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

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Disclosures

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- Consultant: AbbVie, Actavis, Agile Therapeutics, Bayer Healthcare, Endoceutics, Exeltis, InnovaGyn, Merck, Pfizer, Radius Health, Sermonix, Shionogi, Teva Women's Healthcare, and TherapeuticsMD
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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[1]
- Up to 51% of US pregnancies unintended[2,3]
  - No significant decline since 1982[2]
- Staggering costs[4]

  ~1 million unplanned births in US publicly funded in 2010

1. Sedgh G, et al. *Stud Fam Plann*. 2014;45:301-314 2. Mosher WD, et al. *Natl Health Stat Report*. 2012;55:1-28. 3. Finer LB, Zolna MR. *Am J Public Health*. 2014;104:S43-S48
4. Sonfield A, Kost K. Guttmacher Institute, 2015. Available at: https://www.guttmacher.org/report/public-costs-unintended-pregnancies-and-role-public-insurance-programs-paying-pregnancy. Accessed February 22, 2019.

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]

1. Finer LB, Zolna MR. *Am J Public Health*. 2014;104:S43-S48. 2. Gipson JD, et al. *Studies in Family Planning*. 2008;39:18-38.

Overcoming Barriers: Improve Access

- All women must have access to a variety of safe and effective methods[1]
  - Address underserved populations, eg, college-aged women[2] and women without immediate post-partum contraception[3]
  - Minimize barriers to emergency contraception[4,5]
  - Increase use of long-acting reversible contraception (LARC)[6,7]
    - Underutilized as a first-line option (<5%)[1,8]
- Poor patient adherence and intolerance of side effects can lead to nonuse
  - Explore novel methods and formulations to improve uptake

1. American College of Obstetricians and Gynecologists. 2017;615. 1-6. 2. Logan RG, et al. *Matern Child Health J*. 2018;22:1639-1646. 3. Coleman-Minahan K, et al. *Perspect Sex Reprod Health*. 2018;50:189-198. 4. Moore A, et al. *Women Health*. 2018; Jun 19:1-11. 5. The American College of Obstetricians and Gynecologists. 2017;707:1-5. 6. Itriyeva K. *Curr Probl Pediatr Adolesc Health Care*. 2018;48:321-332. 7. Winner B, et al. *NEJM*. 2012;366:1998-2007. 8. Mosher WD, Jones J. *Vital Health Stat*. 2010;23:29:1-44.

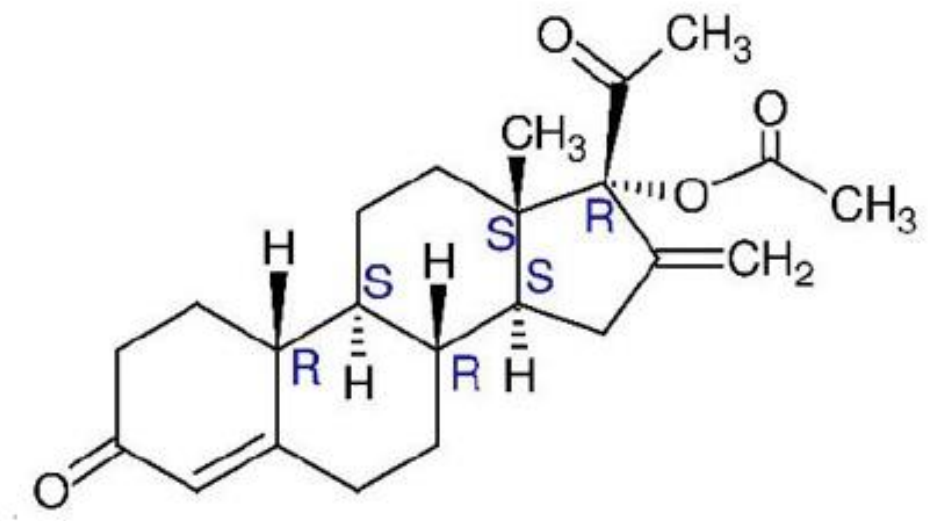
Overcoming Barriers: Novel Methods, Improved Safety

- 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]

1. American College of Obstetricians and Gynecologists. 2017;615;1-6. 2. Sitruk-Ware R. *Fertility and Sterility*. 2016;106:1-6.

