Induction of Labor: An Evidence Based Approach

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Conflicts of Interest/Disclosures

- **Conflicts of Interest:**
  - Sudler & Hennessey

- **Disclosures:**
  - "Investigational" use of medications, drugs, devices including:
    - Misoprostol
    - Foley catheter

Objectives

- **To discuss the epidemiology of inductions**
- **To review various methods of induction of labor**
  - Including results from the FOR MOMI trial - four-armed randomized trial on IOL methods
- **To become familiarized with an on-line calculator for induction success**

4,000,000 million women give birth annually in the U.S.

More than 20% undergo an induction of labor (23.3% in 2012)

One of the most common obstetrical procedures

?? Most effective way to induce labor ??

Background – consequences to an induction

- **Prolonged labor**
  - Increased risk of chorioamnionitis, endometritis, postpartum hemorrhage, and neonatal intensive care unit admission.
- **? Cesarean delivery**
  - Increased risk of blood transfusion, venous thromboembolism, and abnormal placentation in a subsequent pregnancy.
- **Increased cost**
  - Increase in hospital costs and healthcare utilization for both a prolonged labor and cesarean delivery.

Importance of decreasing the length of labor and risk of cesarean delivery among women undergoing an induction of labor cannot be overstated.

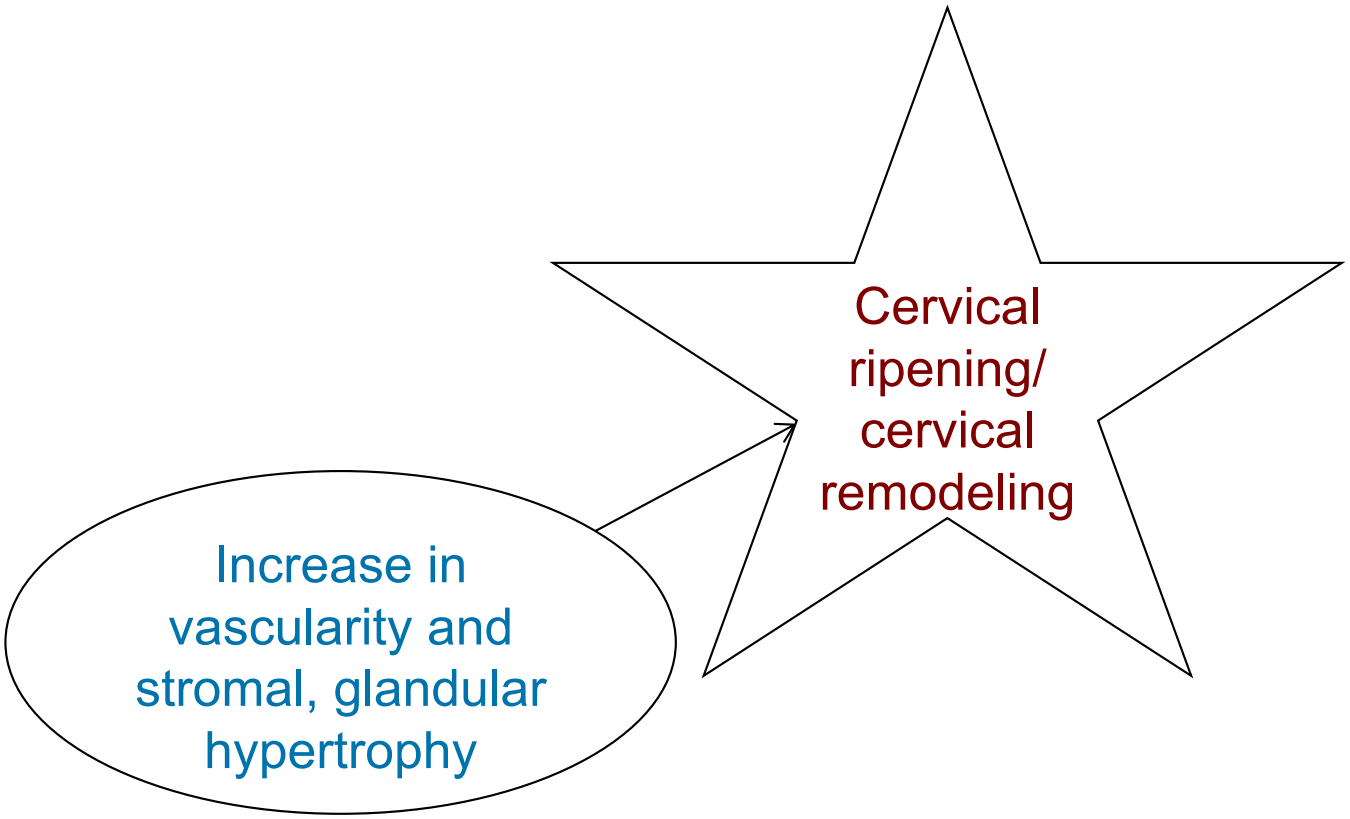
Background – consequences to an induction

- **Patient satisfaction**
  - Survey study evaluating women's satisfaction with induced labor (Shetty EJOG 2004)
  - 40% of women – "most important aspect of their induction they would like to change was the length of labor"

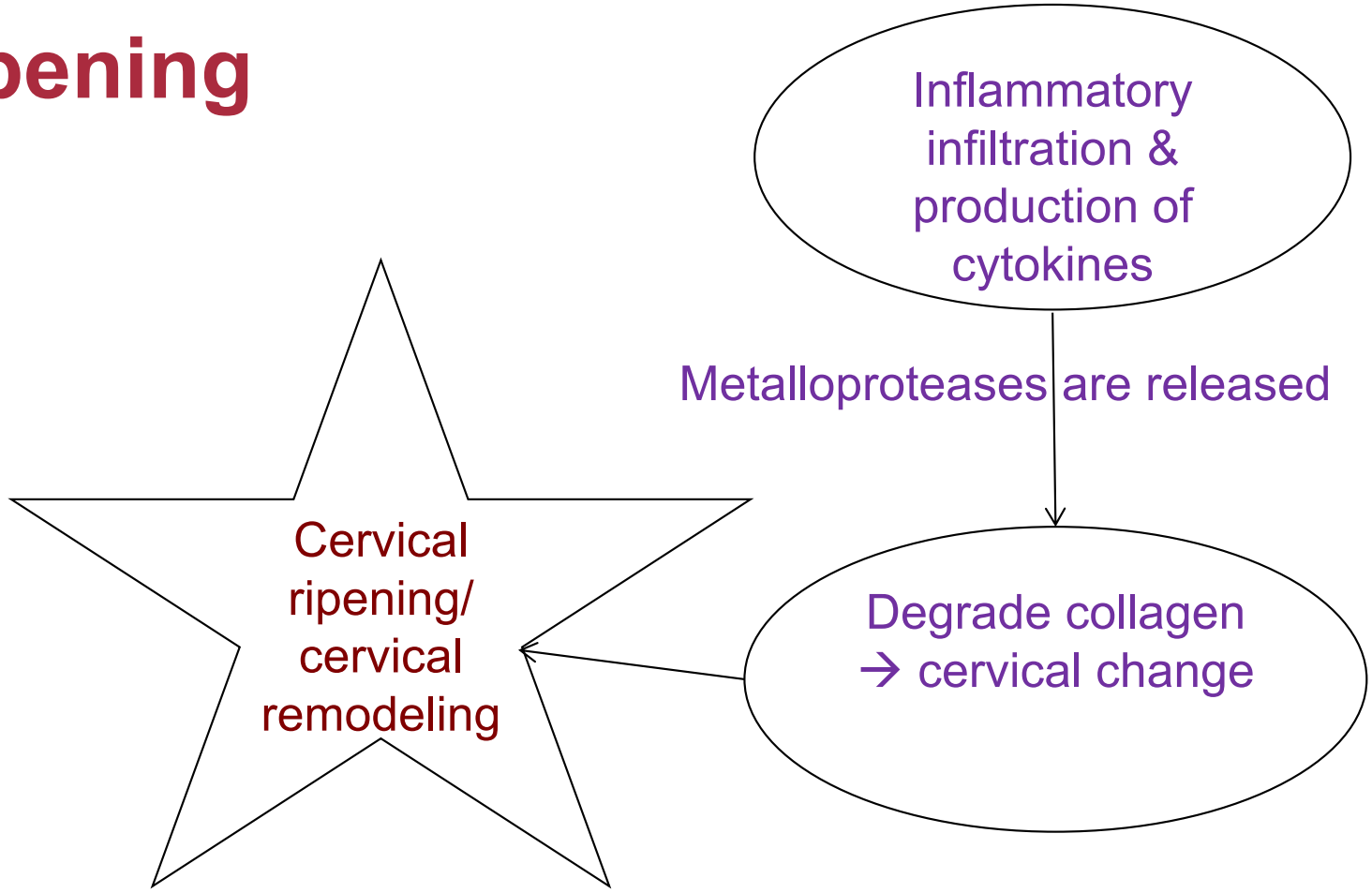
Background

- **Cervical ripening or "softening of the cervix" - required process of ensuing labor**
  - For both spontaneous labor and iatrogenic initiation
- **Cervical composition:**
  - Fibrous connective tissue, collagen (types 1, III, and IV), elastin, vasculature, fibroblasts
  - Minimal smooth muscle

