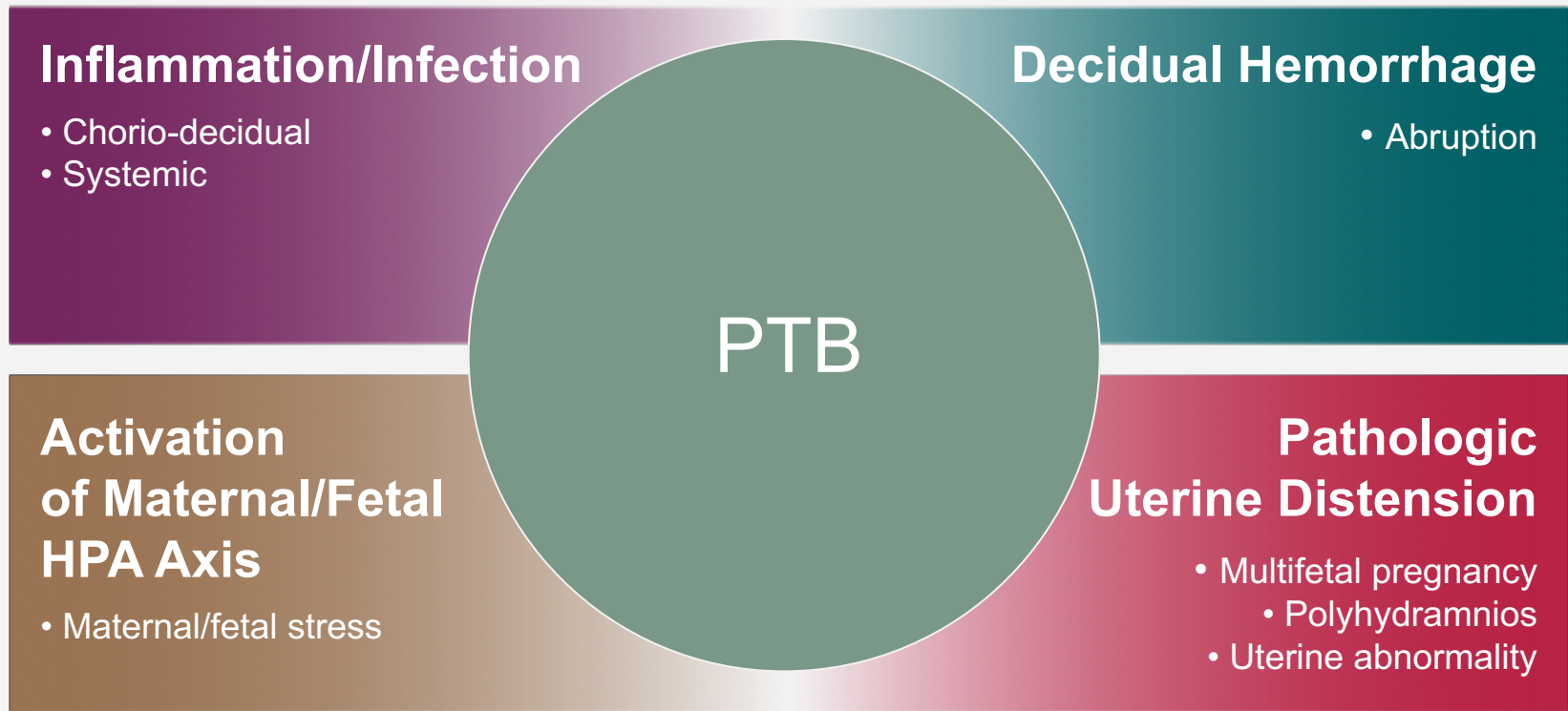A cluster of problems with
a set of overlapping factors:

- Causes

- Mechanisms

- Risk Factors

PTL=preterm labor.
Romero R, et al. Preterm labor: one syndrome, many causes. *Science*. 2014;345(6198):760-765. doi:10.1126/science.1251816.
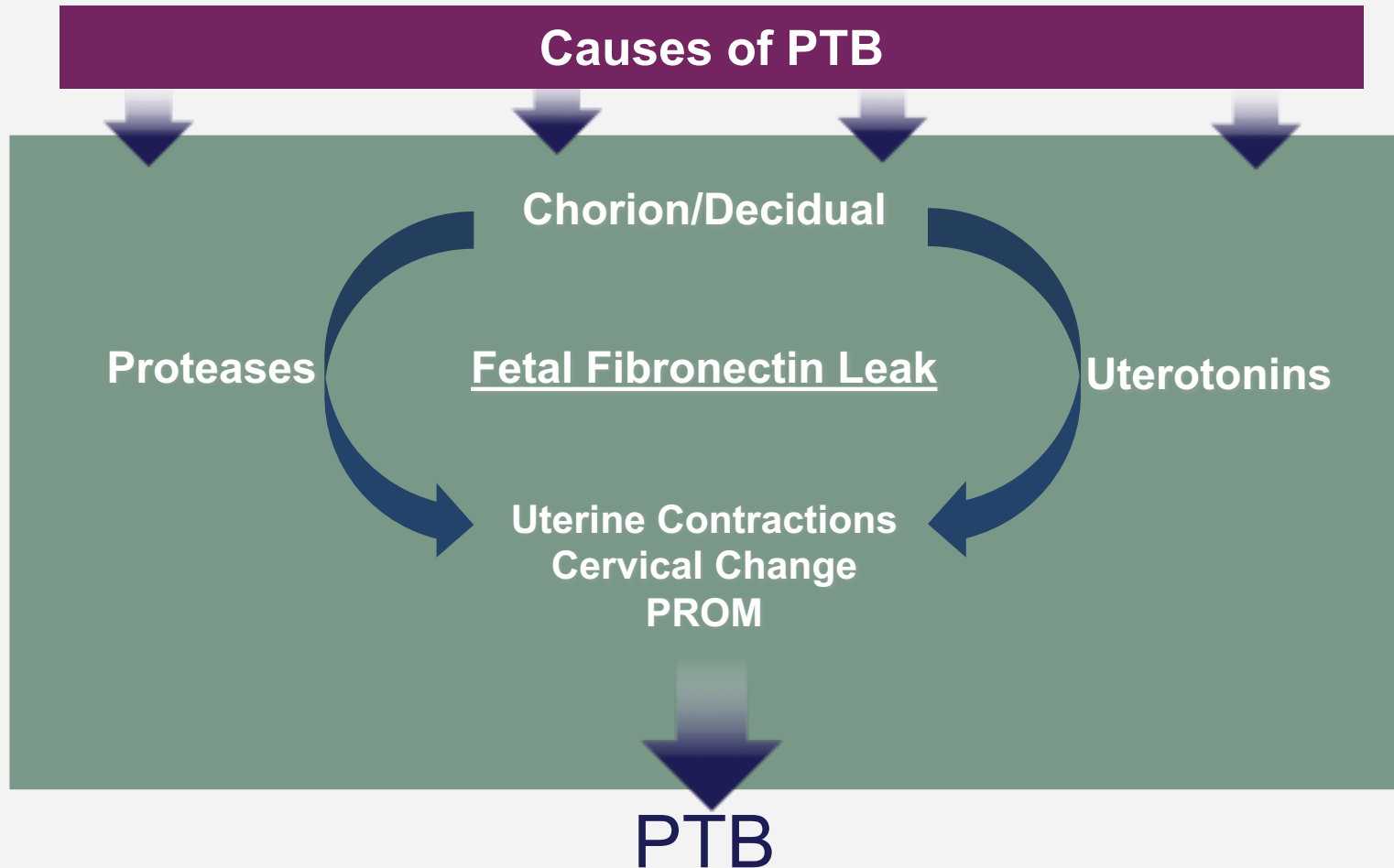
Causes of Preterm Birth

Inflammation/Infection
- Chorio-decidual
- Systemic

Decidual Hemorrhage
- Abruption

PTB

Activation of Maternal/Fetal HPA Axis
- Maternal/fetal stress

Pathologic Uterine Distension
- Multifetal pregnancy
- Polyhydramnios
- Uterine abnormality

Mechanisms of PTB

Causes of PTB

Chorion/Decidual

Proteases

Fetal Fibronectin Leak

Uterotonins

Uterine Contractions
Cervical Change
PROM

PTB

PROM=premature rupture of membranes; PTB=preterm birth.
Lockwood CJ, et al. Risk stratification and pathological mechanisms in preterm delivery. *Paediatr Perinat Epidemiol*. 2001;15(S2):78-89.
doi:10.1046/j.1365-3016.2001.00010.x.

Clinical Risk Factors: SPTB

Clinical Factors

- Prior history of SPTB

- Multiple gestation

- Cervical insufficiency, uterine abnormalities

- Vaginal bleeding

- Anemia

- Low prepregnancy weight

- Infection

Demographics

- African American ethnicity

- Maternal age <17 and >35 years

- Low socioeconomic status

- Maternal stress

- Behavior patterns: cigarette smoking, drug abuse

SPTB=spontaneous preterm birth.
Adapted from: Nawal N. Premature Delivery and the Millennium Development Goal. *Rev Obstet Gynceol.* 2012;5(2):100-105.

