How and why to get earlier diagnosis of endometriosis?

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Presentation outline

- Endometriosis in adolescents and young women
- Lengthy diagnostic delays
- Non-invasive diagnosis of endometriosis
- Can earlier diagnosis impact the outcome?
- Implications for clinical practice
Endometriosis in adolescents and young women

- Endometriosis affects women during the prime years of their lives!

- Women at age ≤ 23 yrs account for > 20% of endo-related outpatient visits

✓ Present in 69% of adolescents with pain refractory to NSAID’s or OCP’s

**Age at first consultation for symptoms**

64% were <30 years

- **Age 10–19**
- **Age 20–29**
- **Age 30–39**
- **Age 40–49**

WERF prospective Global Study of Women's Health (n=1,418)
Lengthy diagnostic delays

Mean of 7 years from the onset of symptoms to diagnosis

Age at the onset of symptoms (yrs)

Length of diagnostic delay

12.1 years

4.5 years

3.3 years

< 20

20 - 29

> 30

Arruda M. Hum Reprod 2003;18:756
Lengthy diagnostic delays

- %47 had to see ≥ 5 MDs, pre-Dx
- Those with the earliest onset of symptoms had to see more MDs (4.2 if onset <15 yrs old, 2.6 if onset started 30-34)
- delay between onset of symptoms and actual diagnosis = 9.28 yrs
- 4.67 yrs delay to report symptoms to MD, another 4.61 yrs delay to Dx (4.1 yrs gyn; 1.4 yrs rep.endo; 5.3 yrs fam. pract)

Biological markers in non-invasive diagnosis of endometriosis

- Surgically diagnosed endometriosis cases in 182 studies
  ✓ high quality - 9 studies
  ✓ sensitivity & specificity could be calculated - 32 studies
  ✓ the most promising markers - nerve fibres and molecules involved in cell-cycle control, cell adhesion and angiogenesis
  ✓ no marker was conclusively shown to be diagnostic

- Se. CA-125 - limited performance in grade I/IV, better in grade III/IV
**Immunological biomarkers in non-invasive diagnosis of endometriosis**

- Genome wide transcriptional profiling indicated that endometriosis has an immunological basis
  Hever A et al. Proc Natl Acad Sci USA 2007;104:12451–6

- Autoimmune involvement proposed

- Among over 200 investigated possible immunological biomarkers, none clearly shown to be of clinical use

- The discovery of biomarkers with high sensitivity, specificity and clinical relevance useful for non-invasive diagnosis is still awaited
Recommendations

Clinicians are recommended not to use biomarkers in endometrial tissue, menstrual or uterine fluids to diagnose endometriosis (May, et al., 2011).

Clinicians are recommended not to use immunological biomarkers, including CA-125, in plasma, urine or serum to diagnose endometriosis (May, et al., 2010, Mol, et al., 1998).
Why diagnose early?
Can earlier diagnosis impact the outcome?

- We do know:
  - Persistent pain becomes chronic

- We don’t know:
  - Who will develop progressive disease
  - Who will regress
  - Who will stay stable
  - Decrease in
    ✓ Chronic pain risk?
    ✓ Infertility risk?

- To explain the pain
  - Improve validation of symptoms and reduce feelings of isolation

“We can cope with almost anything, if we can understand it”
The presence of endometriosis in the adolescent seems similar to a Mona Lisa smile with a mysterious innocence.
A progressive disease?

- Adolescents’ & adults’ lesions are similar (subtle, superficial red, vesicular also extensive adhesions and ovarian endometriomas)

- L/S at age 16.6 yrs; 50% Stage I / II and 50% had Stage III / IV

- no difference in stages between adolescents aged 18–19 vs 19+ yrs
  ✓ 75 vs 66% severe endometriosis

- Adolescent endometriosis is no different from adult endometriosis

- The behavior is unpredictable, independent of stage, lesion, site, sometimes self-limiting its spread, even regressing.
Recurrent endometriosis and repetitive conservative surgery

- In the past two decades the growing popularity and widespread diffusion of operative laparoscopy has fostered a spread of surgical procedures in women with endometriosis.

- The behavior of endometriosis is unpredictable regardless of the type of surgical approach.

  ✓ no data are available on reoperation for DIE.

