Fertility-sparing surgery in young patients with cervical cancer

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Evaluation BEFORE surgery

- Cancer: stage, type
- Patient’s age
- Desire for future pregnancy
- Imaging+++
- Tumor Board, multidisciplinary decision (oncofertility network)
- Early specific oncofertility consultation
Key elements to stage

- Size (volume ?)
- Nodes
- Histology
- Lympho-vascular space involvement (LVSI)

• Clinical examination
• +/- Pathological review
• MRI
• PET CT for advanced stage

IA1, IA2 (microscopic): **conization**
Conization

Obstetrical risks (metanalysis Kirgiou Lancet 2006)

<table>
<thead>
<tr>
<th>Obstetrical risks</th>
<th>Odd ratio (OR, IC 95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm delivery</td>
<td>2.59 (1.80-3.72)</td>
</tr>
<tr>
<td>Premature rupture of the membranes</td>
<td>2.69 (1.62-4.46)</td>
</tr>
<tr>
<td>Caesarean section</td>
<td>3.17 (1.07-9.40)</td>
</tr>
<tr>
<td>Low birth weight (&lt;2500g)</td>
<td>2.53 (1.19-5.36)</td>
</tr>
</tbody>
</table>

Fertility and early pregnancy outcomes after conservative treatment for cervical intraepithelial neoplasia (Review)


<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Relative effect (95% CI)</th>
<th>Number of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Assessed risk</td>
<td>Corresponding risk</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Untreated</td>
<td>Cervical treatment for CIN (ablation or ablative)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2nd trimester miscarriage rates</td>
<td>Study population</td>
<td>Relative risk (1.4 to 4.17)</td>
<td>21/26/288 (8 studies)</td>
<td>Low*</td>
</tr>
<tr>
<td></td>
<td>4 per 1000</td>
<td>18 per 8990 (2 to 16)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Control population</td>
<td>11 per 1000</td>
<td>29 per 8990 (18 to 81)</td>
<td>Low*</td>
</tr>
</tbody>
</table>

Observational studies only. 4 studies assessed as low quality. 1 study changed in very low quality due to study design (high risk of publication bias) and wide confidence intervals. 1 study upgraded to moderate quality due to large study population and magnitude of effect.
1997-2005 (552,678 singletons, 19,049 preterm, 8,180 subsequent to Loop electrosurgical excision procedure): 6% increase in risk of preterm delivery per each additional millimeter of tissue excised (OR: 1.06, 95% CI [1.03-1.09])
LEEP: RRX2 / no LEEP
2 or + LEEP: RR X4 / no LEEP

**New french recommendatons (INCA) in 2017:**
Under colposcopy control to limit excision size
No systematic second procedure if no margin
HPV status more important in follow up

**Fig. 1.** The estimated association between the odds ratio (logistic scale) for preterm delivery and cone depth
*Adjusted for year of delivery, maternal age, smoking during pregnancy, and marital status. The association is fitted by a linear spline with knots placed at the quantiles (i.e., 13, 78, and 20 mm). The reference level is the odds among deliveries not preceded by a loop electrosurgical excision procedure articles.
Note: Cone Depth of LEEP and Premen Delivery. Citrine Gyneco 2009.

IB1, <2cm, no LVSI, N-:
**Radical trachelectomy**

De-escalation ?
(on going studies)
Radical trachelectomy

• Technique of Pr Dargent in 1987
• Conditions
  – Histological review
  – <2cm
  – No LVSI (discussed, demonstrated risk factor)
  – MRI: limited / isthma
  – Desire of pregnancy (fertility ?)
  – Examination: size of cervix after previous conization...
• During surgery
  – Pelvic lymphadenectomy
  – Frozen section for margin
  – Definitive cerclage

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Table 2: MRI Imaging Findings Used to Assess Eligibility for Trachelectomy

