Loop Electrosurgical Excision Procedure, Abnormal Cervical Histology, and Risk of Preterm Delivery: A Retrospective Cohort Study

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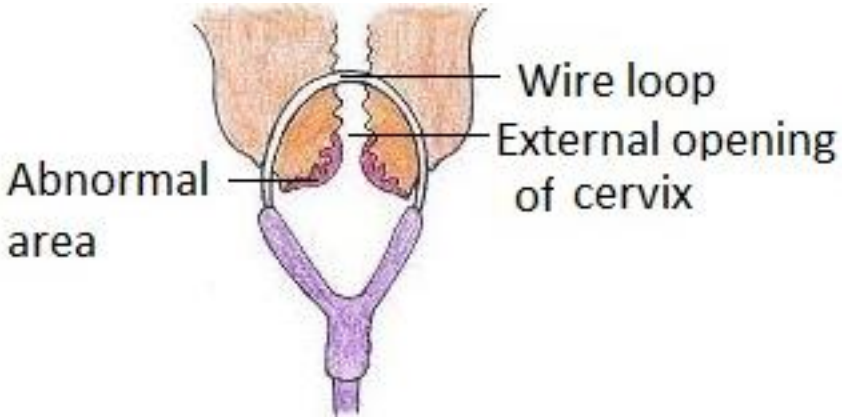
Disclosure

I have no potential conflicts of interest to disclose.

Background

- Cervical intraepithelial neoplasia (CIN) and adenocarcinoma in situ (AIS) are precursors of cancer
- Mainstay of treatment is **L**oop **E**lectrosurgical **E**xcision **P**rocedure (LEEP)



http://www.cancerindia.org.in/cp/index.php/know-about-cancer/cervical-cancer

Background

- Several systematic reviews identified an increased risk of preterm birth in pregnancies after LEEP or in pregnancies after untreated cervical dysplasia
  - None stratified on severity of diagnosis

- Nova Scotia data: increased risk of preterm birth < 37 weeks, low birth weight and preterm rupture of membranes