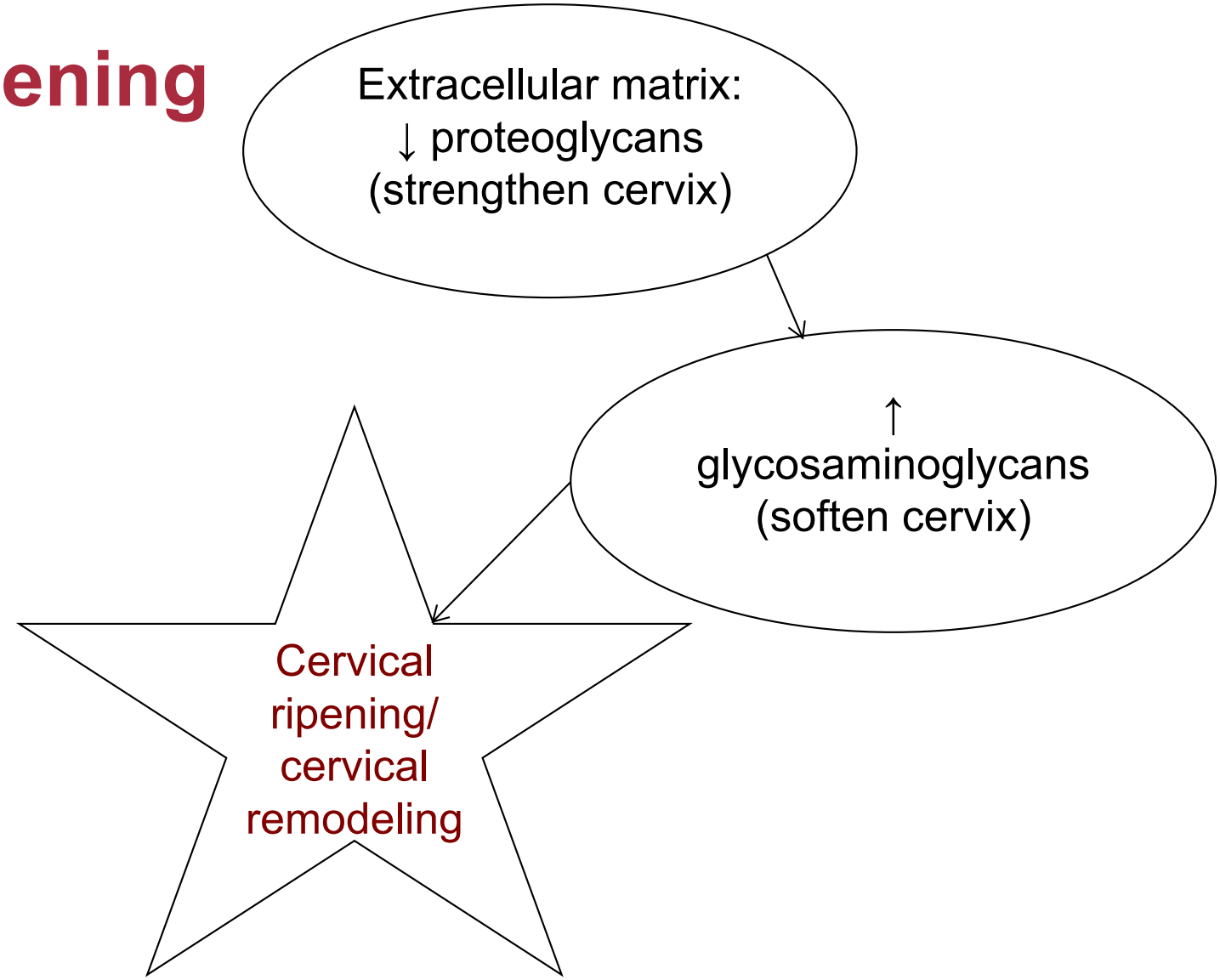
Cervical ripening



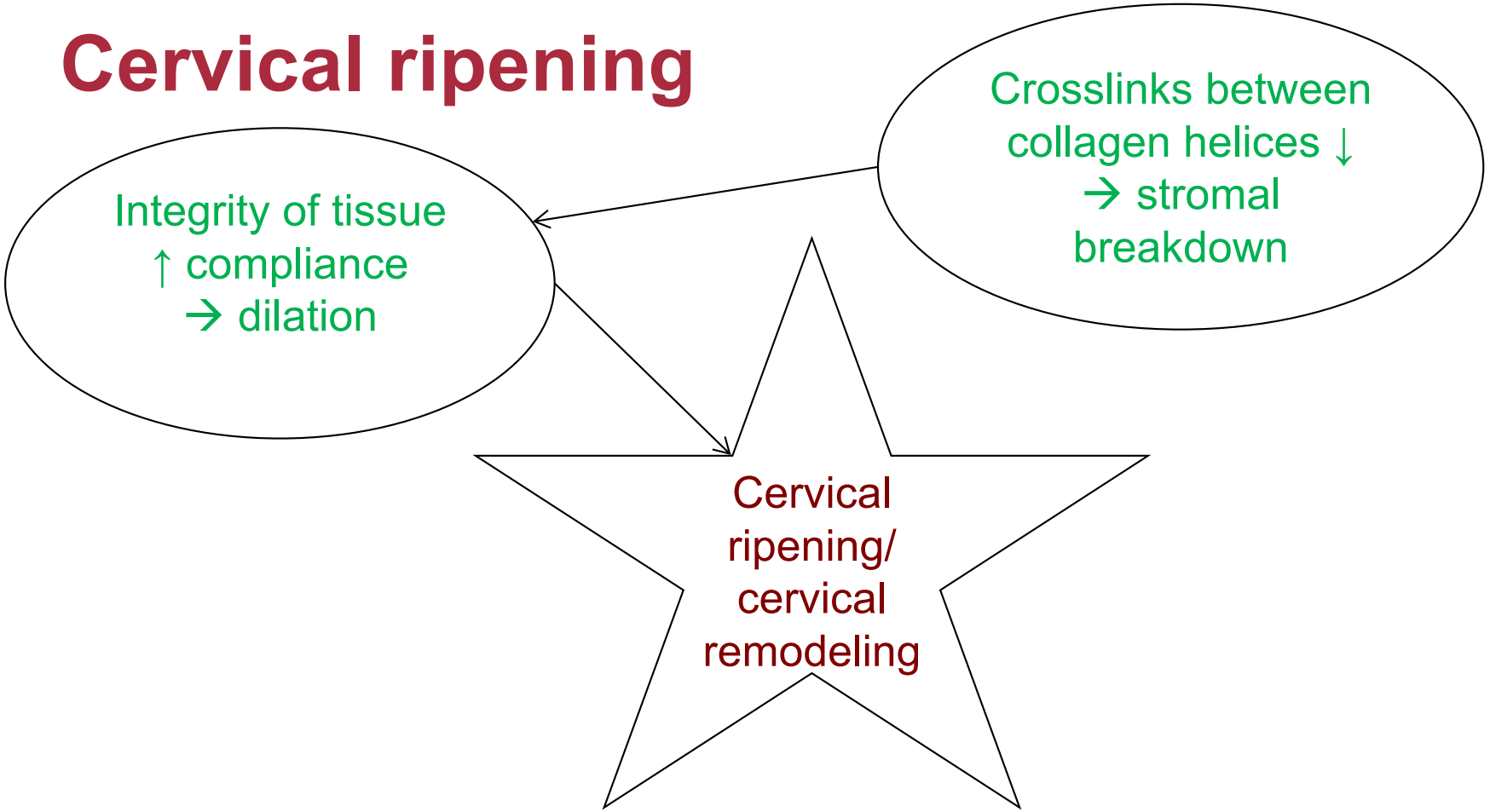
Cervical ripening



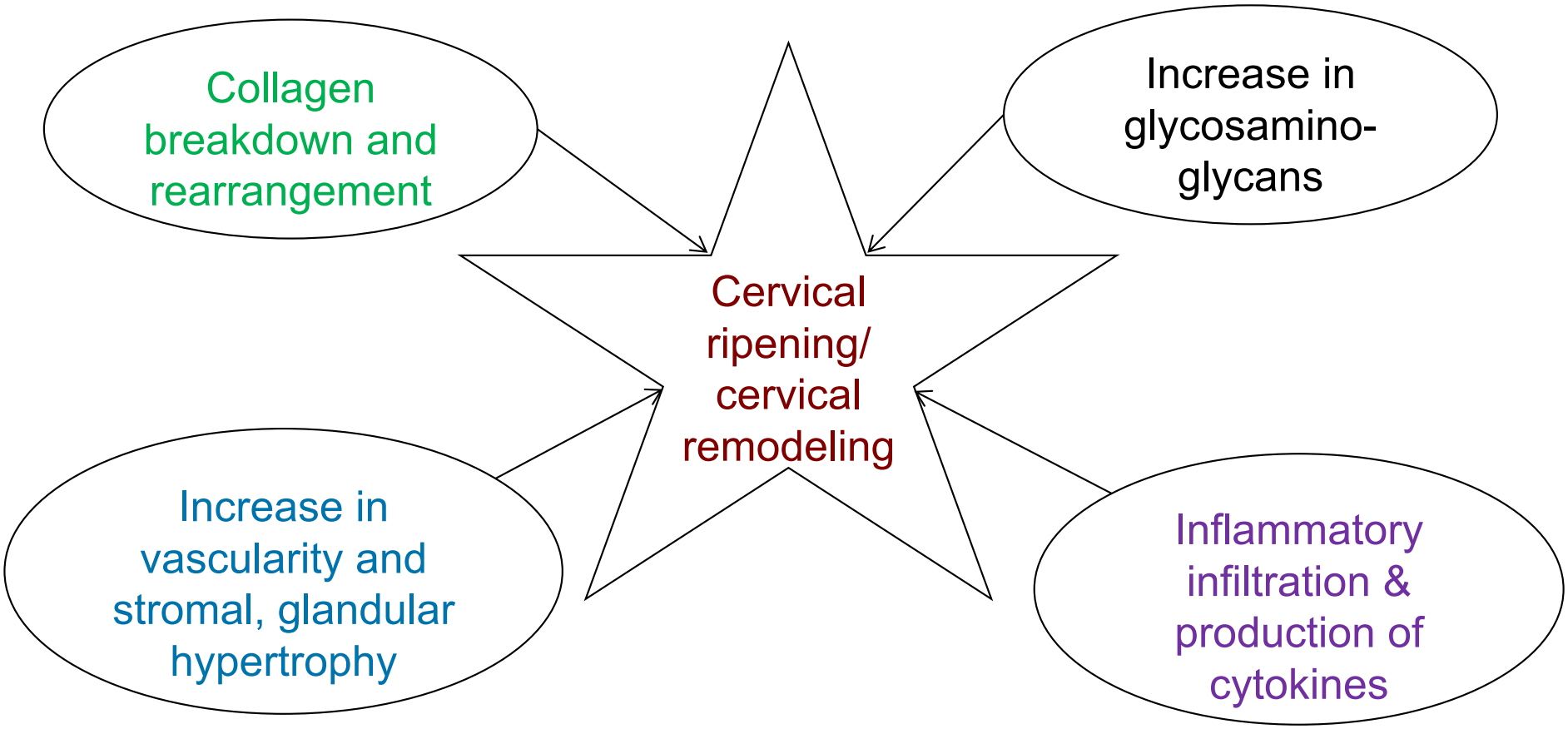
Cervical ripening



Cervical ripening



Cervical ripening



Cervical ripening

When is it needed?

Bishop scoring system

- **Dr. Edward Bishop, 1964**
- **Pre-labor scoring system to assess likelihood of going into spontaneous labor**
  - (NOT for success of induction)
- **Currently utilized to assess the favorability of the cervix prior to induction of labor**
  - ≤6 considered unfavorable →consider cervical ripening prior to IOL
  - ≥8 → probability of vaginal delivery after IOL = spontaneous labor

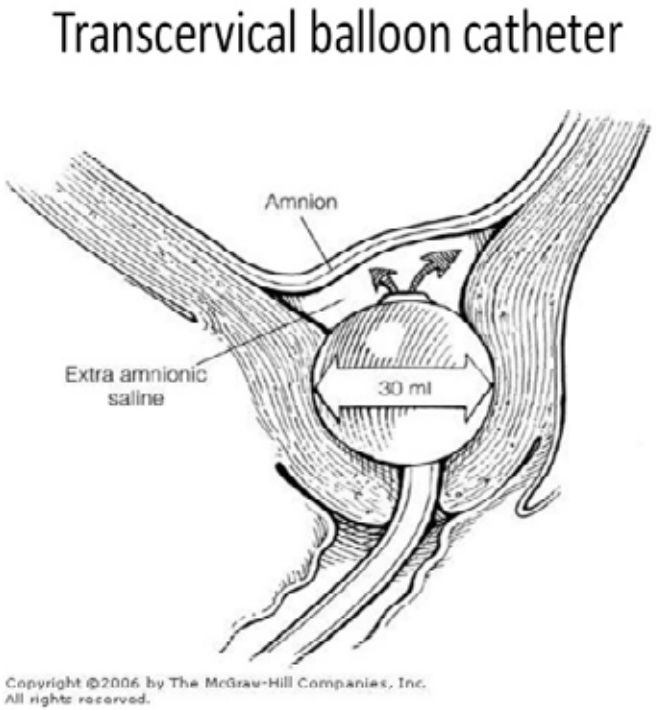
Parameter/Score	0	1	2	3
Position	Posterior	Intermediate	Anterior	-
Consistency	Firm	Intermediate	Soft	-
Effacement	0-30%	31-50%	51-80%	>80%
Dilation	0 cm	1-2 cm	3-4 cm	>5cm
Fetal Station	-3	-2	-1, 0	+1, +2

Cervical Ripening/Induction of labor methods

- **Mechanical methods**
  - Cervical Foley catheter
  - Stripping membranes
  - Laminaria
  - Extra-amniotic saline infusion
- **Pharmacologic methods**
  - Prostaglandins
    - Prostaglandin E2 (dinoprostone)
    - Synthetic prostaglandin E1 (misoprostol)
  - Oxytocin
- **Combination methods (mechanical and pharmacologic)**
  - Cervical Foley + oxytocin
  - Cervical Foley + prostaglandin

Mechanical methods – Foley catheter

- **Enhance stromal breakdown→ ↑ response to oxy & protaglandin**
- **16-18F Foley catheter, 30 mL balloon**
- **Insert past internal os**
- **Inflate balloon 30-80cc**