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]

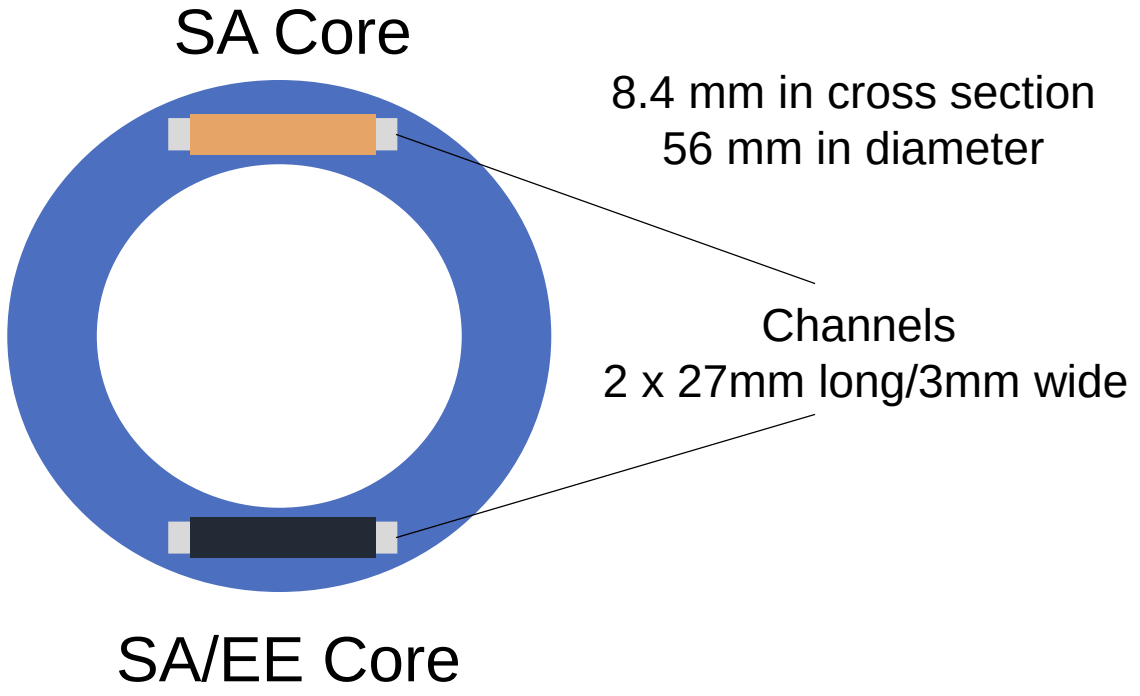


Formerly referred to as Nesterone® or ST 1435

1. Kumar N, et al. *Steroids*. 2000;65:629-636. 2. Zhao X-F, et al. *Contraception*. 2004;69:505-511. 3. Lahteenmaki P. *Contraception*. 1984; 30:143-151.

