Endometrial ablation, supracervicals, and laparoscopic trachelectomy
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Objectives

• Review randomized data about endometrial ablation and supracervical hysterectomy compared with total hysterectomy.
• Review putative risks of ablation and retained cervix.
• Using video and slides, show each surgical step in resection of cervix after a supracervical hysterectomy was done.
Disclosures

• Consultant
  o Applied Medical
  o Olympus
  o Medtronic
  o Caldera Medical
  o Cooper Surgical

Disclosures

• I am not a GYN oncologist

• I am a benign gynecologic surgeon who eagerly looks for oncoreductive opportunities for my patients
Endometrial ablation

True or False?

10% of women who undergo endometrial ablation will ultimately fail and require a hysterectomy

Case 1

• 32yo g0 with premature ovarian failure
• Treated with OCs → Endometrial ablation

“Discussed that we do not need to check estrogen levels but rather can treat her symptoms. We may want to decrease dose in future; however, at this time given her age it is reasonable to use increased dose. Also, we discussed estrogen only is acceptable since she has had endometrial ablation. If she develops spotting or bleeding in future, she will need to let us know since there may be small areas of endometrium which were not burned during procedure which can place her at small risk for hyperplasia.”
Case 2

- 50yo 18 wk fibroid uterus
  - Endometrial ablation two years prior, improved bleeding, but remains “extremely symptomatic” with pelvic pain and dysmenorrhea
  - Pre-ablation bx negative; “I have not been able to biopsy her since the ablation as I might expect.”
  - Tubal ligation 10 years ago
  - Medhx: diabetes, hyperlipidemia, 3-agent HTN with kidney disease
  - BMI 36 kg/m²
Endometrial ablation history

Dührssen Berliner Klinische Wochenschrift 1898
Endometrial ablation history

- 1936: Bardenheuer, Zentralblatt fur Gynakologie 1937; Wortman, JMIG 2015
- 1937: Schultze, Cal West Med; Cahan, AJOG 1967; Droegemueller, Obstet Gynecol 1971
- 1967: UNC Health Care Women's Care
- 1971: UNC Health Care Women's Care
Endometrial ablation history
Resectoscopic endometrial ablation (REA)
- Laser, rollerball, loop electrode

Non-resectoscopic endometrial ablation (NREA)
- AKA global or 2nd gen endometrial ablation devices
- Bipolar radiofrequency (Novasure®)
- Hot liquid filled balloon (ThermaChoice®)
- Cryotherapy (Her Option®)
- Circulating hot water (Hydro ThermAblator®)
- Microwave (Microwave Endometrial Ablation)
Types of Endometrial ablation

<table>
<thead>
<tr>
<th>Method</th>
<th>Pretreatment</th>
<th>Outside Diameter (mm)</th>
<th>Approximate Treatment Time (min)</th>
<th>*Sounded Ultrasound Length (cm)</th>
<th>Treatment in the Presence of Submucosal Leiomyoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thermacsel (thermal balloon)</td>
<td>Mechanical (balloon aspiration)</td>
<td>5.5</td>
<td>8</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>氩热 (cryoablation)</td>
<td>Cryodestruction (cryoablation)</td>
<td>4.5</td>
<td>10-18</td>
<td>Not specified</td>
<td>10</td>
</tr>
<tr>
<td>HydroThermAblator</td>
<td>Mechanical destruction (laser)</td>
<td>7.8</td>
<td>14</td>
<td>4</td>
<td>10.5</td>
</tr>
<tr>
<td>Microwave Endometrial Ablation System (microwave energy)</td>
<td>Mechanical destruction (laser)</td>
<td>8.5</td>
<td>2.5-4.5</td>
<td>6</td>
<td>14</td>
</tr>
<tr>
<td>NovaSure (radiofrequency electricity)</td>
<td>None</td>
<td>7.2</td>
<td>1-2</td>
<td>6</td>
<td>10</td>
</tr>
</tbody>
</table>

* *Sounded device or treatment not applicable

Endometrial ablation complications

- Pregnancy after endometrial ablation
- Pain related obstructed menses
- Hematometra, post-ablation tubal sterilization syndrome (PATSS)
- Treatment failure
- Repeat ablation, hysterectomy
- Risk from pre-existing conditions
- Endometrial hyper-/neoplasia
- Cesarean delivery
- Infection