  - Caughey et al (Obs Gyn 2010) showed that 60cc has shorter time to delivery vs. 30cc
- **+/- Traction**
  - Gibson et al (AJOG 2013) no difference in time to delivery with taping vs. traction
- **Benefits:**
  - Simple
  - Low risk
  - Low cost
  - Stability of mechanism (ie. No breakdown)
  - Widespread availability



Mechanical methods – Foley catheter

- **Safety:**
  - Meta-analysis (McMaster et al. Obs Gyn Sept 2015) on infectious morbidity, 26 studies
    - Compared with prostaglandins alone, no difference in infections:
      - Chorioamnionitis, endometritis, pooled maternal infection, neonatal infection
- **Efficacy:**
  - Cochrane review 2012: Mechanical methods for induction of labor

	Foley vs. PG RR [95% CI]	**Foley vs. oxytocin** RR [95% CI]
Cesarean delivery	1.01 [0.90-1.13]	0.57 [0.38-0.88]*
No vaginal delivery in 24 hours	1.26 [0.94-1.68]	NA
Tachysystole without FHR changes	0.19 [0.08-0.43]*	0.20 [0.01-4.11]

  - Serious maternal and neonatal morbidity rare and no difference

Single vs. double balloon

- **Single (Foley) vs. double balloon (Cook)**
  - Salim et al (Obstet Gynecol 2011) – similar efficaciousness (time to delivery and mode of delivery)
  - Pennel et al (BJOG 2009) – shorter time to delivery and less patient discomfort with single balloon vs. double

- **Cost:**
  - Single (Foley) - $3
  - Double (Cook) - $41

Mechanical methods – Stripping membranes

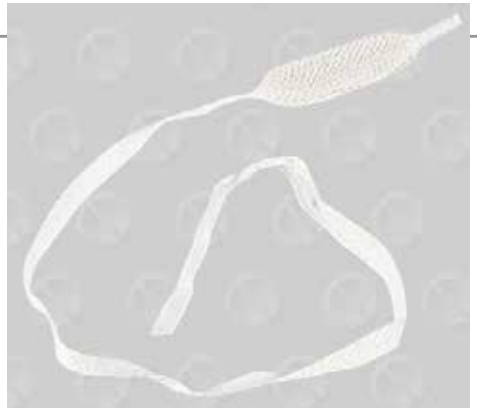
- **"Freeing" of chorionic membrane from decidua of lower uterine segment → Increase phosphilipase A_2 and prostaglandin $F_{2\alpha}$**