**A progressive disease?**

- Retrospective, 90 cases
- Mean age 17 (12-24)
- Mean stage – I (max. III)
- Ablation/medical Rx
- Intersurgical interval median 29 months (6-112 mths)
- Re-LS indication – symptomatic recurrence

**Table 1. Patient Statistics**

<table>
<thead>
<tr>
<th></th>
<th>Median</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>17</td>
<td>12</td>
<td>24</td>
</tr>
<tr>
<td>Stage at 1st Surgery</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Stage at 2nd Surgery</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Stage at 3rd Surgery</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Duration between 1st and 2nd Surgeries (months)</td>
<td>29</td>
<td>6</td>
<td>112</td>
</tr>
<tr>
<td>Duration between 2nd and 3rd Surgeries (months)</td>
<td>27</td>
<td>9</td>
<td>62</td>
</tr>
<tr>
<td>Medical Therapies Used Between 1st and 2nd Surgeries</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Continuous combined oral contraceptives</td>
<td>82</td>
<td>91%</td>
<td></td>
</tr>
<tr>
<td>Progesterone only</td>
<td>11</td>
<td>12%</td>
<td></td>
</tr>
<tr>
<td>Leuprolide acetate +/- addback</td>
<td>70</td>
<td>78%</td>
<td></td>
</tr>
</tbody>
</table>

A progressive disease?

Table 2. Change in Stage of Endometriosis between Surgeries

<table>
<thead>
<tr>
<th></th>
<th>Between 1st and 2nd Surgery</th>
<th>Between 2nd and 3rd Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Improved by Two Stages</td>
<td>1</td>
<td>1%</td>
</tr>
<tr>
<td>Improved by One Stage</td>
<td>17</td>
<td>19%</td>
</tr>
<tr>
<td>Stage Unchanged</td>
<td>63</td>
<td>70%</td>
</tr>
<tr>
<td>Worsened by One Stage</td>
<td>9</td>
<td>10%</td>
</tr>
<tr>
<td>Total</td>
<td>90</td>
<td>100%</td>
</tr>
</tbody>
</table>

Likelihood of increase (worsening) in disease stage

Likelihood of decrease (improvement) in disease stage

*especially stages II-III

Recurrent endometriosis and outcome of repetitive conservative surgery

Repeated conservative surgery for pelvic pain associated with recurrent endometriosis has the same limitations as primary surgery, with long-term cumulative recurrence rates ranging from 20-40%, further surgical procedure between 15-20% \(^1\) \(^2\)

- Reoperations are technically more challenging and more risky
- Potential damage to ovarian reserve, morbidity, and the paucity of skilled surgeons \(^3\)

\(^1\) Berlanda N. Curr Opin Obstet Gynec 2010, 22:320–325
\(^3\) Adamson GD. Fertil Steril 2005; 84:1582–84
Recurrent endometriosis

• Younger age at onset or at surgery represent a risk factor for recurrence for both ovarian and deep endometriosis


✔ ♀ ≤ 21 yrs ; %56 recurrence in 5 years

### Laparoscopy: advantages and disadvantages

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
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<tbody>
<tr>
<td>Gold standard investigation technique</td>
<td>Facilities/surgical expertise not universally available</td>
</tr>
<tr>
<td>Possibility to diagnose and treat during one procedure</td>
<td>Not all patients are suitable for invasive techniques</td>
</tr>
<tr>
<td></td>
<td>False-positive and false-negative findings</td>
</tr>
<tr>
<td></td>
<td>Risk of complications</td>
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Surgery alone is not the answer

There is currently no cure for endometriosis and surgery alone is not an adequate solution.

- Many women (20% to 40%) do not show improvement following conservative surgery.¹
- Removal of lesions may be incomplete.
- Surgical treatment has risks and, in ovarian endometriosis, is associated with damage to the ovarian reserve.²

“Endometriosis should be viewed as a chronic disease that requires a life-long management plan with the goal of maximizing the use of medical treatment and avoiding repeated surgical procedures.”³

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³ Practice Committee of ASRM. Fertil Steril 2008; 90:S260
Is surgical diagnosis always necessary

“The common belief that a preliminary laparoscopy must always be performed (GPP) in order to definitely diagnose the disease should be challenged, as the non-surgical diagnosis of endometriosis has been demonstrated to be highly reliable”

Guidelines for endometriosis management

Empirical treatment for pain symptoms without a definitive diagnosis

ASRM=The American Society for Reproductive Medicine;
ESHRE=European Society of Human Reproduction and Embryology;
RCOG=Royal College of Obstetricians and Gynaecologists;
SOGC=Society of Obstetricians and Gynaecologists of Canada.

Brazil DoH = Brazilian Department of Health
KSOG = Korean Society of Obstetrics and Gynecology

Can earlier diagnosis impact the outcome?

- Yes:
  - When
    - Pathophysiology of the disease
    - Effective treatment
    - Non-invasive diagnostic methods
  - are known.

- When we know:
  - Who will develop the disease
  - Who will develop progressive disease

Thereby, when we manage to prevent
- Symptoms, recurrence…..
- Chronic pain risk
- Infertility risk
- thus improve the quality of life of women