* *Sounded device or treatment not applicable

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**Table 3. Hysteroscopic Endometrial Ablation Device Comparisons**

AOG Practice Bulletin Obstet and Gynecol 2007/2018
Endometrial ablation complications

- **Pregnancy-related complications**
  - Endometrial ablation is not contraception
  - Increased risks:
    - Premature delivery
    - Morbidly adherent placenta
    - Uterine rupture
    - Cesarean delivery
    - Cesarean hysterectomy
    - Perinatal mortality
  - Pregnancy can occur even in women with amenorrhea

Kohn BJOG 2018

- **Pain-related complications**
  - Amenorrhea 13-55%; 95% of pts have functional endometrium on MRI, even if amenorrheic
  - Post-ablation tubal sterilization syndrome (PATSS)
    - Difficult to target cornua with ablation
    - Visceral distension from menses obstruction
    - Treatment: salpingectomy < hysterectomy
    - Hysteroscopic sterilization
    - Ablation scarring prevents adequate post-sterilization HSG, so recommendation is to wait until after 3 mo period before ablation

Sharp AJOG 2012; Turnbull BJOG 1997
Endometrial ablation complications

• 437 women followed median 2 yrs after ablation
• 21% developed pelvic pain
  ○ 46% went on to have hysterectomy
• 15% of total cohort: hysterectomy

• 1/3 pain, 1/3 bleeding, 1/3 both

• Risk factors for post-ablation pain
  ○ Dysmenorrhea
  ○ Age < 40
  ○ Tubal ligation
  ○ Smokers

• 270 women after various NREAs
• 23% developed new or worsening pelvic pain
• 73% of those with new or worsening pain had preop fibroids or adenomyosis
• 19% of total cohort: hysterectomy
  ○ 30% pain, 26% bleeding, 20% both
  ○ 3 hyperplasias, 1 STUMP, 1 CA
  ○ 2 hyperplasias missed on EMBx, one not done

• Risk factors for post-ablation pain
  ○ Dysmenorrhea
  ○ Tubal ligation
  ○ Non-white race (leiomyomas)
Endometrial ablation complications

- Pain is an Independent Risk Factor for Failed Global Endometrial Ablation
- Cramer M et al, JMIG 2018
- 5800 women underwent ablation 2003-15 at Christiana
- Overall 14% failure (some patients undoubtedly had care at other hospitals)
  - 20% among patients with pelvic pain prior to ablation
- Young age and pain independent risk factors for tx failure
- Need to add reference to reference list

Endometrial ablation complications

True or False?

10% of women who undergo endometrial ablation will ultimately fail and require a hysterectomy

~20%

ACOG Practice Bulletin Obstet Gynecol 2007/2018
Endometrial ablation complications

- **Treatment failure**
  - Risk factors
    - Age
    - Parity ≥ 5
    - Prior sterilization
    - Preop dysmenorrhea
    - Ultrasound suggestive of adenomyosis
    - Large uterine cavity
  - Reasons for post-ablation hysterectomy
    - Bleeding (51%), pain (28%), both (21%)
    - Fibroids found in 44% of those with bleeding
    - Hematometra found in 26% of those with pain
  - Repeat ablation
    - Uterine perforation, hemorrhage, excess fluid absorption, and genital tract burns (HTA)
      higher risk in repeat ablation

Sharp AJOG 2012, Shazly JMIG 2016

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Endometrial ablation complications

- **Treatment failure**
  - 500 patients
  - Avg followup 45 mos
  - 19% treatment failure
  - Risk factors
    - Sterilization
    - Dysmenorrhea
    - Fibroids

- **Pain**
  - 5000 patients
  - 14% hysterectomy
  - Risk factors
    - Age
    - Pain
      - 19% hysterectomy among those with pain

Lybol JMIG 2018, Cramer JMIG 2018
Leiomyomata were present in 63% of patients. Endometriosis in association with another benign diagnosis occurred in 4 of these patients. No patients underwent an abdominal hysterectomy. Therefore, most of our patients had a laparoscopic pelvic evaluation.

