What’s new in Induction of Labor?

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CONFLICT OF INTEREST DISCLOSURE STATEMENT

I have/I don't have financial interest or other relationships with the industry relative to the topics being discussed.
Induction of Labor

IOL increased from 9.6% to 23.8% from 1990 through 2010

Osterman, MJ, Martin, JA. NCHS Data Brief 2014
Who?

Accepted indications
- Abruptio placentae
- Chorioamnionitis
- Fetal demise
- Gestational hypertension, Preeclampsia, Eclampsia
- Premature rupture of membranes
- Postterm pregnancy
- Maternal medical conditions (DM, renal disease, chronic HTN, APAS, etc)
- Fetal Compromise (severe IUGR, isoimmunization, oligohydramnios)

Unclear indications
- Advanced maternal age
- Macroamia

Advanced Maternal Age
Risks of Stillbirth

<table>
<thead>
<tr>
<th>Maternal age at delivery</th>
<th>Risk Tri 21</th>
<th>Risk any chromos. Abn.</th>
<th>Risk SB &gt; 37 w, Multipara</th>
<th>Risk SB &gt; 37 w, nullipara</th>
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</thead>
<tbody>
<tr>
<td>20-34</td>
<td>1/1667-1/485</td>
<td>1/562-1/238</td>
<td>1/775</td>
<td>1/269</td>
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<tr>
<td>35-39</td>
<td>1/378</td>
<td>1/192</td>
<td>1/502</td>
<td>1/156</td>
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<tr>
<td>40+</td>
<td>1/106</td>
<td>1/66</td>
<td>1/304</td>
<td>1/116</td>
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</tbody>
</table>

• Other risks:
  - Hypertensive disease
  - Gestational DM
  - Placenta previa
  - Placental abruption
  - Macroamia
  - Stillbirth
SB risk for “postdates” at 41 weeks for women < 35 (0.95/1000) equivalent to:

- Age 35-39 at 40 weeks
- Age 40+ at 39 weeks

The 35/39 trial:
Hypothesis: IOL at 39 weeks would reduce the rate of C/S among nulliparous women at AMA

- Multicenter randomized controlled trial comparing rate of C/S between women assigned to IOL (n=305) between 39+0 – 39+6 weeks vs expectant management (n=314)
- Nulliparas, age 35 and older at EDD, singleton, cephalic

Results:
- No difference in IOL vs expectant group in C/S: 32% vs. 33%
- No difference in maternal or neonatal outcomes
- Could not assess affect on stillbirth but shows safety for performing larger trial

Randomized Trial of Labor Induction in Women 35 years of Age or Older
NEJM March 3, 2016
Induction of labor for suspected fetal macrosomia

- 4 trials involving 1190 women
- No reduction in C/S rates (RR 0.91, 95% CI 0.76-1.09)
- No difference in instrumental delivery (RR 0.86, 95% CI 0.65-1.13)
- Decrease in shoulder dystocia in IOL group (RR 0.60, 95% CI 0.37-0.98)
- Decrease in fracture (any) in IOL group (RR 0.20, 95% CI 0.05-0.79)
- No difference in brachial plexus injury (2 in IOL, 1 in expectant group)
- IOL group had significantly lower mean BW – mean difference 178 grams
- No differences in low 5 minute Apgars, or low arterial cord blood pH (RR 1.01, 95% CI 0.46-2.22)

What?
Induction of labor: techniques for stimulating uterine contractions to accomplish delivery prior to the onset of spontaneous labor

- **Induction: Oxytocin**
  - 1948: Theobald et al described their use of the posterior pituitary extract, oxytocin, by IV drip for labor induction
  - 1953 oxytocin synthesized

- **Other methods for induction:**
  - Membrane stripping
  - Amniotomy
  - Nipple stimulation
  - Prostaglandin E analogues

- **Vs. Cervical Ripening:**
  - Facilitate cervical softening, thinning and dilating
  - Reduce rate of failed induction and induction to delivery time
Where?: Outpatient Cervical Ripening

- **PGE2 gel**
  - 4 studies
  - outpt vs placebo - +efficacy
  - outpt vs inj -
  - No diff efficacy
  - 1 study - 50% kept in hospital

- **Mifepristone (PGE1)**
  - 5 studies
  - 2 outpt vs placebo - fewer IOL and ↓ time to delivery
  - outpt vs inj -
  - No diff efficacy