Clinical Risk Factors: Limited Sensitivity

Risk factors fail in both directions[1,2]

- More than one half of women who deliver preterm do not have identifiable risk factors.

- Approximately two thirds of women with traditional risk factors do not go on to deliver preterm.

1. Iams JD, et al. The preterm prediction study: can low-risk women destined for spontaneous preterm birth be identified? *Am J Obstet Gynecol*. 2001;184(4):652-655. doi:10.1067/mob.2001.111248.
2. Goldenberg RL, et al. The preterm prediction study: fetal fibronectin testing and spontaneous preterm birth. NICHD Maternal Fetal Medicine Units Network. *Obstet Gynecol.* 1996;87(5 Pt 1):643-648. doi:10.1016/0029-7844(96)00035-X.

For Symptomatic Patients

Diagnosis of Preterm Labor

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Diagnosis of Threatened PTL

Determining patients at greatest risk of PTB is a challenge:

- 30% of PTL spontaneously resolves.[1]

- 50% of patients hospitalized for PTL actually give birth at term.[2]

- <10% of women with the clinical diagnosis of PTL actually give birth within 7 days of presentation.[3]

PTB=preterm birth; PTL=preterm labor.
1. Lewit EM, et al. The direct cost of low birth weight. *Future Child.* 1995;5(1):35-56. doi:10.2307/1602506.
2. Fuchs IB, et al. Sonographic cervical length in singleton pregnancies with intact membranes presenting with threatened preterm labor. *Ultrasound Obstet Gynecol.* 2004;24(5):554-557. doi:10.1002/uog.1714.
3. Tsoi E, et al. Ultrasound assessment of cervical length in threatened preterm labor. *Ultrasound Obstet Gynecol.* 2003;21(6):552-555. doi:10.1002/uog.131.

Predictors of PTB in Symptomatic Patients Triage

Subjective clinical signs and symptoms

- Uterine contractions
- Cramping
- Bleeding

Objective findings

- Presence of fFN
- Cervical changes
- Transvaginal CL, as available
- Combination of clinical findings

CL=cervical length; fFN=fetal fibronectin; PTB=preterm birth.
Van Baaren GJ, et al. Predictive value of cervical length measurement and fibronectin testing in threatened preterm labor. *Obstet Gynecol*. 2014;123(6):1185-92. doi:10.1097/AOG.0000000000000229.

Uterine Contractions: A Diagnostic Challenge

- Uterine contractions alone are a poor positive predictor of true PTL.[1]

- Contractions occur 4 or more times an hour in ~25% of pregnancies <32 weeks.[2]

- Many women diagnosed with PTL based solely on criteria of ≥6 uterine contractions per hour will deliver at term.[2]

PTL=preterm labor.
1. Iams JD, et al. Frequency of uterine contractions and the risk of spontaneous preterm delivery. *N Engl J Med*. 2002;346:250-255. doi:10.1056/NEJMoa002868.
2. Iams JD, et al. Care for women with prior preterm birth. *Am J Obstet Gynecol*. 2010;203(2):89-100. doi:10.1016/j.ajog.2010.02.004.

Biochemical Marker for Risk Assessment: fFN

- Adhesive glycoprotein "glue" at the maternal-fetal interface

- Presence in cervicovaginal secretions highly associated with risk of preterm delivery
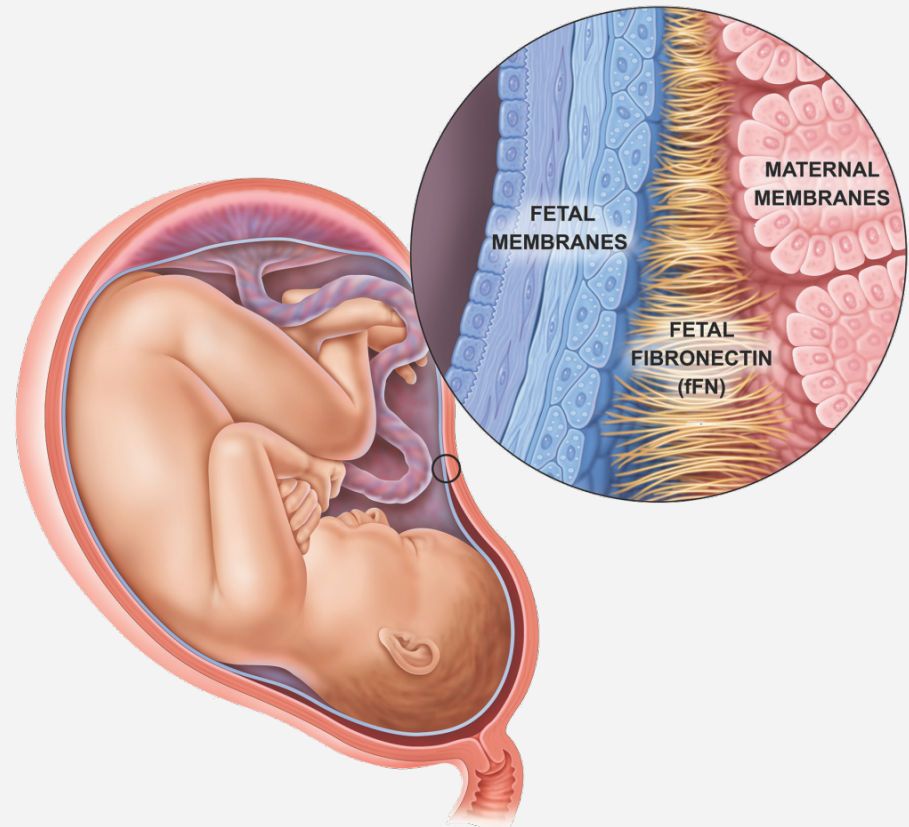
fFN=fetal fibronectin.
Fetal Fibronectin [package insert]. AW-04196-003. Marlborough, MA: Hologic, Inc.; 2015.

The fFN Test: Key Predictor of SPTB

An FDA approved test for use in assessing risk of preterm delivery:

- In conjunction with other clinical information during routine screening of women <u>without symptoms</u> of PTL from 22 weeks, 0 days, through 30 weeks, 6 days of gestation.

- In women <u>with symptoms</u> of PTL from 24 weeks, 0 days, through 34 weeks, 6 days of gestation.

FDA=US Food and Drug Administration; fFN=fetal fibronectin; PTL=preterm labor; SPTB=spontaneous preterm birth.
Fetal Fibronectin [package insert]. AW-04196-003. Marlborough, MA; Hologic, Inc., 2015.

fFN in Symptomatic Patients: Negative fFN

Allows for better targeting of hospital resources.

NPV for Delivery Within:

7 days = 99.5%

14 days = 99.2%

<37 weeks = 84.5%

Benefits of a Negative Test

- Less intervention

- Avoid hospitalizations

- Provider and patient reassurance

fFN=fetal fibronectin; NPV=negative predictive value.
Adapted from: Peaceman AM, et al. Fetal fibronectin as a predictor of preterm birth in patients with symptoms: A multicenter trial.
Am J Obstet Gynecol. 1997;177(1):13-18.

fFN in Symptomatic Patients: Positive fFN

Identifies group for intervention.

PPV for Delivery Within:
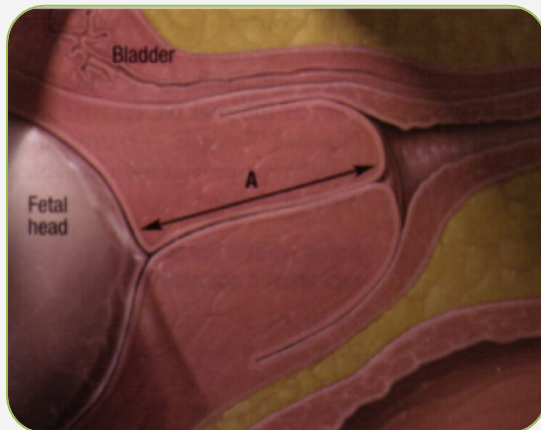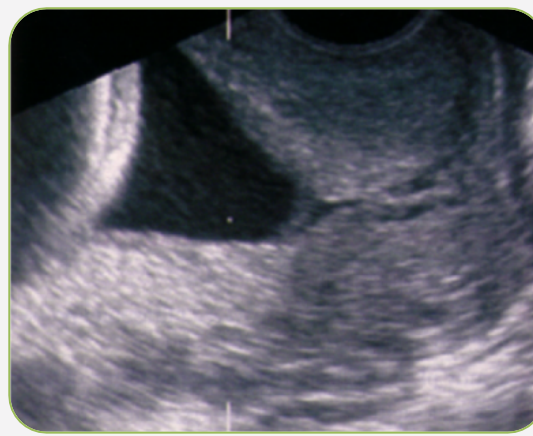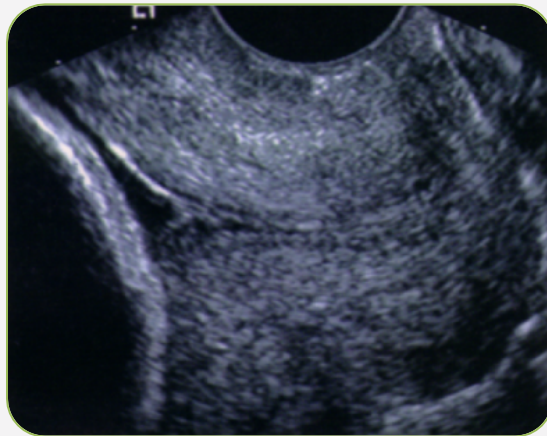
7 days = 12.7%