Kyrgiou et al., 2016
Bruinsma & Quinn, 2011
Jin et al., 2013
Samson et al., 2005

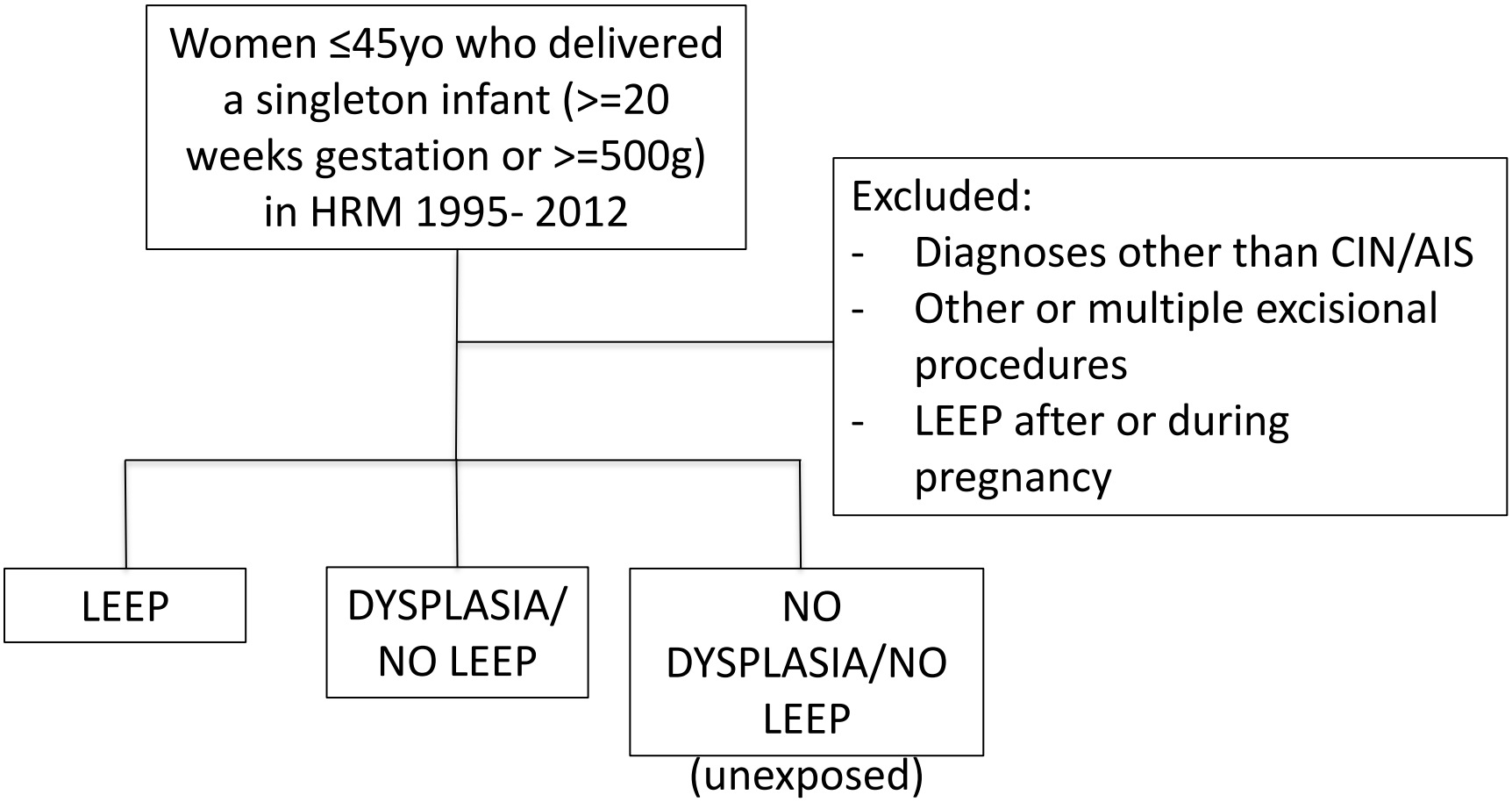
Objectives

1. Is cervical dysplasia, with or without treatment with LEEP, associated with an increased risk of adverse obstetrical outcomes, primarily preterm birth?
2. Is this association heterogeneous by severity of diagnosis?
3. Is there an improvement in risk of preterm birth by time period?

Methods

Study Design

- Retrospective cohort study


Women ≤45yo who delivered a singleton infant (>=20 weeks gestation or >=500g) in HRM 1995- 2012
Excluded:
- Diagnoses other than CIN/AIS
- Other or multiple excisional procedures
- LEEP after or during pregnancy
LEEP
DYSPLASIA/ NO LEEP
NO DYSPLASIA/NO LEEP
(unexposed)

Primary Outcome

- Spontaneous preterm delivery (sPTB)
  - prior to 37 weeks gestation
  - following the onset of spontaneous labour or prelabour rupture of membranes

Secondary Outcomes

- Preterm birth <34, <32, <28 weeks
- Interaction between main independent variable and time period (colposcopy between 1995-2005, and 2006-2012)

Secondary Outcomes

- Information on potential confounders and effect modifiers was derived from the NSAPD
  - Age (<20, >35)
  - Parity
  - Maternal body mass index (BMI)
  - Marital status
  - Socioeconomic status (based on quintile of annual income per person equivalent)
  - Smoking status
  - Maternal or fetal procedures in current pregnancy
  - Substance use
  - Comorbidities

Statistics

- Time to event analyses with follow up starting at 20 weeks of gestation and continued to sPTB (outcome), indicated PTB (censored), or 37 weeks (censored)
  - Cox proportional hazards regression was conducted to estimate hazard ratios for the risk of sPTB for the LEEP and DYSPLASIA-NO LEEP groups relative to the NO DYSPLASIA group.

Statistics

- Supplementary analyses #1 within the DYSPLASIA-NO LEEP group were conducted to examine if the risk of spontaneous preterm birth is associated with histological diagnosis (CIN-1, CIN2-3/AIS)

Statistics

- Supplementary analysis #2 examined if the association between LEEP and sPTB was heterogeneous by histological diagnosis (CIN-1, CIN2-3/AIS)