- **Nitric Oxide donors**
  - 5 studies
  - Most improved
  - Bishop score
  - Mixed results for time from IOL to delivery
  - No diff in C/S rates

- **Foley Balloon**
  - 1 RCT inj vs outpt
  - No difference in outcomes: spent 9.6 h less in hospital
  - 1 cohort study
  - No difference c/s or infection
  - Outpt had longer time from IOL to delivery
  - 86% satisfied

- **Acupuncture**
  - Few good quality studies
  - Most do not show efficacy

When: Indicated late-preterm and early term birth

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**Timing of indicated late-preterm and early-term birth.**

Spong CY, Mercer BM, D’alton M, Kilpatrick S, Blackwell S, Saade G.
When?
Elective induction

- **Con:**
  - Potential for increase in C/S in latent phase, increase in length of labor, cost, neonatal morbidity if < 39 weeks
  - Pro:
  - Reduction in stillbirth, macrosomia, avoid delivery en route to hospital, lifestyle for patients
  - Should not be performed < 39 weeks
  - 3 systematic reviews of RCT's showed no increase in C/S rate*


When?
Preventive (Non-indicated “ni-IOL” or Active Management of Risk in Pregnancy at Term (AMOR-IPAT))

- Data limited but some evidence of benefit to improve outcomes
  - 2 large observational studies found delivery after ni-IOL had lower rates of C/S and stillbirth*
  - 2 RCTs for IOL for reasons not meeting usual indications showed benefit of IOL over expectant mgmt**
  - 2 meta-analyses comparing ni-IOL with expectant mgmt found benefit in IOL group***
  - 5 studies comparing AMOR-IPAT with usual care showed significant associations between the use of preventive IOL and lower rates of common adverse outcomes****
  - Need adequately powered RCT's to definitely study the risks and benefits of modeled risk-based “non-indicated” (i.e. “preventive”) term labor induction

Why?
To induce or not to induce…

- Rising cesarean delivery rates are a major concern

Reasons for increase in C/S?
- Decline in TOLAC
- Increasing rates of obesity
- Advanced maternal age
- Induction of labor (IOL)

- Reducing frequency of IOL often cited as approach to reversing the trend in c/s rates
- Association between IOL and C/S largely based on observational studies

IOL for PROM: large clinical trials and meta-analyses do not show an increase in C/S

2006 Cochrane review for IOL for post-term concluded that there was no difference in the risk of C/S between IOL and expectant management

Does IOL increase the risk of C/S? A systematic review and meta-analysis of trials in women with intact membranes

- 37 RCTs
  - 27 uncomplicated pregnancies 37-42 weeks
  - 10: suspected macrosomia(2), DM (1), oligohydramnios (1), twins (2), IUGR (2), mild pregnancy-induced hypertension (1), women with a high-risk score for C/S (1)

- Meta-analysis of 31 trials determined that a policy of IOL was associated with a reduction in the risk of C/S compared to expectant management (OR 0.83, 95% CI 0.76-0.92)
How? Induction

Oxytocin
- Various regimens with similar efficacy
- 2014 systematic review of 9 randomized trials of high vs low dose oxytocin: high dose reduced induction to delivery interval in high quality trials but no change in C/S rates*
- Higher rates of tachysystole
- Oxytocin and early amniotomy

RCT: early amniotomy vs routine amniotomy
- At physician discretion (mean 7.4 cm) in nulliparous women
- Shortened time to delivery by > 2 hours and increased proportion of deliveries within 24 hours (68 vs 56%, RR 0.72, 95% CI 0.59-0.89)**

*Budden et al Cochrane Database Syst Rev 2014, **Macones et al. AJOG 2012

How? Cervical Ripening

Prostaglandin E1 (misoprostol, cytotec)
- Misoprostol vs other prostaglandins vaginally
  - More effective: Lower failure rate of delivery within 24 hours (RR 0.78, 8 trials, 1995 women)
  - No difference in C/S rates
  - Higher rates of uterine tachysystole associated with FHR changes
- Misoprostol vs. oxytocin
  - Lower C/S rates (RR 0.58, 5 trials, 736 women) but more tachysystole
- Misoprostol vs. balloon catheters
  - No difference in C/S rates, time to delivery or chorioamnionitis but 3X higher rate of tachysystole
How? Cervical Ripening

