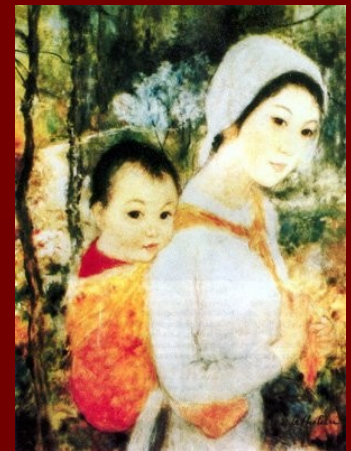


# Preterm delivery outcomes following LEEP treatment of cervical intraepithelial neoplasia (CIN)

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“...etiologic studies focused on homogeneous endpoints are much more likely to yield strong associations than are studies of heterogeneous endpoints.”

Savitz 1991

# Overview

- Classification of CIN and preterm delivery
- Biologic rationale
- Synthesis of LEEP literature prior to 2004
- New Zealand Study
- Subsequent LEEP studies

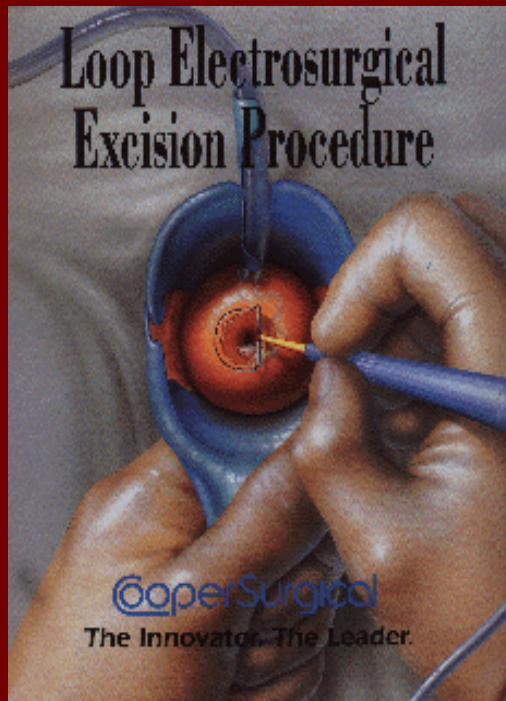
# Cervical Intraepithelial Neoplasia (CIN)

- Pre-invasive lesion of the uterine cervix, which left untreated, can progress to uterine cervical cancer
- Subtypes
  - CIN 1: Mild dysplasia
  - CIN 2: Moderate to severe
  - CIN 3: In situ carcinoma

