Trudy Bush Lecture: Using Progestins in Clinical Practice

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Commercial Disclosure:
I am a consultant on litigation relating to the Mirena IUD

Progestins in Clinical Practice: Outline

• Pharmacology
• Contraception
• Menopausal hormone therapy
• Other non-OB uses
  – Treatment of anovulatory bleeding (DUB)
  – Treatment of endometriosis
  – Infertility due to luteal phase defects

NAMS Definitions

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Full name</th>
</tr>
</thead>
<tbody>
<tr>
<td>ET</td>
<td>Estrogen (E) therapy</td>
</tr>
<tr>
<td>EPT</td>
<td>Combined E+P therapy</td>
</tr>
<tr>
<td>HT</td>
<td>Hormone therapy (ET, EPT)</td>
</tr>
<tr>
<td>MHT</td>
<td>Menopausal hormone therapy</td>
</tr>
<tr>
<td>Progestogen</td>
<td>Progesterone or progestin (P)</td>
</tr>
<tr>
<td>CC-EPT</td>
<td>Continuous-combined E+P therapy</td>
</tr>
<tr>
<td>CS-EPT</td>
<td>Continuous-sequential E+P therapy</td>
</tr>
</tbody>
</table>


Progesterone Physiology

• Three progesterone receptors: A, B, C
• Progestin is not an estrogen receptor antagonist
  – Modifies E action by causing depletion of E receptors
• P-receptor antagonist: mifepristone (RU-486)
  – Affinity of RU 486 for the progesterone receptor is 5 times greater than that of the natural hormone
  – Clinical use: mainly medical abortion
  – Potentially: contraception, endometriosis, induction of labor, syndrome, and various cancers

Fritz and Speroff, Clinical Gyn Endocrinology and Infertility, 8th ed, 2011

FDA Approved Oral Progestins

• 17 acetoxy progestins (aka: pregnanes)
  – Micronized progesterone
  – Medroxy progesterone acetate (MPA)
  – Poorly absorbed, rapidly metabolized, sedating
• 19 nor-testosterone progestins
  – Orally active testosterone derivatives
  – Estranes: norethindrone, norethindrone acetate
  – Gonanes: l-norgestrel, desogestrel, norgestimate
• Drospirenone
  – Spironolactone-like effect
Progestins in Clinical Practice: Contraception

- Mechanism of action
  - Prevent ovulation
  - Thicken cervical mucus
- Products
  - CHCs: OC, contraceptive patch, vaginal ring
  - POMs: progestin only pill, injections, implants
  - IUD: LNG IUS 52 mg (20 mcg/d); LNG 13.5 mg (10 mcg/d)
  - ECP: levonorgestrel 1.5 mg
- Hot topic: role of progestins in DVT rates

Progestins in Contraceptives Clinical Questions

- Venous thromboembolic events (VTE)
  - Do progestins contribute to hypercoagulability?
  - If so, do some progestins have a greater effect than others?
- Other questions
  - Do progestins reduce breast milk quality or quantity?
  - Do progestins cause or worsen depression?

OC “Generations”

- Confusing as reflects changes in both estrogen dose and type of progestin
- Enovid (150 μg mestranol + 9.85 mg norethynodrel) available in 1957 for miscarriages and menstrual disorders
  - 1960= marketed for contraception
  - 1962=Ortho-Novum =“2nd generation”
- Newer formulations less androgenic, less adverse effects on lipid profiles

OCs: Progestins

<table>
<thead>
<tr>
<th>Gen</th>
<th>Metabolite Group</th>
<th>Example</th>
<th>Product Examples</th>
<th>Androgenicity</th>
</tr>
</thead>
</table>
| 2   | Estrane         | Norethindrone
              | Norethindrone acetate
              | Ethynodiol diacetate | Ortho-Novum®
              | Lo-Estrin®
              | Demulen® | Little |
| 2   | Gonane          | Levonorgestrel (dl)
              | Norgestrel
              | Norgestimate | Nordette®
              | Lo-Ovral®
              | TriCyclen® | Moderate |
| 3   | Gonane          | Desogestrel | Desogen®
                                      | OrthoCept® | None |
| 4   | --              | Drosperone | Yasmin®
                                      | Yaz® | Anti-androgenic |

