Endometriosis

Dr PD Didier Chardonnens

Training in Research in Reproductive Health
Geneva 2005
1. Introduction
2. Genetics
3. Endocrinology
4. Immunology
5. Apoptosis
6. Implantation
7. Diagnosis
8. Medical treatment
9. Surgical treatment
10. Future
2-18% of women of reproductive age

5 to 21% of women with admission to the hospital because of chronic pelvic pain

5 to 50% of women suffering from infertility
Epidemiologic findings

- Menstrual history
  - Early Menarche
  - Short cycles
- Body habitus
  - Greater height
  - Lower BMI
- Lifestyle
  - Alcohol, caffeine
  - Dioxine
Epidemiologic findings

- Immune disorders
  - Rheumatoid arthritis (2 vs 0.8%)
  - LED (0.8 vs 0.05%)
  - Hypothyroidism (6.8 vs 1.5%)
  - Hyperthyroidism (1.5 vs 1.1%)
  - MS (0.6 vs 0.1%)
- Family clustering
- Caucasian women
**Epidemiologic findings**


- Progressive disease in a significant proportion of women (30-60 %)
  - Deterioration approximately 50 %
  - Improvement approximately 30 %
  - No change in approximately 20 %
Etiology

- Retrograde menstruation
- Immune system tolerance
- Coelomic metaplasia
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Family clustering
   - 6 to 15 times increased prevalence in first degree relatives

Concordance between monozygotic and dizygotic twins

Future with positional cloning
   - Suggestive linkage has been reported for at least one chromosomal locus (ENDOGENE study)
There are aberrant genes expression in the ectopic endometrium

- Aromatase
- Endometrial bleeding factor
- 17 beta OH-steroid dehydrogenase
- HOXA-10, HOXA-11
- LIF
- MMP 7 and 11
- Progesterone receptors
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Increased endometrial concentrations of E2

- Aromatase overexpression
- Decreased 17 beta OH-steroid dehydrogenase expression
- Decreased progesterone B receptor expression
Origin of estrogen in endometriotic lesions. Estradiol (E$_2$) in a woman with endometriosis arises from several body sites. In an ovulatory woman, estradiol is secreted directly from the ovaries in a cyclic fashion. In the early follicular phase and after menstruation, peripheral tissues (adipose and skin) are the main important source of circulating estradiol. Finally, estradiol is produced locally in the endometriotic implant itself in both ovulatory and postmenopausal women. The most important precursor, androsterone, 

$$\text{AROMATASE}$$

of adrenal origin, becomes converted to estriol, which is, in turn, reduced to E$_2$, in the peripheral tissues and endometriotic implants. We demonstrated significant levels of $$\text{17\textbeta\text{HSD}}$$, aromatase, and type 1 aromatase expression in endometriotic implants. 

Figure 2

The conversion of estriol to E$_2$ is both direct and indirect through catalyzed conversion of PGF ($\text{PGF}_{2\alpha}$) to PGE$_2$ ($\text{PGE}_{2\alpha}$), which gives rise to elevated concentrations of PGE$_2$ in endometriosis. In turn, PGE$_2$ is the most potent known stimulator of aromatase in endometriotic adnexal lesions. Therefore, a positive feedback loop in favor of endometriosis formation is established in endometriosis.
Paracrinology
Gurates et al Sem Reprod Med 2003

