PROGESTERONE
PROGESTINS
SPRMS:
WHAT THEY ARE AND
HOW TO USE THEM

Kirtly Parker Jones MD

DISCLOSURES

none

Objectives

- Counsel patients on the physiologic effects of progesterone and progestins, their risks, side effects, and benefits
- Prescribe progestin only contraceptives to meet patient expectations with respect to their effect on menstrual bleeding patterns and breakthrough bleeding
- Prescribe the safest progestin for use in HRT
- Prescribe selective progestin receptor modulators where appropriate
Question 1

- In 2012, "Natural" Progesterone is made from the corpora lutea of pregnant sows
  - 1. True
  - 2. False

Question 2

- Progesterone is effective in decreasing the effect of traumatic brain injury
  - 1. True
  - 2. False
Question 3

- Ulipristal is
  1. a potent progestin
  2. a complete progestin antagonist
  3. a selective progestin receptor modulator
  4. a potent abortifacient

"THE VAST MAJORITy OF SCIENTISTS PAY LITTLE ATTENTION TO SCIENTIFIC HISTORY"

Carl Djerassi 1992

History of our knowledge

- Natural historians knew of the "yellow body" (corpus luteum) in the ovary that was associated with pregnancy in animals
- Previous names included "luteotropin"
- Some smart pig farmer noticed that the number of yellow bodies correlated with the number of piglets…. 
German biochemists, sausage, and pigs

History of our knowledge

- Progesterone was isolated and characterized before estradiol in the early 1900's
**What is a Progestin**

- A progestin is a molecule that binds to the progesterone receptor and has more or less activation of DNA domains that are activated or suppressed by the receptor/molecule complex.
- (more than you wanted to know….huh?)

**Progesterone receptor, (PR), NR3C1, 11q22, with two main forms, A and B, that differ in their molecular weight, PRB contributes to epithelial growth, Polymorphisms predict responses to therapy.**

**What does Progesterone do?**

- Progesterone is a smooth muscle relaxant
- It causes glands to secrete and stroma to become thickened in the endometrium
- It suppresses the estradiol receptor
- It proliferates cells in the breast lobules
- It binds to GABA receptors in the
What does Progesterone do?

- In humans, progesterone primes the endometrium to make prostaglandins - so when progesterone falls, local prostaglandins are made in the decidua, the blood vessels and myometrium contract, and ... 
- A hormonal D&C that we call a menstrual period occurs
Progesterone causes LH Surge

- Rising progesterone by the follicle may actually cause the LH surge
- Selective Progesterone receptor modulators (like ulipristal) may block ovulation

Progesterone as chemotactant

- Sperm "smell" their way to the egg
- Progesterone made by cumulus cell release progesterone and sperm may find their way to the egg by following an increasing progesterone gradient
- (until the cervical mucous gets too thick for it to get through….it is magic, isn't it?)
PROGESTINS

- **THE ONLY** disease for which progestin-only methods were a MEC category 4: current breast cancer and the data there are poor
- Count on the Canadians’ common sense - “Use of the LNG* ius in the breast cancer survivor may be considered if the unique contraceptive and non-contraceptive benefits outweigh the risk of an unknown effect on recurrence” (same for DMPA and minipill)

SOGC/GOC JOINT CLINICAL PRACTICE GUIDELINES: PROGESTIN ONLY AND NON-HORMONAL CONTRACEPTION IN THE BREAST CANCER SURVIVOR 2006

Progestin Only Methods

- "Mini Pill" – low dose progestin – usually norethindrone
- DMPA – high dose systemic progestin
- Levonorgestrel IUD
- Etonorgestrel implant
- Levonorgestrel implant

ALL DIFFERENT MECHANISMS OF ACTION
WITH DIFFERENT EFFICACY AND SIDE EFFECTS

Highly Effective
Protective against ectopic pregnancy
Possibly protective against PID
Decreases menstrual/uterine blood loss
Causes amenorrhea in >20% of users
Safe, long lasting, convenient

Advantages of LNG-IUD

Adapted from Contraceptive Technology 2004
Subdermal Implant
etongestrel (a desogestrel metabolite)

