The Future of Contraception

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Disclosures

- Nothing to Disclose

1. Recognize the differences between contraceptive progestins

2. Describe the new hormonal formulations for men

3. Discuss the future use of microneedles for contraception

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Evolution of OCs in the United States

- 1960—first OC approved by FDA (150 µg mestranol and 9.85 mg norethynodrel)
- 1974—introduction of low-estrogen pills (<50 µg EE)
- 1989—formulations containing >50 µg estrogen withdrawn from market
- 1990s—introduction of OCs with less androgenic gonane progestins (norgestimate and desogestrel)
- 2001—introduction of spirolactone-derived progestin (drospirenone)

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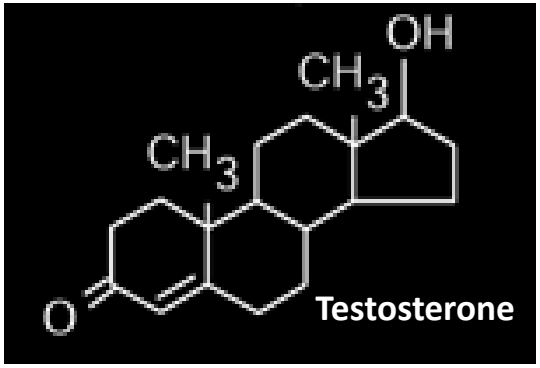
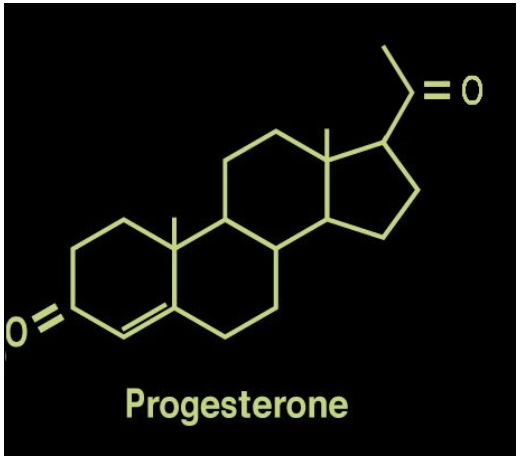
Synthetic Progestins

- Testosterone derivatives (19 C)
  - Estranes
  - Gonanes
- Progesterone derivatives (21 C)
  - Pregnanes
- Spirolactones
- Anti-progestins





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Objectives

- By the end of this lecture, participants should be able to:
  1. Recognize the differences between contraceptive progestins
  2. Understand the new hormonal formulations for men
  3. Discuss the future use of microneedles for contraception

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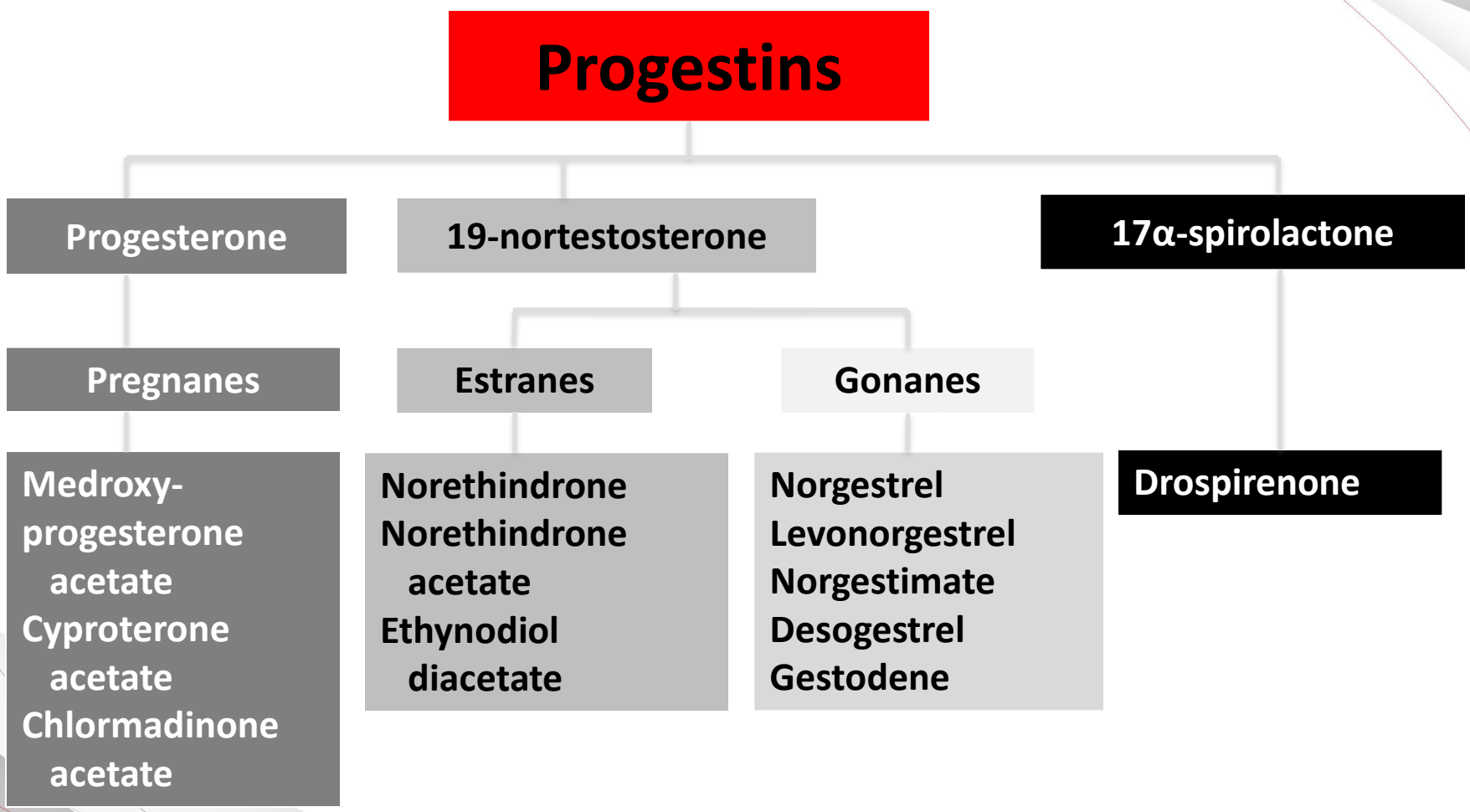
Categorizations of Progestins