Figure 3 Proposed mechanism of regulation of aromatase expression by SF-1, COUP-TF, and WT1 in eutopic endometrium and endometriosis. (A) Binding of COUP-TF to a specific DNA site in nuclear receptor half-site upstream of aromatase promoter II in eutopic endometrium. COUP-TF binds to the nuclear receptor half-site practically in the absence of any competition by SF-1. Receptor SF-1, expression is absent or barely detected in the majority of endometrial samples. Thus, COUP-TF binding induces the silencing of aromatase gene. This mechanism is disrupted in endometriosis because SF-1 is present, sp-1 binds to the nuclear receptor half-site with a higher affinity than COUP-TF. (B) The presence of a stimulatory factor WT1 gives rise to aromatase expression in endometriosis.
Figure 5. Failure of endometriosis tissue to metabolize estradiol: a consequence of progesterone resistance. We propose this model to explain the deficient progesterone action in endometriosis. In the absence of PR-A, the unopposed effects of PR-B may give rise to increased estradiol (E₂) levels, deficient differentiation and apoptosis, and uncontrolled proliferation.
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Cellular immune response

- Increased number of peritoneal macrophages with aberrant immune response
  - Increased release of growth promoting cytokines with impaired scavenger function
- Diminished cytotoxicity of NK cells
  - Increased Killer Inhibitor Receptors (KIR)
**Cellular immune response**

- Polyclonal activation of B lymphocytes with auto antibodies against a certain number of tissues
- Increase in cytokines
  - IL1 and IL1R
  - IL8
  - Monocytic Chemotactic protein (MRCP-1)
  - RANTES
  - TNF alpha
  - VEGF
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There is an increased apoptosis of activated T cells
Apoptosis
Garcia-Velasco et al Sem Reprod Med 2003

Figure 3: (A) Activated T cells express both Fas receptor and Fas ligand, the Fas receptor-bearing cell will undergo apoptosis when Fas ligand binds to it. (B) Different cytokines and growth factors, like Fas ligand expression in shed endometrial cells, these will induce apoptosis in Fas-bearing immune cells when trying to engulf them.
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MMPs and endometriosis
Osteen et al Sem Reprod Med 2003

- Relative insensitivity to progesterone leads to increased MMP3 and 7 in eutopic secretory endometrium of endometriotic women with diminished TIMP3 expression
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Non invasive diagnosis

- Clinical examination
- Ultrasound
- MRI
- Serum markers
Clinical examination

Spaczinski et al. Semin Reprod Med 2003

<table>
<thead>
<tr>
<th>Reference</th>
<th>Finding/Location</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
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<tbody>
<tr>
<td>Rips et al, 1992 (n = 94)</td>
<td>Focal pelvic tenderness (overall)</td>
<td>79</td>
<td>32</td>
<td>65</td>
<td>50</td>
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<tr>
<td></td>
<td>Uterosacral ligaments</td>
<td>56-58</td>
<td>72-80</td>
<td>54-62</td>
<td>60-64</td>
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<td></td>
<td>Cul-de-sac</td>
<td>37</td>
<td>37</td>
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<td>70</td>
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<td></td>
<td>Adnexa</td>
<td>38-43</td>
<td>72-80</td>
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<td>60-64</td>
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<td>Koninckx et al, 1996 (n = 140 and *n = 55)</td>
<td>Pelvic induration and/or nodularities</td>
<td>36</td>
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<td></td>
<td>Pelvic induration and/or nodularities at mensturation (overall)*</td>
<td>79</td>
<td>92</td>
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<tr>
<td></td>
<td>Deep endometriosis*</td>
<td>77</td>
<td>76</td>
<td>88</td>
<td></td>
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<td></td>
<td>Endometrioma*</td>
<td>78</td>
<td>70</td>
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<tr>
<td></td>
<td>Severe cul-de-sac*</td>
<td>52</td>
<td>77</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Esk honazi et al, 2001 (n = 90)</td>
<td>Pelvic induration and/or nodularities of uterosacral ligaments/cul-de-sac and/or fixed adnaxal mass, fixed uterus and/or vaginal endometriotic lesion</td>
<td>76</td>
<td>74</td>
<td>67</td>
<td>81</td>
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<tr>
<td>Chapron et al, 2002 (n = 160)</td>
<td>Painful pelvic induration and/or nodularities (overall)</td>
<td>90</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Bladder endometriosis</td>
<td>73</td>
<td></td>
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<tr>
<td></td>
<td>Uterosacral ligaments</td>
<td>83</td>
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<td>Vaginal endometriosis</td>
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<td></td>
<td>Intestinal endometriosis</td>
<td>94</td>
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Ultrasound
Ultrasound
## Table 3  Reliability of Transvaginal Ultrasound in Diagnosis of Endometriomas