Pro-Drug Metabolism: Progestins

<table>
<thead>
<tr>
<th>Pro-drug</th>
<th>Active metabolite</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norethindrone acetate</td>
<td>Norethindrone</td>
<td>Estrane OC products</td>
</tr>
</tbody>
</table>
| Ethynodiol diacetate | Ortho-Novum®
| | Lo-Estrin®
| | Demulen® |
| Desogestrel | Etonogestrel (3-ketodesogestrel) | Vaginal ring
| | Implant |
| Norgestimate | Norelgestomim | Patch |
Clinical Correlates

- Poor tolerance of gonane or estrane class progestin
  - Switch to an OC from a different class
- Obesity, acne, hirsuitism…PCOS
  - Avoid 1-norgestrel
  - Use a non-androgenic OC: desogestrel, norgestimate
  - Drospirenone OC may be preferred, but is not mandatory

Risk Factors For Venous Thrombosis

- Pregnancy and the post-partum period
- Major surgery with prolonged immobilization
- Older age (especially > 35 years old)
- Obesity (especially BMI >35)
- Personal history of DVT or VTE
- Family history of DVT or VTE
- Inherited thrombophilia (including APL syndrome)
- Inflammatory bowel disease, especially if active
- Systemic lupus with positive or unknown APL
- Current cancer chemotherapy

Figure 1: Likelihood of Developing a VTE

<table>
<thead>
<tr>
<th>Condition</th>
<th>CHC Users</th>
<th>Pregnancy***</th>
<th>Postpartum (12 weeks only)</th>
<th>Non-CHC Users, Non-Pregnant</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ranges: 1 to 5</td>
<td>Ranges: 3 to 12</td>
<td>Ranges from 19 to 50</td>
<td></td>
</tr>
</tbody>
</table>

OC Patient Package Insert

Estrogen and Venous Thrombosis

- Estrogen in CHC methods
  - Increases pro-coagulation factors (Factor VII)
  - Decreases anticoagulant factors (protein C, S, antithrombin III)
  - Fibrinolysis activated; increase in profibrinolysins and a decrease in antifibrinolysins
  - The effect is analogous to revving the engine of a car and applying the brakes at the same time
- VTE in OC users is due to failure of mechanisms that maintain necessary balance in the system

Estrogen and Venous Thrombosis

- Timing
  - Increased within 4 months of starting OC
  - Resolved within 3 months of stopping OC
  - VTE risk declines with increasing duration of use
- No attributable risk of fatal VTE in OC users
- HTN, hypercholesterolemia, and diabetes not risk factors for venous disease
Progestins and Venous Thrombosis
First Wave Of Fear

Mid-1990s
- Desogestrel or gestodene
- “2-3x VTE risk” of levonorgestrel


Bias Due To Preferential Prescribing

- Mixing of new starters and continued users
  - Starters more likely to be prescribed newer products
    - More “first year of use” effect
  - Healthy user effect (aka: attrition of susceptible)
    - Women who did well on older OCs were counted in control group; less “first year of use” effect
- Preferential prescribing
  - Newer pills to given to higher risk, older women due to perception that newer pills are better/safer


Recap: Desogestrel Controversy

- In 2007, 52 dockets calling for a ban on desogestrel were filed with the FDA...
- VTE risk attributable to desogestrel
  - 1 to 2 per 10,000 women-years of use
- Desogestrel COCs remain on market

Progestins and Venous Thrombosis
Second Wave Of Fear

Drospirenone (DRSP) compared to 2nd Generation progestins

Drospirenone (DRSP)

- Synthetic progestin
- Anti-androgenic properties
- Analog of spironolactone
  - Diuretic effect at OC dose approx. equivalent to spironolactone 25mg
- Marketed in the US since 2001
  - Prevention of pregnancy
  - Treatment of moderate acne
  - Treatment of premenstrual dysphoric disorder
  - Treatment of hirsutism/PCOS

Drospirenone Controversy...