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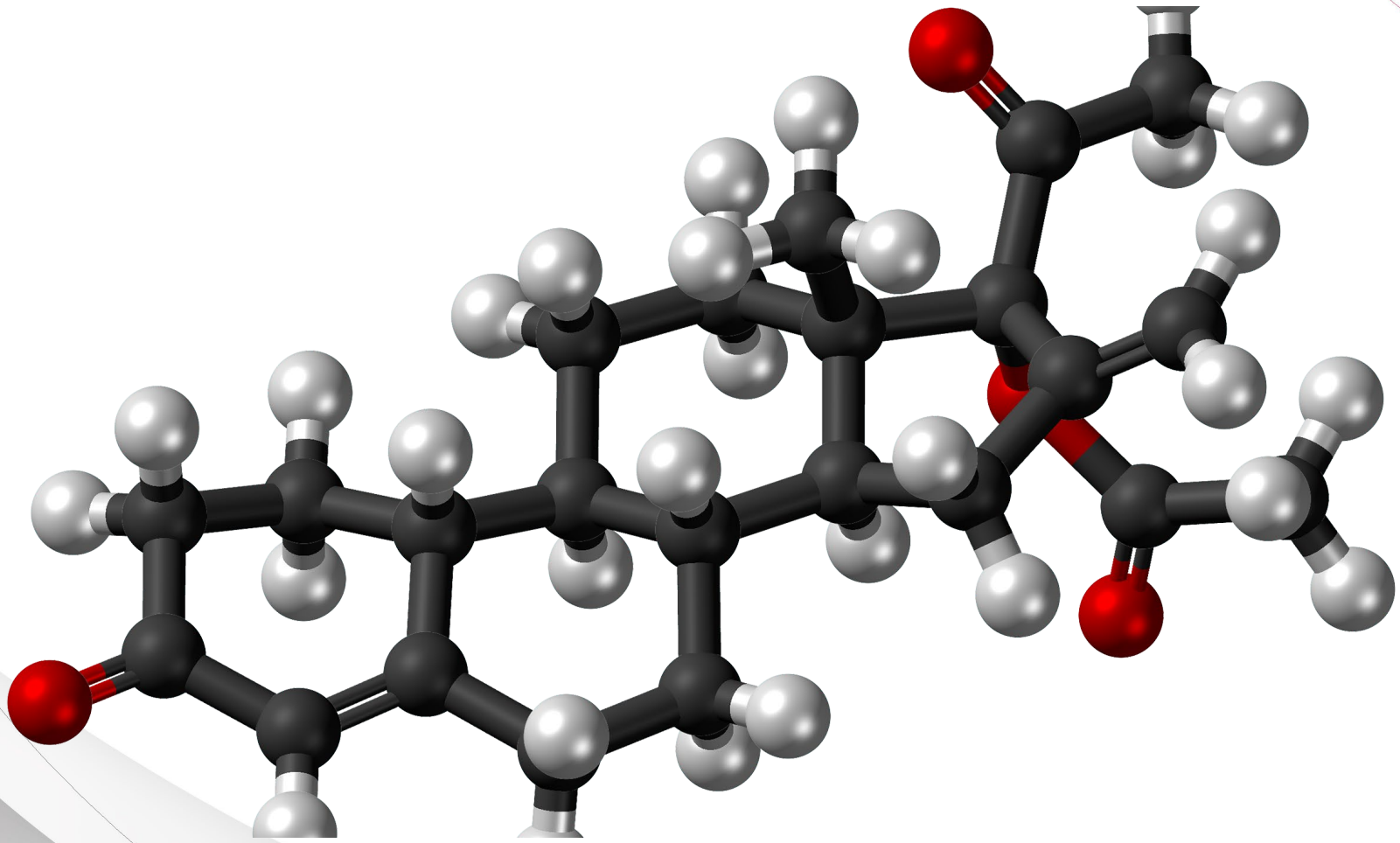
Segesterone Acetate