14 days = 16.7%

<37 weeks = 44.7%

Benefits of a Positive Test

- Identify group that can be targeted for intervention

- Opportunity for antenatal steroids
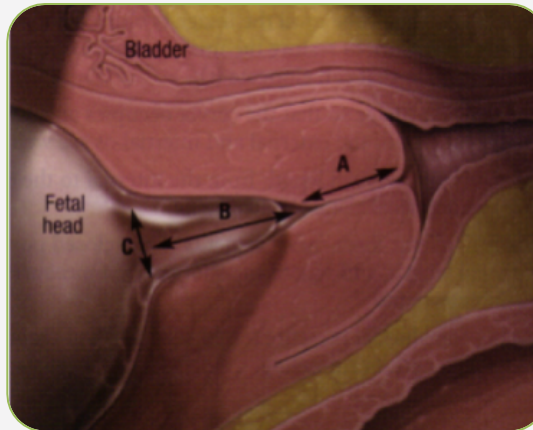
- Preparation for optimal neonatal care

fFN=fetal fibronectin; PPV=positive predictive value.
Adapted from: Peaceman AM, et al. Fetal fibronectin as a predictor of preterm birth in patients with symptoms: A multicenter trial.
Am J Obstet Gynecol. 1997;177(1):13-18.

Another Diagnostic Tool: CL[1]

ACOG Publication – Assessment of Transvaginal Ultrasound Cervical Length Image Quality[2]

- 15% of <u>trained</u> imagers failed to obtain appropriate cervical length imaging.
- There was no difference in pass rate among ultrasonographers, MFM, MFM fellows, and generalists.
- Most common deficiencies were criteria that are central to adequate image acquisition.

Normal Cervix   Short and Funneled Cervix

CL=cervical length. 1. Reprinted with permission from Berghella V. Grand rounds: the short and funneled cervix: what do I do now? *Contemp Ob Gyn*. 2004;49:26-34. 2. Boelig R, et al. Assessment of Transvaginal Ultrasound Cervical Length Image Quality. *Obstet and Gynecol*. 2017; 000(x):000-0.

Role of CL (TVUS) in Symptomatic Women

Study	GA, wk	CL Cutoff, mm	PTD	PPV, %	NPV, %
Murakawa	18–37	<20	<37	100	72
Iams et al	24–35	<30	<36	55	100
Gomez et al	20–35	≤18	<36	67	83
Rizzo et al	24–36	≤20	<36	71	76
Rozenberg et al	24–34	≤26	<37	50	89
Cetin et al	26–35	<30	<37	58	100
Goffient et al	24–34	≤27	<37	40	92
Hincz et al	24–34	≤31	≤28	28	100
Tsoi et al	24–36	≤15	Within 7 d	37	99

CL=cervical length; GA=gestational age; NPV=negative predictive value; PPV=positive predictive value; PTD=preterm delivery; TVUS=transvaginal ultrasound.
Graph adapted from: Gomez R, et al. Cervicovaginal fibronectin improves the prediction of preterm delivery based on sonographic cervical length in patients with preterm uterine contractions and intact membranes. *Am J Obstet Gynecol.* 2004;192(2):350-9.

CL and fFN Combined Improve Prediction

Delivery probability profile for nulliparous patients

Legend:
- fFN − /CL >25mm
- fFN + /CL >25mm
- fFN − /CL <25mm
- fFN + /CL <25mm

Y-axis: Percent remaining pregnant (30–100)
X-axis: Weeks (24, 32, 35, 37, 40)
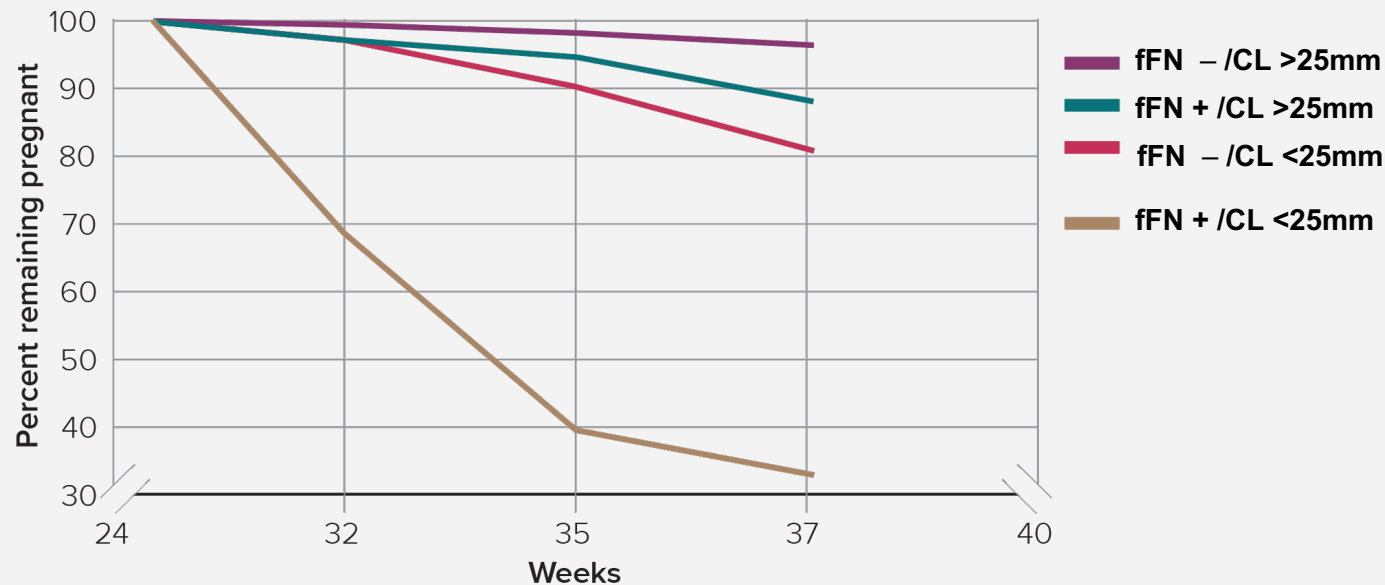
- Majority of patients with a short CL (<25 mm) and negative fFN deliver at term.
- Addition of fFN in patients with a short CL (22–24 weeks) can help to further stratify risk.

CL=cervical length; fFN=fetal fibronectin;
Graph adapted from: Goldenberg, RL, et al. The preterm prediction study: the value of new vs standard risk factors in predicting early and all spontaneous preterm births. HICHD MFMU Network. *Am J Public Health*. 1998;88(2):233-238.

A Powerful Combination of Diagnostic Tools fFN + CL

Symptomatic patients, gestational age ranges: 22-35 weeks.

Screening efficacy of fFN plus CL for prediction of preterm birth (n = 1,194)		
Timing of Birth	**NPV**	**PPV**
<7 days	98.9%	45.4%
<14 days	96.4%	10.3%
<34 weeks	91.5%	36.8%

(Pooled data from 9 studies)
The most common definitions of short cervix were <20 mm, ≤26 mm, and <25 mm.

CL=cervical length; fFN=fetal fibronectin; NPV=negative predictive value; PPV=positive predictive value.
Adapted from: DeFranco EA, Lewis DF, Odibo AO. Improving the screening accuracy for preterm labor: is the combination of fetal fibronectin and cervical length in symptomatic patients a useful predictor of preterm birth? A systematic review. *Am J Obstet Gynecol.* 2013;208:233.e1-6.

Risk Stratification Improves With Combination of Tools

- Patients in the "gray zone" benefit the most from the addition of fFN testing.

  - There is no difference in risk between patients with a negative fFN and a CL between 15–30 mm and patients with a CL >30 mm (<1% risk of PTB in 14 days).

  - The addition of fFN can return patients to baseline risk of a long cervix.

PTD in women who presented with signs and symptoms of PTL and did not deliver within 7 days

Risk Group	SPTB Within 14 Days of Presentation, %	SPTB <34 Weeks, %
CL <15 mm	8.6	28
CL 15–30 mm, fFN +	5.6	25
CL 15-30 mm, fFN –	0.7	19
CL >30 mm	0.4	7.2

CL=cervical length; fFN=fetal fibronectin; PTD=preterm delivery; PTL=preterm labor; SPTB=spontaneous preterm birth.
Hermans FJ, et al. Risk stratification with cervical length and fetal fibronectin in women with threatened preterm labor before 34 weeks and not delivering within 7 days. *Acta Obstet Gynecol Scand*. 2015;94(7):715-721.

For Symptomatic Patients

Management Strategies for Preterm Labor

fFN

Interventions for Fetal Protection

ACS	Magnesium Sulfate for Fetal Neuroprotection
Hospitalization and/or Transport	Tocolytic Therapy

ACS=antenatal corticosteroids.
ACOG. Management of preterm labor. Practice Bulletin No. 159. American College of Obstetricians and Gynecologists. *Obstet Gynecol.* 2016;127:e29–38.

