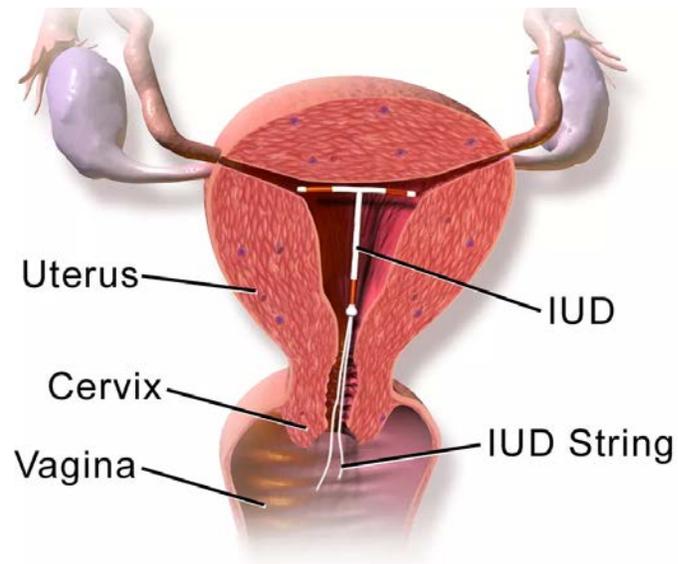


# Relative risk of cervical neoplasms among copper and levonorgestrel intrauterine device users

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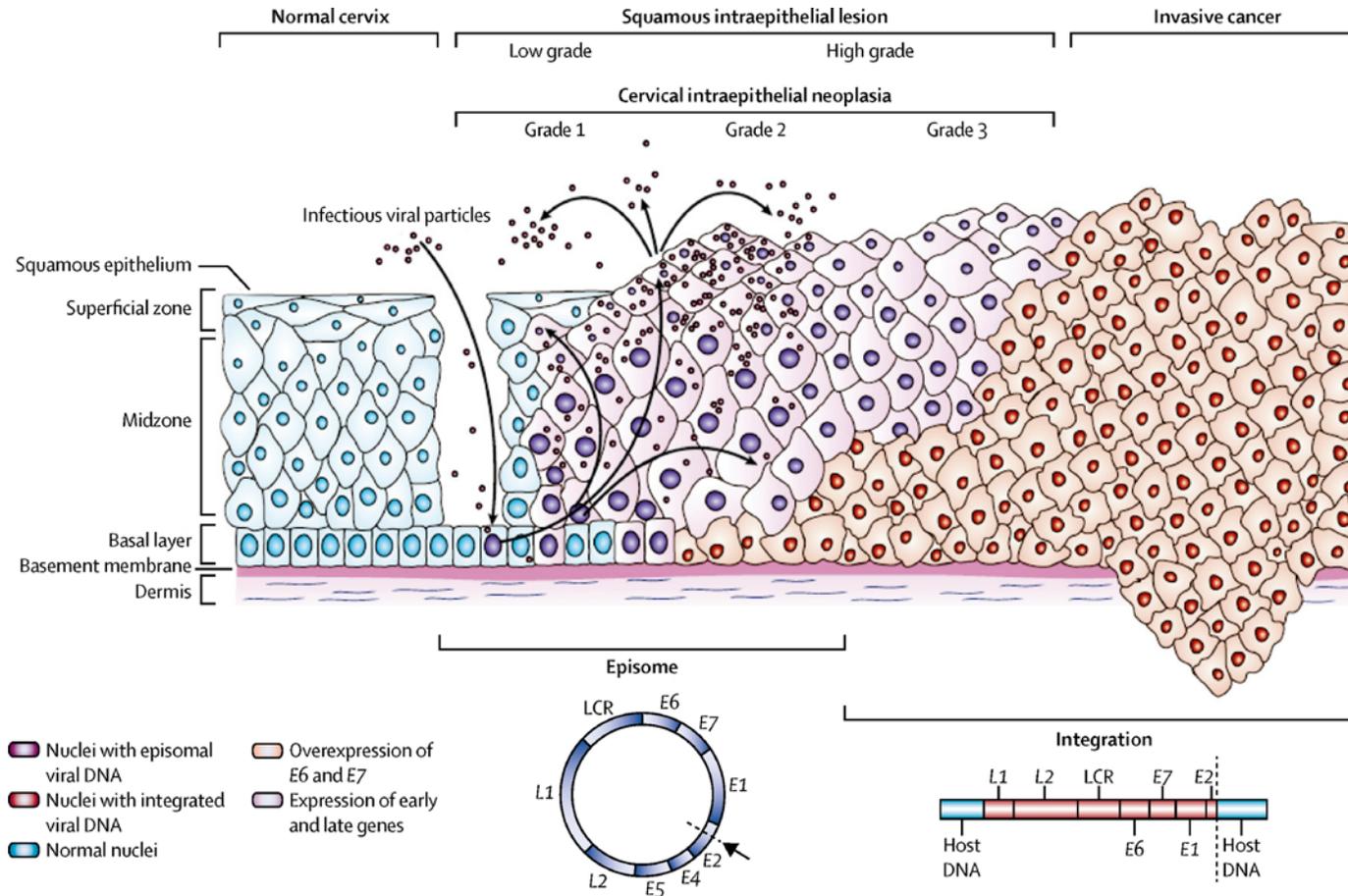
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# Intrauterine Devices (IUDs)