PROGESTIN ONLY – NOT THE SAME

<table>
<thead>
<tr>
<th>METHOD</th>
<th>ENDOMETRIUM</th>
<th>PITUITARY/ OVARIAN SUPP</th>
<th>ESTRADIOL</th>
</tr>
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<tbody>
<tr>
<td>MINI PILL</td>
<td>+/-</td>
<td>+/-</td>
<td>NORMAL</td>
</tr>
<tr>
<td>DMPA</td>
<td>VERY SUPPRESSED</td>
<td>VERY SUPPRESSED</td>
<td>SUPPRESSED</td>
</tr>
<tr>
<td>LEVONORGESTREL REL</td>
<td>VERY SUPPRESSED</td>
<td>NOT SUPPRESSED</td>
<td>NORMAL</td>
</tr>
<tr>
<td>ETONORGESTREL EL</td>
<td>+/-</td>
<td>OVARULATION SUPP</td>
<td>NORMAL</td>
</tr>
<tr>
<td>MINI ANT LEVONORSTRE</td>
<td>+/-</td>
<td>+/-</td>
<td>NORMAL</td>
</tr>
<tr>
<td>REL</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CHC - Tolerance of Progestin BTB

- It is hard to predict which uterus is going to bleed unpredictably on continuous progestins
- It is hard to predict which woman is not going to tolerate break through bleeding
- With all of the progestin only methods, break through bleeding is quantitatively less than normal cyclic bleeding
- There are cultural differences in the tolerance to amenorrhea and BTB (including the culture of teens)
Progestins and Ovulation Suppression

<table>
<thead>
<tr>
<th>Progestin</th>
<th>Dose</th>
</tr>
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<tbody>
<tr>
<td>Levonorgestrel</td>
<td>.05 mg</td>
</tr>
<tr>
<td>Megestrol</td>
<td>2.5 mg</td>
</tr>
<tr>
<td>Norethindrone</td>
<td>5-10 mg</td>
</tr>
<tr>
<td>Megestrol</td>
<td>2.5 mg</td>
</tr>
<tr>
<td>Levonorgestrel</td>
<td>.05 mg</td>
</tr>
</tbody>
</table>

Clinical uses for progestins

- Contraception
- Diagnostic tool in evaluating amenorrhea
- Treatment for precocious puberty
- Hirsutism
- Treatment for dysmenorrhea and mittleschmertz
- Treatment for vasomotor flushes
- Inadequate luteal phase (?)
- Premature labor

Clinical Uses for Progestins

- Suppression of functional ovarian cysts
- Honeymoons, sporting events, beauty pageants
- Threatened abortion (???)
- Endometriosis
- Anovulatory bleeding
- Treatment/prevention of endometrial hyperplasia
- PMS/PMDD
- Male sex offenders
Clinical Uses of Progesterone

- Replacement in IVF cycles
- Replacement after removal of corpus luteum of pregnancy
- Prevention of preterm labor
- Endometrial protection with postmenopausal hormone replacement
- Progesterone decreases traumatic/hypoxic brain injury

Progesterone for Pregnancy

- Luteal phase deficiency – not clear that it exists in spontaneous cycles but we create it in IVF cycles
- Prevention of spontaneous abortion – no good randomized trials - but is necessary if corpus luteum surgically removed before 8 weeks
- Prevention of preterm labor

Preterm Rates in Progesterone vs Control

HRT – THE PROGESTIN WARS

- MPA is an American habit – it is highly effective in suppressing the endometrium and cheap
- The PEPI trial suggested that progesterone had a more favorable impact on lipids
- Norethindrone is making headway into HRT and has been used for years in Europe
- Other progestins are on the way (mini levo IUD, progestin ring, desogestrel for use in HRT, etc
- (Progesterone cream and yam cream......sigh)

The Ideal progestin for HRT

- Protect the endometrium
- Have no adverse physical, psychological, or metabolic effects
- Would not increase the risk of breast cancer
- Would be orally active
- Would be cheap
- (would make you happy, lose weight, improve your libido and your skin tone)
Tibolone

- Synthetic steroid that binds to estrogen, progesterone and testosterone receptors
- Has agonist activities with all these receptors
- Available in Europe

- Protects the endometrium
- Increases bone density
- Decreases hot flushes
- Increases libido
- Better bleeding profile (less bleeding) than continuous estrogen and MPA
- (FDA didn’t like it as high dose increased cholesterol)

How Would and REI Take Progestin

- Hmmm….that’s a tough one
- Probably progesterone (for limited improvement in lipid profile)
- Probably continuously (new data on very significant increase in relative risk of uterine cancer with long interval cyclic progestins (any less frequently than monthly is not frequent enough)
- Progestin options will be increasing (new chemistry, new formulations)
Endometrial Cancer: Estradiol-Progestins

- Finnish Cancer Registry: 224,015 women who used estradiol-progestin therapy for at least 6 months
- Continuous therapy for 5 or more years – 76% reduction (10,759 women: 12 cancers observed, 33 expected)
- Sequential monthly progestin 5 years – 69% increase (25,582 women: 152 cancers observed, 90 expected)
- Sequential q 3 month progestin 5 years – 276% increase (3500 women: 65 cancers observed, 17 expected) Jaakkola et al. Obstet Gynecol 2009

Bleeding that predicts pathology?

