THREATENED PRETERM LABOR (tPTL)

FLAME LECTURE: 124

BURNS/STELLER 3.16.19

LEARNING OBJECTIVES

- Identify risk factors for preterm labor
- Describe the signs and symptoms of preterm labor
- See also:
  - Flame 125 – Mgmt of Preterm Labor
  - Flame 126 – Adverse Outcomes of PTD
  - Flame 127 – Ruling Out ROM
  - Flame 129 – Management of PROM

BACKGROUND
PTD EPIDEMIOLOGY & DEFINITIONS

- 400,000 preterm deliveries (PTDs) in U.S. annually (~10% of all deliveries)
- PTD is responsible for 28% of non-chromosomally-related M&M
- PTD is defined as delivery <37 weeks
  - <34 weeks: early preterm birth
  - 34-37 weeks: late preterm birth

BACKGROUND
PTL DEFINITIONS

- Preterm Labor: Contractions **+ Cervical Change (dilation/effacement)** <37 weeks GA
  - Some women will have cervical changes without contractions (cervical insufficiency)
  - Some women will have symptoms w/o cervical change (threatened PTL (tPTL), or just Braxton Hicks contractions)
- **85% of pts admitted for tPTL do not deliver w/in 7 days**
  - Most get BMZ for fetal lung maturity
  - Avg price of admission for PTL <34wks (w/o delivery) is $20,300[1]

BACKGROUND
RISK FACTORS FOR PTD

- Previous PTD
  - 1.5-2X more likely to have subsequent PTD
  - Risk becomes progressively higher with increased number of PTDs
  - Likewise, risk decreased the more remote a PTD was OR if there has been a subsequent term delivery
- Short cervix (<2.5cm)
- PROM (prelabor rupture of membranes)
- Multiple gestation
- Tobacco and illicit substance abuse
- Underweight pre-pregnancy BMI
- Short interpregnancy interval
- Chorioamnionitis / UTIs / Bacterial vaginosis
- Mullerian anomalies

HOW DO WE EVAL FOR PTL?

- **Standard clinical assessment (SCA)** includes: history, continuous fetal monitoring (CFM), sterile pelvic exam (SPE), and sterile speculum exam (SSE)
- Lofti 2017 evaluated SCA in 148 women 24-36 6/7 wks
  - tPTL symptoms: contractions, cramping, intermittent lower abdominal pain, back pain, pelvic pressure, vaginal bleeding
    - Exclusions: moderate bleeding, previa, SROM, >3cm dilated, intercourse w/in 24 hours of time of evaluation, <18 yo, multiples
  - Prediction of delivery within 7 (& 14 days in parentheses) is BAD (only 10%), however, NPV was good

METRIC	SENSITIVITY	SPECIFICITY	PPV	NPV
SCA	100% (100%)	41% (42%)	10% (14%)	100% (100%)

CAN CERVICAL LENGTH (CL) HELP?

- Nikolova 2015:
  - SCA + CL performed in 203 singletons between 20 0/7 – 36 6/7 weeks for risk of labor <7 days
  - tPTL symptoms: contractions, cramping, intermittent lower abdominal pain, back pain, pelvic pressure, vaginal bleeding
    - Exclusions: moderate bleeding, previa, SROM, >3cm dilated, intercourse w/in 24 hours of time of evaluation, <18 yo, multiples
  - Prediction of delivery within 7 days with CL <2.5 is BAD (~30%)

METRIC	SENSITIVITY	SPECIFICITY	PPV	NPV
CL <2.5cm	57%	73%	30%	89%

- **Interestingly, 100% of patients with CL <1.5 delivered in <7D, and 3% of pts w/ CL >3.5 delivered in <7D; CL between 1.5-3.5 was not helpful**

THUS, THE STANDARD OF CARE (SCA +/- CL) HAS NOT BEEN GREAT FOR PREDICTING PTD!

CAN BIOMARKERS HELP?

FETAL FIBRONECTIN (FFN)

fFN HAS BEEN THE RECENT STANDARD

HOW IT WORKS IN PRACTICE

- Used as an aid to assess risk of delivery w/in 7-14 days between 24 0/7-34 6/7 weeks with tPTL (who have INTACT cervical membranes AND <3cm cervical DILATION)
  - NOT to be used in women >3cm dilated, SROM, cervical cerclage, or bleeding
- In practice, fFN is used for its NPV, not its PPV!
  - If fFN is negative, you can be fairly confident that the patient is unlikely to deliver in the next 7 days (maybe even 14 days)
  - If fFN is positive… then you wish you hadn't even sent it because it is not helpful in determining risk of PTD

BACKGROUND

WHAT IS fFN?

