Lebanese International Fertility Summit

2 – 3 October 2015
Hilton Beirut Habtoor Grand
Conservative treatment of endometrial cancer

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www.cancerologiegynecologique.eu
AUDIT 2013 about cancer and preservation of fertility

- 30 to 50% of women are not informed
- Insufficient mobilisation of practitioners
- Insufficient data on treatments toxicity
- Insufficient knowledge of practitioners of the existing strategies
- Lack of time to inform patients properly
- Difficulties to talk about fertility during the announce of diagnosis
- Underestimation of the importance of fertility in cancer survivors
- Lack of research on the topic
Introduction

- Endometrial cancer: 7200 cas/year in 2012 in France

  5% before 40 years old (360 patients)
  70% are nullipare.

- Increasing of the age of first pregnancy

- Endometrial cancer in young women with desire of childbearing is not rare

- We should be able to propose a conservative treatment when possible

- Multidisciplinarity +++: oncofertility
Context

- **Context of high oestrogens levels**
  - Obesity,
  - Chronic anovulation,
  - Polycystic ovaries syndrome,
  - infertility

- **Patients with infertility and endometrial cancer risk**
  - x 4.8 in patients complaining of infertility
  - x 10.3 in patients with infertility and anovulation

- **Lynch Syndrome**
Lynch Syndrome

**COLON**
- Ascending colon
- Transverse colon
- Descending colon
- Appendix
- Sigmoid colon
- Rectum

**ENDOMETRE**

**OVARIAN CANCER**
- Small bowel cancer
- Stomach cancer
- Urinary tract cancer
- Biliary tract cancer
- Cutaneous Tumours (Muir-Torre)
- Brain tumors

LIFE 2015
« MOLECULAR » definition

Germinal mutation of one gene in the MMR system

MLH1, MSH2 +++ MSH6, PMS2

Specific tumor phenotype

Ac anti-MLH1
Défaut expression protéique IHC

MSI-H
Cancer Risks Associated With Germline Mutations in \textit{MLH1}, \textit{MSH2}, and \textit{MSH6} Genes in Lynch Syndrome

Cumulated risk at 70 yrs

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Total</th>
<th>MLH1</th>
<th>MSH2</th>
<th>MSH6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometrial cancer</td>
<td>33%</td>
<td>54%</td>
<td>21%</td>
<td>16%</td>
</tr>
<tr>
<td>Colo-rectal cancer</td>
<td>31%</td>
<td>41%</td>
<td>48%</td>
<td>12%</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>9%</td>
<td>20%</td>
<td>24%</td>
<td>1%</td>
</tr>
</tbody>
</table>

\textit{Bonadona, JAMA 2011}

Young age
Synchrone ovarian cancer
Non endometrioid carcinoma
Locally advanced stages
High grade?
Tumor located in the isthmus

\textit{Broaddus, Cancer 2006,}
Standard treatment of endometrial cancer

• **Surgical treatment**
  - Total hysterectomy with bilateral salpingo-oophorectomy, pelvic lymphadenectomy, +/- para-aortic lymphadenectomy and omentectomy according to subtype

• **Adjuvant treatment**
  - Radiotherapy
  - Brachytherapy
  - Chemotherapy
  According to stage, pN status
Indications and modalities of conservative treatment

Oncological outcomes

Fertility outcomes
Indications and modalities of conservative treatment

Meta-analysis
370 patients in 24 studies:
- 121 patients with atypic hyperplasia
- 249 patients with endometrial carcinoma

Median age 33 y

Treatment:
- medroxyprogesterone acetate DMPA: 54%
- megestrol acetate: 20%
- Others (analogues…): 26%

Koskas, Fertil Steril 2014
Indications and modalities of conservative treatment

Indications

No recommendations

✓ Before 42 years old
✓ Endometrioïd carcinoma
✓ FIGO Stage IA (without myometrium invasion)
✓ Grade 1
✓ Positive Progesterone Receptors
✓ Patient with a desire of childbearing
✓ Informed consent
Indications and modalities of conservative treatment

Baseline assessment

✓ Pelvic ultrasound and MRI, CA125
✓ Ovarian function evaluation (AMH, FSH and oestradiol at day 3)
✓ Spermogram
✓ Laparoscopic evaluation with peritoneal washing cytology, ovaries observation +/- ovarian drilling
✓ Hysteroscopy and curettage
Technical modalities

- Simultaneous laparoscopy and hysteroscopy
- Peritoneal washing for cytology
- Endometrectomy
- Concomittant tubal occlusion
Fertility preservation via photodynamic therapy in young patients with early-stage uterine endometrial cancer: a long term follow-up study

Inclusion criteria:

< 35 years old,
Endometrioïd carcinoma,
FIGO stage IA without myometrium invasion

Protocole: intravenous injection of a photosensitizing element followed 48 hrs after with exposure to infrared light