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

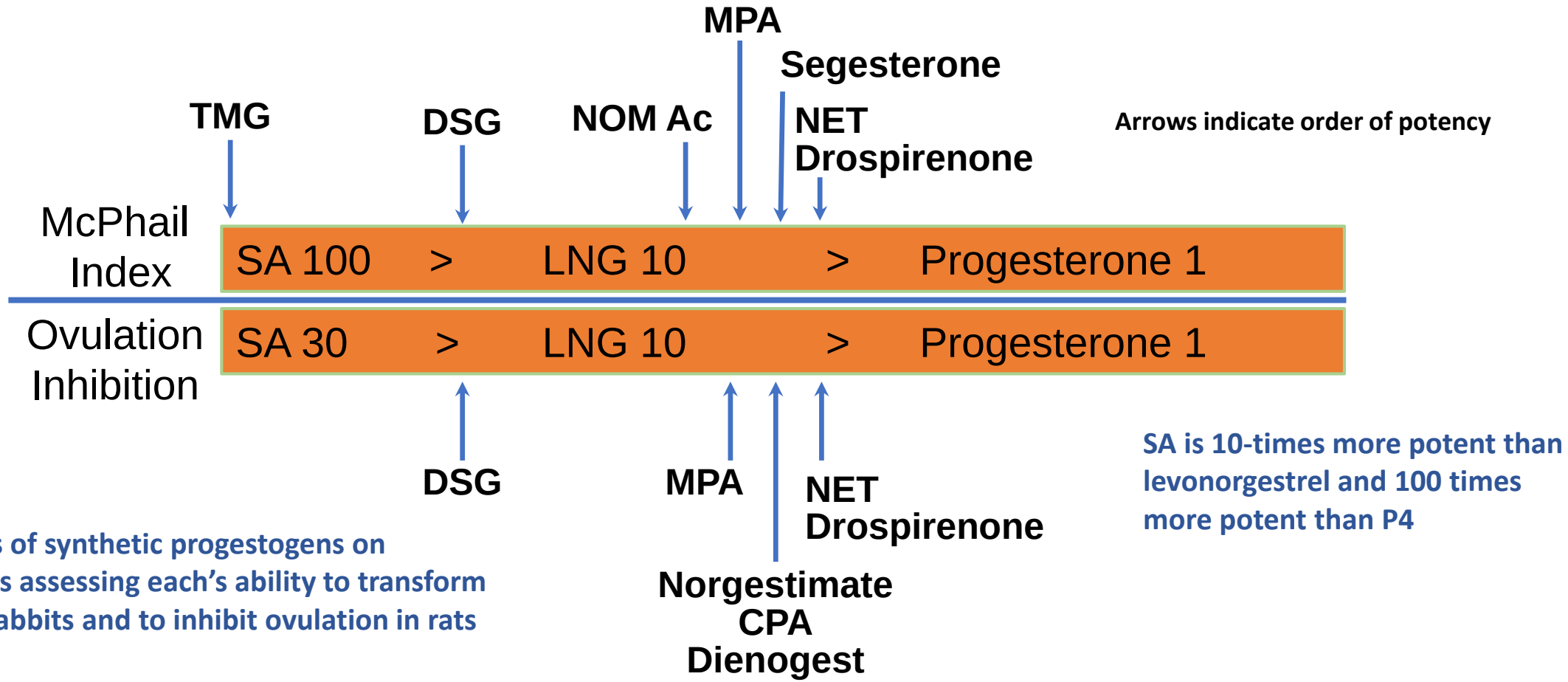
- Only SA-containing contraceptive method available
- Convenient 21-day in/7-day out cycle that can be reinserted up to 13 cycles (1 year)
- Effective ovulation suppression for up to 1 year with low hormone levels
- Does not need to be removed during sex
- Does not require refrigeration



Total drug load = 103 mg SA/17.4 mg EE
Daily release rate = 0.15 mg SA/0.013 mg EE

Annovera™ package insert.