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Segesterone Acetate

- 19-norprogesterone
- Developed by the Population Council
- No binding to estrogen, androgen or mineralocorticoid receptors
- High affinity for glucocorticoid receptor, but no clinical affect
- Treatment option for contraception or endometriosis
- Non-oral administration
  - Vaginal ring
  - Transdermal gel

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Segesterone Acetate

- Approved by the FDA in 2018 as a IVR
- SA 150 mcg/day and EE 13 mcg/day
- Used for 13 cycles
  - Inserted for 21 days
  - Cleaned and removed for 7 days
- NIH CCTN. Contraception 2019; 99:323-28
  - 12 month safety evaluation
  - 2308 recruited, 999 completed 13 cycles of use
  - Headache 26%, Nausea 18%, Vaginal discharge 10%, Abd pain 10%, VTE 0.2% with 1 having Factor V Leiden.
  - Expulsion: Partial 19%, Complete 7%

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Segesterone Acetate

- NIH CCTN 90 day dose IVR finding study
- Chen et al, Contraception 2020; 102:168-173
- 65 subjects
- 7 centers
- SA 200 mg randomized with either E2 75, 100, or 200 mcg/day
- E2 concentrations 2x/week
- Hypothesis: Find E2 levels to avoid hypoestrogenism and suppress ovulation

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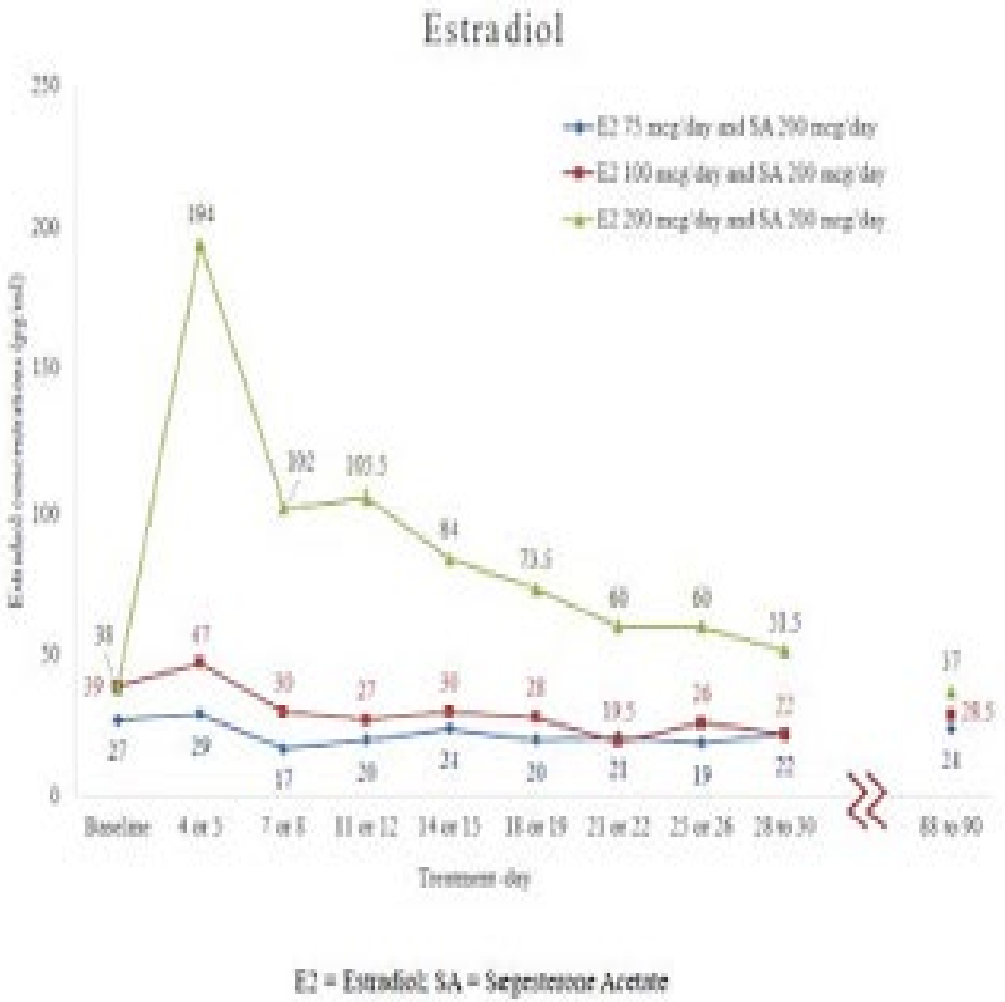

