Male Contraception: Advances, Challenges, Future Directions

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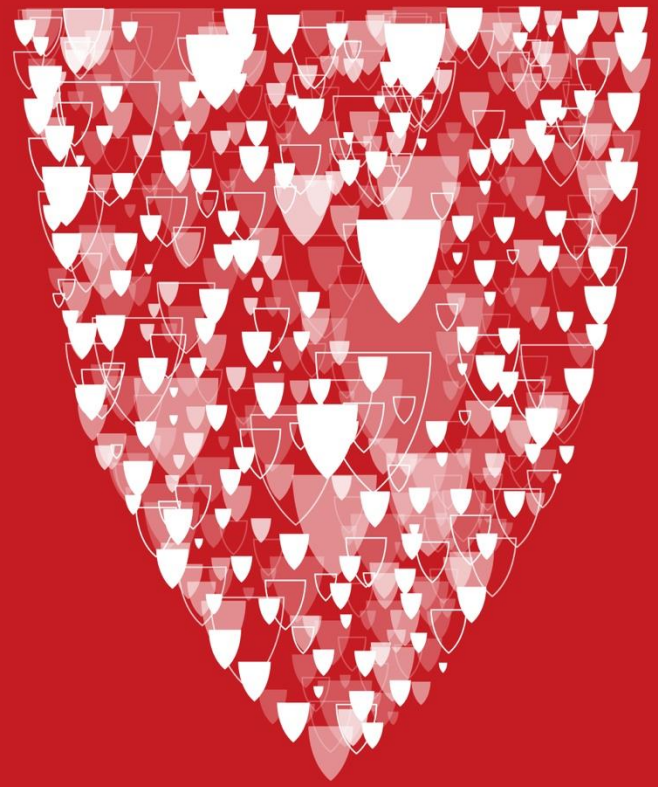


Learning objectives

- Discuss both hormonal and non-hormonal **male contraceptive targets**
- Develop knowledge to counsel patients on emerging male contraceptive options.
- Assess barriers to new male-oriented methods

Disclosures

- No conflicts of interest relevant to this presentation
- No off-label discussion of products

Current options

Female

- Ethinyl estradiol & progestin combo
  - Daily pills
  - Weekly patch
  - Intravaginal ring
- Progestin only systemic
  - Daily POPs
  - Q3 mo DMPA
  - 3-5 yr ENG implant
- Intrauterine
  - Copper
  - Progestin
- Barriers/spermicide
- Sterilization

Male

- Withdrawal
- Condom
- Vasectomy

Global burden of unplanned pregnancy

<u>200 million pregnancies/year</u>

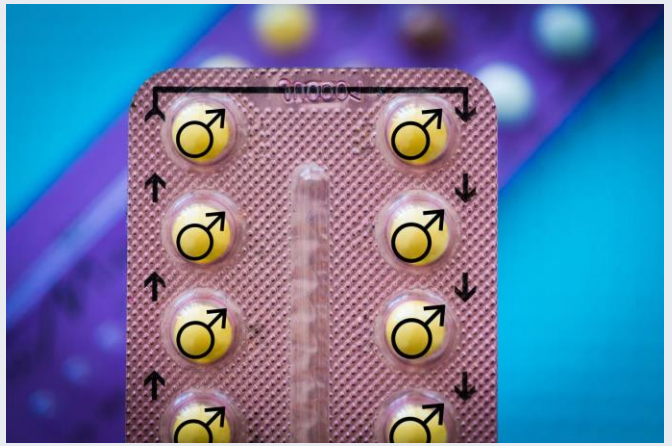
- 85 million unplanned/mistimed
- 56 million abortions

- Health risks
- Economic risks
- Ecologic risks

Sedgh, G et al *Lancet* 388, 258–267 (2016).

Why a male-directed contraceptive?

- Men are affected by unintended pregnancies
- Everyone has the right to control their own fertility
- Some women cannot use contraceptives
- Men and women report they want this option
- Not new concept
  - Historically, main contraceptives have been withdrawal (and LAM)



Male contraceptive methods

Withdrawal

Condoms

Vasectomy

King Minos of Crete. Pasiphae, his wife, employed a goat's bladder in the vagina so that King Minos would not be able to harm her as his semen was said to contain "scorpions and serpents" that killed his mistresses

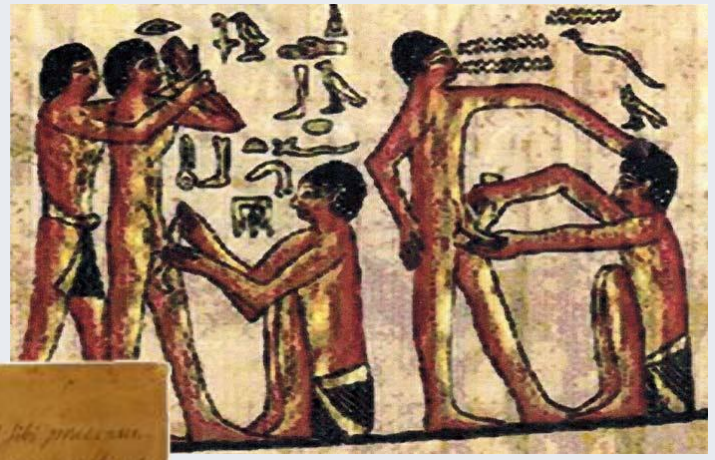
Ancient Romans used the bladder[illegible] to protect the woman; they were wo[illegible] to[illegible] but to prevent contraction of