<table>
<thead>
<tr>
<th>Reference</th>
<th>Ultrasound Mode; Indication for Surgery</th>
<th>Prevalence (%)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>Kappa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mais et al, 1993$^*$(n = 236)</td>
<td>B-mode; infertility, CPP, fibroids, adnexal mass</td>
<td>10</td>
<td>75</td>
<td>99</td>
<td>76</td>
<td>98</td>
<td></td>
</tr>
<tr>
<td>Guerriero et al, 1995$^\dagger$(n = 118)</td>
<td>B-mode; adnexal mass</td>
<td>33</td>
<td>85</td>
<td>97</td>
<td>94</td>
<td>93</td>
<td>0.84</td>
</tr>
<tr>
<td>Alcazar et al, 1997$^\ddagger$(n = 78)</td>
<td>B-mode + color Doppler imaging (CDI); adnexal mass</td>
<td>33</td>
<td>89</td>
<td>91</td>
<td>94</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>Guerriero et al, 1999$^\S$(n = 170)</td>
<td>B-mode Color Doppler energy (CDE); adnexal mass</td>
<td>34</td>
<td>81</td>
<td>96</td>
<td>92</td>
<td>91</td>
<td>0.80</td>
</tr>
<tr>
<td>Passal et al, 2000$^\S$(n = 352)</td>
<td>Color Doppler imaging (CDI); adnexal mass</td>
<td>52</td>
<td>92</td>
<td>95</td>
<td>96</td>
<td>92</td>
<td></td>
</tr>
<tr>
<td>Eskanazi et al, 2001(n = 90)</td>
<td>B-mode; adnexal mass, fibroids, CPP; infertility</td>
<td>23</td>
<td>57</td>
<td>98</td>
<td>95</td>
<td>76</td>
<td>0.58</td>
</tr>
</tbody>
</table>
Table 2  Reliability of CA-125 in Diagnosis of Endometriosis (Cutoff Level used 35 IU/mL Unless Stated Otherwise)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Assay; Timing of Sample Collection</th>
<th>Stage</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barbieri et al, 1996(^{51})</td>
<td>Standard assay; timing of sample collection unknown</td>
<td>All</td>
<td>17</td>
<td>95</td>
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<tr>
<td>(n = 147)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patton et al, 1986(^{77})</td>
<td>Standard assay; timing of sample collection unknown</td>
<td>III+IV</td>
<td>54</td>
<td>95</td>
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<tr>
<td>(n = 113)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pittaway and Faye, 1988(^{12})</td>
<td>Standard assay; cutoff level 30 IU/mL, follicular phase</td>
<td>All</td>
<td>14</td>
<td>93</td>
</tr>
<tr>
<td>(n = 414)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Koninckx et al, 1992(^{54})</td>
<td>Standard assay; late luteal phase</td>
<td>III+IV</td>
<td>18</td>
<td>93</td>
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<tr>
<td>(n = 259)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>O’Shaughnessy et al, 1993(^{36})</td>
<td>Standard assay; menstrual phase</td>
<td>III+IV</td>
<td>17</td>
<td>93</td>
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<tr>
<td>(n = 100)</td>
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</tr>
<tr>
<td>Hornstein et al, 1995(^{87})</td>
<td>Standard assay; early follicular phase</td>
<td>All</td>
<td>13</td>
<td>95</td>
</tr>
<tr>
<td>(n = 123)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>CA 125 II assay; early follicular phase</td>
<td>III+IV</td>
<td>19</td>
<td>93</td>
<td></td>
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<tr>
<td>Mertl et al, 1997(^{114})</td>
<td>Standard assay; timing of sample collection unknown</td>
<td>All</td>
<td>30</td>
<td>92</td>
</tr>
<tr>
<td>(n = 368)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CA 125 II assay; luteal phase</td>
<td>III+IV</td>
<td>61</td>
<td>88</td>
<td></td>
</tr>
<tr>
<td>Chen et al, 1998(^{167})</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n = 157)</td>
<td></td>
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Table 4  Reliability of Magnetic Resonance Imaging in Diagnosis of Endometriosis