<table>
<thead>
<tr>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of the cervix from the external os to the internal os</td>
</tr>
<tr>
<td>Length of the minimal cavity from the external os to the internal os</td>
</tr>
<tr>
<td>Distance of the tumor to the cervix</td>
</tr>
<tr>
<td>Position of the tumor in the cervix</td>
</tr>
<tr>
<td>Tumor growth pattern (e.g., anaplastic, diffuse infiltration)</td>
</tr>
<tr>
<td>Distance of the pelvic edge of the tumor to the internal os, parametrium, or vaginal fornix</td>
</tr>
<tr>
<td>Mediastinal lymphadenopathy (pelvic or para-aortic)</td>
</tr>
<tr>
<td>Incidental finding in other organs (ovaries, rectum, or bladder)</td>
</tr>
</tbody>
</table>

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Figure 3. Assessment of eligibility for trachelectomy. (a) Sagittal T2-weighted MRI image shows soft tissues with intermediate signal intensity (arrow) consistent with a cervical tumor in the anterior lip of the cervix. The tumor is smaller than 2 cm in diameter and more than 1 cm from the internal os, with no evidence of extraneous extension. (b) Sagittal T2-weighted MRI image shows the measurements that must be considered before trachelectomy is considered, namely, the position of the internal os, identified (red line), the length of the external os from the internal os to the external os (solid white line), the length of the anterior edge of the tumor to the internal os (light blue line), and the distance from the anterior edge of the tumor to the external os (red line) should be considered.
Less radical surgery?

- Review of rate of parametrial involvement if N-, <2cm, no LVSI: 0.6% (Uzan 2009, Schmeler 2011)

Management of low-risk early-stage cervical cancer: Should conization, simple trachelectomy, or simple hysterectomy replace radical surgery as the new standard of care? 

Pedro T. Ramirez, Rene Pareja, Gabriel J. Rendón, Carlos Millán, Michael Frumovitz, Kathleen M. Schmeler

Gynecol oncol 2014

- 3 on going trials
  - ConCerv (Shmeler): cohlorte with less radical surgery, 25/100
  - SHAPE (Plante): randomization radical vs non radical, 700 pts
  - GOG 278 (Covens): quality of life after non radical surgery, 200 to 600 pts

Clinical recommendation radical trachelectomy for fertility preservation in patients with early-stage cervical cancer.

*Int Gyn Cancer, Schneider et al 2012*

- Review VRT-ART
- If < 2 cm, Recurrence rate 3-6%
- Death rate 2-5%
- Same fertility
- Risk of preterm delivery RR=2-3
- More info on VRT / ART
- >2cm, chemo and RT: option but limited experience
Fertility after trachelectomy (Bentivegna fertil steril 2016)