# CIN Treatment

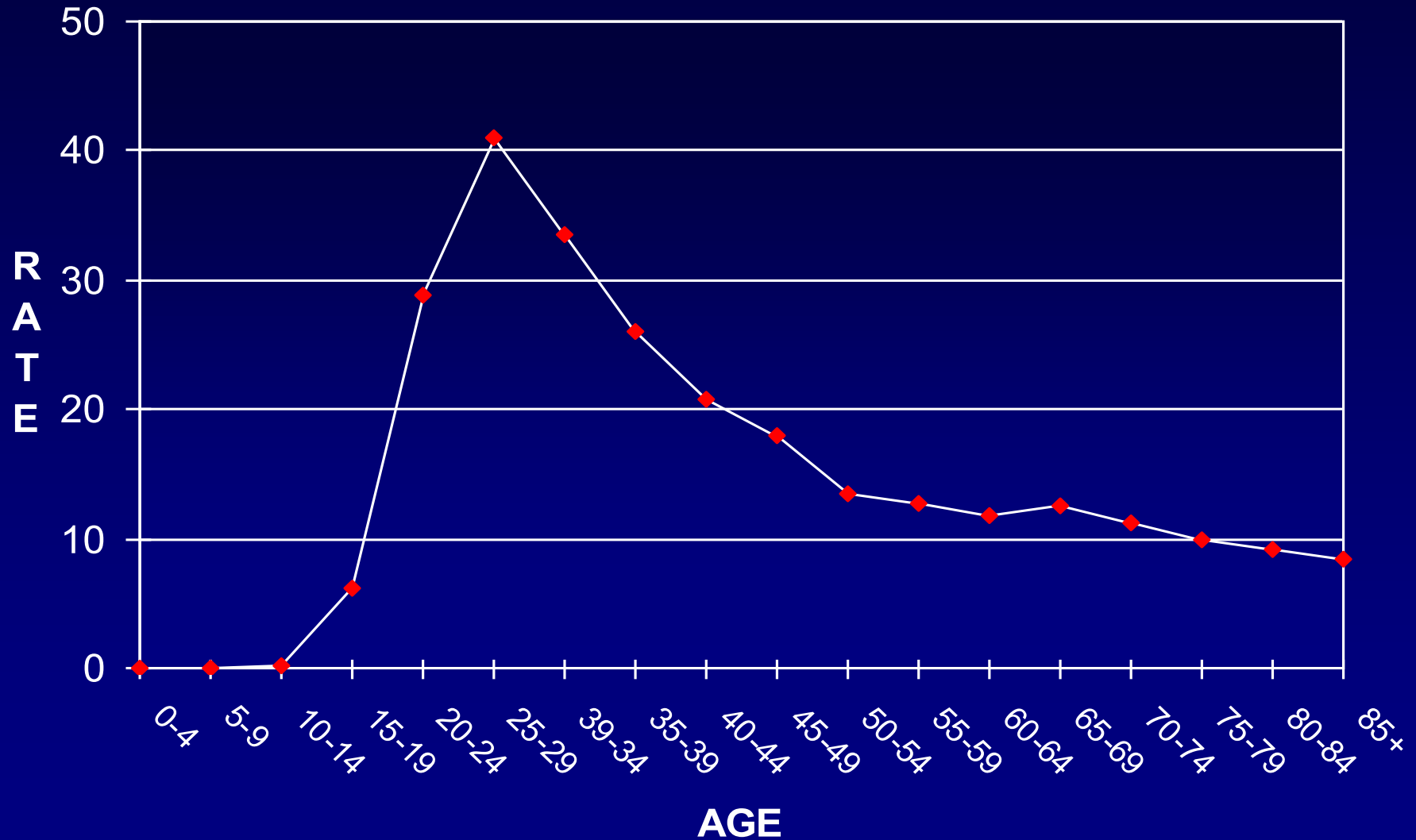
- Prior to 1980s: hysterectomy and cold knife conization
- Since the 1980s, more conservative treatments have been used:
  - Laser conization and ablation
  - Cryotherapy
  - Loop Electrosurgical Excision Procedure: LEEP, also known as LLETZ

# Loop Electrosurgical Excision Procedure (LEEP/LLETZ)



- Allows for outpatient treatment (5 minutes)
- Lower complication rates
- Excision of less tissue volume
- Pathological examination
- Less “burn” than laser conization

# Age-specific CIS rates/100,000 white women, USA (1994-1998)



# Preterm Delivery

- Subtypes
  - Medical Induction
  - Spontaneous Preterm Labor
  - Preterm Premature Rupture of the Fetal Membranes (pPROM)



# Preterm Delivery

## ■ Major risk factors

- Prior preterm delivery
- Low socioeconomic status
- Maternal smoking
- Antepartum infections
- Short cervical length (assessed at 22-24 weeks gestation)

# Biologic Rationale

# LEEP and Spontaneous Preterm Delivery: Hypothesized Mechanisms

- Weakened mechanical support due to removal of stromal tissue in cervix
- Shortening of cervical length, although no studies have established whether LEEP causes persistent shortening
- Alteration and/or reduction of cervical mucus secretions and its antimicrobial defense mechanism

# LEEP and risk of total preterm birth

Author	Year	n	RR	95% CI
Gunasekera	1992	22	----	-----
Blomfield	1993	38	1.4	0.5-4.0
Haffenden	1993	152	1.1	0.5-2.1
Braet	1994	78	2.5	0.8-7.6
Cruikshank	1995	149	1.9	0.9-3.8
Paraskevaidis	2002	28	3.7	0.97-20.3