Ethics

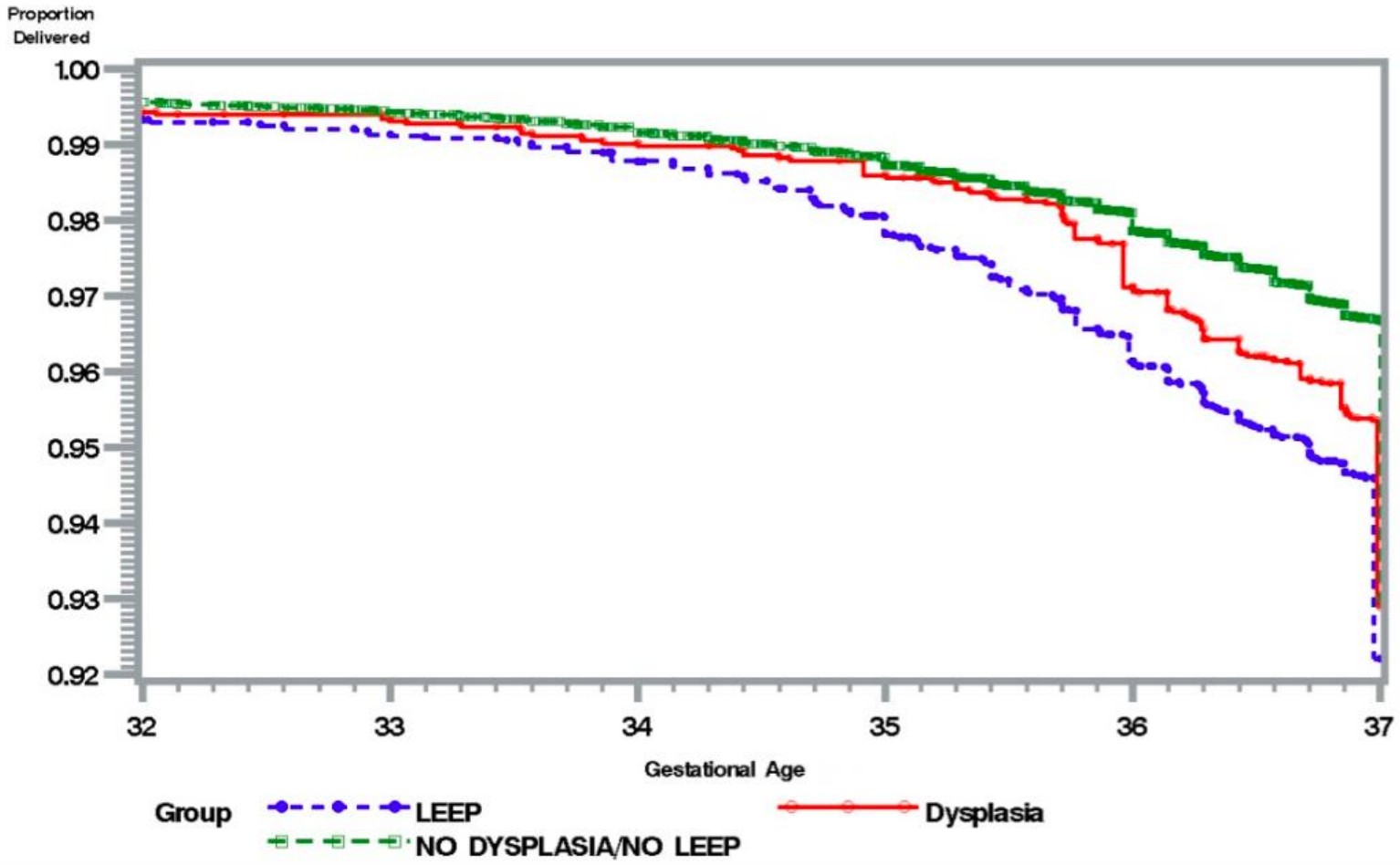
- This study was approved by:
  - The Joint Data Access Committee of the Reproductive Care Program Nova Scotia and the Nova Scotia Department of Health and Wellness
  - Nova Scotia Health Authority Research Ethics Board
  - The IWK Health Center Research Ethics Board

Results

Table I. Maternal Characteristics in Each Group

	Group 1 (LEEP) N=4265	Group 2 (dysplasia/no LEEP) N=3147	Group 3 (no dysplasia) N=63345
Age	30.6 (4.7)	29.0 (4.9)	29.8 (5.5)
Parity			
Primiparous	1685 (39.5)	1272 (40.4)	30367 (47.9)
Multiparous	2580 (60.5)	1875 (59.6)	32978 (52.0)
Grade			
CIN I	692 (16.2)	1983 (63.0)	-
CIN II/III/AIS	2580 (60.5)	764 (24.3)	-
Smoking status			
Never smokers	2595 (60.8)	1794 (57.0)	38672 (61.05)
Quit smoking	238 (5.6)	194 (6.2)	3104 (4.90)
Current smokers	1192 (27.9)	1035 (32.9)	11909 (18.80)
Pre-pregnancy body mass index (kg/m^2)	25.4 (5.8)	25.8 (5.9)	25.5 (6.0)
Marital status			
Single	2004 (47.0)	1758 (55.9)	21879 (34.5)
Married/Common-law	2261 (53.0)	1389 (44.1)	41466 (65.5)
Substance use	91 (2.13)	95 (3.0)	1121 (1.8)
Annual Income (QAIPPE*)			
Low (1-2)	1593 (37.4)	1343 (42.7)	25610 (40.4)
High (3-5)	2634 (61.8)	1768 (56.2)	37095 (58.6)
Antenatal complications$^+$			
Diabetes mellitus	179 (4.2)	139 (4.4)	2084 (3.3)
Antepartum hemorrhage	90 (2.1)	66 (2.1)	1698 (2.7)
Placental/cord anomalies	148 (3.5)	89 (2.8)	1913 (3.0)
Maternal fetal procedures	97 (2.3)	54 (1.7)	3193 (5.0)
IUGR	134 (3.1)	121 (3.8)	2204 (3.5)
Previous preterm birth	111 (2.6)	78 (2.5)	538 (0.85)