ACOG Recommendations on ACS

Timing[1]

- A single course of steroids is recommended for women between 24 and 34 weeks who are at risk of PTD within 7 days (Level A).

- A single course of repeat steroids should be considered in women whose prior course of steroids was administered at least 7 days previously and who remain at risk of PTB before 34 weeks of gestation (Level B).

Dosing[2]

- Betamethasone (12 mg) 24 hours apart for 2 doses

- Dexamethasone (6 mg) every 12 hours for 4 doses

ACOG=American College of Obstetricians and Gynecologists; ACS=antenatal corticosteroids; PTB=preterm birth; PTD=preterm delivery.

1. ACOG. Management of preterm labor. Practice Bulletin No. 159. American College of Obstetricians and Gynecologists. *Obstet Gynecol.* 2016;127:e29–38.
2. ACOG. Premature Rupture of Membranes. Practice Bulletin No. 160. American College of Obstetricians and Gynecologists. *Obstet Gynecol.* 2016;127:e39–51.

Extending ACS to 34-36 Weeks

- Recent data from ALPs trial suggests benefit in extending use of ACS up to 36 weeks of pregnancy for singleton gestations.[1]

  – Significant decrease in neonatal morbidities similar to benefits seen with use of ACS prior to 34 weeks.

- ACOG updated guidance in 2016 to support use of betamethasone in the late preterm birth period.[2]

  – A single course of betamethasone is recommended between 34 and 36 weeks of gestation for those at risk of preterm birth within 7 days, and who have not received a previous course of antenatal corticosteroids.

ACS=antenatal corticosteroids; ACOG=American College of Obstetricians and Gynecologists.
1. Gyamfi-Bannerman C, et al. Antenatal betamethasone for women at risk for late preterm delivery. *N Engl J Med.* 2016;374(14):1311-1320.
2. ACOG. Antenatal Corticosteroid Therapy for Fetal Maturation. Committee Opinion No. 677. American College of Obstetricians and Gynecologists. *Obstet Gynecol.* 2016;128:e187-94.

Why This Matters:

ACS Benefit at 24-34 Weeks

A review of 21 studies (3,885 women and 4,269 infants) showed that ACS led to reduction in:	
NND	30%
RDS	35%
IVH	50%
Cerebroventricular hemorrhage	50%
NEC	55%
NICU admissions	20%
Early systemic infections	50%

ACS=antenatal corticosteroids.; IVH=intraventricular hemorrhage; NEC=necrotizing enterocolitis; NND=neonatal death; RDS=respiratory distress syndrome.
Adapted from: Roberts D, et al. Antenatal corticosteroids for accelerating fetal lung maturation of women at risk of preterm birth.
Cochrane Database Syst Rev. 2006;19(3):CD004454.

Importance of Appropriate Steroid Timing

- Joint Commission measure PC-03 to improve the number of PTL patients that receive a dose of steroids.[1]

- Recognition of the need for protocols that help to determine the patients most likely to benefit from steroids.[1]

Association of neonatal respiratory morbidity and the ACS-to-delivery interval[2]

At Gestational Age 28-29 6/7

Variable	8–14 D	15–21 D
Intubation	5.1	4.7
RDS	2.7	6.8
Chronic lung disease	1.1	8.0
Composite outcome	0.98	6.8

Odds ratio compared to delivery interval of 0–7 days

When delivered within 7 days, steroids demonstrated a reduction in the likelihood of neonatal morbidity.[2]

ACS=antenatal corticosteroids; PTL=preterm labor; RDS=respiratory distress syndrome.
1. Perinatal Care Measure Information Form Version 2015B. The Joint Commission, 2005. Available at:
https://manual.jointcommission.org/releases/TJC2015B/MIF0168.html. Accessed March 8, 2017.
2. Adapted from: Wilms FF, et al. Relationship between the time interval from antenatal corticosteroid administration until preterm birth and the occurrence of respiratory morbidity. *Am J Obstet Gynecol*. 2011;205(1):49.e1-7.

Effect of Timing of ACS on Primary Infant Outcomes

Outcomes	Risk Ratio <24 Hours First Dose to Birth	Risk Ratio <48 Hours First Dose to Birth	Risk Ratio 1–7 Days First Dose to Birth	Risk Ratio ≥7 Days First Dose to Birth
Perinatal death	0.60 (0.39–0.94)	0.59 (0.41–0.86)	0.84 (0.31–2.29)*	1.42 (0.91–2.23)
Fetal death	0.68 (0.34–1.38)	0.78 (0.40–1.51)	1.01 (0.58–1.76)	1.36 (0.73–2.53)
Neonatal death	0.53 (0.29–0.96)	0.49 (0.45-1.54)	0.80 (0.34–1.88)*	0.67 (0.10–4.42)*
RDS	0.87 (0.66–1.15)	0.83 (0.45–1.54)*	0.52 (0.33–0.83)*	0.82 (0.53–1.28)

Risk ratio: As compared to no exposure to ACS

*Random effects model used for these Clinical Practice Guidelines due to significant heterogeneity

ACS=antenatal corticosteroids; RDS=respiratory distress syndrome.
Adapted from: Roberts CPG. New Zealand and Australian Clinical Practice Guidelines, 2015. Accessed March 8, 2017.

How Are We Doing?

14-year study looking at antenatal steroid timing relative to delivery
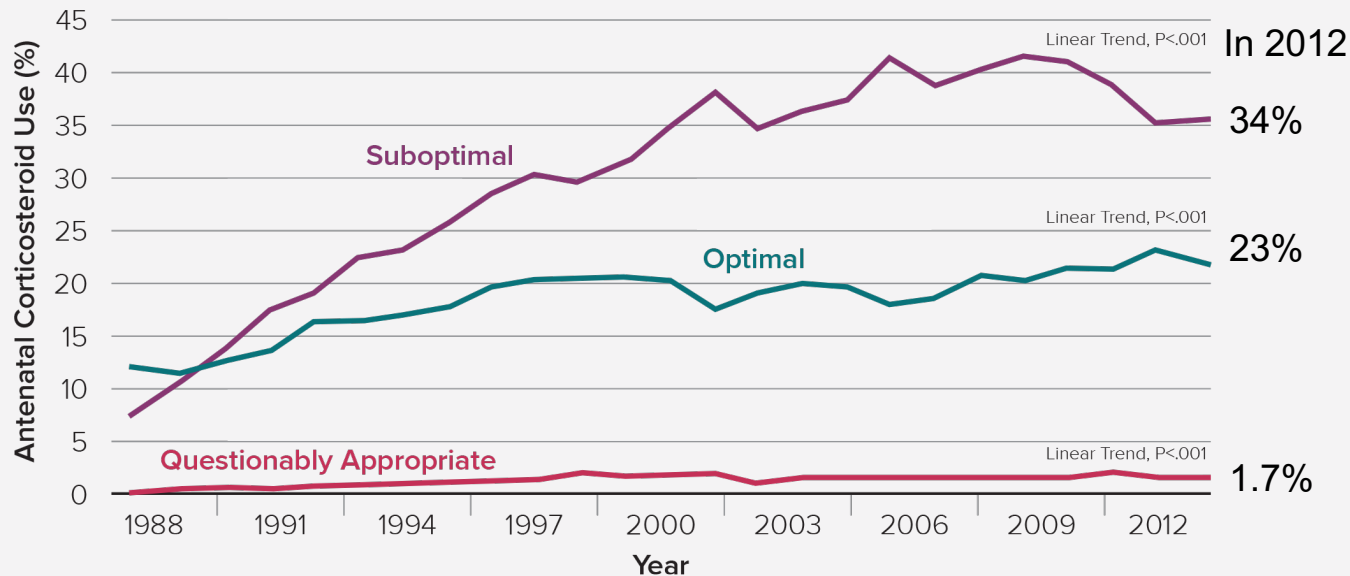
- **Optimal ACS administration**: proportion of live births at 24-34 weeks of gestation exposed to ACS between 24 hours and 7 days before delivery.

- **Suboptimal ACS administration**: proportion of live births at 24-34 weeks of gestation exposed to ACS <24 hours or >7 days before delivery.