- **Cochrane review (Boulvain 2005)**
  - Cesarean delivery risk no different – RR 0.9 [0.7-1.15]
  - No difference in maternal or neonatal infection
  - Decreased frequency of pregnancy beyond:
    - 41 weeks (RR 0.59 [0.46-0.74])
    - 42 weeks (RR 0.28 [0.15-0.50])
  - Increased risk of uterine contractions without labor and bleeding

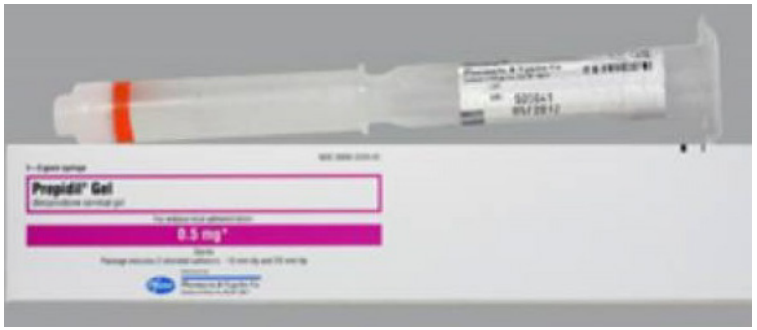
- **<u>NNT=8</u> to avoid a formal induction**
  - Risks/benefits should be individualized

    - **Should not be performed before 39 weeks**

Pharmacologic



- **Prostaglandin E2 - Dinoprostone**
- **Only cervical ripening agent approved by FDA**
- **Examples:**
  1. Cervidil – control release hydrogel suppository
     - 10mg vaginal insert released slowly 0.3mg/hr
     - Replace q12 hours
     - $218
     - Advantage – can be removed as it does not dissolve
  2. Prepidil – intracervical prostaglandin gel
     - Intracervical 0.5 mg/2.5 ml
     - Repeat q 6 hours if needed, max 3 doses in 24 hours
     - $210
  3. Prostin E2 – vaginal suppository
- **Must be kept refrigerated**
- **Work over longer period of time**
- **Expensive ($200)**



Synthetic prostaglandin (PGE1) - Misoprostol

- **FDA approved for prevention of peptic ulcers**
  - Added off-label use (2002) for cervical ripening and induction of labor →No claims regarding efficacy, safety, dosing

- **Advantages:**
  - Cheap ($0.26 per 25 mcg)
  - Can be kept at room temperature

- **Dosing: 25mcg-50mcg q3-6h**
  - Increased rate of tachysystole with 50mcg
  - Lower doses comparable to conventional methods of ripening/induction (Cochrane 2003 & Hofmeyr 1999)

Efficacy of prostaglandins

Study	Agents	Outcomes
Cochrane 2009	PG vs. oxytocin	-Lower cesarean -Higher vaginal delivery within 24 hrs
Cochrane 2009	Miso vs. PGE2	-No difference in cesarean -Higher vaginal delivery within 24 hrs
Wing, AJOG 1995	Miso vs. PGE2	-Shorter time to delivery (5 hours) -Less need for oxytocin -Higher vaginal delivery within 24 hours
Wing 2006	Miso vs. PGE2+oxytocin	-Less epidural -More meconium

Oxytocin

- **Peptide hormone**
  - Produced in hypothalamus
  - Stored in posterior pituitary gland → acts on uterus (myometrial smooth muscle)
    - G-protein coupled receptor → inc [Ca^{+2}] → contractions
  - No direct effect on cervix

- **Receptors increase with gestation**

- **Uterine response within 3-4 minutes**
- **Steady state achieved within 40 minutes**

Use of combination methods

- **Plausibly have synergistic effect in achieving cervical ripening**

Study	Agents	Time to delivery	Delivery w/in 24hrs	Cesarean delivery
Pettker (Obstet Gynecol 2008)	Foley alone vs. Foley +oxytocin *Low dose oxytocin	No * Multips combined shorter	No	No
Huin (AJOG 2004)	Foley+oxytocin vs. Foley +EASI	No	No	No
Hill (AJP 2009)	Oral miso+Foley vs. vag miso	Combined 5hrs faster	No	No
Carbone (Obstet Gynecol 2013)	Vag miso+Foley vs. vag miso	Combined 3hrs faster	No	No
Chung (AJOG 2003)	Vag miso vs. Foley vs. miso+Foley	No	No (vag deliv w/in 24)	No
Rust (J Repro Med 2001)	Vag miso vs. miso+Foley	No		No
Barrilleaux (AJOG 2002)	PGE2+Foley vs. oral miso+Foley vs. oral miso	No		No
Cochrane Jozwiak 2012	Foley+any PG vs. PG	---	Yes (vag deliv w/in 24)	No

4 million women give birth annually in the U.S.

More than 20% undergo an induction of labor
(23.3% in 2012) → 1 million women

One of the most common obstetrical procedures

?? Most effective way to induce labor ??

Lack of head to head studies of multiple agents, limiting ability to directly compare outcomes and effectiveness within one trial

What method → timely delivery without increasing cesarean and maternal/neonatal risks?

Foley OR MisOprostol for the Management of Induction: the FOR MOMI Trial

Objective:

- **To compare the time to delivery among four routinely utilized induction of labor methods, including two different combination methods**
  - Hypothesis: Women that undergo an induction with combined methods will have a shorter time to delivery than those with a single method without an increase in cesarean delivery or maternal and neonatal morbidity

Methods

Study Design

- **Randomized clinical trial evaluating four methods of induction and comparing time to delivery**
  - Misoprostol alone
  - Misoprostol/cervical Foley concurrently
  - Cervical Foley alone
  - Cervical Foley/oxytocin concurrently
- **May 2013-June 2015**
- **Hospital of the University of Pennsylvania**
- **Approval from convened IRB**
- **Registered with clinicaltrials.gov (NCT01916681)**

Inclusion criteria

- ≥ 37 weeks gestational age
- ≥18 years of age
- Singleton gestation
- Cephalic presentation
- Intact membranes
- Bishop score ≤6 and cervical dilation ≤2cm
- All indications for induction were included unless specified in the exclusion criteria
- Both nulliparous and multiparous

Exclusion criteria

- **Contraindication to vaginal delivery**
- **Contraindication to misoprostol**
  - Prior cesarean delivery or contracting >3 times in 10 minutes
- **Fetal demise or major fetal anomaly**
- **Non-English speaking**
- **HIV**
- **Women requiring an assisted second stage**
- **Category 3 fetal heart rate tracing at start of induction**
- **Hemolysis elevated liver enzymes and low platelets (HELLP) or eclampsia**
- **IUGR <10th percentile with reversal of flow in the umbilical artery dopplers**
- **IUGR <5th percentile with any abnormal umbilical artery dopplers (elevated, absent, or reversal of flow)**
- **If already enrolled in a concurrent prospective observational trial (NuMoM2b)**
  - First 12 months only

Recruitment, consenting, randomization

- **Eligible patients were approached for study participation in the obstetrical unit (L&D or triage unit) prior to the start of their induction.**
  - Written consent was obtained prior to participation in the study.

- **Internet based clinical trial management system, Research Electronic Data Capture, (REDCap):**
  - Ensured eligibility
  - Assigned randomization group
    - Randomization scheme was1:1
    - Blocks of 20
    - Stratified by parity

Methods:

- Misoprostol only arm
- Misoprostol/Cervical Foley arm
- Cervical Foley only arm
- Cervical Foley/oxytocin arm

Standard protocols for enrolled patients

- **Oxytocin protocol (hospital based)**
  - 2 mu/min increasing by 2 mu q 15 min
  - 40 mu considered the maximum dose
  - No limit to time at 40 mu

- **Amniotomy**
  - Could be performed at any point during the labor course
  - If not yet ruptured when ≥4 cm dilated, amniotomy recommended

- **Once ≥5cm, proceeded with the active labor protocol**
  - Encouraged close attention to rate of cervical change and recommended
    - Initiation of the oxytocin protocol (if not already initiated) and placement of IUPC if the patient was not making at least 1cm/hr of change.

Other labor interventions/guidelines

- **Amnioinfusion, fetal scalp electrode, tocolysis, and assisted second stage were at discretion of the managing provider.**

- **Cesarean delivery recommendations**
  - Failed induction or arrest of active phase was recommended based on current guidelines by Spong & colleagues.
  - If patient was not in active labor after 36 hours of cervical ripening
  - If patient was undelivered 12 hours after achieving active labor

- **Cesarean delivery for other indications was at the discretion of the provider**

Outcomes

- **Primary outcome: Time to delivery (hours)**
  - Regardless of mode of delivery

- **Secondary outcomes**
  - Cesarean delivery (and indication)
  - Time to vaginal delivery
  - Delivery within 24 hours
  - Time to active labor
  - Maternal and neonatal length of stay
  - Chorioamnionitis
  - NICU admission, NICU admission >48 hours
  - Composite maternal morbidity including ≥1:
    - $3^{rd}/4^{th}$ degree laceration, blood transfusion, endometritis, wound separation/infection, VTE, hysterectomy, ICU admission, and death.
  - Composite neonatal morbidity including ≥1:
    - Severe RDS, culture proven/presumed sepsis, blood transfusion, HIE, IVH grade 3 or 4, NEC, and need for head cooling.