Gestational Age at Delivery



Spontaneous Preterm Birth

Comparison	N (%) women		Effect estimate	p-value
	Exposed	Unexposed	aHR (95% CI)	
LEEP vs No dysplasia/no LEEP				
<37 weeks	227 (5.3)	2059 (3.25)	**1.22 (1.06-1.39)**	**<0.05**
<34 weeks	47 (1.1)	483 (0.8)	**1.73 (1.22-2.39)**	**<0.05**
<32 weeks	27 (0.6)	262 (0.4)	**1.74 (1.04-2.75)**	**<0.05**
<28 weeks	8 (0.2)	128 (0.2)	1.50 (0.62-3.10)	NS
Dysplasia vs No dysplasia/no LEEP				
<37 weeks	144 (4.6)	2059 (3.25)	1.01 (0.86-1.19)	NS
<34 weeks	30 (1.0)	483 (0.8)	0.94 (0.55-1.49)	NS
<32 weeks	18 (0.4)	262 (0.4)	1.10 (0.53-2.02)	NS
<28 weeks	6 (0.2)	128 (0.2)	1.13 (0.34-2.78)	NS

Spontaneous Preterm Birth <37 weeks Grade Comparison

Comparison	N (%) women		Effect estimate HR (95% CI)	p-value
	Exposed	Unexposed		
no dysplasia/ no LEEP vs CIN I	85 (4.3)	2059 (3.25)	1.04 (0.84-1.30)	NS
no dysplasia/ no LEEP vs CIN II-III/AIS	44 (5.76)	2059 (3.25)	**0.67 (0.52-0.88)**	**<0.05**
CIN II-III/AIS no LEEP vs LEEP	129 (5.0)	44 (5.76)	0.90 (0.67-1.22)	NS

Time Interval

- Risk of sPTB in women who had LEEP was not heterogeneous by time period (≤2005 vs >2005)
  - HR 1.121; CI 0.82-1.57, p=0.49

Discussion

- Treatment with LEEP was associated with a higher risk of sPTB, and this association was not heterogeneous by grade
- High grade dysplasia, but not low grade dysplasia, was associated with a higher risk of sPTB

Strengths

- Appropriate study design
- Large sample size
- First study to evaluate the interaction between grade term and risk of preterm birth, and between time period and risk of preterm birth

Comparison with Nova Scotia Data

- Samson et al. (2005)
  - Higher magnitude effect

Limitations

- No data on volume of excision
- Not powered for rare outcomes
- Association not causation
  - What is the biological explanation for this association?

Research Implications

- Why does LEEP increase risk of preterm delivery?
  - Anatomical changes/scarring
    - Adjustment for cervical length
  - Alterations in cervicovaginal microenvironment

Halliwell et al., 2016
Kyrgiou et al., 2012
Miller et al., 2015

Practice Implications

- Expectant management for women with low grade dysplasia is not associated with increased risk of spontaneous preterm birth
- Treatment of high grade dysplasia is associated with an increased risk of of PTB but this risk is comparable to their baseline risk
- Temporal analysis using Nova Scotia data as a marker of change of practice did not show a difference in obstetrical outcomes