# LEEP and risk of preterm birth following pPROM

Author	Year	n	RR	95% CI
Braet	1994	78	3.0	0.6-14.4

# LEEP and risk of preterm birth following spontaneous labor

Author	Year	n	RR	95% CI
Bloomfield	1993	40	1.4	0.5-4.0

# Limitations of studies published prior to 2004

- Most are small retrospective cohort studies examining preterm delivery without regard to subtype
- Sub-optimal control groups
  - Pregnancies of the same women prior to treatment
  - General gynecology patients who delivered at the same hospital, usually matched on age and parity.
- Few studies adjusted statistically for important confounding variables
- Few considered measures of the excised tissue and cone depth

# Treatment for Cervical Intraepithelial Neoplasia and Risk of Preterm Delivery

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# Treatment for Cervical Intraepithelial Neoplasia and Risk of Preterm Delivery

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**Context** It is unclear whether treatments for cervical intraepithelial neoplasia (CIN) increase the subsequent risk of preterm delivery. Most studies have lacked sufficient sample size, mixed heterogeneous subtypes of preterm delivery, and failed to control for confounding factors.

**Objective** To determine whether cervical laser and loop electrosurgical excision procedure (LEEP) treatments increase risk of preterm delivery and its subtypes.

**Design, Setting, and Participants** Retrospective cohort study conducted among women evaluated at a colposcopy clinic serving Auckland, New Zealand (1988-2000), comparing delivery outcomes of untreated women (n=426) and those treated (n=652) with laser conization, laser ablation, or LEEP. Record linkage using unique health identifiers identified women who had subsequent deliveries.

**Main Outcome Measures** Total preterm delivery and its subtypes, spontaneous labor and premature rupture of membranes before 37 weeks' gestation (pPROM).

**Results** The overall rate of preterm delivery was 13.8%. The rate of pPROM was 6.2% and the rate of spontaneous preterm delivery was 3.8%. Analyses showed no significant increase in risk of total preterm delivery (adjusted relative risk [aRR], 1.1; 95% confidence interval [CI], 0.8-1.5) or spontaneous preterm delivery (aRR, 1.3; 95% CI, 0.7-2.6) for any treatment. Risk of pPROM was significantly increased following treatment with laser conization (aRR, 2.7; 95% CI, 1.3-5.6) or LEEP (aRR, 1.9; 95% CI, 1.0-3.8), but not laser ablation (aRR, 1.1; 95% CI, 0.5-2.4). Moreover, risk of pPROM and total preterm delivery increased significantly with increasing height of tissue removed from the cervix in conization. Women in the highest tertile of cone height ( $\geq 1.7$  cm) had a greater than 3-fold increase in risk of pPROM compared with untreated women (aRR, 3.6; 95% CI, 1.8-7.5).

**Conclusions** LEEP and laser cone treatments were associated with significantly increased risk of pPROM. Careful consideration should be given to treatment of CIN in women of reproductive age, especially when treatment might reasonably be delayed or targeted to high-risk cases.

# Treatment exposure measures

- Laser cone and LEEP treatments combined
- Laser cone, laser ablation, LEEP
- Number of treatments
- Height of cone