| Variable             | Cu-IUD<br>("Copper") | LNG-IUS<br>("Hormonal") |
|----------------------|----------------------|-------------------------|
| Available in US      | 1988 (Paragard)      | 2000 (Mirena)           |
| Number of Users      | ~80 Million          | ~20 Million             |
| Prevents Pregnancy   | >99%                 | >99%                    |
| Inhibits Sperm       | Yes                  | Yes                     |
| Thins Uterine Lining | No                   | Yes                     |
| Thickens Mucous      | No                   | Yes                     |
| Decreases Bleeding   | No                   | Yes                     |
| Decreases Pain       | No                   | Yes                     |
| Approximate Cost     | \$700                | \$800                   |

# Cervical Cancer Pathophysiology



# IUDs and Cervical Cancer: Systematic Review

| 1st Author                 | Location                | Data Collection | Control Source       | Case Participants | Control Participants |
|----------------------------|-------------------------|-----------------|----------------------|-------------------|----------------------|
| Celentano <sup>35</sup>    | United States           | 1982–1984       | Mixed                | 153               | 153                  |
| Brinton <sup>32</sup>      | Multisite <sup>s</sup>  | 1986–1987       | Mixed                | 568               | 1,071                |
| Lassise <sup>36</sup>      | United States           | 1982–1984       | Population           | 479               | 789                  |
| Parazzini <sup>37</sup>    | Italy                   | 1990            | Clinic or hospital   | 720               | 820                  |
| Williams <sup>33</sup>     | Kenya                   | 1981–1988       | Clinical or hospital | 112               | 749                  |
| Li <sup>38</sup>           | China                   | 1989–1991       | Population           | 272               | 893                  |
| Shields <sup>34</sup>      | United States           | 1982–1984       | Population           | 235               | 486                  |
| Hammouda <sup>16</sup>     | Algeria                 | 1997–1999       | Clinic or hospital   | 198               | 202                  |
| Castellsagué <sup>10</sup> | Morocco                 | 1991–1993       | Clinic or hospital   | 202               | 214                  |
| Castellsagué <sup>10</sup> | Philippines             | 1991–1993       | Clinic or hospital   | 383               | 387                  |
| Castellsagué <sup>10</sup> | Thailand                | 1990–1993       | Clinic or hospital   | 348               | 385                  |
| Castellsagué <sup>10</sup> | Peru                    | 1996–1998       | Clinic or hospital   | 137               | 140                  |
| Castellsagué <sup>10</sup> | India                   | 1998–1999       | Clinic or hospital   | 76                | 60                   |
| Castellsagué <sup>10</sup> | Spain                   | 1985–1987       | Population           | 480               | 472                  |
| Castellsagué <sup>10</sup> | Colombia                | 1985–1988       | Population           | 448               | 452                  |
| Roura <sup>15</sup>        | Multisite <sup>ll</sup> | 1992–2006       | Cohort               | 134               | 264                  |

# Methods: Cohorts

- Retrospective observational cohort study
- Cohorts and estimation analysis were designed in ATLAS
- Cu-IUD Cohort (T): CPT Code for first IUD placement, no subsequent LNG-IUS exposure
- LNG-IUS Cohort (C): CPT Code for first IUD placement, at least 1 subsequent LNG-IUS exposure
- Cervical Neoplasm Cohort (O): Condition code of a high grade cervical neoplasm (i.e. SNOMED "Primary Malignant Neoplasm of Uterine Cervix")
- All study patients had 365 days prior observation, no history of endometrial or cervical cancer, and were 45 years or younger