<table>
<thead>
<tr>
<th>Reference</th>
<th>Assay</th>
<th>Lesion</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zawin et al.</td>
<td>T1- and T2- weighted imaging</td>
<td>All lesions</td>
<td>71</td>
<td>82</td>
<td>77</td>
<td>76</td>
</tr>
<tr>
<td>Arrive et al.</td>
<td>T1- and T2- weighted imaging</td>
<td>All lesions</td>
<td>64</td>
<td>60</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Implants</td>
<td>13</td>
<td>60</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adhesions</td>
<td>48</td>
<td>60</td>
<td>—</td>
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<td></td>
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<td>Endometrioma</td>
<td>88</td>
<td>60</td>
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<tr>
<td>Togashi et al.</td>
<td>T1- and T2- weighted imaging</td>
<td>Endometrioma</td>
<td>90</td>
<td>98</td>
<td>94</td>
<td>97</td>
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<tr>
<td>Sugimura et al.</td>
<td>T1- and T2- weighted imaging</td>
<td>Endometrioma</td>
<td>82</td>
<td>91</td>
<td>90</td>
<td>84</td>
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<tr>
<td></td>
<td>T1/T2 and fat-suppressed</td>
<td>Implants</td>
<td>11</td>
<td>98</td>
<td>33</td>
<td>90</td>
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<td></td>
<td>imaging</td>
<td>Endometrioma</td>
<td>91</td>
<td>94</td>
<td>94</td>
<td>92</td>
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<td>Implants</td>
<td>47</td>
<td>97</td>
<td>64</td>
<td>94</td>
</tr>
<tr>
<td>Ha et al.</td>
<td>T1- and T2- weighted imaging</td>
<td>Implants</td>
<td>27</td>
<td>98</td>
<td>93</td>
<td>55</td>
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<td></td>
<td>Fat-suppressed imaging</td>
<td></td>
<td>61</td>
<td>87</td>
<td>83</td>
<td>67</td>
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</table>
Invasive diagnosis
Invasive diagnosis
<table>
<thead>
<tr>
<th>Patient's Name:</th>
<th>Date:</th>
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</thead>
<tbody>
<tr>
<td>Stage I (Minimal): 1-5</td>
<td>Laparoscopy</td>
</tr>
<tr>
<td>Stage II (Mild): 6-15</td>
<td>Recommended Treatment</td>
</tr>
<tr>
<td>Stage III (Moderate): 16-40</td>
<td></td>
</tr>
<tr>
<td>Stage IV (Severe): &gt;40</td>
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<tr>
<td>Total</td>
<td>Prognosis</td>
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</tbody>
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<table>
<thead>
<tr>
<th>ENDOMETRIOSIS</th>
<th>&lt;1cm</th>
<th>1-3cm</th>
<th>&gt;3cm</th>
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</thead>
<tbody>
<tr>
<td>Superficial</td>
<td>1</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Deep</td>
<td>2</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>R Superficial</td>
<td>1</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Deep</td>
<td>4</td>
<td>16</td>
<td>20</td>
</tr>
<tr>
<td>L Superficial</td>
<td>1</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Deep</td>
<td>4</td>
<td>16</td>
<td>20</td>
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</tbody>
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<table>
<thead>
<tr>
<th>OVARY</th>
<th>POSTERIOR CULDESAC OBLITERATION</th>
<th>Partial</th>
<th>Complete</th>
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<tr>
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<td>40</td>
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<table>
<thead>
<tr>
<th>ADHESIONS</th>
<th>&lt;1/3 Enclosure</th>
<th>1/3-2/3 Enclosure</th>
<th>&gt;2/3 Enclosure</th>
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<tbody>
<tr>
<td>R Filmy</td>
<td>1</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Dense</td>
<td>4</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>L Filmy</td>
<td>1</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Dense</td>
<td>4</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>R Filmy</td>
<td>1</td>
<td>2</td>
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<tr>
<td>Dense</td>
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<td>8</td>
<td>16</td>
</tr>
<tr>
<td>L Filmy</td>
<td>1</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Dense</td>
<td>4</td>
<td>8</td>
<td>16</td>
</tr>
</tbody>
</table>