DSMB

- A data and safety monitoring board (DSMB) was established to independently evaluate the safety of the study.
- An interim safety analysis was performed for pre-defined adverse outcomes after 50% recruitment
- The primary outcome, time to delivery, was not evaluated at this interim analysis.

- Recommendations: continue with study per current protocol without actions or changes to the study.

Sample size

- **4 hour reduction in time to delivery - clinically meaningful**
  - Mean time to delivery for induction in literature: 18 hours ±8.5
- **No "standard of care" method**
  - *a priori*, chose to compare all groups
  - Requires 6 separate comparisons (Bonferroni) → alpha of 0.008
- **80% power, 1:1 ratio, and a two sided p-value**
- **112 patients in each arm → total sample size of 448**
- **Increased sample sized based on assumed crossover rate of 10%**

- **Final desired sample size 492**

Data Analysis

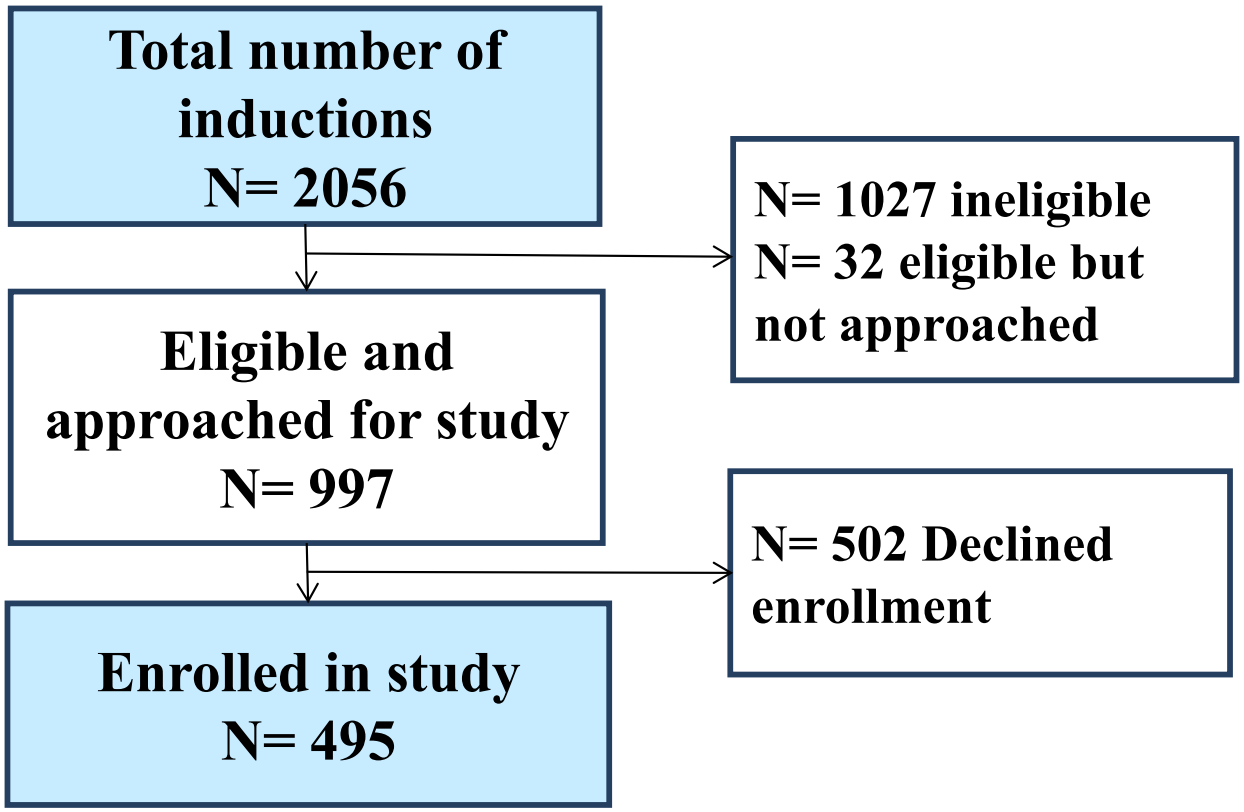
- **Descriptive statistics for labor outcomes:**
  - Overall
  - Stratified by parity
- **Bivariate analyses:**
  - ANOVA and Kruskal-Wallis for continuous variables
  - Fisher exact and Chi-square for categorical variables
- **Intention-to-treat principle**
- **Time to event regression models (Cox proportional hazard model)**
  - Labor length censored for cesarean
- **Risk of cesarean delivery**
  - Modified Poisson approach
- **Sensitivity analysis**
  - "As treated"