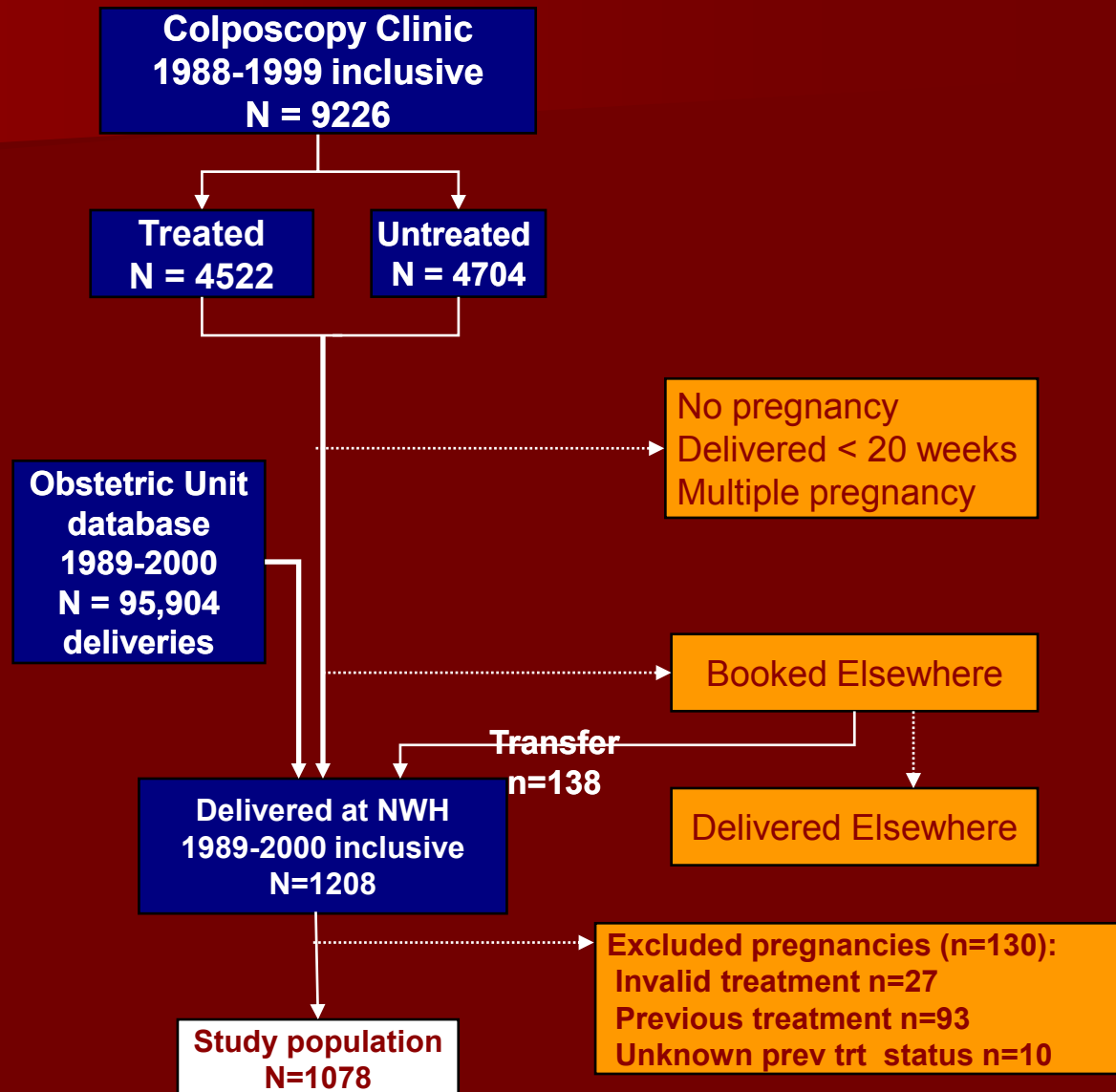
# Outcome measures

- All preterm deliveries
- Spontaneous preterm labor resulting in preterm delivery
- pPROM