*If the fimbriated end of the fallopian tube is completely enclosed, change the point assignment to 16.*

Denote appearance of superficial implant types as red (R), red, red pink, flame-like vascular bluish clear vesicles, white (W) capillaries, peritoneal defects yellow-brown, or black (B) black hemosiderin deposits, blue. Denote percent of total described as R %, W %, B %, and B %. Total should equal 100%.
Fig. 2. The American Fertility Society revised classification of endometriosis. (From American Fertility Society. Revised classification of endometriosis. Fertil Steril 1985;43:351–2; with permission.)
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## Pain treatment

### Table 3
Placebo-controlled trials evaluating medical treatments of endometriosis-associated pain

<table>
<thead>
<tr>
<th>Medication</th>
<th>Sample size*</th>
<th>Duration of therapy</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Danazol [4]</td>
<td>n = 18</td>
<td>6 mo</td>
<td>Significant reductions in pain scores</td>
</tr>
<tr>
<td>600 mg/d</td>
<td></td>
<td></td>
<td>Decrease in number and size of endometriotic lesions</td>
</tr>
<tr>
<td>Provera [4]</td>
<td>n = 16</td>
<td>6 mo</td>
<td>Significant reductions in pain scores</td>
</tr>
<tr>
<td>100 mg/d</td>
<td></td>
<td></td>
<td>Decrease in number and size of endometriotic lesions</td>
</tr>
<tr>
<td><strong>GnRH agonists</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lupron Depot [55]</td>
<td>n = 32</td>
<td>6 mo</td>
<td>90% complete relief of dysmenorrhea</td>
</tr>
<tr>
<td>• 3.75 mg intramuscularly every 28 d</td>
<td></td>
<td></td>
<td>Significant reductions in pelvic pain, tenderness, and nodularity</td>
</tr>
<tr>
<td>Triptorelin [56]</td>
<td>n = 24</td>
<td>6 mo</td>
<td>Significant reductions in pain scores</td>
</tr>
<tr>
<td>• 3.75 mg intramuscularly every 28 d</td>
<td></td>
<td></td>
<td>Decrease in number and size of endometriotic lesions</td>
</tr>
</tbody>
</table>

* Number of participants who received the active study medication.
Box 2. Side effects of progestins

- Breakthrough bleeding (40% – 80%)
- Weight gain, fluid retention (40% – 50%)
- Acne (20%)
- Breast tenderness (10%)
- Headaches (10%)
- Mood changes (10%)
- Muscle cramps
- Adverse lipid changes (↑ LDL, ↓ HDL)

Estimates of prevalence are a composite from published clinical trials [34,36,48].
Side effects

Box 1. Side effects of danazol

Androgenic
- Hot flashes (50%)
- Acne, oily skin (30% – 60%)
- Weight gain, fluid retention (30% – 50%)
- Muscle cramps (30%)
- Adverse lipid changes ([HDL, [LDL]
- Decreased breast size (25%)
- Hirsutism (15%)
- Irreversible deepening of the voice (8%)