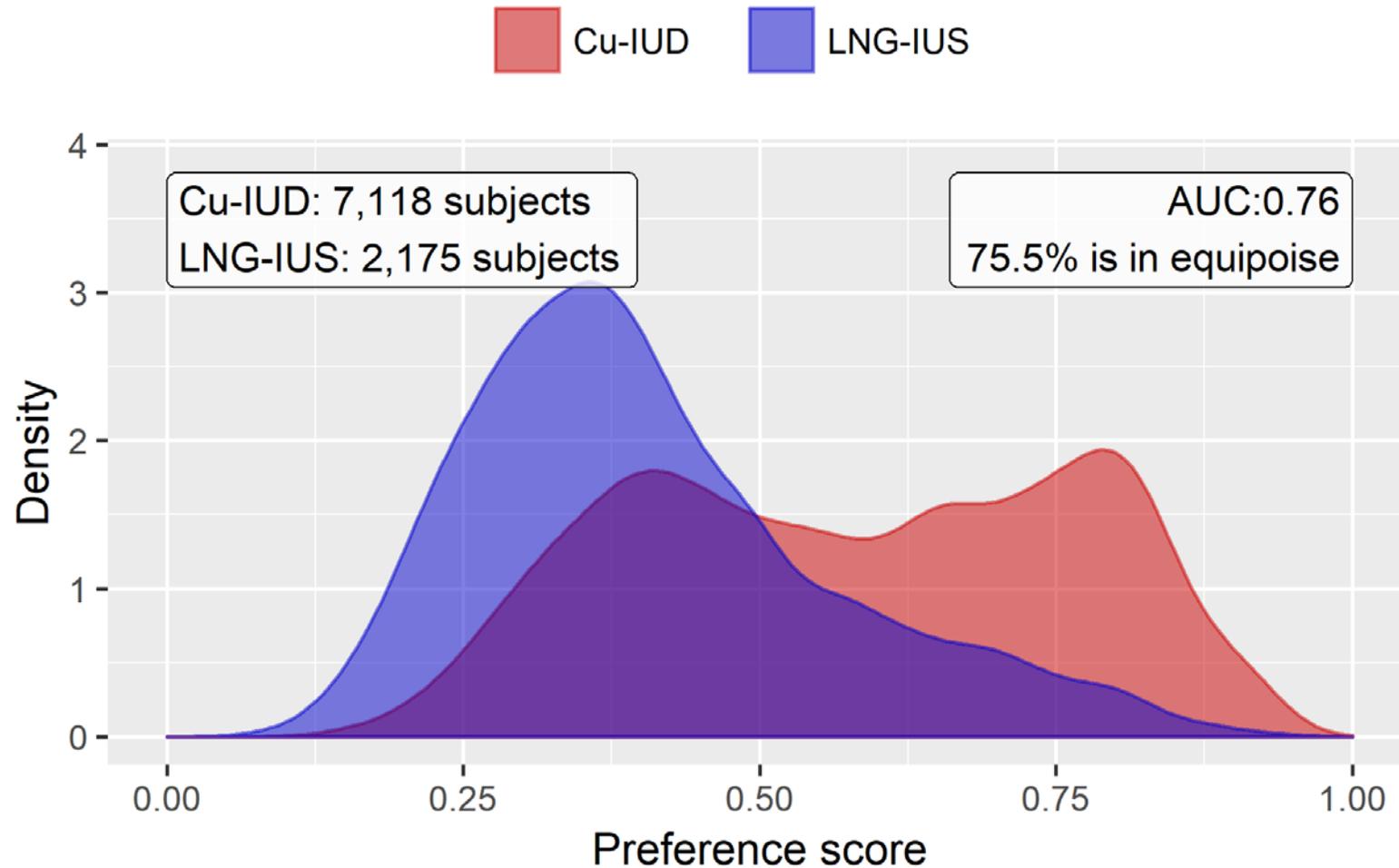
# Methods: Analysis

- Study Window: 1/1/2003 – 12/15/2018
- Study Period: 30 days to 15 years post placement
- Subgroup Analysis: 1 to 15 years post placement
- Propensity score stratification, propensity score matching, and propensity score matching for the subgroup were performed
- Adjusted over more than 10,000 covariates in each analysis and balance was achieved

# Cervical Neoplasm Phenotype Validation

- Under CUIMC IRB approval (IRB #AAAO7805), we identified 115 cervical neoplasm patients with our phenotype
- 90% of cervical neoplasm cases had concordant biopsy diagnosis
- 100% of LNG-IUS exposures were identified properly
- 10% of Cu-IUD exposures were actually LNG-IUS exposures