Of the 51 patients in the cohort studied, 92% (47 patients) expressed concern about both pain and menorrhagia. Of 51 patients, 11 (22%) noted pelvic pain as their chief concern. Of these patients, 8 (73%) were found to have endometriosis. The most common diagnosis was endometriosis, which was found in 46 patients. A vaginal hysterectomy was performed through a minimally invasive approach. Over 90% of patients experienced satisfaction. However, adequate relief after endometrial ablation was noted in only 5% of patients.

Patients who present for hysterectomy after endometrial ablation fail due to persistent symptoms, causing them to choose hysterectomy as the only option for treatment of menorrhagia, pain, or both. Ninety-six percent were Caucasian. Compared with a group previously studied satisfied with endometrial ablation, the only statistically significant difference in age between the 2 groups of patients was 0.01.

Nineteen percent of patients were African American, Hispanic, or other race. Average body mass index was 31 (range 19–47). The different techniques have limitations based on demographic parameters. Statistical differences were found between the 2 groups. These patients had either endometriosis alone or endometriosis and leiomyomata. Leiomyomata were present in 63% of patients. Many patients had multiple benign diagnoses. The average age was 44. One patient had a Novasure endometrial ablation. There were 46 patients who had a thermal balloon ablation. One patient had a C-3 EndoSoft endometrial ablation. Most patients included in this study had a thermal balloon ablation technique for their endometrial ablation. There were no statistical differences in age or demographic parameters.

The purpose of this study is to identify the characteristics of patients who previously had undergone an endometrial ablation. The outcomes following hysterectomy or endometrial ablation for heavy menstrual bleeding were investigated. The Society of Laparoendoscopic Surgeons, Inc. published a paper on this topic. Even with the advances in minimally invasive procedures, the incidence of endometrial ablation complications remains high. The key words for this paper are: hysterectomy, endometrial ablation, complications.

### Endometrial Ablation Complications

#### Rates of Treatment Failure

- **14,078 women**
- **20% subsequent hysterectomy**
- **1169 women**
- **13% subsequent hysterectomy**

#### Hysterectomy Subsequent to Endometrial Ablation

Valerie I. Shavell, MD,*, Michael P. Diamond, MD, James P. Senter, Michael L. Kruger, and D. Alan Johns, MD

#### Outcomes Following Hysterectomy or Endometrial Ablation for Heavy Menstrual Bleeding

K. Cooper,*** A. Lee,*** P. Chien,*** E. Raja,*** V. Himmaja,*** S. Bhatia,***

Shavell JMGI 2012, Cooper BJOG 2011
Endometrial ablation complications

• Post-cesarean delivery
  - GU injuries (bladder and ureteral fistulae) reported
  - Quantitative risk unknown

• Infection
  - Endometritis (1.4–2.0%)
  - Myometritis (0–0.9%)
  - PID (1.1%)
  - TOA (0–1.1%)
  - Endometrial destruction / necrosis thought to be a risk factor different than simple hysteroscopy

Sharp AJOG 2012

Endometrial ablation complications

Long-term Follow-up After Endometrial Ablation in Finland
Cancer Risks and Later Hysterectomies

Twila Soini, MD, Matti Ramonen, MS, Jorma Pauonen, MD, Selja Rinman, MD,
Johanna Mäntylä, MD, Eero Pukkanen, MD, Mika Gissler, MD, and Ritva Hurskainen, MD

Endometrial Cancer After Endometrial Ablation vs Medical Management of Abnormal Uterine Bleeding

Robert L. Dood, MD, MSCE†; Clarisa R. Gracia, MD, MSCE, Mary D. Sammel, ScD,
Kevin Haynes, PharmD, MSCE, Suneepta Senapati, MD, and Brian L. Strom, MD, MPH

From the Center for Clinical Epidemiology and Biostatistics, Department of Biostatistics and Epidemiology, Penn State School of Medicine, University of Pennsylvania (all authors), and Department of Obstetrics and Gynecology, Hospital of the University of Pennsylvania (Dr. Dood, Gracia, Sammel, and Senapati), Philadelphia.