- **Questionably appropriate ACS administration**: proportion of live births ≥35 weeks of gestation exposed to ACS.
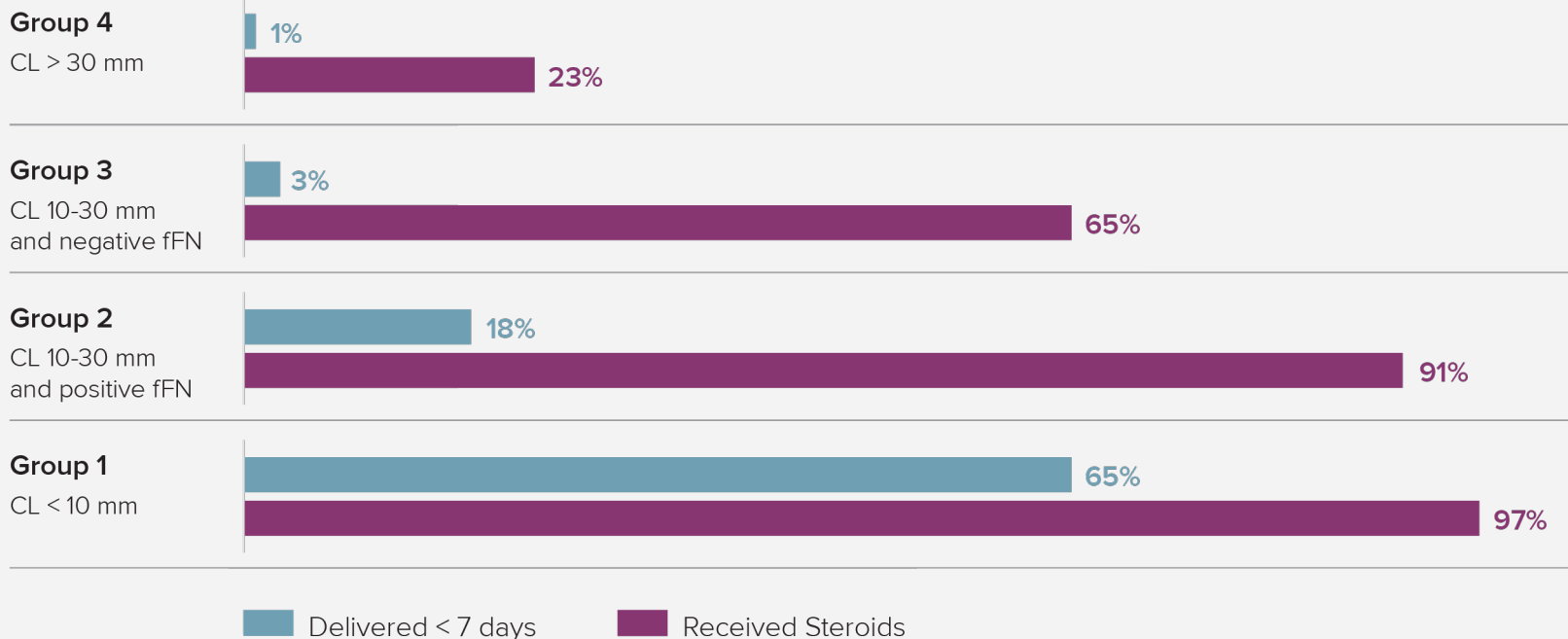
ACS=antenatal corticosteroids.
Adapted from: Razaz N, et al. Trends in Optimal, Suboptimal, and Questionably Appropriate Receipt of Antenatal Corticosteroid Prophylaxis. *Obstet Gynecol.* 2015;125(2):288-296.

Women Who Did Not Receive ACS

20% of neonates born at 28–32 weeks of gestation

50% of neonates born at 33–34 weeks of gestation

ACS=antenatal corticosteroids.
Adapted from: Razaz N, et al. Trends in Optimal, Suboptimal, and Questionably Appropriate Receipt of Antenatal Corticosteroid Prophylaxis. *Obstet Gynecol*. 2015;125(2):288-296.

How Are We Doing?

2015 Study: ACS delivery in relation to fFN and CL results

- ACS is frequently administered to women with symptoms of preterm labor but at low risk for delivery <7 days.

Group 4
CL > 30 mm
1%
23%

Group 3
CL 10-30 mm
and negative fFN
3%
65%

Group 2
CL 10-30 mm
and positive fFN
18%
91%

Group 1
CL < 10 mm
65%
97%

Delivered < 7 days   Received Steroids

ACS=antenatal corticosteroids; CL=cervical length; fFN=fetal fibronectin.
Adapted from: Wilms FF, et al. Prescribing patterns of antenatal corticosteroids in women with threatened preterm birth. *Eur J Obstet Gynecol Reprod Biol*. 2015;192:47-53.

Harms of Repeat Prenatal Corticosteroid Treatment

- Could increase risk of infection.[1]

- Suppressed pituitary-adrenal function for mother and baby.[1]

- Reduction in size at birth.[1]

- Trends toward higher rate of cerebral palsy among children at 2-3 years.[2]

- Animal studies have shown delayed myelination and decreased growth in all areas of the fetal brain, especially the hippocampus.[3,4]

1. Cochrane. Repeat doses of prenatal corticosteroids for women at risk of preterm birth for preventing neonatal respiratory disease. Available at: http://www.cochrane.org/CD003935/PREG_repeat-doses-prenatal-corticosteroids-women-risk-preterm-birth-preventing-neonatal-respiratory. Accessed March 8, 2017.
2. Wapner RJ, et al. Long term outcomes after repeat doses of antenatal corticosteroids. *N Engl J Med*. 2007;357:1190-1198.
3. Huang WL, et al. Effect of corticosteroids on brain growth in sheep. *Obstet Gynecol* 1999;94:213-218.
4. Dunlop SA, et al. Repeated corticosteroids delay the myelination bovine central nervous system. *J Mater Med.* 1997. 6:309-313.

Positive fFN Can Help to Reduce Unnecessary Exposure to ACS

Number needed to treat with steroids to prevent
1 case of RDS

fFN Testing: Negative	509
No fFN Testing	109
fFN Testing: Positive	17
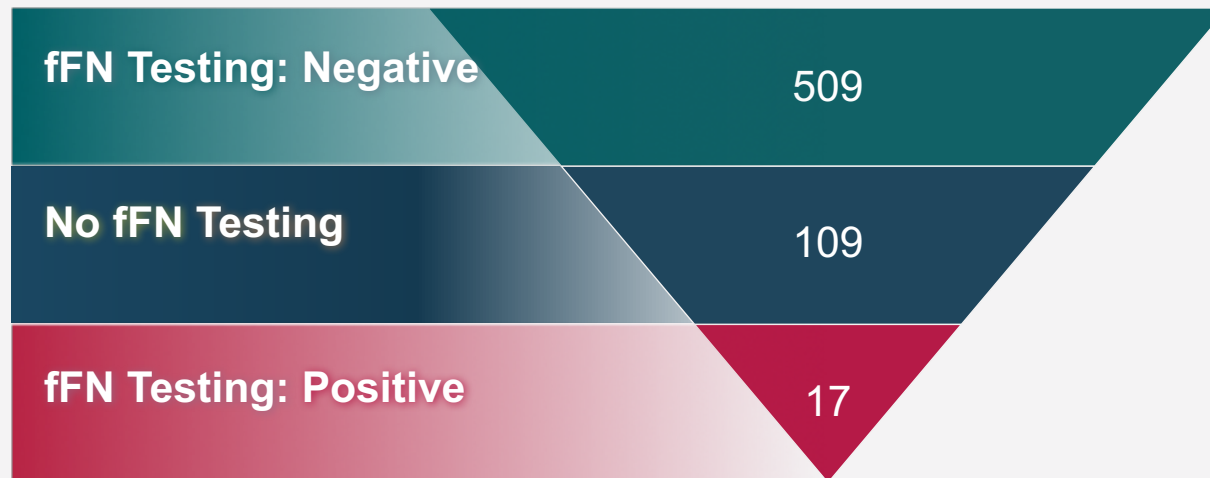
ACS=antenatal corticosteroids; fFN=fetal fibronectin; RDS=respiratory distress syndrome.
Adapted from: Honest H, et al. Accuracy of cervicovaginal fetal fibronectin test in predicting risk of spontaneous preterm birth: systematic review. *BMJ*. 2002;325:301.

ACOG Guideline on Tocolytic Agents

- The evidence supports the use of first-line tocolytic treatment with beta-adrenergic agonist therapy, calcium channel blockers, or NSAIDs for short-term prolongation of pregnancy (up to 48 hours) to allow for the administration of ACS.

- Maintenance therapy with tocolytics is ineffective for preventing PTB and improving neonatal outcomes and is not recommended for this purpose.

> The benefits of tocolytics are to safely transport patient to optimal level hospital and to get a full course of steroids on board.

ACOG=American College of Obstetricians and Gynecologists; ACS=antenatal corticosteroids; NSAIDs=nonsteroidal anti-inflammatory drugs; PTB=preterm birth.
ACOG. Management of preterm labor. Practice Bulletin No. 159. American College of Obstetricians and Gynecologists. *Obstet Gynecol.* 2016;127:e29–38.

ACOG Guidance on Magnesium Sulfate for Fetal Neuroprotection

- Evidence suggests potential neuroprotective benefit.

- Decreased severity and risk of cerebral palsy in surviving infants if administered when birth is anticipated before 32 weeks of gestation.

- Institutions should develop guidelines regarding inclusion criteria, treatment regimens, concurrent tocolysis, and monitoring in accordance with one of the larger trials.

ACOG=American College of Obstetricians and Gynecologists.
ACOG. Management of preterm labor. Practice Bulletin No. 159. American College of Obstetricians and Gynecologists. *Obstet Gynecol.* 2016;127:e29–38.