Results

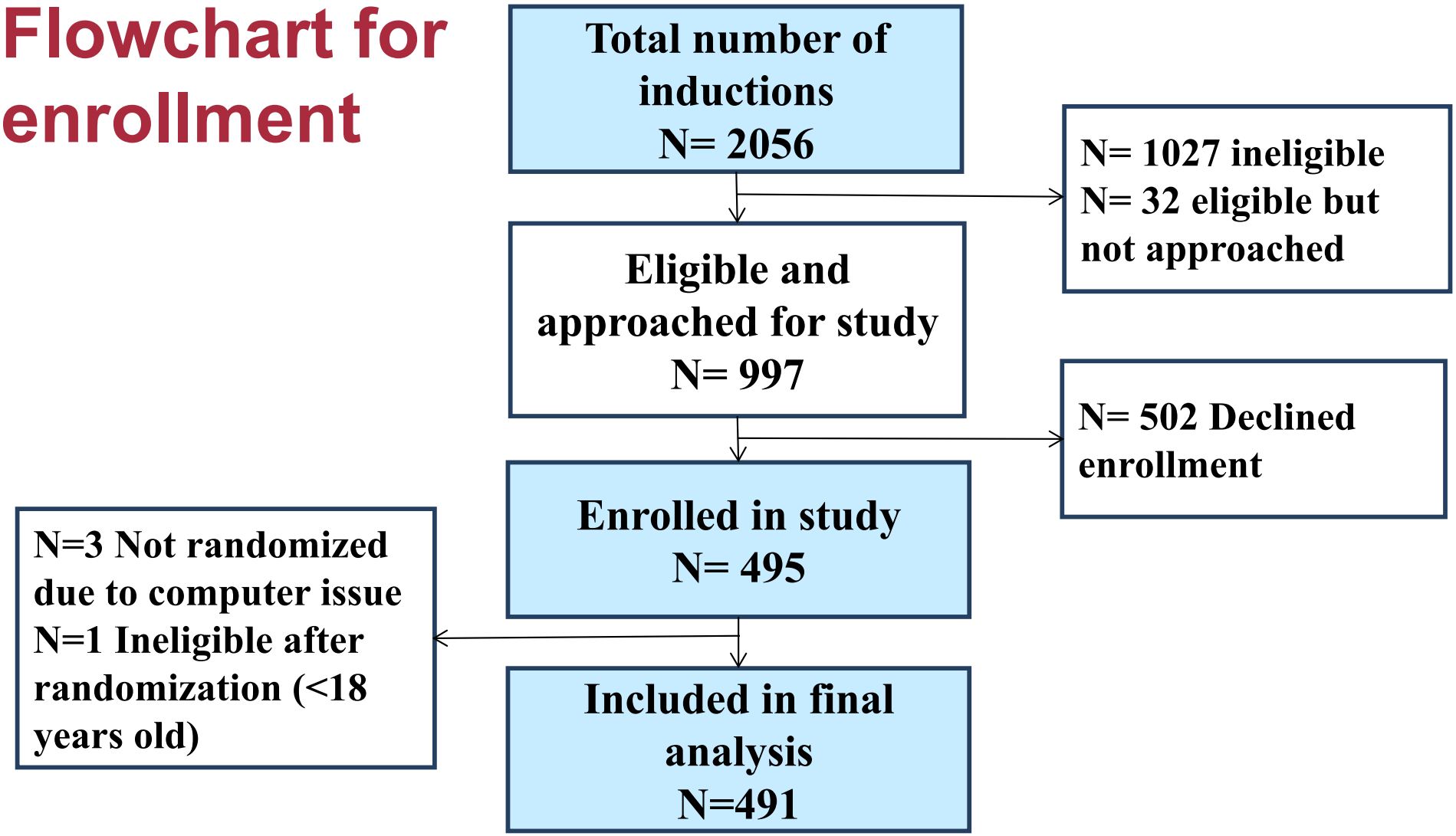
Flowchart for enrollment

Total number of inductions
N= 2056

Flowchart for enrollment



Flowchart for enrollment



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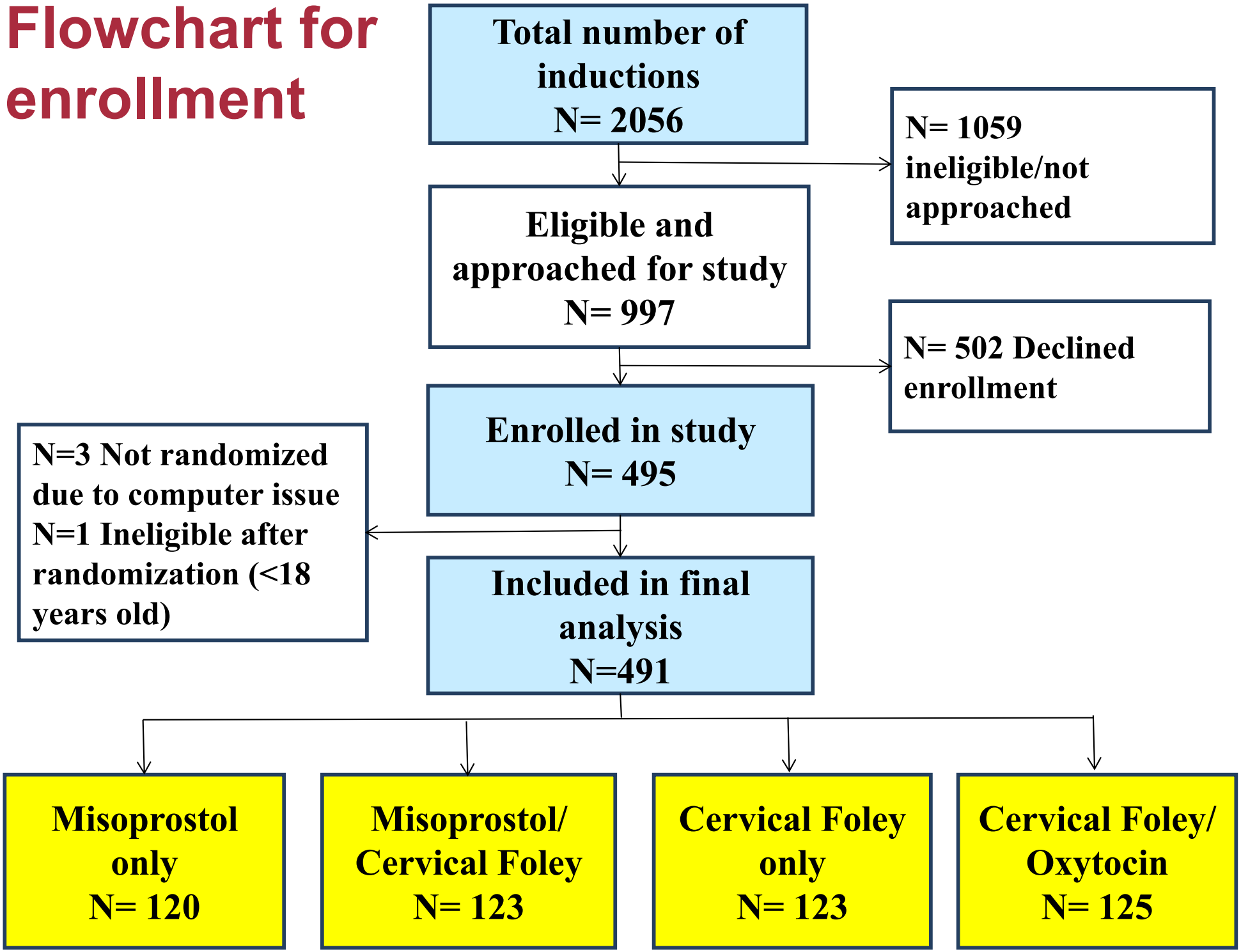


Patient demographic and clinical characteristics

	Miso Only (n=120)	Miso/Foley (n=123)	Foley Only (n=123)	Foley/ Oxytocin (n=125)	P-value
Maternal Age	26.7 [21.8-31.0]	28.0 [22.4-33.1]	27.3 [22.3-32.9]	26.5 [22.4-31.7]	0.3
BMI	27.5 [24.3-35.9]	28.3 [23.9-32.6]	29.1 [24.4-35.7]	30.1 [24.6-35.8]	0.3
Race					0.6
Black	94 (78.3)	93 (75.6)	99 (80.5)	95 (76.0)	
White	15 (12.5)	24 (19.5)	16 (13.0)	21 (16.8)	
Other	11 (9.2)	6 (4.9)	8 (6.5)	9 (7.2)	
Insurance					0.8
Private	40 (33.3)	45 (36.6)	42 (34.2)	38 (30.4)	
Public	80 (66.7)	78 (63.4)	81 (65.9)	87 (69.6)	
# prenatal visits	9.5 [7-11]	10 [8-12]	10 [8-12]	10 [7-12]	0.1
Nulliparous	70 (58.3)	73 (59.4)	73 (59.4)	74 (59.2)	0.9
GA at induction	39.1 [37.9-40.1]	39.6 [38.3-40.7]	39.3 [38.3-40.4]	39.1 [38.3-40.6]	0.2

Data presented as median [IQR] or n(%)

Patient demographic and clinical characteristics

	Miso Only (n=120)	Miso/Foley (n=123)	Foley Only (n=123)	Foley/ Oxytocin (n=125)	P-value
Bishop score at randomization	3 [2-4]	3 [2-4]	3 [2-4]	3 [2-4]	0.5
Dilation at randomization	1 [0.5-1.5]	1 [1-1.5]	1 [0.5-1.5]	1 [0.5-1.5]	0.04
Bishop score at induction	3 [2-4]	3 [3-4]	3 [2-4]	3 [2-4]	0.5
Dilation at induction	1 [1-1.5]	1.5 [1-2]	1 [1-1.5]	1 [1-1.5]	0.07
Gestational diabetes	6 (5.0)	8 (6.5)	5 (4.1)	14 (11.2)	0.1
Pre-gestational DM	3 (2.5)	2 (1.6)	4 (3.3)	2 (1.6)	0.8
CHTN	7 (5.8)	10 (8.1)	10 (8.1)	12 (9.6)	0.8
Preeclampsia	35 (29.1)	41 (33.4)	45 (36.6)	43 (34.4)	0.8
Tobacco use	9 (7.5)	9 (7.3)	10 (8.1)	15 (12.0)	0.5
Indication for induction					0.4
Postdate	12 (10.0)	20 (16.3)	18 (14.6)	17 (13.6)	
Maternal	28 (23.3)	37 (30.1)	38 (30.9)	44 (35.2)	
Fetal	64 (53.3)	57 (46.3)	54 (43.9)	50 (40.0)	
Elective/Other	16 (13.3)	9 (7.3)	13 (10.6)	14 (11.2)	

Data presented as median [IQR] or n(%)