Soini Obstet Gynecol 2017; Dood JMIG 2014
Endometrial ablation complications

- **Patients at risk for hyperplasia / neoplasia**
  - Nulliparity, chronic anovulation, obesity, diabetes
  - Tamoxifen tx, HNPCC, existing hyperplasia (contraindications)
- Ablation might mask the symptom that makes EMCA early diagnosis
- **Endometrial sampling post-ablation**
  - What is abnormal bleeding after an ablation?
  - Don’t know the utility of office biopsy after ablation
  - Office biopsy only samples 4% of the endometrium
  - U/S EM thickness not reliable after ablation
  - Probably obligated to do hysteroscopic bx / D&C
  - Post-ablation hysteroscopy can be challenging
  - May require hysterectomy
    - (at a time when they were likely less healthy than ablation)
  - If cancer present, then additional procedures indicated

16 patients s/p ablation undergoing hysterectomy
- EMB insufficient 50% of the time
- D&C insufficient 73% of the time
- EMB agreed with hysterectomy only 27% of the time
- D&C agreed with hysterectomy only 20% of the time

Pierce JMIG 2015
Comparisons among treatments

- Hysterectomy associated with highest satisfaction and most cost-effective (despite low numbers of TLH)
Comparisons among treatments

### A Systematic Review Comparing Hysterectomy with Less-Invasive Treatments for Abnormal Uterine Bleeding


- 9 RCTs reviewed
  - Some studies: better SF-36 for pain, vitality, general health, social function with hysterectomy
  - Most studies: no statistical difference in satisfaction (one favored hysterectomy)
  - One study: 73% (hyst) vs 48% (ablation) “health much better” compared w 1 year ago
  - Hysterectomy superior for dysmenorrhea
  - Pelvic pain: 18-64% ablation vs. 5-19% hysterectomy
  - 2-19% of ablation patients underwent repeat ablation; 10-29% underwent hysterectomy
  - Similar results comparing hysterectomy to LNG-IUS
  - Very small numbers of laparoscopic hysterectomy

### Hysteroscopic Endometrial Resection Versus Laparoscopic Supracervical Hysterectomy for Abnormal Uterine Bleeding: Long-term Follow-up of a Randomized Trial

Enrico Zupi, MD*, Gabriele Centini, MD, Lucia Lazzeri, MD, PhD, Andrea Finco, MD, Caterina Evacoustos, MD, PhD, Karolina Afoto, MD, Pelvio Zullo, MD, and Felice Petraglia, MD

- RCT of LSH vs Hysteroscopic endometrial ablation for abnl uterine bleeding
  - Initial trial: 1995-1997, 203 randomized patients
    - Two-year outcomes favored LSH
    - No difference in hospitalization, complications, resumption of activities
    - Higher reoperation rate with HEA (13% vs 1%), greater satisfaction LSH
  - Contacted patients 15 years later
  - Results
    - 153 subjects
    - Reoperation rate: 28% vs 0%
    - All HEA patients initially received repeat ablation, 75% of those went on to have hysterectomy
    - Hysterectomy: higher mental and physical scores on SF-12
3.3. Hemoglobin levels

LNG-IUS, 3 were lost to follow-up, 1 had a hysterectomy performed using paired Student’s test, and comparison before and after treatment was significant. In the same way, the TBA group had increased MBL, and 35.3% patients presented with amenorrhea. No significant differences were observed in the intermenstrual bleeding pattern between the two treatment modalities in the studies included in our meta-analysis: endometrial ablation versus the levonorgestrel-releasing intrauterine system. Both treatment modalities were associated with similar reductions in menstrual blood loss after 6 months of treatment (Fig. 6). To the statement, “I am very satisfied with my health,” women favored the levonorgestrel-releasing system over endometrial ablation; however, if the black square and 95% CIs are to the right of the solid vertical line, then overall satisfaction rate were significantly higher in women with the levonorgestrel-releasing system compared with those with endometrial ablation (Fig. 7). To the statement, “Overall, I am very satisfied with my sex life,” 11% (21/196) and 10% (19/194) for the LNG-IUS and endometrial ablation, respectively. Because there are, 195 reported by 100% in the LNG-IUS group vs. 95% in the endometrial ablation group.