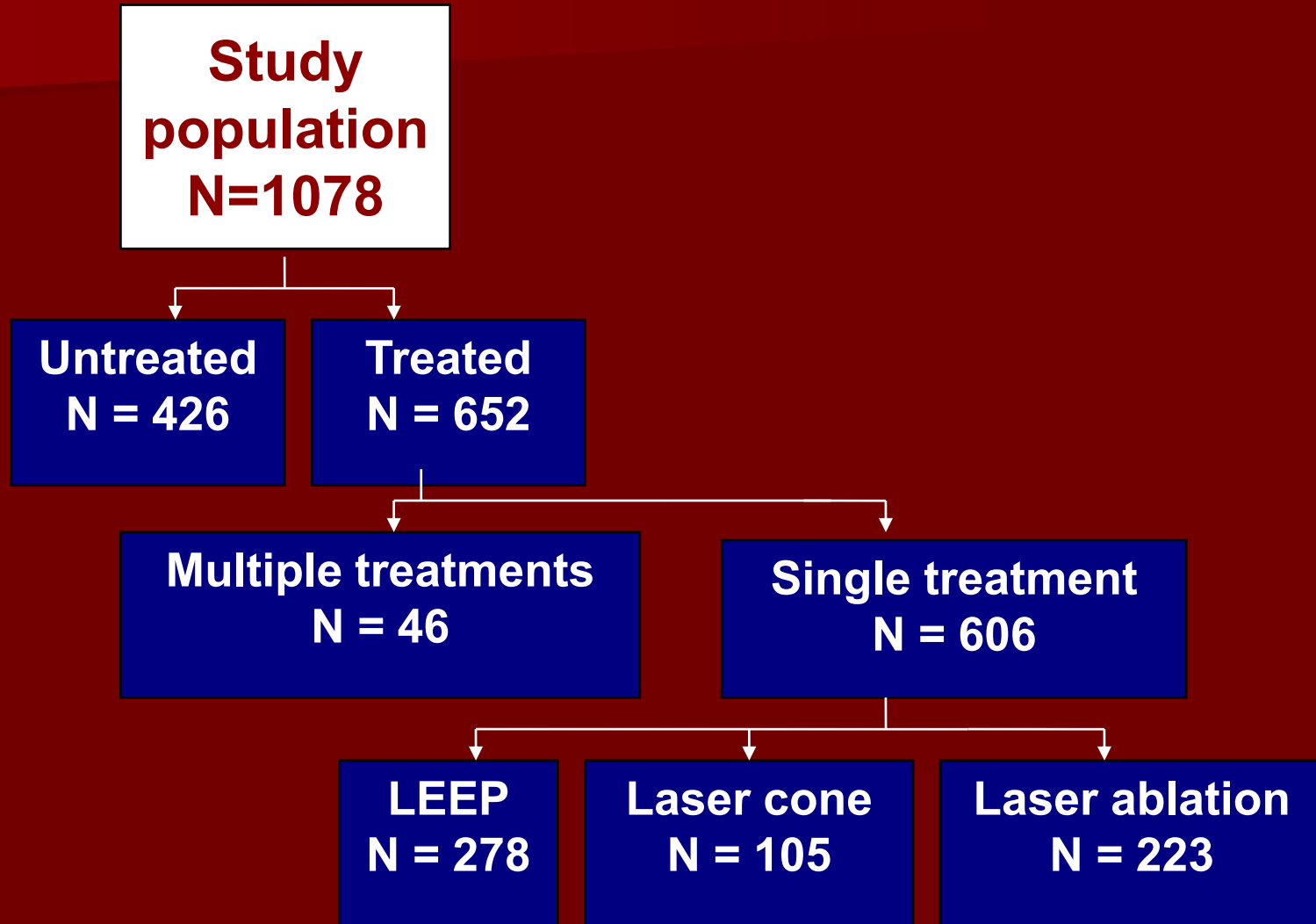
# Confounders

- Maternal age
- Ethnicity
- Socioeconomic status
- Smoking in pregnancy
- Previous obstetric history
- Infection in pregnancy
- Transferred from another hospital
- Antepartum hemorrhage

# Description of Study Cohort



# Final delivery population by treatment status



Maternal characteristics		Treated n=652	Untreated n=426	P value
Age (yrs)	<25	20.6	23.9	0.5
	25-34	64.5	61.9	
	≥35	14.9	14.1	
Ethnicity	European/oth	68.5	54.7	<.0001
	Asian	2.2	7.6	
	Maori	16.9	18.2	
	Pacific Island	12.5	19.6	
Deprivation Index	high	21.3	20.7	0.6
	intermediate	30.2	27.6	
	low	48.6	51.7	
Smoking		41.6	31	0.0006
History of PTD		9.2	12.6	0.2
Bacterial vaginosis		8.4	5.9	0.1

# Preterm delivery subtypes by treatment status

	Treated (n=652)	Untreated (n=426)	P value
	%	%	
All PTD	14.9	12.2	0.2
<32 weeks	3.7	3.1	0.6
pPROM	8.0	3.5	0.004
Spontaneous	4.0	3.5	0.6
Iatrogenic	2.9	5.2	0.09



# Preterm delivery outcomes by treatment modality

	LEEP n=278	Laser cone n=105	Laser ablation n=223	Untreated n=426
	%	%	%	%
All PTD	15.8	19.1	10.3	12.2
<32 weeks	3.2	5.7	3.1	3.1
pPROM	8.6	15	4.8	3.5
Spontaneous preterm labor	5.3	3.4	3.9	3.5