Perinatal Care:
Improving Outcomes

fFN

Standardization of Practice to Improve Outcomes

In a recent committee opinion, ACOG stated:

- Protocols and checklists should be recognized as a guide to the management of a clinical situation or process of care that will apply to most patients; and

- Obstetrician-gynecologists should be engaged in the process of developing guidelines and presenting data to help foster stakeholder buy-in and create consensus, thus improving adherence to guidelines and protocols.

ACOG=American College of Obstetricians and Gynecologists.
ACOG. Committee Opinion No. 629. Clinical Guidelines and Standardization of Practice to Improve Outcomes. Published April 2015. Accessed March 8, 2017.

Benefits of Standardization in PTL Management: In Practice

- Identifying those patients in true labor will benefit all women who present in triage with signs and symptoms of suspected PTL.

- Hospitals providing all levels of care will achieve the following outcomes within a relatively brief timeframe:

  - Timely and appropriate interventions

  - Optimal maternal-fetal safety

  - Hospitalization of only those patients at greatest risk for PTD

  - Effective transport of PTL patients to higher, more appropriate levels of care

  - Avoidance of unnecessary treatment, interventions, and medications

PTD=preterm delivery; PTL=preterm labor.
Used with permission. Byrne, J. Benefits of Standardization in PTD Management. Presented at: American College of Nurse-Midwives Annual Meeting & Exposition; June 2-7, 2002; Long Beach, CA.

Cost Savings – Protocol Adherence

- Standardizing PTL evaluation reduces unnecessary admissions for observation, resulting in significant cost savings.[1]
  - When compared with prior year:
    - 56% reduction in admission rate for PTL
    - Estimated annual savings of $40,000

- Introducing fFN to triage reduces length of stay.[2]
  - Average length of stay before and after fFN introduction:
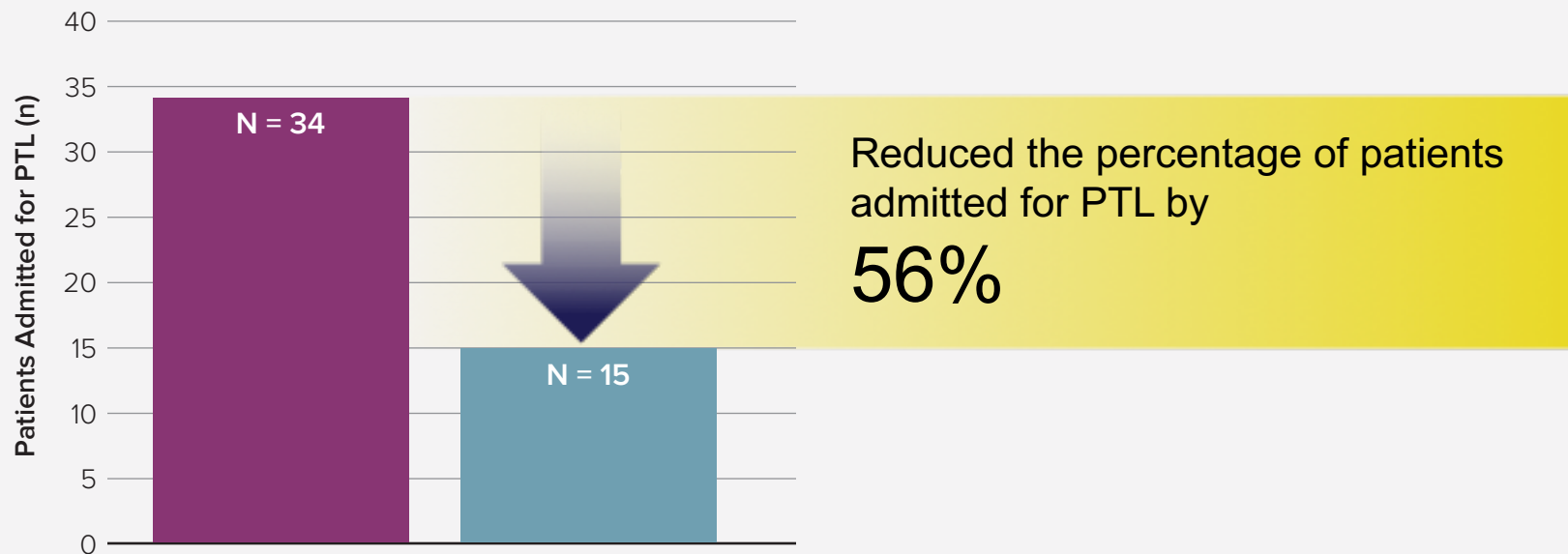   - 5.2 days before fFN
    - 0.6 days after fFN

This information is intended for insurers.

fFN=fetal fibronectin; PTL=preterm labor.
1. Rose CH, et al. Cost-effective standardization of preterm labor evaluation. *Am J Obstet Gynecol.* 2010;203(3):250.e1-5.
2. Abenhaim HA, et al. Does availability of fetal fibronectin testing in the management of threatened preterm labour affect the utilization of hospital resources? *J Obstet Gynecol Can.* 2005;27(7):689-694.

Standard Protocols Help Avoid Unnecessary Healthcare Costs

If a standard protocol was adopted nationally, it would lead to approximately $560 million in cost savings.

Reduced the percentage of patients admitted for PTL by
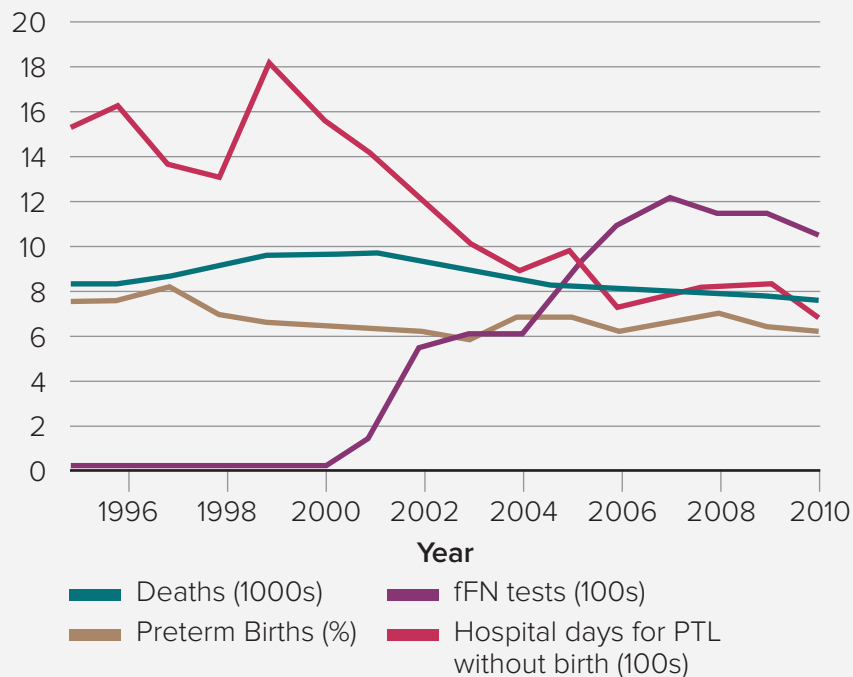
56%

This information is intended for insurers.

PTL=preterm labor.
Rose CH, et al. Cost-effective standardization of preterm labor evaluation. *Am J Obstet Gynecol.* 2010;203(3):250.e1-5.

Standard Protocols Help Avoid Unnecessary Healthcare Costs

Hospital admissions trends before, during, and after the introduction of fFN

Year

- Deaths (1000s)
- fFN tests (100s)
- Preterm Births (%)
- Hospital days for PTL without birth (100s)

- **$963K** annual decrease in cost of admissions for PTL without delivery

- **$811K** net decrease in cost of PTL

- **51%** reduction in average number of hospital days for admissions without PTL

This information is intended for insurers.

fFN=fetal fibronectin; PTL=preterm labor.
Iyer S, et al. The association of fFN testing on hospital admissions for preterm labor. *Open J Obstet Gynecol.* 2013;3(1):126-129.

