An Evidence-Based Update on Methods of Labor Induction: How can we improve our care?

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In 2013, 23% of all pregnant patients in the US underwent IOL.

National Vital Statistics Report

I have nothing to disclose.
Objectives

- Improved quality of inductions: Tailored patient-centered approach
  - Obesity
  - TOLAC
  - PROM and PPROM
  - Termination inductions
  - Prolonged pregnancy/Postdates
- Decreased Cost
  - Outpatient IOL methods

Clinically relevant outcomes for IOL studies

- Duration of labor (cervical ripening and active labor)
- Rates of spontaneous vaginal delivery
- Need for additional augmentation
- Adverse neonatal and maternal outcomes
- Satisfaction (patient and caregiver)
- Length of hospital stay

Induction Methods

- PGE1 Misoprostol
- PGE2 Dinoprostone
- Mechanical dilators
  - Foley ballon, Cook cervical ripening balloon, laminaria
- Oxytocin
- Isosorbide mononitrate: nitric oxide donor
- Mifepristone: termination inductions

Labor Induction and Obesity

- Obesity epidemic with childbearing women
- Increased comorbidities requiring IOL
- Increased rates of labor induction by obesity class
  - 30.4% class I to 34% women class III
- Increased failed IOL
- Increased complications with c sections
- Obesity class — independent predictor of IOL failure — C section*
  - OverWeight OR 1.4 (CI 1.2-1.7 p<0.001), Obese OR 2.3 (1.9-2.7 p<0.001)

*Wolfe et al AJOG 2014
*Ronzoni et al AM J Perinatal 2015
Labor Outcomes of Obese Patients Undergoing Induction of Labor with Misoprostol compared to Dinoprostone

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- Retrospective review 2008-2013
- Misoprostol 25µg vaginal or 50µg oral vs Dinoprostone vaginal insert 10-mg
- 564 women (297 misoprostol, 267 dinoprostone)
- **Misoprostol: more successful cervical ripening**: 78.1% vs 66.7% (OR 1.79) p=0.002
- Lower CD rate 39.1% vs 51.3% (OR 0.61) p=0.003
- Significance persisted with multivariate model adjusted for parity, GA, birth weight, indication for IOL

Differences with obese and non-obese patients with miso

- Secondary analysis of Misoprostol Vaginal Insert Trial: multisite, double-blind RCT
- 1,273 patients stratified by BMI—> Analyzed duration, characteristics and outcomes of labor
- Obese women:
  - Take longer to deliver spont (up to 4 hours longer for morbidly obese patients)
  - Higher CD rates: Obese (29.8%) and Morbidly Obese (36.5%) compared to non-obese (21.3%)
  - Increased need for oxytocin augmentation and increased amounts of oxytocin for longer time periods

Pevzner et al Obstet Gyn 2009

Labor Induction and TOLAC

- Decreased likelihood of VBAC: less likely with unfavorable cervix
- Potential increased risk of uterine rupture
- ACOG states **IOL should be an option for TOLAC (Level B)**
- Baseline uterine rupture risk in spontaneous labor: 0.5%
- Which method?
  - Prostaglandins (PGE1 and PGE2)
    - Misoprostol increased risk of uterine rupture (case reports or halted trials)
    - Sequential use of PGE2 and oxytocin increased risk of rupture, not PGE2 alone
  - ACOG: Against misoprostol, unclear statement about PGE2

1ACOG PB 115
2Cahill et al AJOG 2008
Labor Induction and TOLAC

- Which methods?
  - Oxytocin
    - Unclear risk: No increased risk of rupture vs doubles risk of rupture to 1% \(^1\)
    - Dose response noted: higher doses associated with increased uterine rupture \(^2\)
  - ACOG: No established upper limit dose for oxytocin
- Mechanical dilation:
  - Limited mixed data: two studies show no increase in risk, one with increased risk of rupture after mechanical dilation
  - ACOG: Foley/mechanical dilations can be used

\(^1\) ACOG PB 115
\(^2\) Cahill et al AJOG 2008

Induction Methods for PROM and PPROM

- Sparse data on preferred method for PPROM, extrapolate from PROM evidence
- Conflicting evidence about superiority of prostaglandins vs oxytocin in PROM
- Prolongation of latency >24 hours —> increased chorio