December 2011

- FDA advisory panel vote: “in the general population of women desiring contraception, do the benefits of drospirenone-containing OC for prevention of pregnancy outweigh the risks?”
  - YES (vote: 15 to 11)
- Labels should highlight risks of VTE (vote: 21 to 5)
- Drospirenone OC remain on the market
ACOG Statement of DRSP OCs

- Decisions regarding the choice of OCs should be left to clinicians and their patients, taking into account the following factors
  - Slightly increased absolute risk of VTE
    - DRSP: 10 /10,000 woman-years
    - Other OCs: 3–9 /10,000 woman-years
  - Patient preference
  - Available alternatives

ACOG Committee Opinion #540. Obstet Gynecol 2012; 120:1239

International Active Surveillance Study, 2014

- Prospective observational new-user cohort
  - Pharma funded
  - 85,109 women, followed for 2-6 years
  - 22% new-users of COC
  - 142,475 woman years of observation
  - Loss to follow-up 3.3%


Different COCs And The Risk Of VT: Systematic Review And Network Meta-analysis

- Combining different preparations of OCs into generations may not be an appropriate way to present the risk of thrombosis, because the risk depends on the dose of EE as well as on the progestogen provided
- We suggest abstaining from any classification of contraceptives, but to compare the risk of venous thrombosis per OC preparation

Stegeman B, BMJ Sept 2013;347:f5298
FDA Approved Modification in NuvaRing Labelling 10/2013

- Two well done epidemiologic studies assessed the risk of VTE associated with the use of contraceptive vaginal ring (CVR)
- In these studies, which were required or sponsored by regulatory agencies (the FDA), CVR users had a risk of VTE similar to combined OC (COC) users

FDA Approved Modification in NuvaRing Labelling 10/2013

A large prospective, observational study, TASC, investigated the risk of VTE for new users of NuvaRing and women starting, switching to, or restarting OCs

- Women were followed for 24 to 48 months
- Similar incidence of VTE events per 10,000 WY
  - CVR users 8.3
  - Using COCs 9.2
  - Using COCs (except desogestrel) 8.9

FDA Approved Modification in NuvaRing Labelling 10/2013

- A retrospective cohort study using data from 4 health plans in the US (Kaiser/Medicaid)
- Sidney S, Contraception. 2013; 87(1):93-100
- Incidence of VTE events per 10,000 WY
  - New users of CVR 11.4
  - New users of a LNG COC 9.2
  - Users of other available COCs 8.2

Summary: Venous Disease and CHC

- All low-dose OCs, regardless of progestin type, have an increased risk of VTE in the first 1–2 years of use
- The actual risk of VTE with low-dose OCs is lower in the new studies compared with previous reports
- The risk increases with increasing age and body weight
- Smoking has a lesser effect on the risk of VTE compared with arterial thrombosis

Fritz and Sperooff, Clinical Gyn Endocrinology and Infertility, 8th ed, 2011

Venous Risks: Messages for Clinicians

- Some studies show that VTE risk is slightly higher with CVR, compared to a variety of OCs; others do not
  - The best prospective study: no greater risk than OC
- The increased risk is confined to the first year of use
- If using Patch, CVR, or DRSP OC, no need to discontinue
- Place in context of DVT risk in pregnancy and postpartum
- While there has been a voluntary label change of the CVR, there are NO new FDA restrictions

Venous Risks: Advice to Clients

- There are many contraceptive choices available to you
- Discuss your medical history with your provider to determine if there are reasons not to use a method
- The risk of VTE in CVR users is similar to OC users
- DVT risk with all combined hormonal contraceptives
  - Is less than in pregnancy
  - Far less than the post-partum period
- The absolute risk of a DVT is very low
Summary: VTE Risk and Combined Hormonal Contraception

- More than baseline risk and much less than pregnancy
- Pharmacologic profile
  - Estrogen dose + progestin product
  - Estrogen effect much stronger than progestin effect
  - Unique to each E+P combination (not P generation)
  - Ring and Patch VTE risks similar to OCs
- Mainly in women predisposed to VTE
- Mainly in the first year of use

Contraceptives With NO Increased Risk Of VTE

- LNG Intrauterine contraceptive (Mirena®, Skyla®)
- Contraceptive implant (Nexplanon®)
- Contraceptive Injection (DMPA; DepoProvera®)
- Progestin only pills (norethindrone; Micronor®)
  are usually more effective!