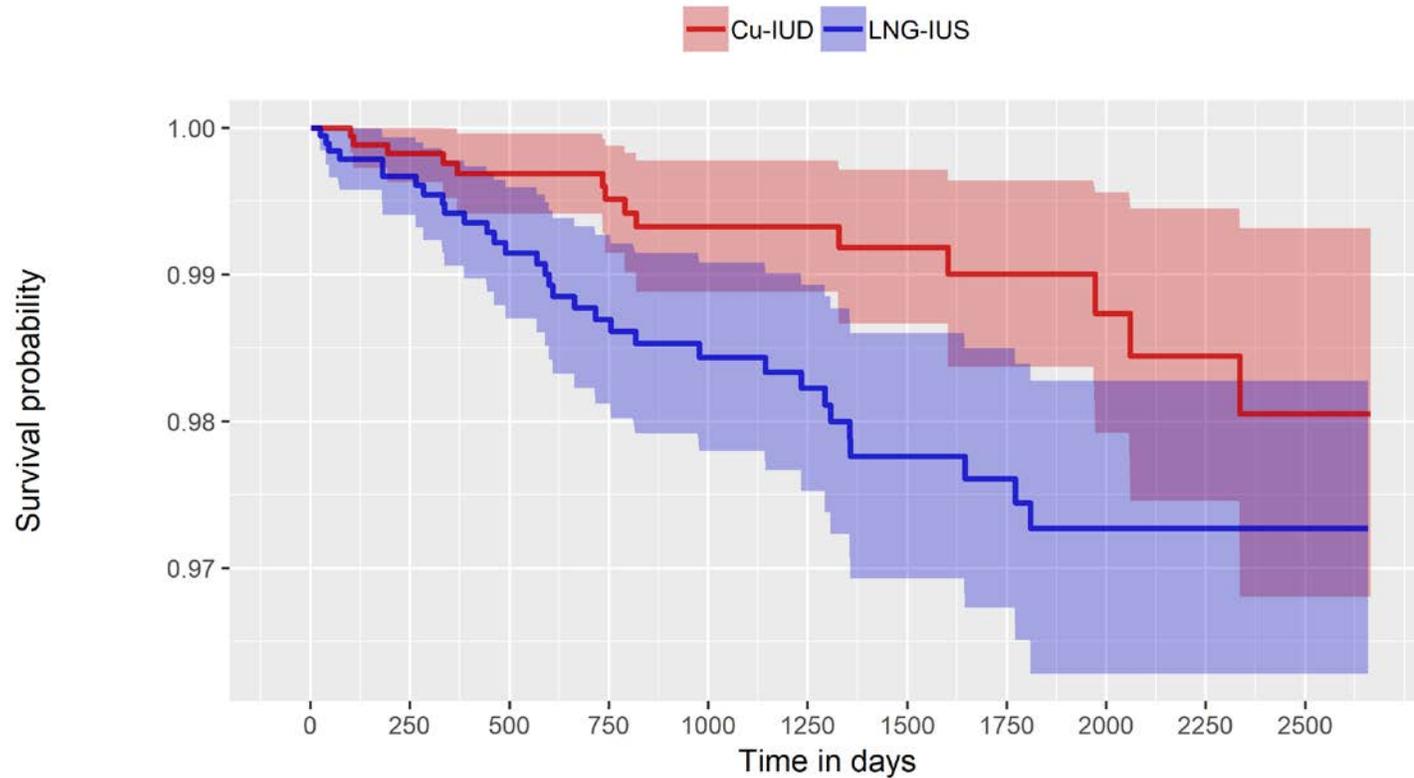
# Propensity Score Distribution



# Matched Cervical Cancer Risk Factors

| Variable (n, %)          | Copper Before Matching (n=8274) | Hormonal Before Matching (n=2400) | Before PS Matching Std. Diff |
|--------------------------|---------------------------------|-----------------------------------|------------------------------|
| Tobacco Smoking Behavior | 3261 (39.4%)                    | 1290 (53.8%)                      | 0.49*                        |
| HPV Vaccine              | 43 (0.5%)                       | 27 (1.1%)                         | -0.07                        |
| HPV Test Positive        | 210 (2.5%)                      | 59 (2.5%)                         | 0.03                         |