Induction Methods for PROM and PPROM

- Oxytocin better than PGE2: Kunt et al Taiwan J Obstet Gyn 2010: PGE2 vs pit for PROM
  - RCT 240 low-risk, nullips, PROM for ≥12 hours and Bishop ≤ 6
  - Mean time from labor induction to active labor and to delivery significantly shorter for pit group
  - No difference in neonatal outcomes and c section rates
  - Supported previous findings, Butt et al Obstet and Gyn 1999
- Miso better than pit? Lin et al Obstet Gyn 2005: Metaanalysis of miso vs placebo or pit for PROM IOL
  - 15 RCTs (6 studies 453 women miso vs placebo) (9 studies 1130 women miso vs pit)
  - Miso compared to placebo increased vaginal delivery rates in < 12 hrs
  - Miso better than pit for vag delivery < 12 hrs, equivalent for <24 hrs
  - No increased rates of hyperstim or adverse maternal or neonatal outcomes compared to pit
  - Decide oxytocin vs miso based on Bishop score.

Induction Methods for PROM and PPROM

- Mechanical dilators with ruptured membranes: theoretical concern for ascending infection
- Mackeen et al J Am Osteopath Assoc 2014
  - Retrospective cohort: Nullips with ROM, ≥36 wks
    - 122 Induced with Foley compared to 33 with miso
  - Time to delivery halved in Foley cohort
    - Foley group received higher dose of oxytocin compared to miso
    - No differences in mode of delivery
    - Trend toward higher infection rate in miso group
  - Two large multicenter RCTs recruiting patients now: FOLCROM Study and Eval of CRB in PROM
Termination induction in the second and third trimester

- Dodd et al Cochrane Review 2010
  - RCTs compared vaginal misoprostol with other agents and routes
  - Oral miso less effective than vaginal miso for 2nd and 3rd tri induction terminations
  - Sublingual miso may be more effective than both oral and vaginal

- Mifepristone and Miso vs Miso Alone
  - Panda et al J Family Reprod Health 2013
    - Prospective enrollment of 52 women, 3rd tri IUFD
    - IOL to delivery time shorter with combo (p<0.001)
    - Total miso dose lower with mifepristone preTx
    - No difference in complication of labor
    - RCT 100 patient IUFD ≥20 weeks, mifepristone 200mg vs placebo, then vaginal miso 36-48 h after
    - Shorter delivery interval with mifepristone pre treatment: mean 9.8 h vs 16.3 h, (p<0.001)

Induction for Prolonged pregnancy

- Complicates 15% of all preg
- Most have an unfavorable cervix —> increased CD rate

Nitric Oxide Donors: isosorbide mononitrate (IMN)

- IMN vascular dilation, rearranges cervical collagen —> ripening
- Does not induce contractions
- PRIM study: Osman et al AJOG 2006: miso vs IMN inpt: faster cervical ripening with miso, fewer fetal heart changes with IMN
- Agarwal et al Int J Gyn Ob 2012 : improved Bishop scores on admission for IOL in IMN group
- IMOP study: Bollapragada et al BJOG 2009
  - 350 pts: Nullips, singleton 37 or > weeks requiring cervical ripening prior to IOL
  - Self administered vaginal IMN 48, 32 and 16 hrs before admission —> then induced
  - IMN improved Bishop score but did not shorten admission to delivery time interval
  - Overall women appreciated home treatment
    - Patient satisfaction higher with placebo: IMN group with more headaches
Outpatient Labor Induction?

- Ideal agent: cervical ripening without significant uterine contractions
- Important outcomes:
  - Safety profile
  - Patient experience
  - Cost-saving: decreased hospital time
- Any inherent physiologic differences?