**Preterm  
delivery rate (%)                      aRR (95%CI)**

No treatment	12.2	1.0 Referent
Any treatment	14.9	1.1 (0.8-1.5)

**Treatment type**

Laser cone	19.1	1.3 (0.8-2.2)
LEEP	15.8	1.2 (0.8-1.8)
Laser ablation	10.3	0.8 (0.5-1.2)

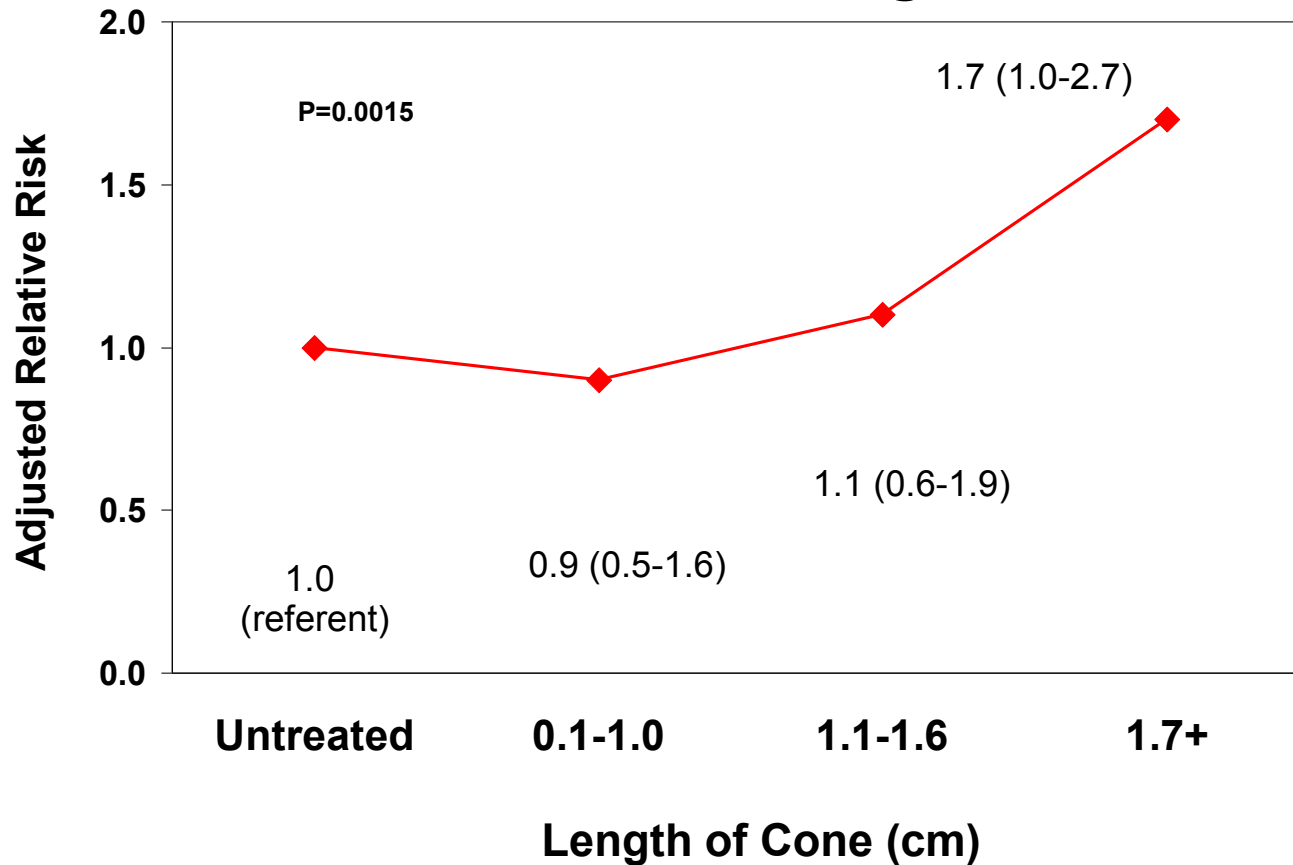
**# Treatments**

1 treatment	14.4	1.0 (0.7-1.5)
>1 treatment	21.7	1.3 (0.6-2.6)

