NEW MEDICAL THERAPIES FOR ENDOMETRIOSIS

William D. Schlaff, M.D.
Professor and Vice-Chairman
Department of Ob-Gyn
University of Colorado
Health Sciences Center
Denver, CO
Dr. Schlaff discloses the following relationships within the past 2 years:

Consultant: Pfizer, Solvay
Sponsored research: Organon, Wyeth, Pfizer
MEDICAL TREATMENT OF ENDOMETRIOSIS

PSEUDO-PREGNANCY (OVULATION SUPPRESSION)

– OCP’s
– Progestins
– Danazol
– GnRH analogs
MEDICAL TREATMENT OF ENDOMETRIOSIS

Approach to treatment has traditionally been indirect, i.e. suppression of ovulation. Is the future of treatment evolving?
ENDOMETRIOSIS IS DIFFERENT FROM ENDOMETRIUM

• Lesions differ histologically from endometrium obtained from the same patient at the same time.
• Lesions obtained at the same time commonly differ histologically from each other.
Endometrium was obtained at various stages of the menstrual cycle from nonmenopausal fertile controls and compared to peritoneal endometriotic lesions from women undergoing laparoscopy for pain (n=10) or infertility (n=20)

ENDOMETRIOSIS IS DIFFERENT FROM ENDOMETRIUM

- Maximal proliferation of endometrium is in the proliferative phase and decreases throughout the secretory phase. Proliferative activity in endometriosis tissue was less than in endometrium and constant throughout the cycle.

- ER and PR in endometrium highest in the proliferative phase.

ENDOMETRIOSIS IS DIFFERENT FROM ENDOMETRIUM

• ER and PR did not vary during the cycle in endometriotic lesions
• PR receptors were higher in endometriotic lesions than endometrium
• Endometriotic lesions demonstrated less apoptosis which could promote the dissemination and implantation of these cells to ectopic sites

ESTROGEN RECEPTORS AND ENDOMETRIOSIS

13 baboons underwent experimentally induced endometriosis by peritoneal injection of menstrual endometrium

- ER alpha and PR expressed in both endometrium and endometriosis from 1 to 10 months after inoculation
- ER beta was also expressed at all stages, but only in ectopic endometriotic lesions
- Aromatase expression was only evident in lesions 10 months after inoculation

Fazleabas et al, Fertil Steril, 2003; 8820-8827
Anastrozole, an aromatase inhibitor, decreases conversion of androgen to estrogen in endometriotic cells

- 16 patients with endometriosis randomized to receive either Anastrozole or Danazol for 3 months

- Both Anastrozole and Danazol reduced levels of aromatase activity (equally)

- Luteal phase progesterone reduced with Danazol but increased with Anastrozole

Moegini et al, Abstract 0-38, World Congress on Endometriosis, 9/05
Ovarian endometrioma cyst tissue (n=22) and endometrium (n=13) were obtained from women undergoing endometriosis surgery:

- ER and PR expression varied in ectopic vs. eutopic endometrium; RU-486 down-regulated ER and PR in both tissues.
- “Different steroid receptor expressions indicate different hormonal regulation between endometriotic and endometrial cells.”

Jiang et al. 2002 Fertil Steril. 77:995-1000 (China)
CLINICAL APPLICATION OF ANGIOGENESIS INHIBITORS

• Vascular endothelial growth factor (VEGF-A) is the most abundantly expressed angiogenic factor in human endometrium.

• Anti (human) VEGF-A antibody (Avastin, Genentech, San Francisco, CA) has been shown in concept to be effective in treatment of human cancer

Ferrara, Semin Oncol, 2002. 29 (Suppl16);10-14
ANGIOGENESIS INHIBITORS AND ENDOMETRIOSIS

- Proliferative endometrium obtained from laparoscopy performed in 6 women with normal ovulatory cycles and transplanted into a nude mouse model
- Angiostatic compounds (anti-human VEGF, TNP-470, endostatin, and anginex) inhibited angiogenesis and reduced growth and proliferation of established endometriosis
- Overall health of the mice unaffected

Nap, et al, JCEM 2004;1089-1095 (Maastricht, Netherlands)
Anti-angiogenic factors (anti-human VEGF-A) dramatically reduced the effectiveness of inoculating cultured endometrium into the nude mouse model.