Figure 2. Median estradiol concentration with use of a contraceptive vaginal ring releasing estradiol 75, 100, or 200 mcg/day and segesterone acetate 200 mcg/day. Serum hormone concentrations were not assayed between day 30 and day 88.

Segesterone Acetate

- Conclusions:
  - IVR with SA 200 mg and E2 200 mcg
    - Avoids hypoestrogenism
    - Presumed ovulation suppression
    - Decreased bleeding irregularities
  - Future option
    - SA/E2 transdermal gel for women
    - SA/Testosterone transdermal gel for men

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Other Progestin on the Horizon

- Nomegestrol Acetate
  - 19-nortestosterone
  - Decreased affinity to the androgen receptor
  - Oral contraceptive (E2)

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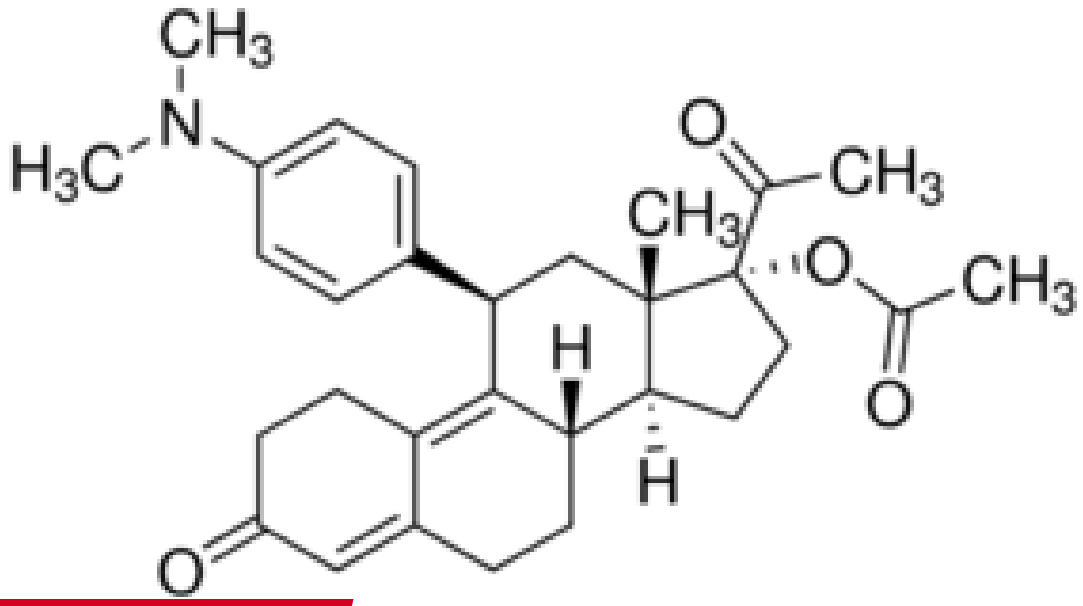
Ulipristal Acetate



Emergency Contraception

- Previous EC agents
  - High dose estrogen
  - Danazol
  - Copper IUD
  - Combination OCP (Yuzpe method)
  - Progestin only pill
  - Anti progestin (Mifepristone)

Ulipristal Acetate

- UPA or CDB-2914
  - Second generation selective progesterone receptor modulator (SPRM)
  - Blocks progesterone (P4) action in target cells
  - Has little glucocorticoid receptor activity like mifepristone
  - Method of action
    - Delay ovulation
    - Prevent implantation

Ulipristal Acetate

- Antagonistic and partial agonistic effects on P4 receptor
- Binds to P4 receptor
  - Prevents endogenous P4 receptor attachment
  - Inhibits P4-activated DNA transcription

Ulipristal Acetate

- Effect is cycle dependent
  - Mid-follicular
    - Inhibits folliculogenesis
    - Reduces E2 concentrations
  - At LH surge
    - Delays follicular rupture for 5-9 days
  - Early luteal phase
    - Decreases endometrial thickness by 0.6 mm
    - No effect on endometrial maturation