Lidegaard et al BMJ. 2011 Oct 25;343:d6423

Progestins in Clinical Practice: Menopausal Hormone Therapy

- Mechanism of action
  - Prevent endometrial hyperplasia by reducing endometrial E receptors in women using systemic E
  - P generally not indicated with local ET for GSM
- Clinical use (in a woman with a uterus)
  - Continuous combined (continuous E + P)
  - Continuous sequential (continuous E, cycle P)
  - Progestins alone
- Hot topic
  - Contribution of P to breast cancer risk

Progestogen Indication

- Primary menopause-related indication for progestogen use is endometrial protection from systemic ET
- Adequate progestogen recommended for women with an intact uterus using systemic ET

NAMS Position Statement Menopause 2012;19:257-71

Hormone Therapy Regimens

<table>
<thead>
<tr>
<th>Month 1</th>
<th>Month 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrogen Therapy (ET)</td>
<td>Estrogen</td>
</tr>
<tr>
<td>Estrogen</td>
<td>Progestin</td>
</tr>
<tr>
<td>Continuous combined (CC) EPT</td>
<td>Continuous-sequential (CS) EPT</td>
</tr>
<tr>
<td>Estrogen</td>
<td>Progestin</td>
</tr>
<tr>
<td>Progestin 14d</td>
<td>Off for 14 d</td>
</tr>
<tr>
<td>Continuous-pulsed (CP) EPT</td>
<td></td>
</tr>
</tbody>
</table>

Choice of HT Regimen

- If no uterus: estrogen only
- If uterus present
  - Goal is to avoid vaginal bleeding entirely, or, at least, to make it predictable
  - Endometrial activity predicts bleeding pattern
  - Recent spontaneous or induced bleeding
    - Use continuous sequential
  - No bleeding for >2-3 cycles
    - Use continuous combined
**HT Starting Dosages**

- Typical lowest doses of progestogen
  - 1.5 mg oral MPA
  - 0.1 mg oral norethindrone acetate
  - 0.5 mg oral drospirenone
  - 50-100 mg oral micronized progesterone
- Lower daily doses typically used with systemic ET
  - 0.3 mg oral CE
  - 0.5 mg oral micronized 17β-estradiol
  - 0.014-0.025 mg transdermal 17β-estradiol patch

**Progestin Equivalence**

- In the continuous combined regimen, progestins are combined with estrogen in comparable dosages
  - 1.5 or 2.5 mg medroxyprogesterone acetate
  - 0.5 or 1.0 mg norethindrone acetate
  - 0.35 mg norethindrone
  - 2 mg drospirenone
  - 100 mg micronized progesterone

**HT and Breast Cancer: Pre-WHI**

- Case-control and cohort studies have reported an increased risk of breast cancer associated with hormone therapy, greater with combined estrogen-progestin.
- The reported increased risks of breast cancer associated with HT are due to ER-positive tumors, perhaps mostly tumors with lobular tissue
- An increased risk of breast cancer is observed only in current users and is detected relatively rapidly

**Women’s Health Initiative (WHI)**

- 1993-2005: RCT with 17,000 women
- Postmenopausal women 50-79 years old
  - 33%: 50-59 yrs old; 45%: 60-69 yo; 22% 70-79 yo
  - Average age: 64 years old
- End points
  - Primary prevention of MI and stroke
  - Hip fracture, various cancers
- Treatment arms
  - If uterus: CC-EPT (CEE+MPA) vs. placebo
  - If no uterus: ET (CEE) vs. placebo