- It is a protein typically localized in the extracellular matrix of the choriodecidual junction
- It is unclear exactly how fFN appears in cervico-vaginal secretions
  - Mechanical stress caused by uterine contractions and cervical change leading to choriodecidual separation?
  - Localized inflammation (from infection) leading to breakdown of the choriodecidual interface?

NEWER BIOMARKERS

PAMG-1 (PARTOSURE)

PHIGFBP-1 (ACTIM PARTUS)

BACKGROUND

WHAT IS PAMG-1?

- Human placental alpha macroglobulin-1 historically is a protein isolated from amniotic fluid
  - It can also be found in cervico-vaginal discharge (however at several thousand times lower concentration)
  - Thus, it was originally extensively used as AmniSure to evaluate for ruptured membranes

BACKGROUND

WHAT IS phIGFBP-1?

- Also called placental protein 12, it is a protein synthesized in decidualized endometrial cells during pregnancy
- Appears to be regulated by HCG and progesterone
- Has abundant functions during implantation and throughout pregnancy
- Absent in the vagina under normal conditions

BACK TO LOFTI 2017

- 148 singletons between 24 0/7 – 36 6/7 weeks were evaluated for risk of labor within 7 and 14 days
- Previously hidden from the 1st slide was that PAMG-1 was also collected and clinicians were blinded to its outcome
- Results for prediction of delivery <7D (and <14D in parentheses), and PAMG-1 greatly improved PPV, while retaining very high NPV

METRIC	SENSITIVITY	SPECIFICITY	PPV	NPV
SCA	100% (100%)	41% (42%)	10% (14%)	100% (100%)
PAMG-1	63% (55%)	98% (99%)	71% (86%)	98% (96%)

- Conclusion of investigators: 81/132 pts had been admitted for observation 2/2 concern or tPTL by SCA → 8/81 delivered <7D → thus potentially 73/81 of the admissions "may have been prevented with help of PAMG-1"

PAMG-1 COMPARED TO fFN?
BACK TO NIKOLOVA 2015

- 203 singletons between 20 0/7 – 36 6/7 weeks for risk of labor <7D
  - Previously hidden from the slide was that *PAMG*-were also collected and clinicians were blinded to its outcome

METRIC	SENSITIVITY	SPECIFICITY	PPV	NPV
CL <2.5cm	57%	73%	30%	89%
PAMG-1	80%	95%	76% (82%)	98% (93%)
fFN	50%	72%	25% (42%)	91% (82%)

- Results for prediction of delivery <7D (and <14D in parentheses)
- PAMG-1 has better (but not perfect) PPV, and still better NPV

RECENT META-ANALYSIS
MELCHOR 2018

- Evaluated SCA + CL + all 3 biomarkers and compared them (after separating pts into three groups by CL) for their ability to predict PTD w/in 7 days
  - Low risk (CL >3cm), High risk (CL <1.5cm), Mod. risk (CL 1.5-3cm)
  - PAMG-1 was found to be generally better in most aspects
  - Below are the statistics for theses markers irrespective of CL

METRIC	SENSITIVITY	SPECIFICITY	PPV	NPV
fFN	68%	84%	34%	83%
PAMG-1	76%	97%	76%	97%
phIGFBP-1	93%	76%	35%	99%

CONCLUSIONS

- There is no perfect way to rule out PTL, thus extended observation of patients with concern for PTL remains important for decreasing fetal morbidity/mortality
- A biomarker such as PAMG-1 retains strong NPV, while having the strongest predictive accuracy and may assist with evaluation of tPTL
  - Further, in Melchor 2018, the positivity rate for PAMG-1 in pts with tPTL was 7.9% (compared to 23-30% for the other two markers)
    - Thus, a lower overall positivity rate + a higher PPV may reduce the rate of unnecessary hospitalization and/or transfer for tPTL
- Remember that blood, lubricating jelly, betadine, and antibiotic creams can interfere with biomarkers
- Generic soaps, creams, semen, urine, vaginitis will not interfere

REFERENCES

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