Ulipristal Acetate

- Side effect profile
  - Headache, nausea, abdominal pain, dysmenorrhea, fatigue, vertigo
  - Not indicated and no effect on ongoing pregnancy
  - Rapid return to fertility
- Metabolism
  - Cytochrome P450 pathway
- Half life (30 mg tablet)
  - 32.4 hours

Emergency Contraception

- FDA approved in 2010
- 30 mg tablet given within 120 hours of intercourse

UPA as an EC (study 1)

- PR Modulator for EC: A Randomized Study
  - Creinin MD et al, Obstet Gynecol 2006;108:1089
- U Cincinnati, U Pittsburgh, U Colorado, Eastern Virginia, NYU, California Health Council
- 1:1 randomization within 72 hours of IC
  - UPA 50 mg, then placebo 12 hrs later
  - LNG 1.5 mg divided over 12 hours

Creinin Conclusions

- UPA as effective as LNG
- Overall averted pregnancies
  - UPA 85%
  - LNG 69%
  - Effectiveness rate ratio 1.2
- No pregnancies noted if UPA given more than 24 hrs post-ovulation

UPA to treat fibroids

- UPA as a treatment for uterine leiomyomas
  - Liu JH et al, Obstet Gynecol 2018;132:1241
- Placebo vs UPA 5 or 10 mg
  - Phase 3, prospective, randomized, double blind, double dummy, placebo controlled, crossover study
  - 12 week treatment periods x 2

Liu et al Conclusions

- UPA 5 and 10 mg dosing superior to placebo
  - Increased rates of and time to amenorrhea
  - Reduced fibroid volume
  - Improved Health related QOL
- UPA noted higher rate of hot flashes
- One subject had severe hemorrhage in the UPA 5 mg (course 2)

Ulipristal Acetate

- Emergency Contraception
  - FDA approved in 2010
- Uterine fibroids
  - Ongoing clinical trials

DILI! DILI!

- Drug induced liver injury (DILI)
  - Intrinsic – hepatotoxicity with potential to affect all individuals to a varying degree
    - Acetaminophen
  - Idiosyncratic – hepatotoxicity affecting only rare susceptible individuals. Less dose dependent and more varied in latency, presentation and course
- Since 2012 in Europe, UPA 5 mg (ulipristal acetate) used for fibroids with reduction in bleeding, size, and volume

DILI! DILI!

- 5 cases of confirmed DILI out of 765,000 users
  - 4 of 5 needed liver transplant
- European Medicines Agency restricted UPA use in February 2018
  - Because of this, NICHD CCTN daily UPA 5-10 mg contraceptive study placed on hold

Other SPRMs

- Asoprisnil
  - Endometriosis
  - Uterine fibroids
- Telapristone (CDB-4124)
  - Endometriosis
  - Uterine fibroids
  - Possible chemopreventive effects

Microneedle Patches

- Array of hundreds of needles in a small patch
- Painlessly penetrate the upper layer of skin
- Delivers levonorgestrel in a water soluble formulation
- Needles dissolve in skin
- Use for ≥ one month

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Design and fabrication of effervescent MN patches.