- **Misoprostol oral administration**
  - Peaks quickly and declines rapidly
  - No consensus on dosing (50 mcg q 4 hours – max 6 hours)

- **Buccal or sublingual**
  - More rapid onset of action and greater bioavailability
  - **Sublingual vs oral**
    - RCT of 50 mcg SL vs 100 mcg oral q. 4 hours X max 5 doses: similar efficacy for vaginal delivery within 24 hours and = tachysystole
  - **Sublingual vs. vaginal**
    - Meta-analysis of 5 RCTs found no difference for rates of vaginal delivery within 24 hours, tachysystole or C/S
    - 3 small trials – need more data

How: Balloon catheters

- **Single balloon catheters**
  - Larger is better
    - 30mL balloon vs. 60mL balloon: greater % delivery within 12 hours (26 vs 14%) and greater cervical dilation (4cm vs 3 cm)

- **Double balloon catheters**
  - No difference in outcomes between single and double balloon catheters*
    - 1 study showed lower c/s rates and shorter interval to delivery when balloon placements included extra-amniotic saline infusion**

*Prenel BJOG 2009, ** Mei-Dad J Mat Fet Neon Med 2014
How: Balloon catheters

- Balloon catheters vs. prostaglandins
  - 2012 Cochrane database meta-analysis:
    - No difference in vaginal deliveries within 24 hours (RR 1.28, 95% CI 0.94-1.68, 7 trials, 1142 women)
    - No difference in C/S rates (RR 1.01, 95% CI 0.90-1.13, 21 trials, 3202 women)
    - Balloon catheters had higher rates of oxytocin augmentation (RR 1.51, 95% CI 1.15-1.97, 6 trials, 613 women)
    - Balloon catheters: significant decrease tachysystole with FHR changes (RR 0.19, 95% CI 0.08-0.43, 9 trials, 1931 women)

How: combination methods

- Foley bulb + vaginal misoprostol (25 mcg) vs. vaginal misoprostol alone (25 mcg)
  - Foley with 60mL NS
  - Included nulliparas and multiparas
  - Primary outcome: induction to delivery time
  - Median Bishop score equal (3, range 0-6)
  - Results:
    - Decrease in induction to delivery by 3 hours in combination group (15.3 vs 18.3 hours)
    - No difference in delivery within 24 hours or mode of delivery
    - No difference in neonatal outcomes

Carbone et al Obstet and Gynecol 2013
How: combination methods

- Transcervical Foley Catheter with and w/o oxytocin for cervical ripening: an RCT*
  - Nulliparas and multiparas
  - 30mL NS
  - No difference in delivery within 24 hours (65 vs 60%)
  - No difference in interval to delivery (21 vs 23.5 hours)

- RCT of Foley balloon Induction of labor Trial in Nulliparas (FIAT-N)**
  - Randomized to simultaneous oxytocin + foley (60 mL) or foley alone (followed by sequential oxytocin after expulsion)
  - No difference in Bishop score (mean 1, range 0-6)
  - Results:
    - Simultaneous group delivered 3 hours earlier (15.9 vs 18.9 hrs, p=0.004)
    - Of those delivering vaginally, Simultaneous group delivered earlier (14.8 vs. 17.6 hours, p=0.02)
    - No difference in C/S rates
    - Increase rate of C/S performed for NRFHRT in simultaneous group

*Pettker et al Obstet Gynecol 2008, **Connolly et al AJOG Sept 2016

How: combination methods

Methods:

- Misoprostol/Cervical Foley arm
  - Misoprostol only arm
    - 25ug q 3 hours per vagina
    - Repeated up to 5 times for max of 24 hours
  - Cervical Foley only arm
  - Cervical Foley/oxytocin arm

Levine et al SMFM 2016
It seems reasonable to induce for AMA although large trials needed

- Induction for impending macrosomia may reduce shoulder dystocia, fracture and lower birth weight

- Outpatient cervical ripening with foley bulb appears safe and no major difference in outcomes

- Non-indicated IOL and preventive inductions may lower C/S rates and reduce adverse outcomes but need more studies

- Balloon catheters are equally efficacious to prostaglandins without the issue of tachysystole associated with FHR changes

- Combination cervical ripening agents reduce time to delivery without an effect on C/S rates
The employees are loafing again. I'm going to go out there and induce labor.