# Kaplan-Meier Plot: PS Matching



| Number at risk | 0     | 250   | 500   | 750   | 1000  | 1250 | 1500 | 1750 | 2000 | 2250 | 2500 |
|----------------|-------|-------|-------|-------|-------|------|------|------|------|------|------|
| Cu-IUD         | 2,039 | 1,579 | 1,327 | 1,115 | 937   | 759  | 601  | 464  | 359  | 277  | 203  |
| LNG-IUS        | 2,039 | 1,639 | 1,413 | 1,213 | 1,057 | 895  | 730  | 599  | 457  | 373  | 299  |

# Possible Explanations for Effect

- Differences in risk factors or screening uptake
- Harmful effect of synthetic hormones
- Protective effect from copper

# Screening Uptake Characterization

| Variable (n, %)                      | Copper<br>(n=8274) | Hormonal<br>(n=2400) |
|--------------------------------------|--------------------|----------------------|
| Median Follow-Up Years               | 2.8 [0.5-6.5]      | 2.6 [0.6-5.0]        |
| Subsequent Cervical Cancer Screening | 2560 (30.9%)       | 835 (34.8%)          |
| Subsequent Preventive Health Visits  | 1893 (22.9%)       | 695 (29.0%)          |

# Premarket Randomized Control Trial (RCT): Mirena FDA Application, 2000

- “In the study report based on annual PAP smear data from 2758 women, investigators reported no difference in the rate of dysplasia or cancer between women using Mirena (1821) and those using a copper IUD (937). There were 46 subjects who developed abnormal cervical cytology (Class III, IV, V), 13 in the copper IUD group and 33 in the Mirena group. There was one invasive cervical cancer in the Mirena group (described in section 3.10.1). These differences were not statistically significant.”
- No reporting of cervical neoplasms in peer reviewed publications

# Proportional Copper vs. Hormonal Results

| Cohort  | RCT  | CUIMC<br>PS Strat | CUIMC<br>PS Match | CUIMC<br>Crude |
|---------|------|-------------------|-------------------|----------------|
| Cu-IUD  | 1.4% | 1.1%              | 0.7%              | 0.9%           |
| LNG-IUS | 1.8% | 1.7%              | 1.8%              | 1.5%           |

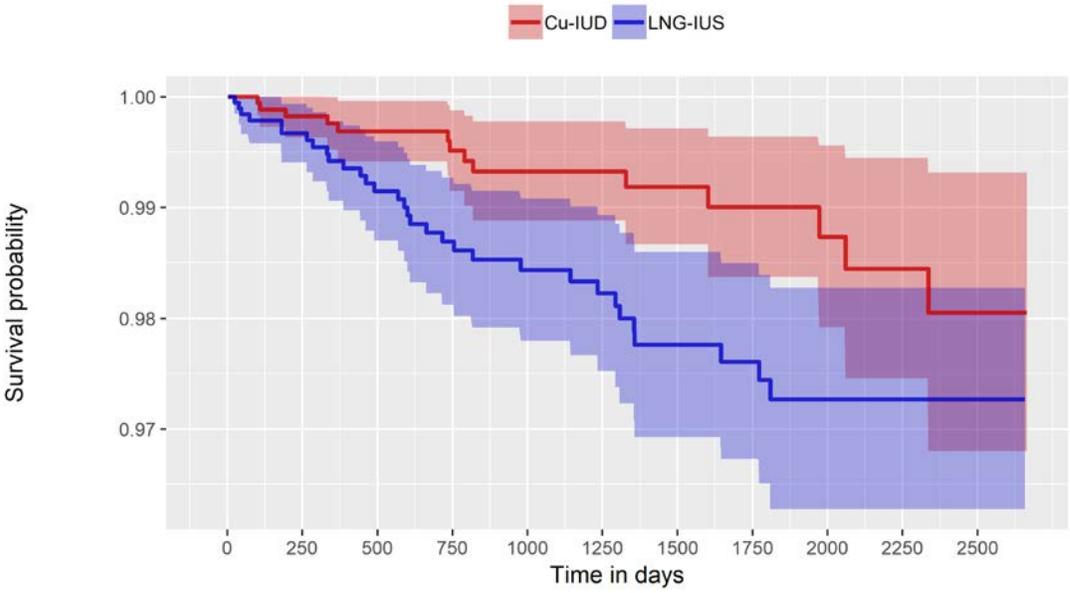
# Analysis Summary

| Analysis                           | RR [95% CI]      |
|------------------------------------|------------------|
| Propensity Score Stratification    | 0.49 [0.32-0.76] |
| Propensity Score Matching          | 0.38 [0.16-0.78] |
| Propensity Score Matching Subgroup | 0.64 [0.27-1.47] |
| Premarket RCT (n=2758)             | 0.76 [0.40-1.40] |