March of Dimes Preterm Labor Assessment Toolkit (PLAT)
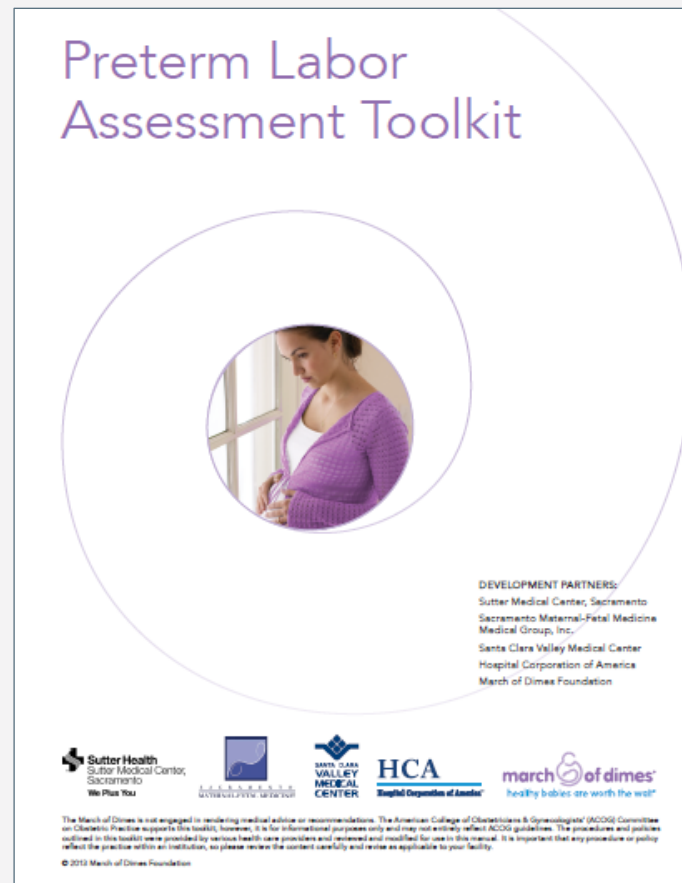
March of Dimes Assessment Algorithm
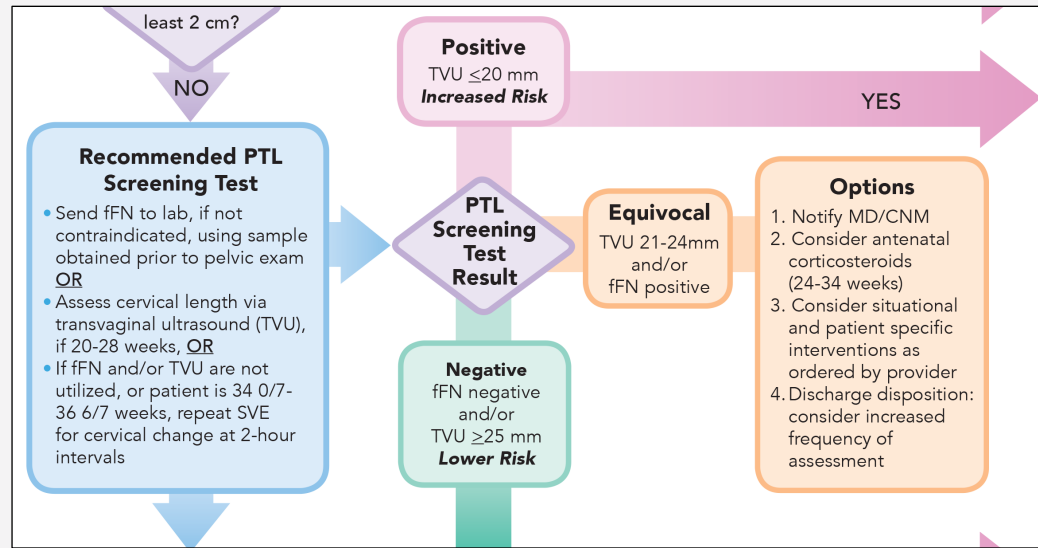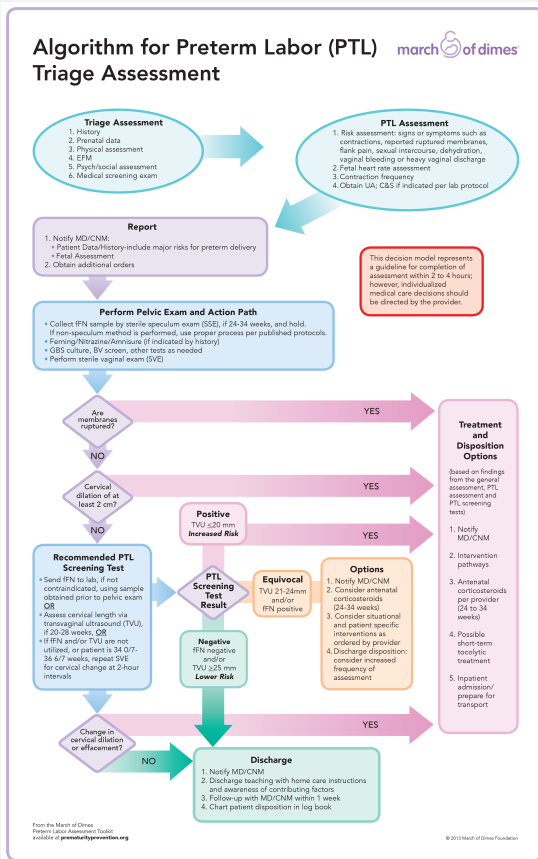
fFN=fetal fibronectin; PTL=preterm labor; SVE=sterile vaginal exam.
March of Dimes. March of Dimes Preterm Labor Assessment Toolkit, 2016. Available at: http://www.marchofdimes.org/professionals/preterm-labor-assessment-toolkit.aspx. Accessed March 8, 2017.
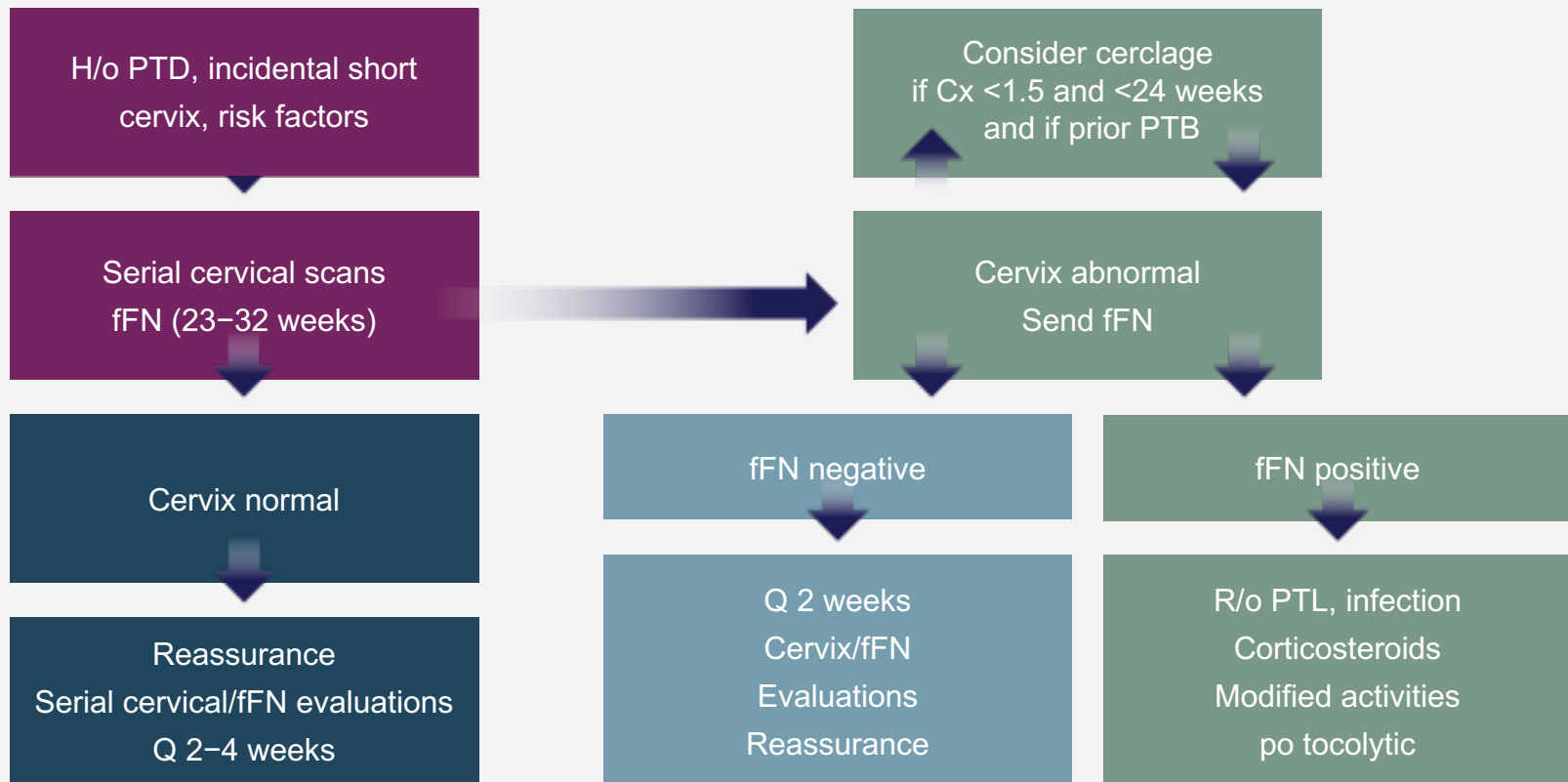
PLAT Resources

- Toolkit implementation guide

- PTL protocol poster

- PowerPoint slide deck overview

- Implementation tools

- Patient education materials

Prematurity Prevention Resource Center:
www.prematurityprevention.org

PLAT=preterm labor assessment toolkit; PTL=preterm labor.

Example Algorithm:

Virtua Health Clinical Management Flowchart

H/o PTD, incidental short cervix, risk factors	Consider cerclage if Cx <1.5 and <24 weeks and if prior PTB
Serial cervical scans fFN (23−32 weeks)	Cervix abnormal Send fFN
Cervix normal	fFN negative / fFN positive
Reassurance Serial cervical/fFN evaluations Q 2−4 weeks	Q 2 weeks Cervix/fFN Evaluations Reassurance / R/o PTL, infection Corticosteroids Modified activities po tocolytic

Cx=cervix; fFN=fetal fibronectin; H/o=history of; PO=per os; PTB=preterm birth; PTD=preterm delivery; Q=every; R/o=rule out.
Used with permission from Dr Shailen Shah.