Jaakkola et al. Maturitas 2000

Progestin Frequency and Endometrial Cancer

Jaakkola et al, Obstetr Gynecol 2009
**Bioidenticals** are available in FDA approved forms

2. Compounding pharmacy forms are not safer

3. Saliva testing is unreliable and lack standards

4. Critical window of safety for HRT

5. Progestins appear to play a role in breast Ca risk

6. Stay tuned

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**RR of Invasive Breast CA in HT Progestin Users**

<table>
<thead>
<tr>
<th>Progestin</th>
<th>Route</th>
<th>Women-years</th>
<th>RR</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progesterone</td>
<td>TDerf</td>
<td>35,513</td>
<td>1.08</td>
<td>0.89-1.31</td>
</tr>
<tr>
<td>Medroxyprogesterone</td>
<td>Oral</td>
<td>7,035</td>
<td>1.48</td>
<td>1.02-2.16</td>
</tr>
<tr>
<td>Norethindrone Acetate</td>
<td>Oral</td>
<td>7,401</td>
<td>2.11</td>
<td>1.56-2.86</td>
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<tr>
<td>Dydrogesterone</td>
<td>TDerf</td>
<td>25,405</td>
<td>1.18</td>
<td>0.95-1.48</td>
</tr>
<tr>
<td>Nomegestrol Acetate</td>
<td>TDerf</td>
<td>18,826</td>
<td>1.60</td>
<td>1.28-2.01</td>
</tr>
<tr>
<td>Promegestone</td>
<td>TDerf</td>
<td>14,910</td>
<td>1.52</td>
<td>1.19-1.96</td>
</tr>
</tbody>
</table>


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**MOTHER’S LITTLE HELPERS**

- PMB (Premarin and meprobamate – a tranquilizer)
- Menrium – chlordiazepoxide and esterified estrogens
- Medriatic – conjugatedestrogen, methyltestosterone, multivitamins and minerals, methamphetamine
Progesterone and Sleep

- Progesterone improves sleep quality in menopausal women directly as a gaba agonist
- Progesterone does NOT act as a sedative hypnotic – it promotes “normal” sleep
- Progesterone decreases sleep disordered breathing
- Progesterone decreases hot flushes (not as much as estradiol…)

Spark MJ. Maturitas 2012
Caufrez A et al. JCEM. April 2011

Progestins for EC

- 1974 Yuzpe demonstrates efficacy of high dose (EE and levonorgestrel) for EC
- 1998 Preven (COCs packaged for EC
- 1999 – progestin only (levonorgestrel) Plan B marketed with less side effects
- 2006 FDA approves Plan B for OTC for women over 17 (by Rx for women <18)

SPRMS

- Selective progesterone receptor modulators
- Tibolone could be considered in this class
- Mifepristone
- Ulipristal
Mifepristone

- Originally formulated as a cortisol receptor antagonist – has strong progesterone antagonist activity and moderate cortisol receptor antagonist
- Use for Cushing’s Syndrome, some brain tumors, induction of labor, etc… but use as an antiprogestrone for medical abortion became the primary use

- By occupying the progesterone receptor but not activating the DNA pathway, it signals progesterone withdrawal, prostaglandins production, uterine arteriospasm and myometrial contractions leading to… menses, abortion, labor depending on when it is used
- Mifepristone is a potent emergency contraceptive but is marketed in low dose for EC only in China
Ulipristal

- Selective progesterone receptor antagonist
- Primary mechanism of action is thought to be blocking the progesterone mediated LH surge and ovulation
- When given prior to LH surge is effective in blocking ovulation
- May also block ovulation (postpone ovulation for several days) if given during LH surge

Follicular rupture was postponed for 5 days in 8/8 women who had a dominant follicle but had not started LH Surge
Follicular rupture was postponed for 5 days in 11/14 women in whom the LH surge had begun

Brache V et al. Human Reproduction 2010

Probably will not work if you have already ovulated
- Although marketed to work up to 5 days after intercourse, that is ONLY if the woman hasn’t ovulated yet
- Women should still take it ASAP
- Available only by RX
Meta analysis suggests that ulipristal is superior to levonorgestrel at 72 hours and at 120 hours after unprotected intercourse.

It won’t work if women still have unprotected intercourse in the weeks to come......

Glasier A et al. Lancet. 2010
POST COITAL CONTRACEPTION

THE FUTURE WELFARE OF HUMAN KIND RESTS MORE HEAVILY AT THIS POINT IN HISTORY ON THE PROGESTINS THAN IT DOES ON ATOMIC WEAPONS

ROY O. GREEP 1976
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