PRIMARY OUTCOME

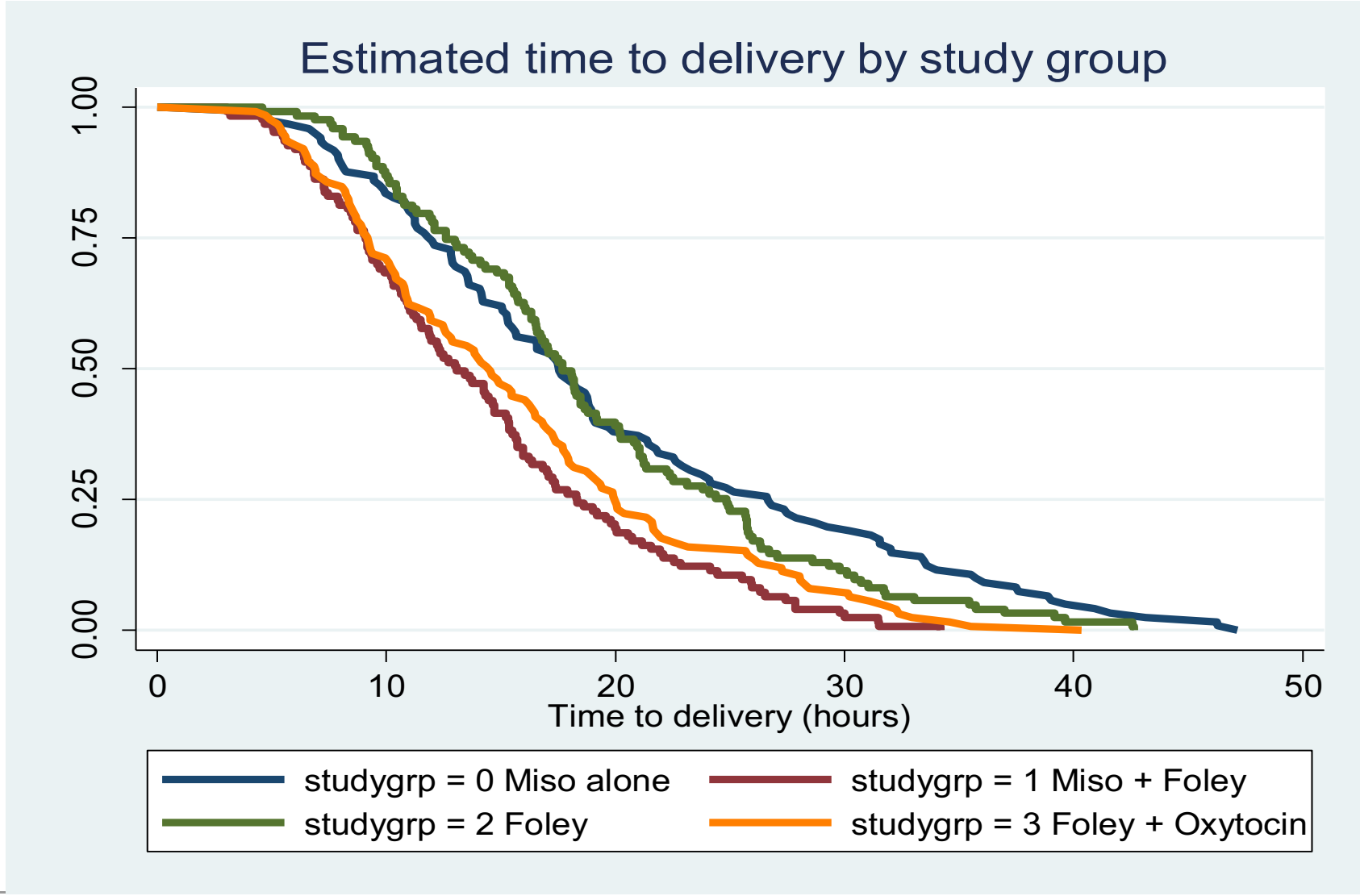
Time to delivery by study group

	Miso Only (n=120)	Miso/Foley (n=123)	Foley Only (n=123)	Foley/ Oxytocin (n=125)	P-value
***Time to delivery (hours)	17.6 [11.9-26.7]	**13.1 [9.1-18.3]**	17.7 [12.6-24.9]	**14.5 [9.3-20.0]**	<0.001
Nulliparous	21.4 [15.6-33.3]	**16.2 [11.5-21.6]**	21.0 [15.8-26.4]	**17.7 [11.9-22.0]**	<0.001
Multiparous	12.9 [9.9-18.7]	**9.3 [6.7-13.0]**	15.5 [10.1-18.2]	**10.4 [6.8-14.8]**	<0.001

Data presented as median [IQR], p<0.008 is statistically significant

PRIMARY OUTCOME

Time to delivery by study group: Survival Curve



SECONDARY OUTCOME

Time to vaginal delivery by study group

	Miso Only (n=120)	Miso/Foley (n=123)	Foley Only (n=123)	Foley/ Oxytocin (n=125)	P-value
Time to vaginal delivery (hours)	16.6 [11.2-23.8]	**11.0 [8.0-15.5]**	16.3 [11.2-21.0]	**11.0 [8.4-16.5]**	<0.001
Nulliparous	19.1 [15.1-28.7]	**15.3 [10.2-17.9]**	18.2 [13.4-24.4]	**15.2 [9.7-20.0]**	<0.001
Multiparous	12.9 [9.9-18.2]	**9.1 [6.6-12.6]**	14.8 [10.1-17.7]	**10.1 [6.6-13.5]**	<0.001

Data presented as median [IQR]

SECONDARY OUTCOME

Cesarean delivery by study group

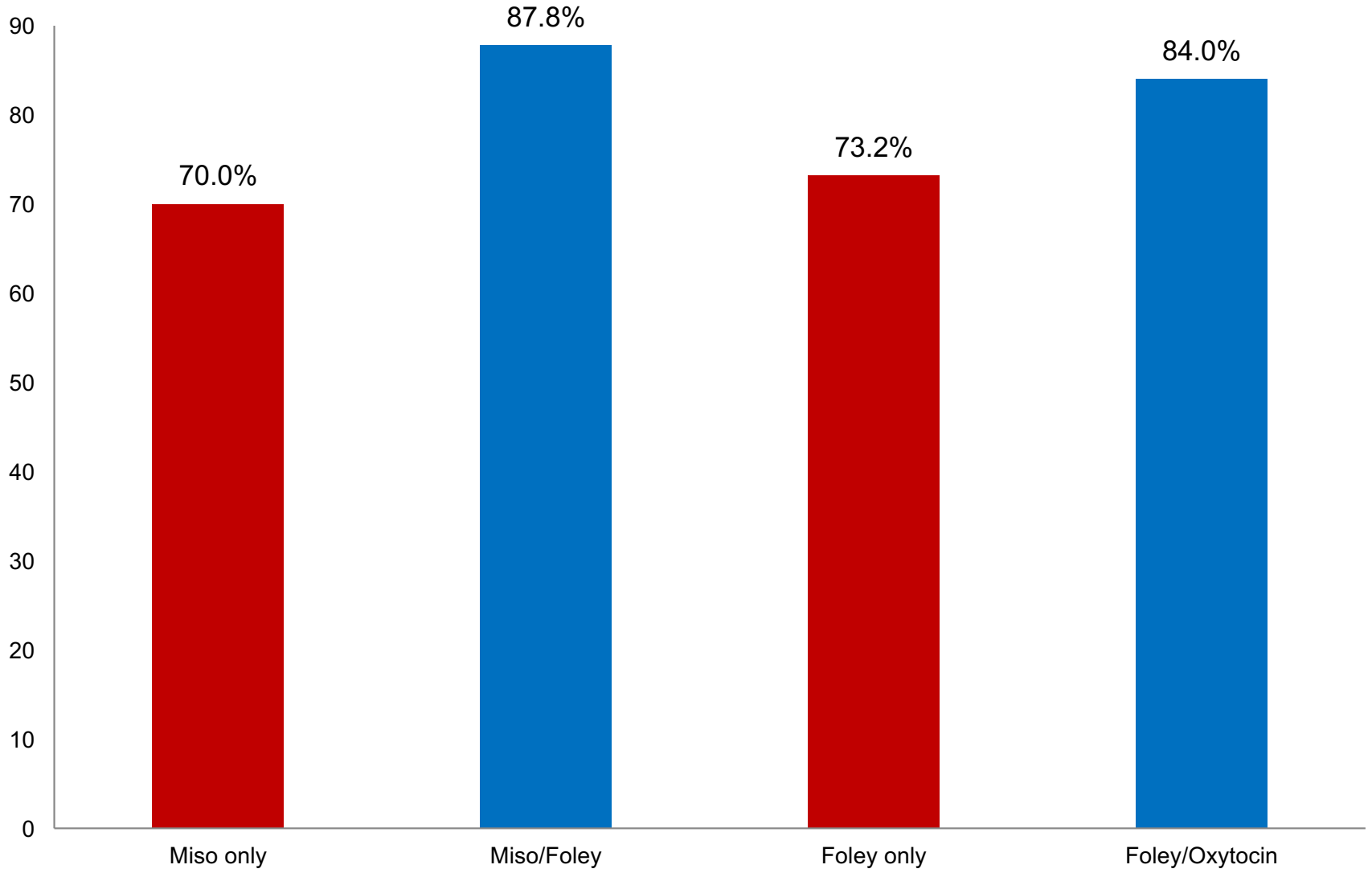
	Miso Only (n=120)	Miso/Foley (n=123)	Foley Only (n=123)	Foley/ Oxytocin (n=125)	P-value
CD (%) overall	29 (24.2)	**34 (27.6)**	35 (28.5)	**38 (30.4)**	0.7
Nulliparous	23 (32.9)	**32 (43.8)**	30 (41.1)	**30 (40.5)**	0.6
Multiparous	6 (12.0)	**2 (4.0)**	5 (10.0)	**8 (15.7)**	0.3

Data presented as n(%)

SECONDARY OUTCOME

Delivery within 24 hours

P<0.001



Labor length censoring for cesarean delivery

- **Hazard ratio=event rate (delivery)**
  - HR>1 = event happening faster, HR<1=event happening slower