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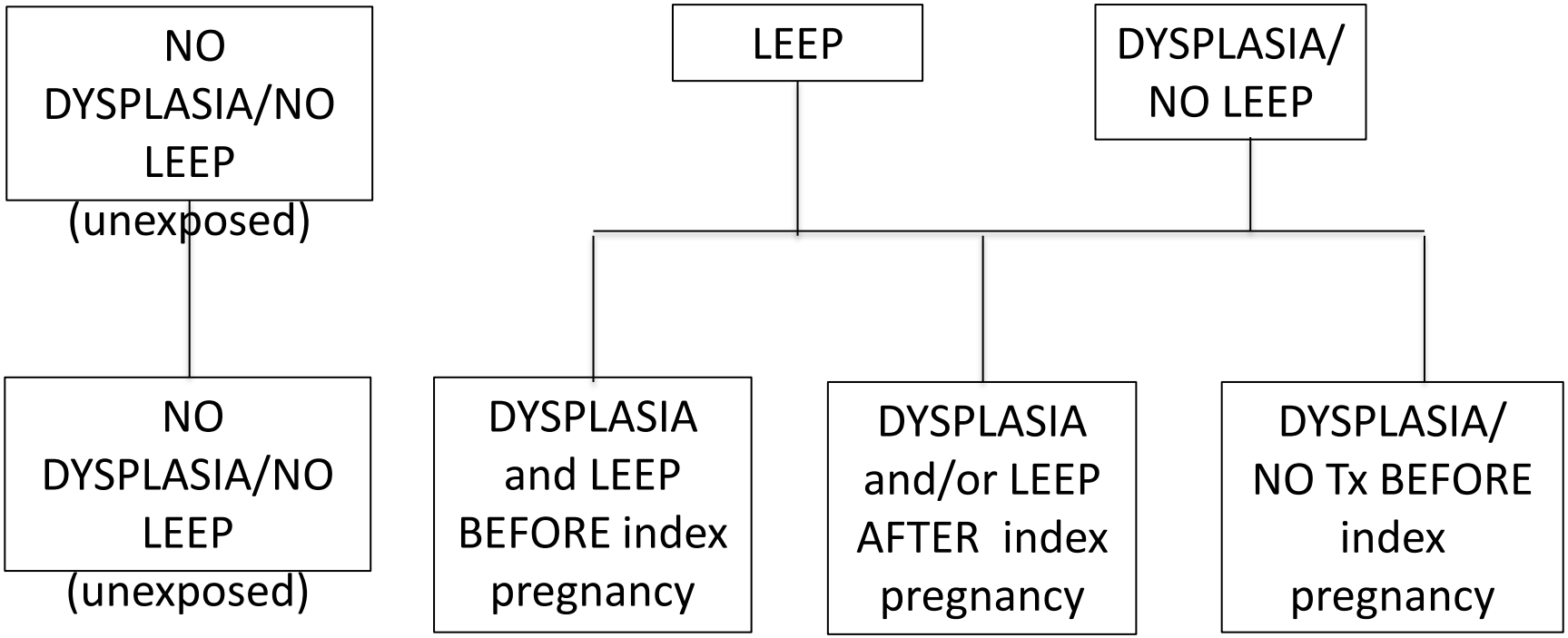
Thank you!
Questions…?


NO DYSPLASIA/NO LEEP
(unexposed)
NO DYSPLASIA/NO LEEP
(unexposed)
LEEP
DYSPLASIA/ NO LEEP
DYSPLASIA and LEEP BEFORE index pregnancy
DYSPLASIA and/or LEEP AFTER index pregnancy
DYSPLASIA/ NO Tx BEFORE index pregnancy

Secondary Outcomes - Maternal

- sPTB<34 weeks gestation, <32 weeks, and <28 weeks
- Preterm prelabour rupture of membranes (PPROM)
- Mode of delivery (Cesarean section vs vaginal)
- Administration of steroids, tocolysis
- Maternal infection

Secondary Outcomes - Fetal

- Stillbirth (fetal death >20 weeks gestation)
- Neonatal mortality (defined as a live birth and subsequent death <28
- Birth weight: days)
- Perinatal mortality (defined as stillbirths plus neonatal deaths <7 days)
- Birth weight:
  - Low birth weight (<2500g)
  - Birthweight percentile for gestational age
  - Small for gestational age (<10^{th} percentile)
  - Large for gestational age (>90th percentile)
- Admission to neonatal intensive care units
- Length of hospital stay
- Complications of prematurity:
  - Intraventricular hemorrhage grades III and IV
  - Moderate to severe respiratory distress syndrome
  - Necrotizing enterocolitis
  - Bronchopulmonary dysplasia
  - Sepsis or other infectious morbidity

Secondary Outcomes- Fetal

- Composite adverse neonatal outcome (CROWN initiative):
  - maternal infection
  - gestational age at delivery
  - perinatal mortality
  - birth weight
  - complications of prematurity (NEC, BPD, RDS, sepsis, IVH grade III and IV)

Future directions

- Individual patient data meta-analysis (IPDMA)
  - Volume of LEEP
  - Cervical cancer outcomes