Outpatient Vaginal gels/vaginal insert (PGE2)

- O’Brien et al AJOG 1995
  - RCT compared 2mg intravaginal PGE2 to placebo placed as outpatient over 5 consecutive days
  - 100 low risk patients, well-dated between 38-40 weeks, Bishop score ≤ 6,
  - PGE2: significantly shorter mean time to delivery (4 d vs 10d p=0.002)
  - 54% of PGE2 group admitted in spont labor, vs 20% of placebo group
  - Hyperstim noted in one PGE2 patient

  - RCT compared outpatient vs inpatient vaginal CR PGE2
  - 300 term women, Bishop score ≤ 6
  - Similar times to labor onset and spontaneous delivery by 24 hours in both groups
  - **Outpatient group with higher levels of satisfaction (56% to 39 % p<0.008)**
  - Outpt group at home for median 8 hours before labor

Outpatient Cervical Ripening by Nitric Oxide Donors for Prolonged Pregnancy

- Does outpt cervical ripening at 41 wks with isosorbide mononitrate reduce c section rate in nullips with an unfavorable cervix
- Powered to detect a 25 % reduction in tx group, 685 women in each group
- Treatment: 40mg vaginal dose at 41wks, 41+2, 41+4—> induced with miso or oxytocin at 41+5 if not yet in labor
- Equivalent CD rate: ( 27.3% tx, 27.2 % plac)
- Tx increases SEs: HA, n/v

A randomised controlled trial of outpatient compared with inpatient cervical ripening with prostaglandin E2 (OPRA study)

- 827 women, outpatient vs inpatient PGE2
- No differences in pit use, CD rate, epidural use and NSVD within 24 hours
- Outpt women : increased hyperstim and non reassuring monitoring, < half went home and remained home overnight
- Cost analysis: Adelson et al Aust Health Review 2013
  - Outpatient care: cost saving of $433/woman, offset by costs of “priming” clinic—> overall savings $156
Outpatient Misoprostol: Background

- Misoprostol (PGE1)
- Effective cervical ripening agent compared to dinoprostone, oxytocin or placebo
- Trend to more c sections for fetal distress and fewer for failure to progress
- Miso compared to Foley
  - Trend to higher rates of tachysystole with miso
  - No difference in CD rates or adverse fetal outcomes
- Miso compared to dinoprostone
- Miso: Higher vaginal delivery rates within 12 and 24 hrs, similar heart rate changes and CD rates

1 Hofmeyr et al Cochrane Review 2010
2 Fox et al BJOG 2011
3 Jozwiak et al Am J Perinat 2014
4 Austin et al AJOG 2010

Outpatient Misoprostol

- Stitely et al Obstet Gyn 2000: 25 µg vaginal miso for 2 days vs placebo, then IOL on day 3
- Small RCT: Low risk singleton pregnancies ≥41 wks, low Bishop
- 88.9% miso patients entered active labor within 48 hrs of 1st dose, compared to 16.7%
- Additional studies show efficacy, all too small to be powered for safety
- Increased rates of tachysystole with and without fetal heart rate changes

Outpatient Foley Balloon: Background

- Effective method with lower rates of uterine hyperstim compared to prostaglandins
- Oxytocin needed more often in labor IOL with Foley compared to misoprostol
- → Capitalize on cervical ripening with fewer contractions for outpatient setting

Outpatient Foley Balloon

- Sciscione et al Obst Gyn 2001
  - RCT 61 patients, Bishop score ≤5
  - Inpatient vs outpatient Foley: no difference in duration or dose of oxytocin, IOL time, neonatal outcomes
  - No adverse events in either group
  - Outpatient group in hospital an average of 9.6 hours less
- Sciscione et al Am J Perinatol 2014
  - Retrospective char review of 1,905 term singleton preg with Foley, excluded TOLAC, ROM, fetal anomaly, HTN, IUFD
  - Looked at timing of adverse outcomes: CD for NRFHT, VB, placental abruption and IUFD after for interval of Foley
  - No adverse outcomes → Safe mechanism for IOL as an outpatient
Conclusions

- Obesity: Miso more effective than PGE2
- TOLAC: Pitocin and mechanical dilator can be used, no misoprostol, PGE2?
- PPROM/PROM: Decide on oxytocin vs miso based on need for cervical ripening, Foley balloon?
- Termination Inductions: Vaginal miso over oral, consider adding mifepristone 24-48 hrs before IOL
- Post dates: Nitric oxide donor —> no difference
- Outpatient IOL: Mechanical Dilator most promising option: need more data

Questions? | Thank you.