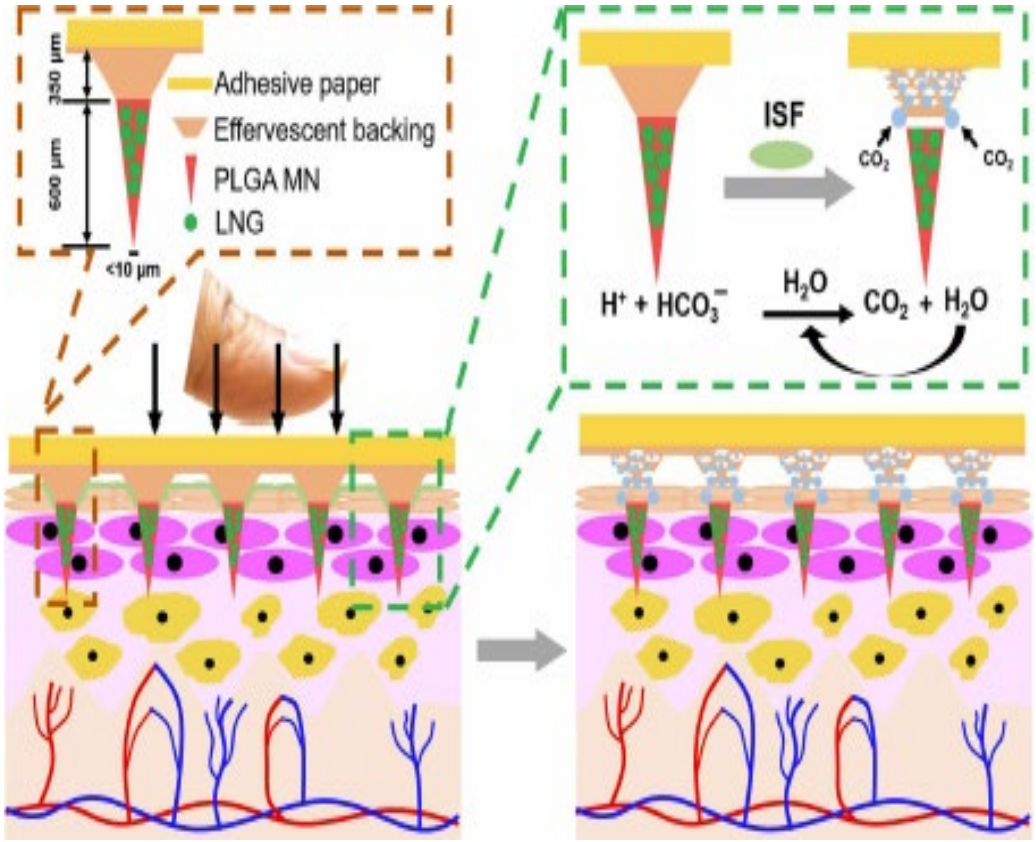

Fig. 1. Design and fabrication of effervescent MN patches. Schematic illustration of the design of an MN patch with effervescent backing and of the process of MN patch application to skin to rapidly deliver MNs into the skin by fast dissolution of the effervescent backing. Photo credit: Wei Li, Georgia Tech.

Li et al., Sci. Adv. 2019; 5 : eaaw8145 6 November 2019

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Application of effervescent MN patches to human participants.