Choi MC, Int J Gynecol Cancer 2013
**Fertility preservation via photodynamic therapy in young patients with early-stage uterine endometrial cancer: a long term follow-up study**

**Results**

- 16 patients included
- Mean age: 30.7 y
- Mean follow-up: 78 months
- 11 initial treatments and 5 recurrences
- Complete response: 75%
- 57% of pregnancy among women with desire of childbear

Choi MC, Int J Gynecol Cancer 2013
Conservative treatment

✔ In first intention: progestatives treatment, megestrol acetate 160 mg for 3 months

✔ Hysteroscopy (HSC)-curettage after 3 months to ensure complete response

✔ In case of incomplete response:
  ✔ Standart surgery
  ✔ Or second medical treatment with GnRH analogues for 3 months, followed by hysteroscopy-curettage
Follow-up after conservative treatment

Follow-up modalities for patients with complete response

- HSC + endometrial biopsy every 3 months until pregnancy
- Hysterectomy to be discussed after pregnancy(ies)
- If completion surgery is refused: HSC + endometrial biopsy every 6 months
- Imaging, CA125?
Follow-up after conservative treatment

Indications of AMP

- If no previous infertility, wait for a spontaneous pregnancy
- If associated infertility, AMP without delay
Oncological outcomes

Complete response: 75%

✓ Median time: 5.4 months
✓ Factors associated with complete response: patients with infertility, patients receiving megestrol acetate, patients with previous pregnancy

Progression: 15%

Recurrence: up to 35%

✓ Median time: 24 months
✓ 70% of recurrences occurred within 3 years.
✓ Recurrence probability at 6, 12 and 24 months: 9.6%, 17.2% and 29% according to Koskas et al.
Fertility outcomes

Review of Tong et al 2013, pregnancy rate= 60% n= 152 patients

Table 1. Methods for achieving pregnancy and outcomes of patients with early-stage endometrial carcinoma who desire to conceive

<table>
<thead>
<tr>
<th>Methods for pregnancy</th>
<th>Natural pregnancy (n)</th>
<th>ART group (n)</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Induction of ovulation</td>
<td>IUI</td>
<td>IVF-ET</td>
</tr>
<tr>
<td>No. of patients desiring pregnancy</td>
<td>81</td>
<td>7</td>
<td>13</td>
</tr>
<tr>
<td>No. of patients achieving pregnancy</td>
<td>35</td>
<td>4</td>
<td>12</td>
</tr>
<tr>
<td>Intrauterine pregnancy</td>
<td>38</td>
<td>5</td>
<td>15</td>
</tr>
<tr>
<td>Spontaneous abortion</td>
<td>7</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Ectopic pregnancy</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Heterotopic pregnancy</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Delivery</td>
<td>31</td>
<td>4</td>
<td>11</td>
</tr>
<tr>
<td>Live birth</td>
<td>31</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>Complication of pregnancy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple pregnancies</td>
<td>0</td>
<td>2 (twins)</td>
<td>1 (twins)</td>
</tr>
<tr>
<td>Preterm labor</td>
<td>2</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Fetal abnormality</td>
<td>Down syndrome: 1</td>
<td>IUGR: 1</td>
<td>0</td>
</tr>
<tr>
<td>Maternal complications</td>
<td>Pre-eclampsia: 1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>HELLP syndrome: 1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Conservative treatment of borderline ovarian tumors and ovarian cancer

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Borderline ovarian tumors

• Age at diagnosis: 40-60 yrs
• In women under 40, borderline ovarian tumors are more frequent than ovarian cancer
• 25-50% serous subtype
• 10% of mucinous tumors are bilateral
• 6-27% of borderline tumors are invasive at final pathology

• **Baseline assessment:**
  - Markers
  - Pelvic MRI
  - CT scan
Standard surgical treatment of borderline ovarian tumors

- Laparoscopy or laparotomy
- Peritoneal evaluation
- Peritoneal washing cytology
- Total hysterectomy and bilateral salpingo-oophorectomy
- Infracolic omentectomy
- Appendectomy if mucinous tumor
- Multiple peritoneal biopsies
Indications and modalities of conservative treatment

Oncological outcomes

Fertility outcomes
Indications and Modalities of conservative treatment of borderline ovarian tumors

- Unilateral tumor stage IA: standard conservative treatment
  - Laparoscopic evaluation
  - Peritoneal wash,
  - Unilateral salpingo-oophorectomy,
  - Infracolic omentectomy,
  - Multiple peritoneal biopsies,
  - Appendectomy (in case of mucinous tumor),
  - No lymphadenectomy
Indications and Modalities of conservative treatment of borderline ovarian tumors

- Bilateral tumor stage IB
  
  - Laparoscopic evaluation
  - Peritoneal wash,
  - Unilateral salpingo-oophorectomy, and contralateral partial oophorectomy
  - Infracolic omentectomy,
  - Multiple peritoneal biopsies,
  - Appendectomy (in case of mucinous tumor),
  - No lymphadenectomy

