Low Systemic Levels of Segesterone Acetate Are Required to Inhibit Ovulation in Women

David F Archer, MD1; Regine Sitruk-Ware, MD2; Sebastian Mirkin, MD3; Vivian Brache, BS4; Ruth B Merkatz, PhD2; Narender Kumar, PhD2

1Eastern Virginia Medical School, Norfolk, VA, USA
2Population Council, New York, NY, USA
3TherapeuticsMD, Boca Raton, FL, USA
4Profamilia, Santo Domingo, Dominican Republic
Disclosures

Dr. Archer

• Consultant: AbbVie, Actavis, Agile Therapeutics, Bayer Healthcare, Endoceutics, Exeltis, InnovaGyn, Merck, Pfizer, Radius Health, Sermonix, Shionogi, Teva Women’s Healthcare, and TherapeuticsMD

• Research support: Actavis, Bayer Healthcare, Endoceutics, Glenmark, Merck, Radius Health, Shionogi, and TherapeuticsMD

Dr. Mirkin

• Employee: TherapeuticsMD with stock/stock options

Drs. Sitruk-Ware, Merkatz, and Kumar

• Employees: Population Council

Dr. Brache

• No conflicts of interest
Unintended Pregnancy Is a Costly Global Issue

• Worldwide rate of unintended pregnancy in 2012 was 53 per 1,000 women aged 15-44\textsuperscript{1}

• Up to 51% of US pregnancies unintended\textsuperscript{2,3}
  • No significant decline since 1982\textsuperscript{2}

• Staggering costs\textsuperscript{4}
  ~1 million unplanned births in US publicly funded in 2010

---

Consequences of Unintended Pregnancy

• Not only an economic concern
• Higher proportions of unintended pregnancies observed among adolescents, young women, racial or ethnic minorities, and lower income and/or education level\(^1\)
• Negative impact on health of infant, child, and parental health\(^2\)

Overcoming Barriers: Improve Access

• All women must have access to a variety of safe and effective methods
  • Address underserved populations, eg, college-aged women and women without immediate post-partum contraception
  • Minimize barriers to emergency contraception
  • Increase use of long-acting reversible contraception (LARC)
    • Underutilized as a first-line option (<5%)
• Poor patient adherence and intolerance of side effects can lead to nonuse
  • Explore novel methods and formulations to improve uptake

Overcoming Barriers: Novel Methods, Improved Safety

• Numerous oral, transdermal, injectable/implantable/insertable and intrauterine devices are available\(^1\)
  • Progestin-only or (more commonly) hormonal combination products\(^2\)
• Combined hormonal contraceptives (CHCs) are FDA approved as safe and effective
  • Venous thromboembolism (VTE) is rare in young CHC users\(^2\)
• Novel methods and/or safer formulations could improve patient convenience and adherence
  • Modify estrogen dose and type in CHC\(^2\)
  • Select new progestins closer to progesterone\(^2\)
  • Develop and/or improve alternate, non-oral routes of delivery\(^2\)

Segesterone Acetate

• Highly specific progestin with selective binding to progesterone receptor (PR)\(^1\)

• Prevents ovulation through inhibition of luteinizing hormone (LH) secretion with no effect on LH synthesis\(^2\)

• Low dose is highly potent with parenteral delivery, but inactive with oral administration due to extensive first-pass metabolism\(^3\)

• No interaction with SHBG, or estrogen or androgen receptors\(^1\)

• No androgenic activity and antiestrogenic\(^1\)

Formerly referred to as Nesterone® or ST 1435

Segesterone Acetate/Ethyl Estradiol Contraceptive Vaginal System (SA/EE CVS)

- Only SA-containing contraceptive method available
- Convenient 21-day in/7-day out cycle that can be reinserted up to 13 cycles (1 year)
- Effective ovulation suppression for up to 1 year with low hormone levels
- Does not need to be removed during sex
- Does not require refrigeration

- 8.4 mm in cross section
- 56 mm in diameter
- 2 x 27mm long/3mm wide
- Total drug load = 103 mg SA/17.4 mg EE
- Daily release rate = 0.15 mg SA/0.013 mg EE
Progestational Activity of SA and Other Progestogens

Relative potencies of synthetic progestogens on standard bioassays assessing each’s ability to transform endometrium in rabbits and to inhibit ovulation in rats.