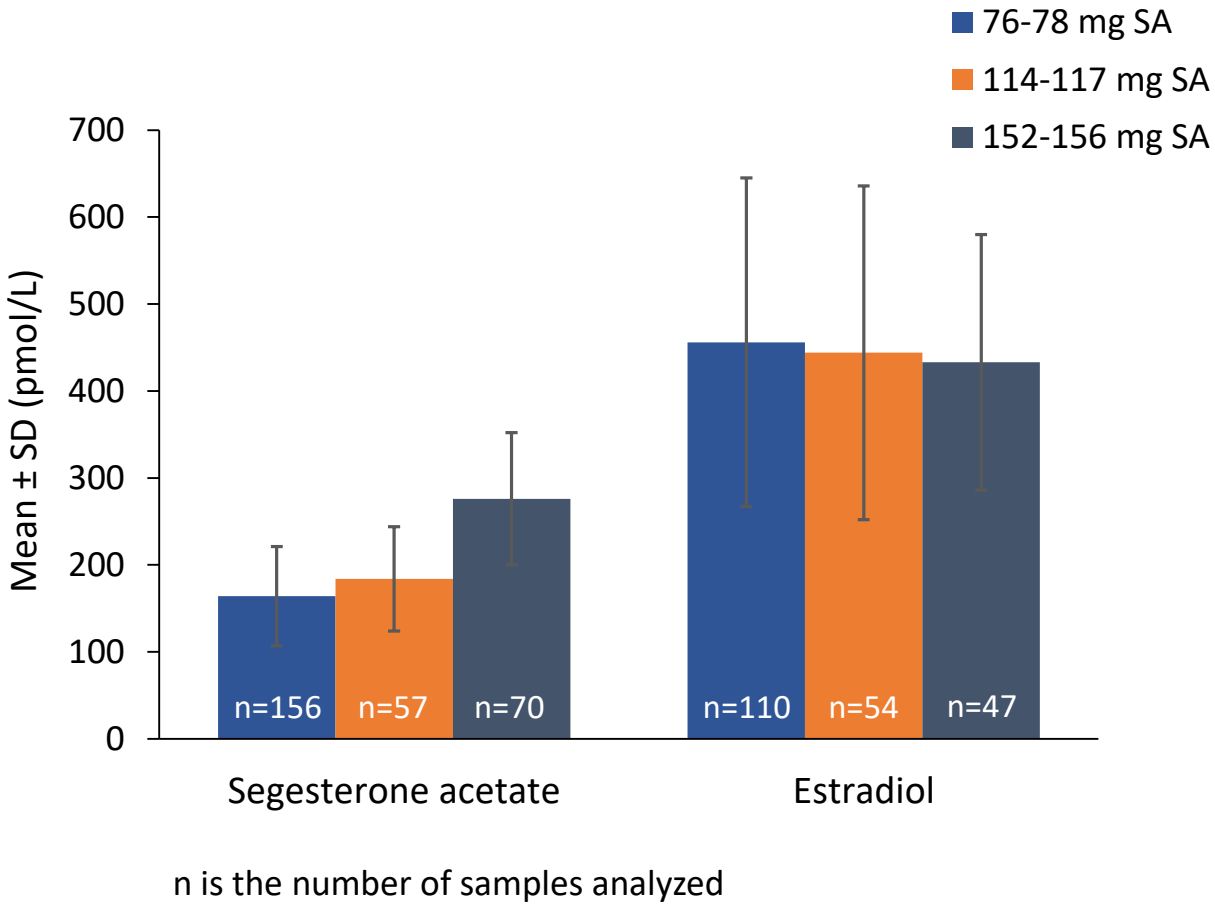
Progestational Activity of SA and Other Progestogens



CPA: cyproterone acetate; DSG: desogestrel; LNG: levonorgestrel; MPA: medroxyprogesterone acetate; NET: norethisterone; NOM Ac: nomegestrol acetate; TMG: trimegestone.
Adapted from Sitruk-Ware R. *Menopause*. 2002;9:6-15. Data from Kumar N, et al. *Steroids*. 2000;65:629-636.

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]