- In case bilateral disease is too important: bilateral adnexitomy and uterus conservation
Indications and Modalities of conservative treatment of borderline ovarian tumors

- Stages II and III (Uzan et al. 2010)
  - Laparoscopic evaluation
  - Peritoneal wash,
  - Unilateral salpingo-oophorectomy, and contralateral partial oophorectomy
  - Infracolic omentectomy,
  - Multiple peritoneal biopsies,
  - Appendectomy (in case of mucinous tumor),
  - Excision of all peritoneal implants
  - No lymphadenectomy
Follow-up after conservative treatment

- **Follow-up**: no consensus, no recommendation
  - Every 6 months for 5 years, then once a year
    - Clinical examination
    - Biology: CA125, HE4
    - Imaging: alternatively ultrasound or MRI, CT scan once a year if advanced stage

- **MAP possible**

- **Completion of surgery**:  
  - No consensus  
  - Probably not necessary if stage IA  
  - Probably recommended if advanced stage
Borderline ovarian tumors: oncological outcomes of conservative treatment

- Recurrence: 7 to 30% of increasing risk, if recurrence of borderline tumor, a second conservative treatment can be performed (Uzan et al. 2010)

- Factors associated with recurrence: presence of peritoneal implants, cystectomy versus adnexectomy

- Progression towards invasive implants: 2-3% (Morice et al. 2012)

- No impact on overall survival: mortality 0.5% without peritoneal implants, 2% with peritoneal implants
Borderline ovarian tumors: fertility results of conservative treatment

- review Darai et al. 2013

- Spontaneous pregnancies: 54% (up to 88% in pooled analysis)
- Better rate if: age < 40 yrs, cystectomy versus adnexectomy, mucinous tumors
- Rate of pregnancies in advanced stages: 34%
- With MAP: 80% of pregnancies, without increasing the recurrence rate (23%)
Ovarian cancer

• 4600 new cases per year in 2012
  • 9% before 40 yrs
  • 30% early stage

• Standard treatment stage
  • Radical surgery: total hysterectomy and bilateral adnexitomy, total omentectomy, appendectomy, pelvic and para-aortic lymphadenectomy and excision of all visible intra-peritoneal disease
  • Stage > IA: Chemotherapy: carboplatin/paclitaxel/+/-bevacizumab
Indications and modalities of conservative treatment

Oncological outcomes

Fertility outcomes
Indications of conservative treatment in ovarian cancer

- **Baseline assessment**
  - Markers
  - Pelvic MRI
  - CT scan

- **Indications of conservative treatment**
  - Epithelial carcinoma (clear cell carcinoma excluded)
    - Stage IA grade 1 (grade 2 possible)
    - Desire of childbearing

- Cancer non épithéial
  - Receivable even in advanced stage
Modalities of conservative treatment in ovarian cancer

- Unilateral tumor stage IA: standard conservative treatment
  - Laparoscopic evaluation
  - Peritoneal wash,
  - Unilateral salpingo-oophorectomy,
  - Total omentectomy,
  - Multiple peritoneal biopsies,
  - Appendectomy (in case of mucinous tumor),
  - Pelvic and para-aortic lymphadenectomy
Modalities of conservative treatment in ovarian cancer

- Bilateral tumor stage IB (only for non epithelial tumor)
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- In case bilateral disease is too important: bilateral adnexectomy and uterus conservation
Modalities of conservative treatment in ovarian cancer

- Stages II and III (only for non epithelial tumor)
  - Laparoscopic evaluation
  - Peritoneal wash,
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  - Multiple peritoneal biopsies,
  - appendectomy (in case of mucinous tumor),
  - Excision of all peritoneal implants
  - Pelvic and para-aortic lymphadenectomy
Oncological outcomes

- Review Zapardiel *et al.* 2014 (early stage)
  - Recurrence: 9 à 29%, mean 11.5%
  - 5 year overall survival: 83 to 100%, mean 91.1%
  - Controlateral recurrence < 5%
  - Recurrence rate is higher in case of grade 2 and grade 3
  - These rates are not different from those obtained with radical surgery (equal grade and stage)
Fertility outcomes

- Conception rate: 60 – 100%, mean 74%
- Miscarriage rate: 17%
Conclusions

FEASIBILITY: conservative treatment is feasible with good oncological and fertility outcome

SELECTION: conservative surgical treatment of endometrial and ovarian cancer should be proposed to eligible patients

STAGING: pre-therapeutic staging should be complete to ensure early stage

INFORMATION: the patient and the couple should be informed that the proposed treatment is not standard and of oncological and fertility outcomes

MULTIDISCIPLINARITY: surgery, oncology, assisted reproduction

FOLLOW-UP: no standard, but close follow-up

COMPLETION OF SURGERY: no standard, but completion of surgery should always be discussed with the patient after pregnancies
THANK YOU FOR YOUR ATTENTION

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