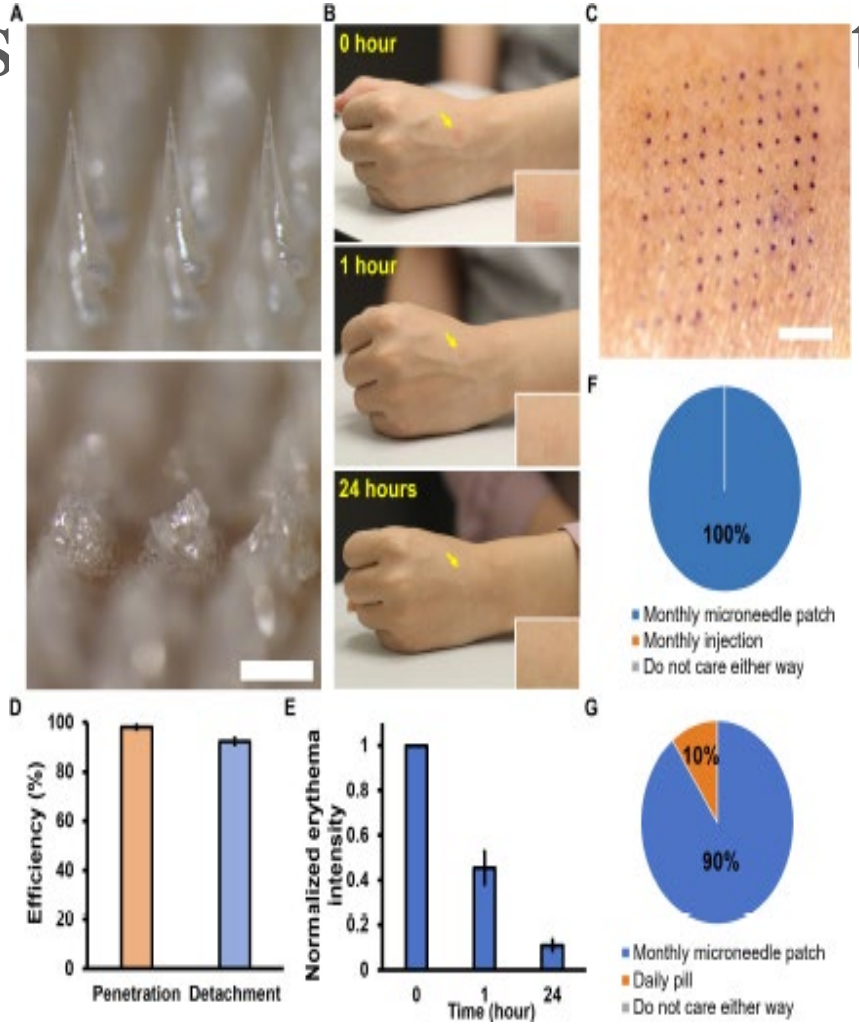

Fig. 6. Application of effervescent MN patches to human participants. (A) Representative bright-field microscopy images of a section of an effervescent MN patch before (top) and after (bottom) application to human skin. Scale bar, 500 mm. (B) Representative images of the site of effervescent MN patch application (yellow arrows) to the skin of a human participant over time. Inset shows magnified images of the skin application site. These images are all from the same participant. (C) Representative photographic image of skin of a human participant stained to show where a 10 × 10 array of MNs punctured into skin. Scale bar, 2 mm. (D) The efficiency of penetration and detachment of effervescent MN patches in skin of human participants. Each point represents mean ± SD (n = 3). (E) Normalized erythema intensity of human skin over time at the site of effervescent MN patch application. Each point represents mean ± SD (n = 10). (F) Preference of human participants for monthly application of effervescent MN patch compared to monthly hypodermic injection for delivery of contraceptive (n = 10). (G) Preference of human participants for monthly application of effervescent MN patch compared to daily oral administration by pill for delivery of contraceptive (n = 10). Photo credit: Wei Li, Georgia Tech.

Microneedle Patches

- Rat model
  - Concentrations of LNG levels higher than therapeutically needed in human
  - Slow release of LNG after needle detachment from patch
- Human model
  - Non-hormonal MN patch
  - Well tolerated
  - Short term erythema at patch site (Lasts 1-24 hours)
  - No tenderness or swelling
  - High tolerability and preference

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Multipurpose Technology (MPT)

- Previous MPT's have used progestins and antivirals to prevent pregnancy and HIV
  - Usually IVR platform

- Current MPT studies using monoclonal antibodies
  - MB66
    - Vaginal film
    - Neutralizes HSV and HIV
    - Adding another monoclonal ab will lower vaginal pH to agglutinize sperm

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Scanning electron micrograph showing agglutination of HCA-treated washed human spermatozoa.

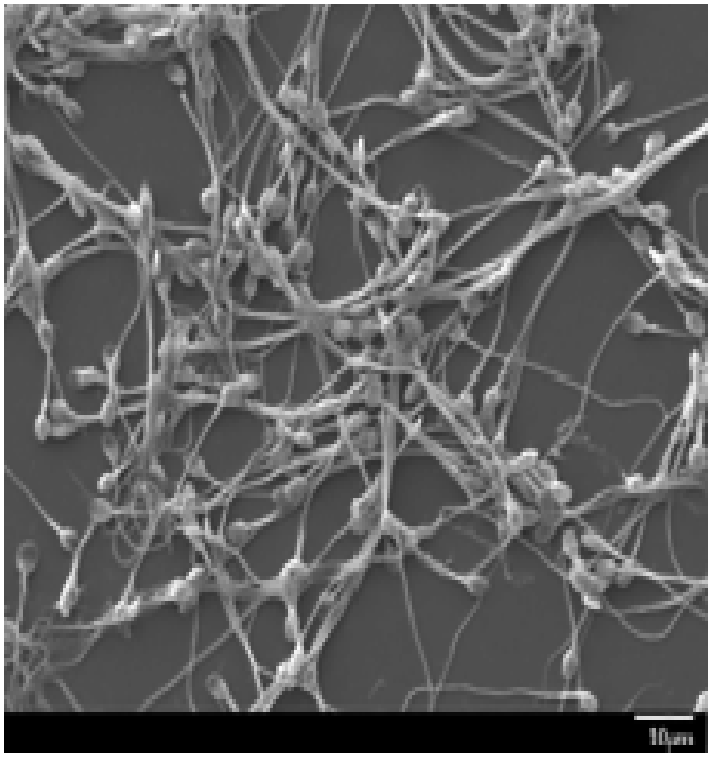

Figure 1. Scanning electron micrograph showing agglutination of HCA-treated washed human spermatozoa.
Since it is difficult to produce IgM antibodies in the Nico-tiana system, we converted the isotype of the antibody to IgG. Genes containing the variable region sequences of H6-3C4 were cloned into TMV and PVX plant expression vectors [16] containing codon-optimized human lambda and human IgG1 constant regions. The vectors were then transformed into Agrobacterium tumefaciens strain ICF320 for transfection into Nicotiana benthamiana plants by vacuum infiltration as previously described [17]. After 7 days of post-infiltration, antibody was extracted from the leaf tissue and purified by Protein A chromatography [17, 18]. We refer to this IgG1 antisperm mAb as HCA.