SA 100 > LNG 10 > Progesterone 1
SA 30 > LNG 10 > Progesterone 1

SA is 10-times more potent than levonorgestrel and 100 times more potent than P4.

CPA: cyproterone acetate; DSG: desogestrel; LNG: levonorgestrel; MPA: medroxyprogesterone acetate; NET: norethisterone; NOM Ac: nomegestrol acetate; TMG: trimegestone.
SA-containing Subdermal Implants

- Dose-dependent increase in SA levels (Figure)$^1$
- All doses inhibited ovulation in 11 women given different doses for up to 2 years$^1$
  - Serum progesterone $<2$ pg/mL
- E2 levels ($>100$ pmol/L)$^2$ indicated some ovarian activity$^1$
- No pregnancies$^1$
- Variable bleeding control$^1$

SA-only Vaginal Rings

- SA levels were high the first day, gradually declined, and then remained stable (~125, 200, and 250 pmol/L, resp.)
- Luteal activity (progesterone >3.14 ng/mL) was observed in 1.2% to 2.6% of cycles with no difference by dose
- E2 levels were inversely correlated with SA dose; the highest E2 levels indicated the most ovarian activity

Dose Finding for SA/EE Vaginal Rings

- Median serum concentrations of SA for all weeks were well above levels needed for ovulation inhibition
- Luteal activity was detected in 15 of 126 (12%) women with cycles measured, and in 22 of 356 measured cycles (6%)
- Seven women using the 150/15 ring had luteal activity
- Luteal activity was not associated with dose

# Systemic SA Level Required for Ovulation Inhibition

<table>
<thead>
<tr>
<th>Study</th>
<th>Formulation</th>
<th>Dose per Day</th>
<th>SA mean levels (pmol/L)</th>
<th>Ovulation inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diaz et al 1995¹</td>
<td>SA subdermal implant</td>
<td>45-50 mcg</td>
<td>&gt;105</td>
<td>Yes</td>
</tr>
<tr>
<td>Brache et al 2001²</td>
<td>SA-only vaginal ring</td>
<td>50 mcg 75 mcg 100 mcg</td>
<td>100-150 170-210 220</td>
<td>Yes (not dose dependent)</td>
</tr>
<tr>
<td>Brache et al 2015³</td>
<td>SA/E2 transdermal gel (daily application)</td>
<td>1.5 mg/0.5 mg* 3.0 mg/1.0 mg* 4.5 mg/1.5 mg*</td>
<td>&gt;250</td>
<td>Yes</td>
</tr>
<tr>
<td>Fraser et al 2005⁴</td>
<td>SA/EE vaginal ring on a bleeding-signaled regimen</td>
<td>50 mcg/10 mcg 50 mcg/20 mcg 150 mcg/15 mcg</td>
<td>106 (median) 99 (median) 227 (median)</td>
<td>Yes (10% luteal activity)</td>
</tr>
<tr>
<td>Sivin et al 2005⁵</td>
<td>SA/EE vaginal ring 21-day in/7-day out regimen</td>
<td>150/15, 150/20, 200/15 mcg/mcg</td>
<td>&gt;200 (median)</td>
<td>Yes (12% luteal activity)</td>
</tr>
</tbody>
</table>

*Ten percent of transdermal gel is absorbed, resulting in a dose of 150, 300 and 450 mcg SA, respectively.

Body Weight was Inversely Correlated with Luteal Activity during CVS Use

- Three CVS doses: SA/EE 0.15/0.015, 0.15/0.02, 0.2/0.015 mg
- Logistic regression found body weight to correlate significantly with increased risk of luteal activity
- Correlation coefficient by individual body weight: $r = 0.33$, $P < 0.001$
  - Phase 3 study does not show an effect of BMI on efficacy
- Odds ratio predicting luteal activity increased by a factor of 1.055 (95% CI 1.022–1.090) per kg of body weight above a baseline of 45 kg

Conclusions

• Unintended pregnancy is a worldwide social and economic problem
• SA inhibits ovulation when levels remain no lower than 105 pmol/L
  • Circulating SA levels were dose dependent
• Ovulation inhibition occurs without fully suppressing ovarian function
• Because BMI did not affect efficacy in phase 3 trials, further study is warranted
• Women have another contraceptive choice with the FDA approval of the SA/EE CVS (as Annovera™) that is a user-controlled, procedure-free, long-term, reversible option

Annovera™ is a trademark of TherapeuticsMD, Boca Raton, FL