Breakthrough bleeding (40%)
Mood changes (20%)
Liver damage

* Estimates of prevalence are a composite from published clinical trials [4,34,38].
Side effects

Box 3. Side effects of GnRH agonists

- Hot flashes (80% – 90%)
- Sleep disturbances (60% – 90%)
- Vaginal dryness (30%)
- Joint pain (30%)
- Breakthrough bleeding (20% – 30%)
- Headaches (20% – 30%)
- Mood change (10%)
- Bone loss (↓ bone density 5% – 6%)
- Adverse lipid changes (↑ LDL, ↓ HDL)

Estimates of prevalence are a composite from published clinical trials [19,55,56,65].
**Add back therapy**

Box 4. Add-back regimens proven to preserve bone density for 1 year

- Norethindrone acetate 5–10 mg orally every day
- Premarin 0.625–1.25 mg + norethindrone acetate 5 mg orally every day
- Cyclic etidronate 400 mg + Os Cal 500 mg + norethindrone acetate 2.5 mg orally every day
Medical treatment strategy for endometriosis pain

Box 6. Suggested approach to endometriosis-associated pain

1\textsuperscript{st} line: continuous low-dose monophasic oral contraceptive with NSAIDs as needed
2\textsuperscript{nd} line: progestins (start with oral dosing, consider switching to levonorgestrel intrauterine device or depo if well tolerated)
3\textsuperscript{rd} line: GnRH agonist with immediate add-back therapy
4\textsuperscript{th} line: repeat surgery, followed by 1, 2, or 3\textsuperscript{a}

\textsuperscript{a} May consider low-dose (100–200 mg every day) danazol if other therapies poorly tolerated.
Post operative medical treatment

Box 5. Postoperative therapies proven to delay the recurrence of endometriosis if given for at least 6 months

- Medroxyprogesterone acetate 100 mg orally every day [34]
- Danazol 600 mg orally every day [34]
- Nafarelin 200 g intranasally twice daily [91]
- Goserelin 3.6 mg sc every month [95]
### Post op medical treatment for pain RCT trials


<table>
<thead>
<tr>
<th>Trial Identifier</th>
<th>Pain Recurrences / Patients</th>
<th>Conservative surgery and post-operative medical treatment better</th>
<th>Conservative surgery only better</th>
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</thead>
<tbody>
<tr>
<td>Hornstein et al. (42)</td>
<td>15/49 25/44</td>
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<tr>
<td>Bianchi et al. (47)</td>
<td>7/31 9/29</td>
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<tr>
<td>Vercellini et al. (46)</td>
<td>19/81 27/74</td>
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<tr>
<td>Muzii et al. (43)</td>
<td>3/33 6/35</td>
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<tr>
<td>Busacca et al. (48)</td>
<td>10/44 11/45</td>
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<td></td>
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</tbody>
</table>

**Common odds ratio**

Breslow-Day = 2.12 ($P = 0.71$)
### Post op medical treatment RCT trials for fertility

**Vercellini et al. Obstet Gynecol Clin N Am 2003**

<table>
<thead>
<tr>
<th>Trial Identifier</th>
<th>Pregnancies / Patients</th>
<th>Conservative surgery only better</th>
<th>Conservative surgery and post-operative medical treatment better</th>
</tr>
</thead>
<tbody>
<tr>
<td>Telimaa et al. (45)</td>
<td>5/40* 3/20</td>
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<tr>
<td>Parazzini et al. (44)</td>
<td>7/36 7/39</td>
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<tr>
<td>Busavica et al. (48)</td>
<td>5/15 6/15</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Common odds ratio**