	Miso Only	Foley Only	Miso/Foley	Foley/Oxytocin
Miso	-----	1.03 [0.76-1.38] (P=0.87)	**1.92 [1.42-2.59] (p<0.001)***	1.39 [1.03-1.87] (p=0.03)
Foley	0.9 [0.72-1.31] (p=0.87)	-------	**1.87 [1.39-2.52] (p<0.001)***	1.35 [1.00-1.82] (p=0.047)

- ***statistically significant p<0.008**

Labor length censoring for cesarean delivery

- **Hazard ratio=event rate (delivery)**
  - HR>1 = event happening faster, HR<1=event happening slower

	Miso Only	Foley Only	Miso/Foley	Foley/Oxytocin
Miso	-----	1.03 [0.76-1.38] (P=0.87)	**1.92 [1.42-2.59] (p<0.001)***	1.39 [1.03-1.87] (p=0.03)
Foley	0.9 [0.72-1.31] (p=0.87)	-------	**1.87 [1.39-2.52] (p<0.001)***	1.35 [1.00-1.82] (p=0.047)
Miso/Foley	**0.52 [0.39-0.74] (p<0.001)***	**0.53 [0.40-0.72] (p<0.001)***	------	0.72 [0.54-0.97] (p=0.03)

- ***statistically significant p<0.008**

Labor length censoring for cesarean delivery

- **Hazard ratio=event rate (delivery)**
  - HR>1 = event happening faster, HR<1=event happening slower

	Miso Only	Foley Only	Miso/Foley	Foley/Oxytocin
Miso	-----	1.03 [0.76-1.38] (P=0.87)	**1.92 [1.42-2.59] (p<0.001)***	1.39 [1.03-1.87] (p=0.03)
Foley	0.9 [0.72-1.31] (p=0.87)	-------	**1.87 [1.39-2.52] (p<0.001)***	1.35 [1.00-1.82] (p=0.047)
Miso/Foley	**0.52 [0.39-0.74] (p<0.001)***	**0.53 [0.40-0.72] (p<0.001)***	------	0.72 [0.54-0.97] (p=0.03)
Foley/ Oxytocin	0.72 [0.54-0.97] (p=0.03)	0.74 [0.55-1.00] (p=0.047)	1.38 [1.03-1.87] (p=0.03)	--------

- ***statistically significant p<0.008**

Secondary maternal outcomes by study group

	Miso Only	Miso/Foley	Foley Only	Foley/Oxytocin	P-value
Indication for CD*					
Failed IOL	10(34.5)	12(35.3)	16(45.7)	14(36.8)	0.8
Arrest of Dilation	4(13.8)	9(26.5)	8(22.9)	12(31.6)	0.4
Arrest of Descent	5(17.2)	5(14.7)	0(0)	4(10.5)	0.05
NRFHT	15(51.7)	19(55.9)	20(57.1)	16(42.1)	0.6
Elective/ Other	5(17.2)	2(5.9)	5(14.3)	4(10.5)	0.5
Regional Anesthesia	111(92.5)	114(92.7)	114(92.7)	121(96.8)	0.4
Terbutaline used	32(26.7)	19(15.5)	23(18.7)	25(20.0)	0.2
Oxytocin in active labor	72(68.6)	82(70.7)	98(89.9)	115(98.3)	<0.001
Chorioamnionitis	9(7.5)	15(12.2)	17(13.8)	20(16.0)	0.2
Maternal morbidity	8(6.7)	5(4.1)	13(10.6)	10(8.0)	0.3
Endometritis	1(0.8)	0(0)	0(0)	0(0)	0.2
3rd /4th degree laceration	2(2.2)	1(1.1)	6(6.8)	3(3.5)	0.2
Blood transfusion	2(1.7)	1(0.8)	5(4.1)	4(3.2)	0.4
Wound separation/ infection	1(0.8)	1(0.8)	1(0.8)	3(2.4)	0.7
Readmission	2(1.7)	2(1.6)	3(2.4)	7(5.6)	0.2
Total maternal LOS	3[3-4]	3[3-4]	3[3-4]	3[3-4]	0.2
Postpartum LOS	2[2-2]	2[2-2]	2[2-2]	2[2-3]	0.6

*If reported as the primary or secondary indication, counted in summary. Therefore, % do not sum to 100%
Data presented as median [IQR] or n(%)

Neonatal outcomes by study group

	Miso Only	Miso/Foley	Foley Only	Foley/ Oxytocin	P-value
Female sex	61 (50.8)	65 (52.9)	54 (43.9)	60 (48.0)	0.5
Birth weight	3178 [2635-3625]	3240 [2875-3600]	3230 [2855-3575]	3240 [2920-3595]	0.3
Apgar at 1 min	8 [7.5-9]	8 [8-9]	8 [8-9]	8 [8-9]	0.06
Apgar at 5 min	9 [9-9]	9 [9-9]	9 [9-9]	9 [9-9]	0.3
Neonatal LOS	2 [2-3]	2 [2-3]	2 [2-3]	2 [2-3]	0.8
NICU admission	15 (12.5)	10 (8.1)	17 (13.8)	11 (8.8)	0.4
NICU >48hrs	6 (5.0)	4 (3.3)	5 (4.1)	2 (1.6)	0.5
Severe RDS	1 (0.8)	0 (0)	2 (1.6)	0 (0)	0.3
Neonatal sepsis	2 (1.7)	1 (0.8)	1 (0.8)	1 (0.8)	0.8

Data presented as median [IQR] or n(%)

Sensitivity Analyses

- 8.5% of women received different initial induction method (n=31) or had the agent changed during their induction (n=11)

- When analyzed "as treated," results were unchanged

Conclusions

- **First randomized trial comparing four methods of induction in one head to head trial**
- **Combined methods achieve a faster delivery time than single agent methods overall and stratified by parity**
  - Higher chance of delivery within 24 hours
- **When censoring for cesarean, Miso/Foley is superior, achieving delivery ~2x faster than single agents**
- **No difference in cesarean delivery or maternal/neonatal morbidity**

Strengths/Limitations

- **STRENGTHS**
- **Induction/active labor standardized**
  - Differences among groups attributed to agents and not labor management
- **Excluded few indications**
  - Increases generalizability
- **One institution**
  - Limits practice variation; ensures compliance with protocols

- **LIMITATIONS**
- **Patients and providers were not blinded**
  - Not practical since examinations required
  - Labor protocols helped minimize variations in practice by un-blinded providers

Clinical Impact

- **One of the most common obstetrical procedures (23.2% in 2012)**
  - If ~1,000,000 women undergo induction with combined methods → 3.5 million fewer hours spent in labor → large impact on healthcare utilization and delivery

- **Shortening labor without increasing cesarean or maternal/neonatal complications → clinical and financial implications**
  - Known maternal and neonatal risks associated with prolonged labor and cesarean delivery as well as the associated costs

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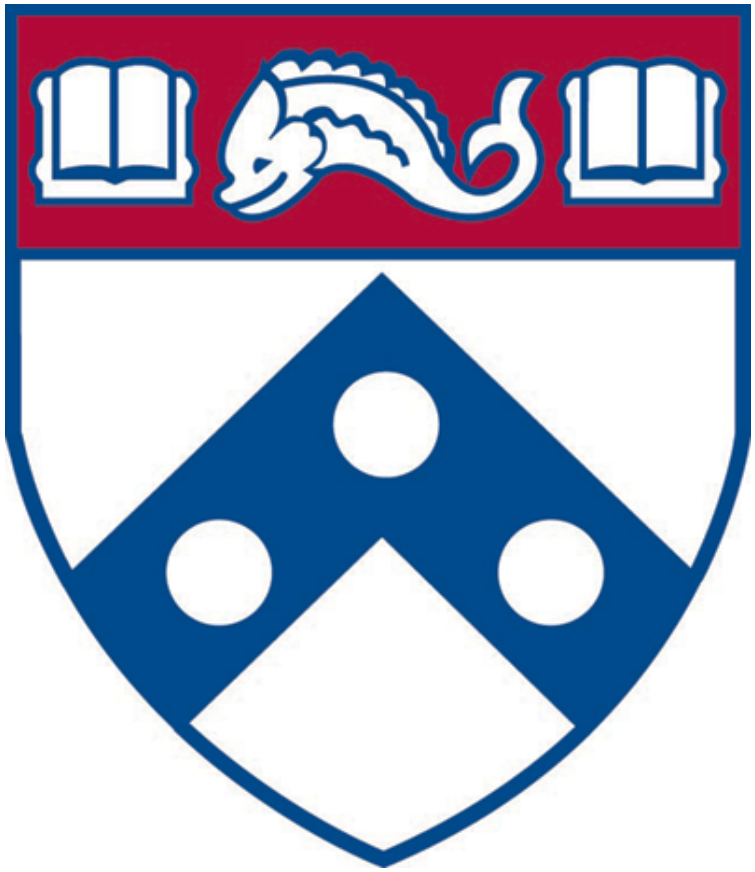

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