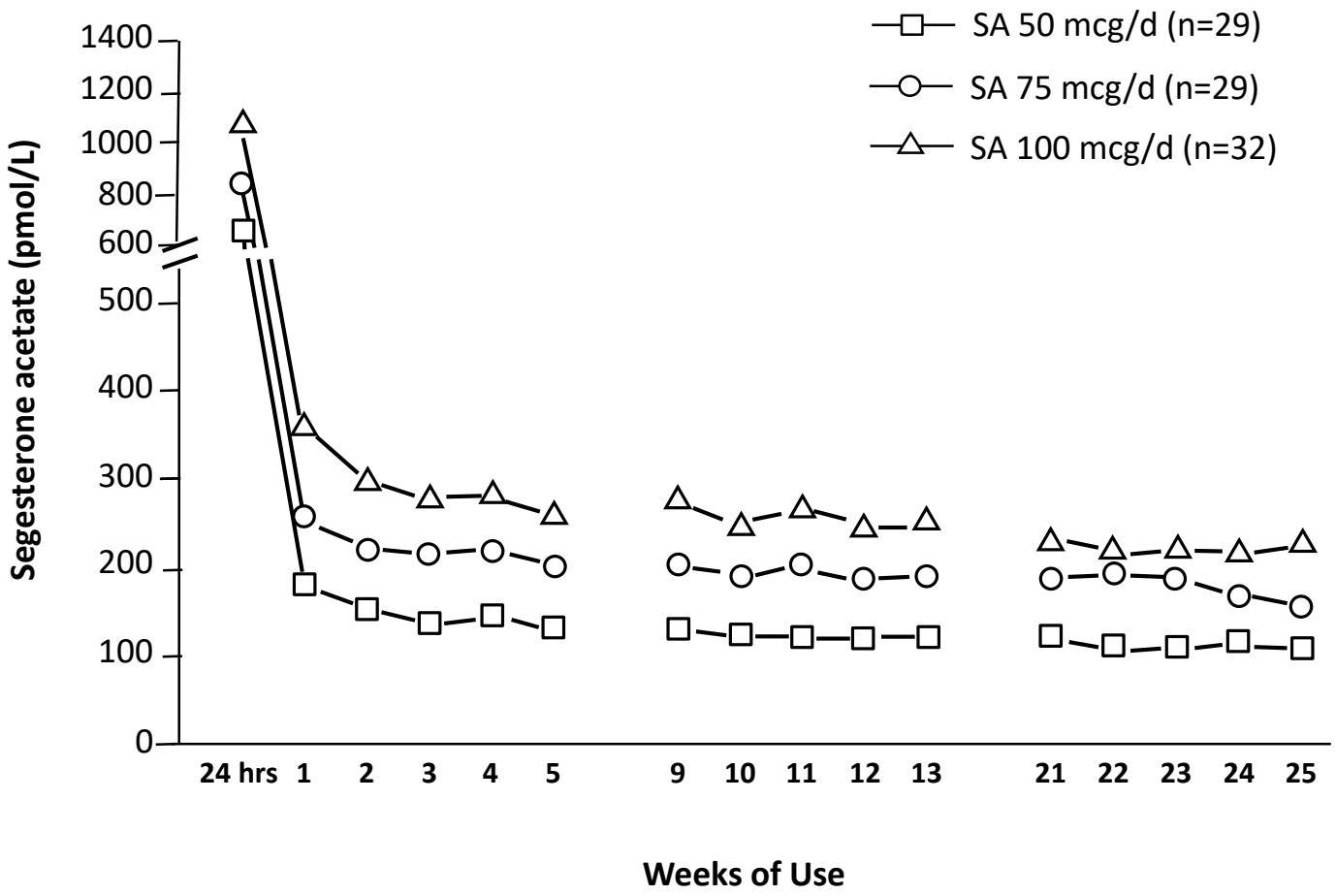


n is the number of samples analyzed

1. Haukkamaa M, et al. *Contraception.* 1992;45:49-55. 2. Brache V, et al. *Contraception.* 2000;61:199-204.

SA-only Vaginal Rings

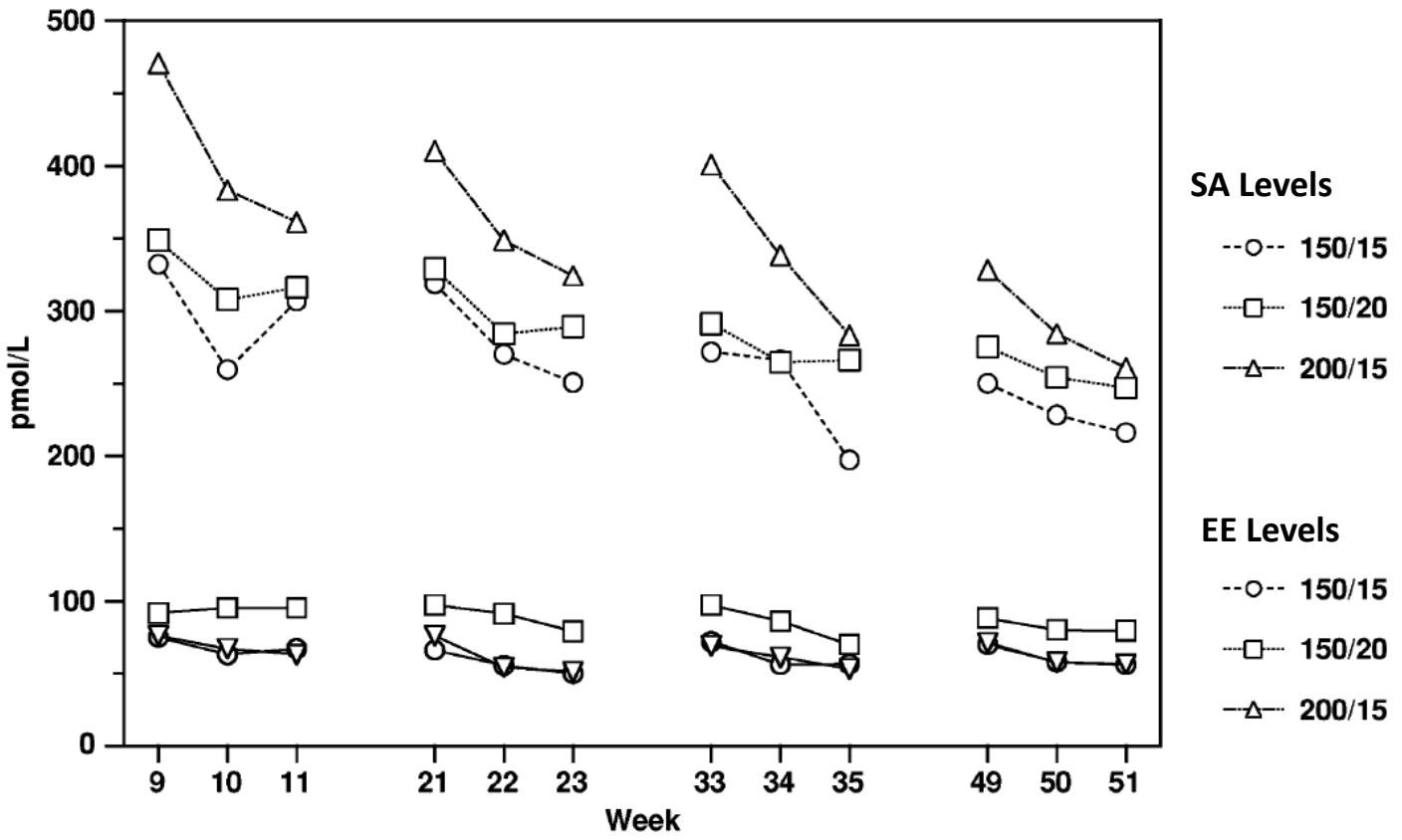
- SA levels were high the first day, gradually declined, and then remained stable (~125, 200, and 250 pmol/L, resp.)
- Luteal activity (progesterone >3.14 ng/mL) was observed in 1.2% to 2.6% of cycles with no difference by dose
- E2 levels were inversely correlated with SA dose; the highest E2 levels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



Adapted from Brache V, et al. *Contraception*. 2001;63:257-261.

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



Adapted from Sivin I, et al. *Contraception* 2005;71:122-129.