# Hormonal Device Toxicity

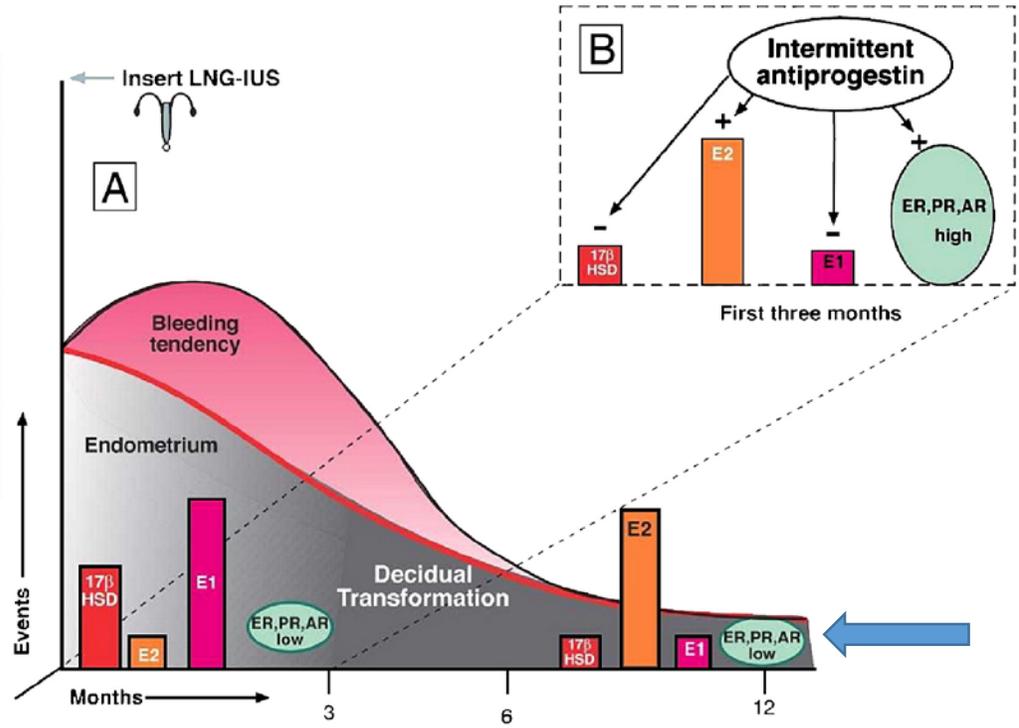
- “The local endometrial concentrations of levonorgestrel, however, are over 100 times higher in Mirena users than in users of oral contraceptive containing 0.25 mg levonorgestrel.”
- Continuous intrauterine exposure for years

# Endometrial Effects of Progesterone Exposure



| Number at risk | 0     | 250   | 500   | 750   | 1000  | 1250 | 1500 | 1750 | 2000 | 2250 | 2500 |
|----------------|-------|-------|-------|-------|-------|------|------|------|------|------|------|
| Cu-IUD         | 2,039 | 1,579 | 1,327 | 1,115 | 937   | 759  | 601  | 464  | 359  | 277  | 203  |
| LNG-IUS        | 2,039 | 1,639 | 1,413 | 1,213 | 1,057 | 895  | 730  | 599  | 457  | 373  | 299  |

## Working Hypothesis



- Increased Angiogenesis
- Increased MMP Activity

# Absolute vs. relative effects

- Although a direct comparison between IUD users and non-IUD users would be informative, it is difficult to do so in practice
- Confounding by intermittent vs. continuous contraception use, and number of pregnancies during the study interval
- Therefore, we focus on relative effects of Cu-IUD vs. LNG-IUS

# Conclusion

- The relative risk of cervical neoplasms for Cu-IUD users was less than that of LNG-IUS users
- Our findings were internally consistent and consistent with a premarket RCT
- High external validity with healthcare implications for approximately 1 million women
- OHDSI is uniquely situated to study the relative risk for other device related adverse events

# Future Studies

- IUD Cervical Neoplasms Network Study
- IUD Cervical Neoplasms Prediction Studies
- IUD Ovarian Cancer Network Study

# Thanks!

- Dr. Carolyn Westhoff
- Dr. Karthik Natarajan
- Dr. Patrick Ryan
- CUIMC DBMI
- Maura Beaton
- OHDSI Community