<table>
<thead>
<tr>
<th>6 mos</th>
<th>12 mos</th>
<th>24 mos</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barrington et al. 2003</td>
<td>Malak and Shawki 2006</td>
<td>Burfield et al. 2006</td>
</tr>
<tr>
<td>Burfield et al. 2006</td>
<td>Crossan et al. 1997</td>
<td>Rauroa et al. 2004</td>
</tr>
<tr>
<td>Overall (95% CI)</td>
<td>Overall (95% CI)</td>
<td>Overall (95% CI)</td>
</tr>
</tbody>
</table>

- 6 RCTs
- No difference in HMB or quality of life improvements
- Ablation assoc w higher risk of perioperative and long-term complications

Five-year follow-up of levonorgestrel-releasing intrauterine system versus thermal balloon ablation for the treatment of heavy menstrual bleeding: a randomized controlled trial

Agnaldo L. Silva-Filho*, Francisco de A.N. Pereira, Sérgio S. de Souza,

- Hysterectomy more common w ablation
  - (24% vs 4%, p=0.04)
- Hgb higher in LNG-IUS grp
  - (14.1 vs 12.7, p=0.01)
- Bleeding profile favors LNG-IUS
- Patient ratings higher LNG-IUS
  - Acceptability
  - Perceived clinical improvement
  - Overall satisfaction
Comparisons among treatments

- LNG-IUS resulted in the most QALYs over the model’s 5-year horizon
- Ablation had more treatment failures and complications than hysterectomy
- LNG-IUS most cost effective
- Hysterectomy associated with greater quality of life than either type of ablation, but at a higher cost

Louie IJOG 2017; Spencer AJOG 2017

<table>
<thead>
<tr>
<th></th>
<th>Endometrial Ablation</th>
<th>LNG-IUS</th>
<th>Hysterectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer</td>
<td>No protection</td>
<td>Temporary protection</td>
<td>Permanent protection</td>
</tr>
<tr>
<td>Dysmenorrhea</td>
<td>Risk for failure</td>
<td>Improves</td>
<td>Definitive treatment</td>
</tr>
<tr>
<td>Contraception</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Future pregnancy</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>In-office</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Procedure cost</td>
<td>Middle</td>
<td>Least expensive</td>
<td>Most expensive</td>
</tr>
<tr>
<td>Reimbursement</td>
<td>Best</td>
<td>Least</td>
<td>Middle</td>
</tr>
<tr>
<td>Procedure risk</td>
<td>Middle</td>
<td>Least</td>
<td>Most</td>
</tr>
<tr>
<td>Cost-effectiveness</td>
<td>Least</td>
<td>Most</td>
<td>Middle</td>
</tr>
<tr>
<td>Endometrial sampling</td>
<td>Problematic</td>
<td>Yes</td>
<td>Not needed</td>
</tr>
<tr>
<td>Return to activities</td>
<td>Middle</td>
<td>Fastest</td>
<td>Slowest</td>
</tr>
<tr>
<td>Hormonal side effects</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>
Special populations

- **Submucosal myomas**
  - HSC or LSC myomectomy

- **Pelvic pain**
  - Risk factor for treatment failure
  - Post-ablation post-tubal ligation syndrome

- **Differently abled**
  - Age most consistent significant risk factor for ablation failure
  - Ablation is not contraception & pregnancy post-ablation assoc w/ risk
  - Ablation can be difficult in small nulligravid uteri

Supracervical hysterectomy

- **History**
  - 1st hysterectomy: vaginal, 1813 (Conrad Langenbeck)
  - 1st abdominal hysterectomy: supracervical, 1863 (Charles Clay)
  - 1st total hysterectomy: 1929 (EH Richardson)
  - Laparoscopy → increased numbers of supracervicals
    - Rates approach 50% in certain parts of Scandinavia
    - 7.5% in the US, 20% in California
Supravercial hysterectomy

- Postulated reasons to retain cervix:
  - Avoid vaginal shortening
  - Prevent prolapse
  - Preserve urinary, bowel function
  - Preserve sexual functioning
  - Avoid poor cuff healing or fallopian tube prolapse
  - Faster operation, less complications