Could this be a potential approach to reducing recurrence in surgically treated women or reducing the risk of developing endometriosis in women at risk?

FUTURE DIRECTIONS IN DIAGNOSIS

- PCR analysis for estrogen beta and progesterone receptors showed an increase in menstrual blood samples of women with endometriosis compared to controls.
- No difference in peripheral blood levels

Kissler et al, abstract PA.3, Ninth World Congress on Endometriosis 9/05
FUTURE DIRECTIONS IN DIAGNOSIS

PCR performed on whole blood obtained from 132 Japanese women with surgically confirmed endometriosis and compared to umbilical cord blood from Japanese female infants.

Polymorphisms in the estrogen receptor beta gene but not the alpha gene are associated with an increased risk of developing endometriosis.

PROGESTIN TREATMENT
Mechanisms of Action

INDIRECT EFFECTS
Suppression of ovulation
Decidualization and atrophy

DIRECT EFFECTS
Inhibition of angiogenesis
Inhibition of matrix metalloproteinases
Suppression of intraperitoneal inflammation
  --reduction of intraperitoneal macrophages
  --increase in natural killer cells
MIRENA INTRAUTERINE DEVICE

• Delivers levonorgestrel directly into the uterine cavity at a steady rate of 20 ug/day over a 5 year period
• Systemic levels of levonorgestrel are lower than achieved with oral administration
• Use of this device has been shown to be effective in reducing menstrual flow in many women
TREATMENT OF ENDOMETRIOSIS WITH MIRENA IUD

34 women with endometriosis confirmed by laparoscopy (stage 1=13, 2=15, 3=6). Mirena inserted at the time of surgery; endometriosis was not treated.

- Continuation rate=85% at 6 mos; 68% at 12 mos; 62% at 24 mos; 56% at 36 mos
- 8/15 removed for persistent pain; remainder removed for acne, weight gain, bleeding, personal reasons

Lockhat et al. 2005, Hum Reprod. 20:789-93 (Leicester, UK)
# TREATMENT OF ENDOMETRIOSIS WITH MIRENA IUD

Lockhat et al, 2005 Hum Reprod 20:789-93, (Leicester, UK)

<table>
<thead>
<tr>
<th>Month</th>
<th>N</th>
<th>VAS</th>
<th>VRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>34</td>
<td>7.7</td>
<td>25</td>
</tr>
<tr>
<td>6</td>
<td>29</td>
<td>4.6</td>
<td>19</td>
</tr>
<tr>
<td>12</td>
<td>23</td>
<td>3.5</td>
<td>14</td>
</tr>
<tr>
<td>18</td>
<td>23</td>
<td>3.2</td>
<td>11</td>
</tr>
<tr>
<td>24</td>
<td>21</td>
<td>2.8</td>
<td>10</td>
</tr>
<tr>
<td>36</td>
<td>19</td>
<td>2.7</td>
<td>8.4</td>
</tr>
</tbody>
</table>

VAS = Visual analog scale. VRS = Verbal rating score
MIRENA IUD AND ANGIOGENESIS

- Vascular endothelial growth factor (VEGF) is a potent angiogenic factor
- Mirena IUD significantly reduced VEGF expression in endometrial glands and stroma when sampled 3 months after insertion (Laoag-Fernandez et al. 2003, Hum Reprod 18:694-9)
- Levonorgestrel levels in peritoneal fluid are similar to serum levels (Lockhat et al. 2005, Fertil Steril 83:398-404)
THE FUTURE MEDICAL OF MEDICAL THERAPY FOR ENDOMETRIOSIS?

DIRECT ACTION, INDIRECT ACTION, OR BOTH?
CONCLUSIONS

• Intensive, collaborative investigation is succeeding in better characterizing the differing biochemical, hormonal, and genetic characteristics of women with endometriosis as well as endometriotic implants.

• Better understanding of these relationships coupled with developing pharmacologic options will allow more focused treatment of endometriosis.
CONCLUSIONS

• While encouraging data have been published, as of yet these factors have not been clearly characterized.

• Recent clinical studies from all over the world provide new and valuable insights, but I do not think we are to the point where these new therapeutic approaches are beyond the pilot stage of development.