There is NO CHARGE for collection kits!

Before digital exam

Collect fFN specimen first!

Guidelines for fFN Specimen Collection

Obtain specimen before any examination or manipulation of the cervix:	Specimen should not be obtained in the presence of:
• Digital examination	• Cervical dilatation ≥3 cm
• Vaginal ultrasound	• PPROM
• Microbiologic culture	• Soaps, gels, lubricants, or disinfectants
• Pap test	• Cervical cerclage
	• Moderate or gross vaginal bleeding
	• **Sexual intercourse within 24 hours,* but NEGATIVE results are valid**

*Positive results should be disregarded and patient should be retested in 24 hours.

fFN=fetal fibronectin; PPROM=preterm premature rupture of membranes.
The Hologic Specimen Collection Kit, instructions for use. PI AW-04196-003. Marlborough, MA; Hologic, Inc., 2015.

fFN Specimen Collection Procedure
Collection kits available at no charge

For accurate patient results, please ensure that you follow these instructions.

▶ During speculum examination, lightly rotate swab across posterior fornix of vagina for 10 seconds to absorb cervicovaginal secretions.
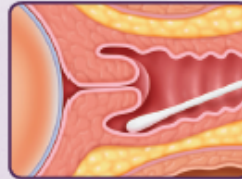
▶ Remove swab and immerse polyester tip in buffer; break shaft at score even with top of tube.

▶ Align the shaft with hole inside the tube cap and push down tightly over shaft, sealing tube; ensure shaft is aligned to avoid leakage.

Specimens should be collected prior to:

- Digital cervical exam
- Collection of culture specimens
- Vaginal probe ultrasound exams

Do not contaminate swab or specimen with:

- Lubricants
- Soaps
- Disinfectants
- Creams

Do not test if patients have:

- Had sexual intercourse within 24 hours prior to sampling*
- Moderate or gross vaginal bleeding
- Advanced cervical dilation (3 centimeters or greater)
- Rupture of membranes
- Suspected or known placental abruption or placenta previa

*If the test result is negative, it is a valid result.

Rapid fFN® Test for the TLi IQ® System

fFN

Conclusions

- PTB is still the leading cause of neonatal morbidity and mortality.

- Etiology is heterogeneous and complex with only retrospective diagnosis and not amenable to a single diagnostic test.

- fFN can assist with management decisions for the symptomatic patient.

Thank you.

Ancillary Slides

fFN

Patients with signs and symptoms of preterm labor

fFN and Cervical Length

fFN

A Powerful Combination of Diagnostic Tools

"Combining fFN testing with cervical length in women with symptoms of preterm labor has been shown to reduce unnecessary transfers and treatment, leading to cost savings that don't compromise neonatal outcomes." – DeFranco EA, et al.

- Adding fFN testing of patients with a CL of 10–30 mm was the most cost-effective strategy.

  – Savings of approximately $4,100 per patient

- The cost reduction was driven by unnecessary admissions and treatment.

This information is intended for insurers.

CL=cervical length; fFN=fetal fibronectin.
DeFranco EA, et al. Improving the screening accuracy for preterm labor: is the combination of fetal fibronectin and cervical length in symptomatic patients a useful predictor of preterm birth? A systematic review. *Am J Obstet Gynecol*. 2013;208(3):233.e1-6.

Another Diagnostic Tool: Clinical Assessment

- Cervical dilatation was inversely proportional to time to delivery in women assessed for initial PTL episodes.

- At the time of clinical presentation, factors significantly (P<0.0001) associated with PTB were:
  - Increased cervical dilatation;
  - Earlier gestational age; and
  - Greater effacement.

Cervical Dilatation on Admission and Time to Delivery

Cervical Dilatation, cm	Deliveries by Time From Admission, %			
	<24 h	24–48 h	3–7 d	>7 d
0–1 (n=104)	6	5	6	84
2 (n=54)	13	9	9	68
3 (n=29)	21	7	14	59
4 (n=22)	50	9	23	18
5 (n=16)	50	12	0	38
6–10 (n=19)	89	11	0	0

PTB=preterm birth; PTL=preterm labor.
How HY, et al. Cervical dilatation on presentation for preterm labor and subsequent preterm birth. *Am J Perinatol*. 2009;26(1):1-6.

Clinical Assessment in Symptomatic Patients

- The most recent ACOG practice bulletin on the management of PTL states[1]:
  - "The diagnosis of preterm labor is generally based on clinical criteria of regular uterine contractions accompanied by a change in cervical dilatation, effacement, or both on initial presentation with regular contractions and cervical dilatation of ≥2 cm."
  - "Less than 10% of women with the clinical diagnosis of preterm labor actually give birth within 7 days of presentation."

- This equates to a PPV of ~10% using only clinical assessment.

ACOG=American College of Obstetricians and Gynecologists; PPV=positive predictive value; PTL=preterm labor.
1. Practice bulletin no. 171: Management of preterm labor. *Obstet Gynecol.* 2016;128(4):e155-164.

Clinical Assessment and fFN Combined Improve Prediction of Preterm Birth

- fFN was the best predictor of delivery within 7 days in patients with intact membranes, cervical dilatation <3 cm, and symptoms of early PTL.[1]

- The fFN test was 3-fold better at predicting delivery within 7 days compared with cervical dilatation and contraction frequency.[1]

  - May lead to fewer false admissions
  - May be useful for steroid targeting

fFN Compared to Cervical Dilatation >1cm and Contractions ≥8/h for Delivery Within 7 Days[1]
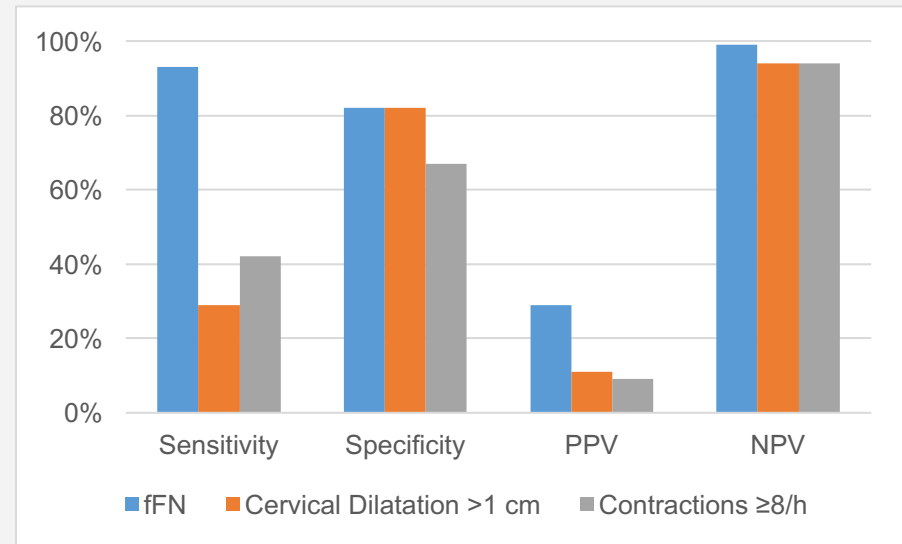
fFN=fetal fibronectin; NPV=negative predictive value; PPV=positive predictive value; PTL=preterm labor.
1. Iams JD, et al. Fetal fibronectin improves the accuracy of diagnosis of preterm labor. *Am J Obstet Gynecol*. 1995;173(1):141-145.

Rapid fFN® Test for the TLi$_{IQ}$® System

- The analyzer can produce results in <30 minutes after specimen is dispensed into the well.

- This moderately complex assay requires a CLIA-approved laboratory.

CLIA=Clinical Laboratory Improvement Amendments; fFN=fetal fibronectin.
Fetal Fibronectin [package insert]. AW-04196-003. Marlborough, MA; Hologic, Inc., 2015.

Use of fFN as a Tool for PTL Assessment

- Meta-analysis of fFN[1]:
  - Interventions were not reported for negative fFN results.
  - In almost all the referenced studies, it was physician discretion that drove the study outcome.
  - The included studies had no consistent protocol for treating negative versus positive fFN.

- fFN results are not expected to affect preterm birth rate
  - Multiple, well-designed trials have shown improvement in admission, intervention and transfer rates.[2]
  - There is value in having a diagnostic tool and management guideline.
  - A physician protocol should be established with direct management guidance.

fFN=fetal fibronectin, RCT=randomized controlled trial.
1. Berghella V and Saccone G. Fetal fibronectin testing for prevention of preterm birth in singleton pregnancies with threatened preterm labor: a systematic review and metaanalysis of randomized controlled trials. *Am J Obstet Gynecol.* 2016;215(4):431-438. 2. Rose CH, et al. Cost-effective standardization of preterm labor evaluation. *Am J Obstet Gynecol.* 2010;203(3):250.e1-5.