**Breslow-Day = 0.95 (P = 0.91)**
Effect of medical treatment on IVF outcome
Surrey et al Fertil Steril 2002

Fig. 3. IVF cycle outcomes for patients with endometriosis who were pretreated with a GnRH agonist for 3 months (group I) immediately before controlled ovarian hyperstimulation or undergoing standard controlled ovarian hyperstimulation (group II). $p<0.05$ versus group I (a). (From Surrey ES, Silverberg KM, Surrey MW, Schultcraft WB. The effect of prolonged GnRH agonist therapy on in vitro fertilization-embryo transfer cycle outcome in endometriosis patients: a multicenter randomized trial. Fertil Steril 2002;78:699–704; reprinted with permission from the American Society for Reproductive Medicine.)
IUI and ovarian stimulation in endometriosis

Tummon et al Fertil Steril 1997

Fig. 2. Cumulative proportion of endometriosis patients with live births after undergoing superovulation and intrauterine insemination versus expectant management. (From Tummon IS, Asher LJ, Martin JSG, Tulandi T. Randomized controlled trial of superovulation and insemination for infertility associated with minimal or mild endometriosis. Fertil Steril 1997;68:3-12; reprinted with permission from the American Society for Reproductive Medicine.)
Endometriosis

1. Introduction
2. Genetics
3. Endocrinology
4. Immunology
5. Apoptosis
6. Implantation
7. Diagnosis
8. Medical treatment
9. Surgical treatment
10. Future
Surgical treatment
Surgical treatment
Endometriosis surgical treatment and infertility
Meta-analysis of surgical vs medical management of endometriosis related infertility

Adamson et al AM J Obstet Gynecol 1994
Endometriosis surgical treatment and pain

- Improves pain score in approximately 80% of patients
- Recurrence rate
  - 5-20% per year
  - 50% after 5 years
Endometriosis

1. Introduction
2. Genetics
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7. Diagnosis
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Lack of progress in endometriosis research

- Unknown length of time of disease at the time of diagnosis
- Lack of adequate study design
  - No proper control group easily available
- Endometriosis should be studied in multidisciplinary groups not only on a surgeon perspective
- Endometriosis natural occurrence
  - Humans
  - Non human primates (baboons, cynomolgus monkey, pigtailed macaques, rhesus monkey, de Brazza monkeys)
New medications

- Hormonal treatments
  - SERM
  - Aromatase inhibitors
  - Progesterone antagonists
    - Slayden et al. Hum Reprod 2001
  - Selective progesterone receptor modulators
    - Chwalisz et al. Ann NY Acad Sci 2002
  - GnRH antagonists
New medications

- Non hormonal treatments
  - Selective blockade of TNF-α activity
    *D’Antonio et al. J Reprod Immunol 2000*
  - Interferon α
    *Ingelmo et al. Fertil Steril 1999*
  - Interleukin 12
    *Somigliana et al. Hum Reprod 1999*
  - Loxoribine, lovamizole
    *Keenan et al. Fertil Steril 2000*
  - Anti VEGF
    *Taylor et al. Ann NY Acad Sci 2002*
  - Anti MMPs
    *Bruner et al. JCI 1997*
The rodent model

- **Advantages**
  - Low cost

- **Disadvantages**
  - No spontaneous endometriosis
    - Induced endometriotic lesions are different histologically and clinically in the rodent when compared to spontaneous endometriotic lesions in the primates or the humans
  - Lack of menstrual cycle
The baboon model

- Phylogenetically close to humans
- Reproductive anatomy and physiology are close to humans
- Continuous breeder with cycles throughout the year
- Proven accepted model in
  - cardiovascular and endoscopic surgery
  - endocrinology
  - teratology
  - toxicology
  - contraception
  - placental development
The baboon model

- Strong primates
  - Repetitive blood sampling
  - Complex surgical procedures
- Spontaneous presence of peritoneal fluid
- Direct access to uterine cavity without the need of hysterotomy
- Different stages of spontaneous endometriosis similar to humans
The baboon model

- Allows adequate observations for endometriosis
  - Etiology
  - Natural history
  - Infertility
  - Pain
  - Surgical treatments
  - Medical treatments
    - Prevention
    - Treatment