Multipurpose Technology (MPT)

- Future Intravaginal rings
  - Known for delivering small molecules
  - Larger molecules, like monoclonal antibodies can be utilized
  - Sustained delivery of contraceptive progestins and anti-HIV neutralizing antibodies

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(A) MB66 film
(B) IVR bearing antibody-loaded capsules

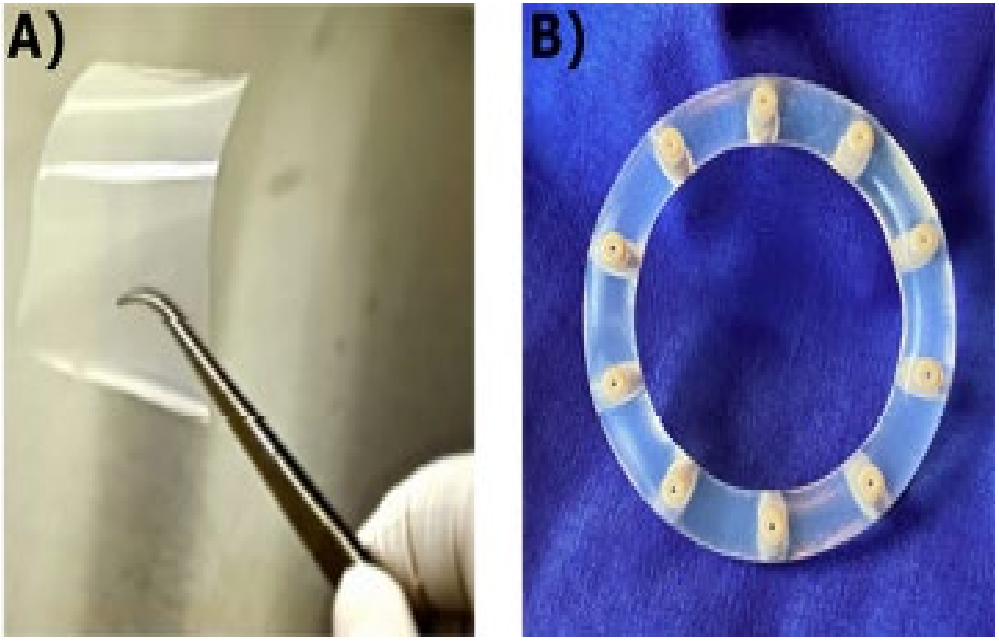

Figure 3. (A) MB66 film containing 10 mg of VRC01 anti-HIV bNAb, and 10 mg of HSV8 anti-HSV antibody; (B) IVR bearing antibody-loaded capsules for contraception or MPT protection.
D.J. Anderson et al., 2020, Vol. 103, No. 2

Male Contraception

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Goals of Male Hormonal Contraception

- Azoospermia
  - Inconsistent results with hormonal agents
- Severe oligospermia
  - <1-3 million/mL
  - Failure rate <1%
    - Similar to hormonal agents used by female patients

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Categories of Experimental Male Contraceptives

Hormonal

- Pill, injection, implant, gel
- Testosterone alone
  - Enanthate, undecanoate, buciclate, 19NT
- Progestin with testosterone
  - LNG, desogestrel, DMPA/MPA, CPA, etonorgestrel, norethistrone enanthate
- GnRH antagonist with testosterone

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On the Horizon

- Combination segesterone acetate/Testosterone Gel
  - NES has no androgenic, estrogenic or glucocorticoid activity
  - 89% had sperm concentration ≤1 million/mL
- Dimethandrolone undecanoate (DMAU)
  - 19-norandrogen with activity at androgen and progesterone receptors

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On the Horizon

- 7-alpha-methyl-19-nortestosterone (MENT)
  - More potent than testosterone
  - Resistant to 5-alpha reduction
  - Lacks progestogenic activity
  - Formulated as in implant
  - Supports bone health
  - Reduces intraprostatic androgen activity
  - Inconsistent implant release with progestin

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Contraceptive Clinical Trials Network

- NIH Contract established in 1995
- Originally 9 Centers, now 19 Female programs and 5 Male programs
- Projects:
  - Ulipristal acetate (CDB 2914) for EC
  - Acidform Gel, C31G
  - Depot levonorgestrel
  - nonhormonal cervical cap
  - UPA as a daily contraceptive pill

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Ideal Contraceptive

- Safe
- Effective
- Reversible
- Acceptable
- Generally available
- Affordable
- Dual Protective

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Words of Wisdom

- Get to know the culture
- Find a mentor or two
- Make a niche for yourself
- Don’t let yourself be taken advantage of
- Make yourself indispensible
- Be ready to move if you are not getting what you need
- Never stop being a learner

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Questions?

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- Which contraceptive progestin is made up of 21 carbons?
  1. Spironolactone
  2. Levonorgestrel
  3. Segesterone acetate
  4. Medroxyprogesterone acetate

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- In contrast to a first generation SPRM, Ulipristal acetate:
  1. Blocks progesterone receptor activity
  2. Delays ovulation
  3. Less glucocorticoid activity
  4. Causes degeneration of chorionic villi

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- Exogeneous androgen utilization in male contraception causing intraprostatic activity is associated with:
  1. Benign prostatic hypertrophy
  2. Prostate cancer
  3. Female partner hyperandrogenism
  4. Increased percentage of male offspring

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