Supravercial Hysterectomy

- 9 randomized trials, 1553 subjects
- Updates from 2006 Cochrane review:
  - Six new trials
  - Twice as many subjects
  - Included long-term (>5 years) followup
  - Stratified by open or LSC approach for short-term outcomes
Supracervical Hysterectomy

• **Primary outcomes**
  o Urinary function
    • Stress incontinence
    • Urinary urgency
    • Voiding dysfunction (incomplete emptying
  o Bowel function
    • Constipation
    • Incontinence (stool)
  o Sexual function
    • Pain symptoms or dyspareunia
    • Satisfaction, relationship and functioning combined
  o Quality of life (validated scales)
  o Operating time
  o Recovery from surgery
  o Length of hospital stay
  o Return to normal activities
  o Short term complications (pre-discharge)
    • Surgical injury
    • EBL, blood transfusion
    • Pelvic hematoma
    • Vaginal bleeding
    • UTI or other infection, fever
    • Urinary retention or bowel obstruction

• **Secondary outcomes**

Supracervical Hysterectomy

• **Secondary outcomes (continued)**
  o Intermediate complications (up to two years post-surgery)
    • Ongoing cyclical bleeding
    • Persistent pain
    • Need for removal of cervical stump
    • Pelvic organ prolapse
    • Gynecologic cancer

• **Long term complications (> two years post-surgery)**
  o Fistulae
  o Pelvic organ prolapse
  o Gynecologic cancer
Supraventricular Hysterectomy

- **Urinary function**
  - No difference in incontinence, incomplete emptying or urinary urgency
  - Both short-term and long-term
  - Both open and laparoscopic

- **Bowel function**
  - No difference in constipation or incontinence
  - Both short-term and long-term (incontinence)
  - No LSC studies

- **Sexual function**
  - No difference in sexual satisfaction
  - No difference in dyspareunia
  - Both short-term and long-term
  - Both open and laparoscopic

- **Quality of life**
  - Subjects reported improved quality of life, regardless of type of hysterectomy (no differences)

- **Operation time**
  - TAH 11 min longer than open SCH
  - No difference between TLH and LSH

- **Recovery**
  - No difference in hospital stay
  - No difference in resumption of normal activities

- **Blood loss**
  - TAH 57mL greater than open SCH for EBL
  - No difference between TLH and LSH
  - No difference in transfusion rate, open or LSC

- **Fever and urinary retention**
  - More common TAH vs open SCH

- **Intermediate outcomes**
  - Cyclic bleeding higher in SCH
  - No differences: persistent pain, prolapse, trachelectomy or GYN cancer (rare outcomes)

- **Long-term outcomes**
  - No difference: prolapse, alleviation of preop sxes
  - Not enough data for GYN cancer

Lethaby Cochrane 2012
Supravcervical Hysterectomy

Risks of supravcervical hysterectomy
- Cyclic bleeding (up to 11%)
  - Especially for those with h/o “fundectomy”
- Cervix dysplasia or neoplasia
- Endometrial cancer
  - 23% of trachelectomy specimens with residual endometrium
  - Combined HRT in menopause
- Need for future surgery (up to 24%)
  - Bleeding, cervical allodynia, residual endometriosis
- Morcellation

Risks of total hysterectomy
- Delayed resumption of penetration intercourse
- Vaginal cuff dehiscence

Supravcervical Hysterectomy

- Contraindications/special populations
  - Precancerous/cancerous conditions of the cervix, smoking
  - Endometriosis
  - Pelvic pain
  - Obesity
    - Increases surgical risk
    - Higher risk for endometrial cancer
Supracervical hysterectomy

- **Counseling** (US east coast, 2003)
  - 45% OBGYNs always perform total
  - 18% counsel about advantages / disadvantages
  - 63% rarely or never counseled about advantages / disadvantages
  - 19% always offered a choice
  - 61% rarely or never offered a choice
  - Of those that offered SCH
    - 36% believed SCH offered benefits such as protection against prolapse
    - 28% would perform SCH despite abnormal pap history

- **ACOG**
  - "The supracervical approach should not be recommended by the surgeon as a superior technique for hysterectomy for benign disease."

Laparoscopic trachelectomy

References

- Dührssen. Berliner Klinische Wochenschrift, 1898, No. 36.


References


References


References