Systemic SA Level Required for Ovulation Inhibition

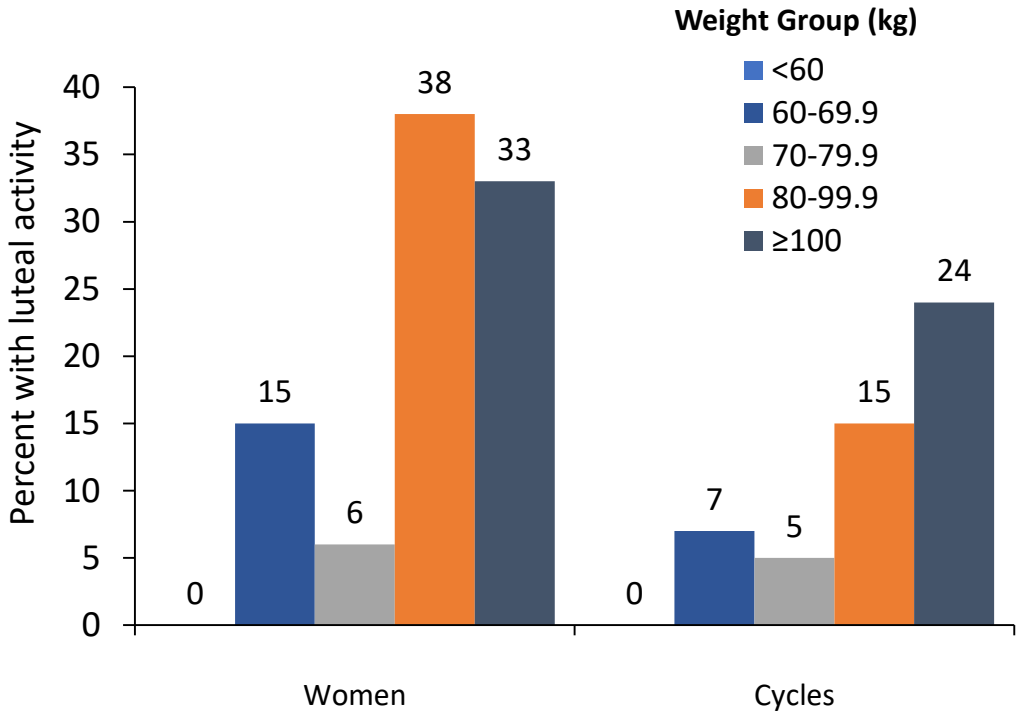
Study	Formulation	Dose per Day	SA mean levels (pmol/L)	Ovulation inhibition
Diaz et al 1995[1]	SA subdermal implant	45-50 mcg	**>105**	Yes
Brache et al 2001[2]	SA-only vaginal ring	50 mcg 75 mcg 100 mcg	100-150 170-210 220	Yes (not dose dependent)
Brache et al 2015[3]	SA/E2 transdermal gel (daily application)	1.5 mg/0.5 mg* 3.0 mg/1.0 mg* 4.5 mg/1.5 mg*	>250	Yes
Fraser et al 2005[4]	SA/EE vaginal ring on a bleeding-signaled regimen	50 mcg/10 mcg 50 mcg/20 mcg 150 mcg/15 mcg	106 (median) 99 (median) 227 (median)	Yes (10% luteal activity)
Sivin et al 2005[5]	SA/EE vaginal ring 21-day in/7-day out regimen	150/15, 150/20, 200/15 mcg/mcg	>200 (median)	Yes (12% luteal activity)

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

1. Diaz S, et al. *Contraception*. 1995;51:33-38. 2. Brache V, et al. *Contraception*. 2001;63:257-261. 3. Brache V, et al. *Contraception*. 2015;92:289-297. 4. Fraser IS, et al. *Contraception*. 2005;72:40-45. 5. Sivin I, et al. *Contraception* 2005;71:122-129.

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[1]
- Logistic regression found body weight to correlate significantly with increased risk of luteal activity[1]
- Correlation coefficient by individual body weight: $r = 0.33$, $P < 0.001$[1]
  - Phase 3 study does not show an effect of BMI on efficacy[2]
- 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[1]



1. Sivin I, et al. *Contraception* 2005;71:122-129. 2. Archer DF, et al. *Lancet Global Health*, submitted.

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