CONSERVATIVE TREATMENT OF ENDOMETRIAL CANCER
A MULTICENTRE REGISTRY STUDY

PROTOCOL OUTLINE
April 2013

Gynecologic Oncology - National Cancer Institute of Naples, Italy
ENDOMETRIAL CANCER IN YOUNG WOMEN

Two main questions

• Is it possible to preserve fertility in young EC pts? In whom?
• Is it possible to achieve pregnancy in pts conservatively treated for EC?
Age-specific Incidence of Endometrial Cancer

about 25% premenopausal women
almost 5% <40 years

FIGO Annual Report, 2006
Endometrial Cancer
*Disease profile in young women*

- endometrioid histotype
- well differentiated tumor
- minimal / absent myometrial invasion
- ER+ / PR+

**Type 1 Endometrial Cancer**

**Favorable prognosis**
Endometrial Cancer

Patient profile in young women

obesity..................................50%
nulliparity..............................60%
infertility...............................30%
Conservative Treatment of Endometrial Ca.

Preservation of fertility regardless of the wish of conceiving

?
## Survey - 1992-2011

<table>
<thead>
<tr>
<th>Study Setting</th>
<th>Histo Grade</th>
<th>HSC Res</th>
<th>Hormone Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retrosp 17</td>
<td>Endo 354 (100%)</td>
<td>20 (6%)</td>
<td>MA / MPA (56%)</td>
</tr>
<tr>
<td>Prosp 11</td>
<td>G1 344 (97%)</td>
<td></td>
<td>LNG-IUD (14%)</td>
</tr>
<tr>
<td>Case rep 7</td>
<td>G2-3 10 (3%)</td>
<td></td>
<td>TAM (+) (9%)</td>
</tr>
</tbody>
</table>

### 1992-2011 (n=354)

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response</td>
<td>72%</td>
<td>18-100</td>
</tr>
<tr>
<td>Relapse Rate</td>
<td>23%</td>
<td>0-67</td>
</tr>
<tr>
<td>Patients who conceived (complete responders)</td>
<td>28%</td>
<td>0-100</td>
</tr>
</tbody>
</table>

### Regression, relapse, and live birth rates with fertility-sparing therapy for endometrial cancer and atypical complex endometrial hyperplasia: a systematic review and metaanalysis

By Joannis D. Gallos, MD; Jason Yap, MBChB; Madhurima Rajkhowa, MD; David M. Luesley, MD; Arri Coomarasamy, MD; Janesh K. Gupta, MD

<table>
<thead>
<tr>
<th>Study</th>
<th>Regressed</th>
<th>Total of patients</th>
<th>Rates [95% CI]</th>
<th>Regression rates (Random), 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subtotal (95% CI)</td>
<td>301</td>
<td>408</td>
<td>76.2 [68, 85.3]</td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity: $Q = 17.463$ on 31 degrees of freedom ($p=0.976$)

<table>
<thead>
<tr>
<th>Study</th>
<th>Relapsed</th>
<th>Total of patients</th>
<th>Rates [95% CI]</th>
<th>Relapse rates (Random), 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subtotal (95% CI)</td>
<td>89</td>
<td>267</td>
<td>40.6 [33.1, 49.8]</td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity: $Q = 26.132$ on 28 degrees of freedom ($p=0.566$)

<table>
<thead>
<tr>
<th>Study</th>
<th>Live births</th>
<th>Total of patients</th>
<th>Rate* [95% CI]</th>
<th>Live birth rates (Random), 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subtotal (95% CI)</td>
<td>75</td>
<td>325</td>
<td>28 [26.6, 36.3]</td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity: $Q = 30.773$ on 25 degrees of freedom ($p=0.197$)

- **34 sel. papers** (408 EC pts)
- **Prospective** 50%
- **G2-3** 5%
- **>5y FU** 18%
Limited amount of data
Retrospective studies in most cases
Often short follow-up
Insufficient information on reproducibility outcome
Lack of pretreatment fertility counseling
Prospective, multicentre registry study to systematically collect data (oncological and obstet. outcomes) on consecutive pts treated according to institutionally defined protocols
Protocol Outline

Eligibility

Inclusion Criteria
- age up to 45 years
- histologically proven EC
- strong desire to preserve fertility and complete the follow-up program
- oncology and fertility counseling and informed consent

Exclusion Criteria
- history of previous/concomitant cancer (except for adequately treated skin basal cell or in situ cervical cancer)
- patient belonging to a family with HNPCC (Lynch II syndrome)
- synchronous ovarian cancer at MRI or laparoscopy
- contraindications for progestin treatment or LNG-IUS insertion

Treatment
- Not one defined protocol (registry study) but treatment, however, administered according to IRB approved protocols
- Pretreatment counseling and patient informed consent mandatory
- Definitive surgery planned and pathological data available
**Protocol Outline - 1**