**Cone depth**

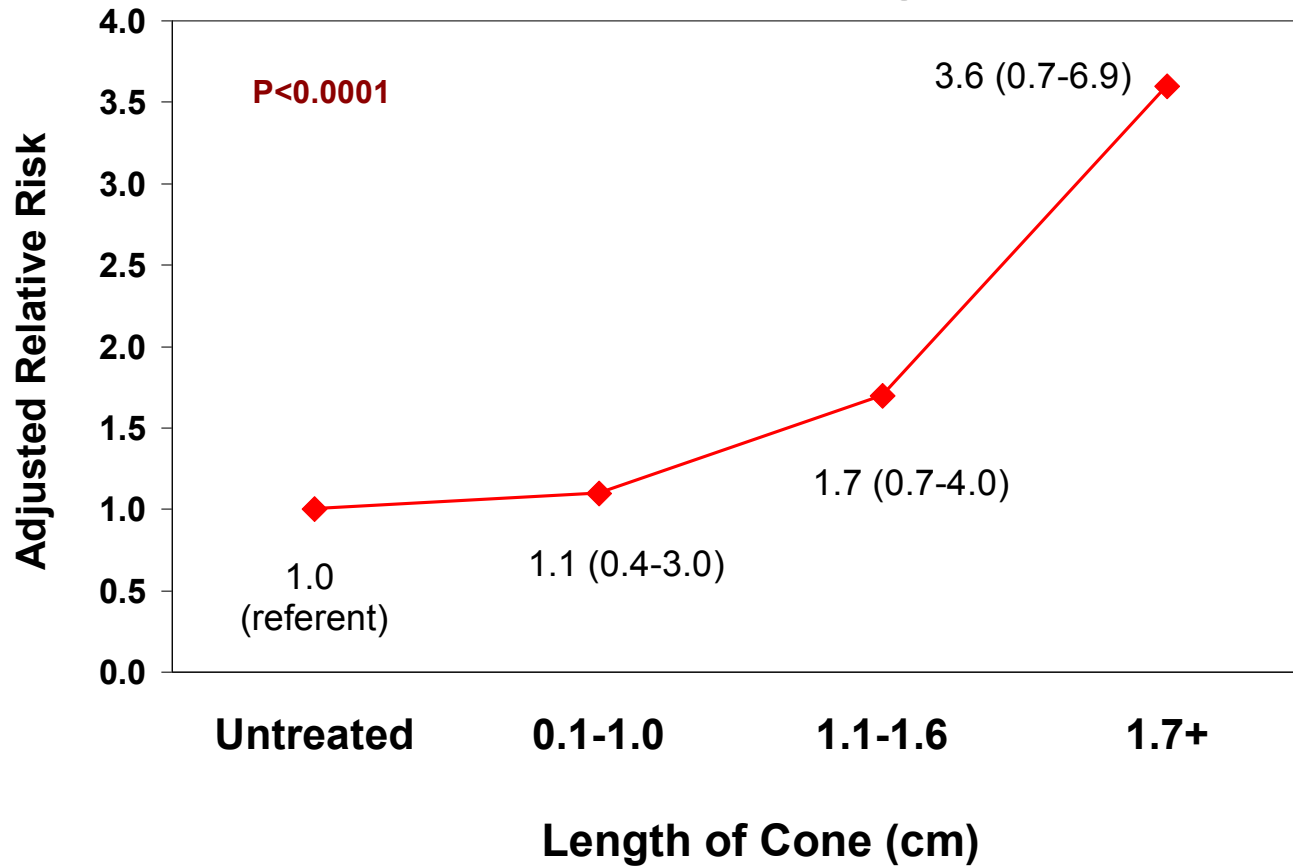
0.1-1.0 cm	12.1	0.9 (0.5-1.6)
1.1-1.6 cm	15.8	1.1 (0.6-1.9)
<u>≥ 1.7 cm</u>	24.8	1.7 (1.0-2.7)