Pregnancy rate 55%
Live Birth rate 70%
Prematurity rate 38%

Sexuality after trachelectomy

**Table 1:** Details of the mean fertility results of this systematic review according to FSS procedures for cervical cancer.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Simple trachelectomy</th>
<th>Segmental procedure</th>
<th>Radical trachelectomy, laparoscopic</th>
<th>Radical trachelectomy, microsurgical</th>
<th>Neoadjuvant chemotherapy</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systems</td>
<td>212</td>
<td>31</td>
<td>195</td>
<td>334</td>
<td>161</td>
<td>2,777</td>
</tr>
<tr>
<td>Cervical included†</td>
<td>13.7</td>
<td>23.7</td>
<td>161</td>
<td>233</td>
<td>17.3</td>
<td>309</td>
</tr>
<tr>
<td>Recurrence</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>5</td>
<td>3</td>
<td>13</td>
</tr>
<tr>
<td>Previous gynecologic history</td>
<td>4</td>
<td>11</td>
<td>4</td>
<td>6</td>
<td>5</td>
<td>17</td>
</tr>
<tr>
<td>Age of participants</td>
<td>103</td>
<td>60</td>
<td>109</td>
<td>92</td>
<td>96</td>
<td>365</td>
</tr>
<tr>
<td>Total lost, 1st trimester</td>
<td>5</td>
<td>0</td>
<td>5</td>
<td>1</td>
<td>5</td>
<td>11</td>
</tr>
<tr>
<td>Total lost, 1st trimester</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Transuterine and other complications</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>Clinical pregnancy</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Preterm delivery 1&lt;6 weeks</td>
<td>14</td>
<td>16</td>
<td>14</td>
<td>16</td>
<td>14</td>
<td>44</td>
</tr>
<tr>
<td>Between 6 and 36 weeks</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Between 36 and 39 weeks</td>
<td>2</td>
<td>4</td>
<td>2</td>
<td>4</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Between 39 and 40 weeks</td>
<td>2</td>
<td>5</td>
<td>2</td>
<td>5</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>Between 40 and 39 weeks</td>
<td>2</td>
<td>7</td>
<td>2</td>
<td>7</td>
<td>2</td>
<td>16</td>
</tr>
<tr>
<td>Between 39 and 40 weeks</td>
<td>2</td>
<td>8</td>
<td>2</td>
<td>8</td>
<td>2</td>
<td>16</td>
</tr>
<tr>
<td>Sex limited†</td>
<td>323 (96%)</td>
<td>36 (46%)</td>
<td>323 (96%)</td>
<td>36 (46%)</td>
<td>323 (96%)</td>
<td>1,269</td>
</tr>
<tr>
<td>Prematurity rate</td>
<td>0.18 (16)</td>
<td>12.8 (16)</td>
<td>0.18 (16)</td>
<td>12.8 (16)</td>
<td>0.18 (16)</td>
<td>0.63</td>
</tr>
</tbody>
</table>

Sexuality after trachelectomy: While FSS may allow for post-treatment fertility, it may not confer a significant benefit with regard to sexual satisfaction or sexual QOL.

- Decision to perform FSS should not be dictated based on preservation of sexual functioning.
2-4 cm, N-

**French standard:**
Radical hysterectomy (RH) or brachytherapy-RH (5 year survival rate 95% Uzan et al 2012)

**Option to spare fertility:**
Neoadjuvant chemotherapy (NAC) trachelectomy / conization

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Oncological and pregnancy outcomes after high-dose density neoadjuvant chemotherapy and fertility-sparing surgery in cervical cancer

Helena Robova a, Michael J. Halaska a, Marek Pluta b, Petr Skapa a, Jan Matecha a, Jiri Lisy c, Lukas Rob a, b

- 28 patients <35y, > 2 cm or >50% stroma infiltration
- Dose-dense NAC (cisplatine-ifo for SCC/ cisplatin-doxo for ADK)
- Pelvic laparoscopy and simple trachelectomy
- Median FU 42 months
- 10 lost fertility
- 10/20 pregnant, 10 babies/ 8 wo (4 preterm)
- 20% recurred (2/4 DCD)

Conclusions: Downstaging by NAC in IB1 and IB2 cervical cancer before fertility-sparing surgery is still an experimental procedure, but shows some promise. Long-term results in relation to oncological outcome for this concept are still needed.
112 patients
Cisplatine-ifosfamide FU / cisplatine ifosfamide placitaxel
6 recurrences (4/28 in the largest series)

> 4cm:

**Standard Chemo-radiation Brachytherapy**
Option to spare fertility: NAC tracheectomy ???
To inform patients

- Risk of non eligibility during surgery (N+ or invaded margin in frozen section)
- Switch to Chemo-radiation if N+
- Results on fertility and pregnancy after this procedure
- De-escalation of surgery for limited lesions?
- Increase indications of conservative treatment???
How to improve our management?

• To evaluate
  – stage,
  – desire and needs of the patient

• To anticipate
  – Risk of modification of treatment planification
  – Explain all the possibilities
  – Evolution of treatments (up-to-date)

• To collaborate
  – Imaging
  – Early consultation in oncofertility (network)
  – Learn from one other-international register (patient included)

Livebirth after uterus transplantation

Brannstrom team

Easier to preserve than to restore (for now…)

9 patients (8 Rokitanski, 1 cervical cancer)
2 graft removal
7 persistent (1 year report in fertil steril 2015 Jan)
5 livebirth to the last report (2016)