**Purpose**
To learn more about the safety of conservatively treating EC and about subsequent fertility outcome

**Study Type**
Observational (Patient Registry)

**Study Design**
Observational Model: Cohort

**Time Perspective**
Prospective

**Endpoint Classification**
Treatment and outcome registry study

**Interventions**
Data collected in the registry includes patient characteristics/demographics, disease characteristics, treatment details (hormonal therapy ± surgery), disease and survival outcomes, post-intervention reproductive and obstetric outcomes
Protocol Outline - 2

Outcome Measures

Primary Outcome Measures
- Prevalence of causes of patient exclusion
- Prevalence of complete regression
- Duration of response
- Prevalence and pattern of relapse
- Prevalence of metachronous ovarian cancer
- Prevalence of DOD

Secondary Outcome Measures
- Prevalence of treatment related morbidity
- Prevalence of spontaneous pregnancies
- Prevalence of pregnancies after ART
- Prevalence and pattern of residual disease on definitive surgical specimens
Data to be collected - 1

Patients excluded
- Causes of exclusion (pt refusal / Stage >IA M0 / non endometrioid histotype / G>1 / PR- / P53+ / previous-concomitant ca / Lynch II syndrome / contraindications for progestins or LNG-IUS insertion / other)

Patients enrolled
- Patient ID code
- Centre
- Age at enrolment
- Body Mass Index (Kg/m2)
- Comorbidity (no / diabetes / hypertension / PCO syndrome / other)
- Age at menarche (yrs)
- Estroprogestin use (N/Y)
- Wish to conceive (N/Y)
- Gravidity (n)
- Spontaneous abortion (n)
- Voluntary abortion (n)
- Stillbirth (n)
- Sterility (N/Y)
- ART (N/Y)

Diagnosis
- Histologic diagnosis procedure (hysteroscopy / D&C / D&C + hysteroscopy)
- Histotype (endometrioid / serous-papillary / clear cell / other)
- Grade (1 / 2 / 3)
- FIGO stage (IA M0 / IA M<50% / > IA)
- PR (not available / negative / <50% / >50%)
- ER (not available / negative / <50% / >50%)
- P53 (not available / negative / <50% / >50%)
- Staging transvaginal ultrasonography (not performed / performed)
- Staging MRI (not performed / performed)
- Tumor pattern (not available / unifocal / multifocal)
- Tumor site (not available / corpus / isthmus)
- Tumor diameter (not available / ≤ 2 cm / > 2 cm)
- Pretreatment fertility counseling (N/Y)
- Pretreatment psychological counseling (N/Y)
Data to be collected - 2

**Primary treatment**
- Hysteroscopic resection (no / endometrium only / endometrium + myometrium)
- Oral progestin therapy (no / MPA / MA / others)
- Oral progestin dosage per day (mg)
- Intrauterine progestin therapy - LNG-IUS (N/Y)
- Planned duration (6 mos / 12 mos / > 12 mos)
- Real duration (months)
- Treatment related adverse events (no / surgical / medical / surgical + medical)

**Response**
- Hysteroscopic controls during treatment (N/Y)
- Complete regression (N/Y)
- Time to CR (mos)
- Evaluation of CR (TV-USG / hysteroscopy without biopsy / hysteroscopy with biopsy)

**Follow-up**
- Last follow-up date
- Last follow-up status (NED / AWD / DOD / death of other cause / not available)
- Compliance to follow-up (N/Y-according to protocol)
First relapse
• Relapse (N/Y)
• Date
• Histology (complex hyperplasia without atypia / hyperplasia with atypia / EC G1 / EC G2 / EC G3)
• Pattern (not applicable / uterine / abdomen / distant / combined)
• Treatment (not applicable / conservative / definitive surgery)

Second+ relapse (as above)

Fertility outcome
• Attempts to conceive (N/Y)
• ART (N/Y)
• Pregnancy (n)
• Spontaneous abortion (n)
• Voluntary abortion (n)
• Normal full term delivery (n)
• Stillbirth (n)

Definitive surgery
• Definitive surgery (not yet planned / planned / performed)
• Date
• Pathology (not applicable / negative / complex hyperplasia without atypia / hyperplasia with atypia / endometrioid EC / non endometrioid EC)
• Grade (not applicable / G1 / G2 / G3)
• FIGO stage (not applicable / IA M0 / IA M<50% / IB / > IB)
Background

Approximately one fourth of EC cases diagnosed in premenopausal women (approximately 40% wish to preserve their fertility)

In young women, EC usually presents with favorable prognostic features, that is, as a focal, well differentiated endometrioid tumor, with minimal or absent myometrial invasion (Type 1 EC with ER+/PR+ pattern)

Primary progestin therapy has been demonstrated to be effective in early well differentiated EC and in poor operative candidates (response rates 58-100%)

The worldwide experience on conservative management of EC is limited. Most reports based on cases retrospectively collected, harboring potential methodological bias, using different therapeutic modalities and drugs. Some systematic reviews have been published in the last decade: 75% regression; 25-40% relapse; 30% pregnancy rate in pts attempting to conceive

Need for a prospective, multicentre cooperative project to systematically collect data (oncological and obstet. outcomes) on consecutive pts treated according to defined protocols