**WHI: EPT Arm Study Results**

Released July 2002: Findings after 5.2 years

<table>
<thead>
<tr>
<th>Event</th>
<th>RR</th>
<th>Attributable Risk /10K/yr</th>
<th>Benefit/10K/yr</th>
<th>Number needed to harm or benefit/ year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart attack</td>
<td>1.29</td>
<td>7</td>
<td>1,100</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>1.41</td>
<td>8</td>
<td>1,200</td>
<td></td>
</tr>
<tr>
<td>Breast CA</td>
<td>1.26</td>
<td>8</td>
<td>1,300</td>
<td></td>
</tr>
<tr>
<td>TE event</td>
<td>2.11</td>
<td>18</td>
<td>600</td>
<td></td>
</tr>
<tr>
<td>Colorectal CA</td>
<td>0.63</td>
<td>6</td>
<td>1,700</td>
<td></td>
</tr>
<tr>
<td>Hip fractures</td>
<td>0.66</td>
<td>5</td>
<td>2,000</td>
<td></td>
</tr>
</tbody>
</table>

Discontinued early, as “risks greater than benefits”

Writing Group for WHI, JAMA. 2002;288:321-333

**WHI: ET-Only Study Arm**

Released 2004: Findings after 7 years

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Change vs. Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary heart disease</td>
<td>No difference in risk</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>No difference in risk</td>
</tr>
<tr>
<td>Stroke</td>
<td>Increased risk</td>
</tr>
<tr>
<td>Hip fractures</td>
<td>Decreased risk</td>
</tr>
<tr>
<td>Dementia, cognitive change (&gt; 65 years old)</td>
<td>Trend toward increased</td>
</tr>
</tbody>
</table>

**Risks: HT and Breast Cancer**

- Conventional wisdom
  - Estrogen may be a weak promoter, but not an initiator, of breast cancer
  - Based on finding of the Women's Health Initiative, progestogens may add a further degree of risk
  - Women with a history of breast cancer should not use estrogen or progestin as it may cause recurrence of tumor


**Can The EPT vs. ET Arms of the WHI Be Compared?**

- WHI investigators cautioned against comparing the two arms, as participants differed considerably
- Women in the ET arm had a higher rate of previous exposure to hormones and for longer durations of use
  - Earlier and greater use of HT before the study identified those with pre-existing tumors who were then excluded
- The WHI does not allow us to answer whether EPT has a greater risk of breast cancer or whether pre-existing tumors respond differently to various hormone regimens


**EPT vs. ET and Breast Cancer**

- The relative risk of breast cancer is higher in users of EPT compared to ET
- The increased risk is observed sooner with the use of combined EPT regimens
- Confined to ER+, PR+ tumors, mainly lobular cancers
- May reflect early detection of better differentiated tumors, a consequence of a favorable response of pre-existing tumors to EPT exposure


**EPT vs. ET and Breast Cancer**

- Studies reflect an effect of HT on pre-existing tumors
- Hormone users who develop breast cancer have a reduced risk of dying because their tumors are better differentiated, more localized, and smaller
- Contrary to the prevailing belief, EPT may cause *greater differentiation* and earlier detection of pre-existing tumors, resulting in better outcomes


**Progestins in Clinical Practice: Other non-OB uses**

- Treatment of anovulatory bleeding (DUB)
- Treatment of endometrial hyperplasia
- Treatment of endometriosis
- Infertility due to luteal phase defects
Oral MPA and COCs for Acute Uterine Bleeding

- 40 women with non-anatomic AUB randomized to
  - MPA 20 mg TID x1 week, then QD for 3 weeks vs.
  - COC (1 mg nor + 35 mcg EE) TID x1 week, QD x3 weeks
- Results
  - Median time to bleeding cessation was 3 days
  - Cessation in 88% OC group, 76% in MPA group
  - Surgery avoided in 100% MPA, 95% COC subjects
  - Compliance similar in both groups
  - “Would use again”...81% MPA, 69% COC

Munro MG, et al Obstet Gynecol 2006;108:924-9