## Adjusted Relative Risk of Preterm Delivery Associated with Length of Cone



	<u>pPROM Rate</u>	<u>aRR (95%CI)</u>
No treatment	3.9	Referent
Any treatment	8.6	1.8 (1.0-3.2)
<u>Modality</u>		
Laser cone	15	2.7 (1.3-5.6)
LEEP	8.6	1.9 (1.0-3.8)
Laser ablation	4.8	1.1 (0.5-2.4)
1 treatment	8.3	1.8 (1.0-3.2)
>1 treatment	12.2	1.8 (0.6-5.1)
<u>Depth of cone</u>		
0.1-1.0 cm	6.4	1.1 (0.4-3.0)
1.1-1.6 cm	8.6	1.7 (0.7-4.0)
≤ 1.7 cm	18.3	3.6 (1.8-7.5)

## Adjusted Relative Risk of PPROM Associated with Length of Cone



**Spontaneous  
PTD Rate (%)**

**aRR (95%CI)**

No treatment 3.9 1.0 Referent

Any treatment 4.5 1.3 (0.7-2.6)

**Modality**

Laser cone 3.4 0.9 (0.3-3.2)

LEEP 5.3 1.5 (0.7-3.2)

Laser ablation 3.9 1.4 (0.6-3.2)

1 treatment 4.4 1.3 (0.7-2.6)

>1 treatment 5.3 1.5 (0.3-7.0)

**Depth of Cone**

0.1-1.0 cm 3.8 1.1 (0.4-3.6)

1.1-1.6 cm 4 1.0 (0.3-3.0)

≥ 1.7 cm 7.3 1.9 (0.7-5.1)

# Summary

- Women treated with LEEP had a 1.9-fold increased risk of pPROM
- Laser conization associated with a 2.7-increased risk of pPROM
- Dose-response relationship between cone height and risk of pPROM and all preterm delivery

# Study Strengths

- Largest cohort of LEEP and laser cones
- Obstetrical charts reviewed to categorize outcomes by preterm delivery subtype
- Colposcopy patients as comparison group
- Multivariate analysis that controlled for important confounding variables
- Assessed depth of tissue excised



# Weaknesses

- Limited to women delivering at NWH
- Transfers from other centers inflates outcome rates
- Residual confounding due to lack of detailed information on some risk factors
- No data on outcomes before 20 weeks

# LEEP and risk of all preterm birth: 2004 - present

Author	Year	n	RR	95% CI
Tan	2004	105	1.6	0.6-2.6
Sadler*	2004	278	1.2*	0.8-1.8
Samson	2005	571	<b>3.0</b>	<b>1.7-5.5</b>
Acharya	2005	79	1.1	0.5-2.3
(loop 25mm)	2005	79	<b>4.0</b>	<b>1.0-16.0</b>
Sjoborg*	2007	742	<b>3.4</b>	<b>2.3-5.1</b>
(LEEP & laser cone)				
Nohr*	2007	349	<b>1.8</b>	<b>1.1-2.9</b>
Jakobsson**	2007	440	<b>1.8</b>	<b>1.6-2.0</b>

\*Significant dose response of cone depth with increasing PTD risk

\*\* Any conization procedure including cold knife, laser, LEEP

# LEEP and risk of pPROM

	Year	n	RR	95% CI
Sadler	2004	278	1.9*	1.0-3.8
Samson	2005	571	4.1**	1.5-14.1
Sjoborg	2007	742	10.5**	3.7-29.5

**\*Adjusted RR**

**\*\*Odds ratio**

# Conclusions

- LEEP and laser conization treatments are associated with a 2-3-fold increased risk of spontaneous preterm delivery, particularly pPPROM
- Risk increases with increasing cone depth

# Implications

- Future studies should more accurately assess the amount of tissue excised and the mechanisms by which treatment increases risk of spontaneous preterm birth and its role in infertility, and 1<sup>st</sup> and 2<sup>nd</sup> trimester fetal loss
- Excisional treatment should be minimized, when possible, for women desiring future fertility
- Ablative methods such as cryotherapy, should be considered as first line of treatment; or new treatment options should be developed and explored
- Educate and inform patients and physicians
- Primary prevention through implementation of vaccination programs worldwide

Thank you!