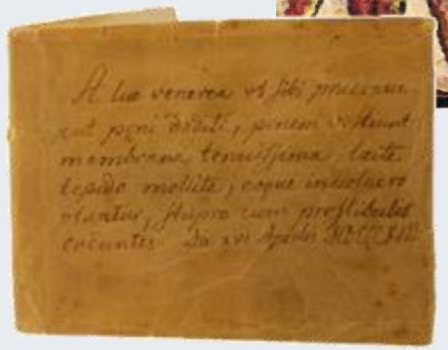
1000 C.E. sta[illegible] specifically to prev[illegible]

Current market $18 BILLION/year

Replaced by inte[illegible] ength and more comfortable

Goodyear rubber vulcanization leads to modern condoms:
1860s, made to fit, reusable
1920s latex

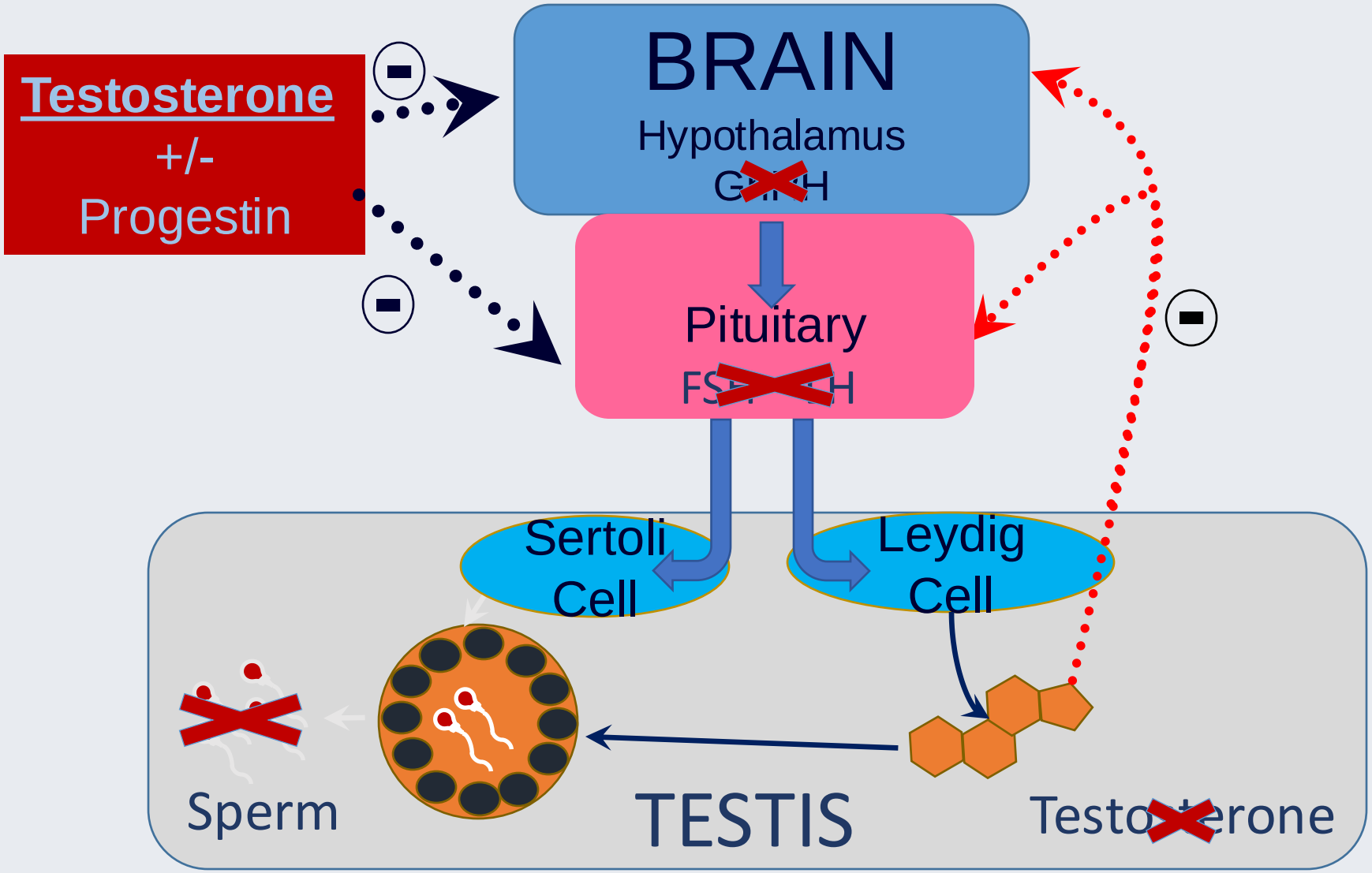




Mechanism of Hormonal Action

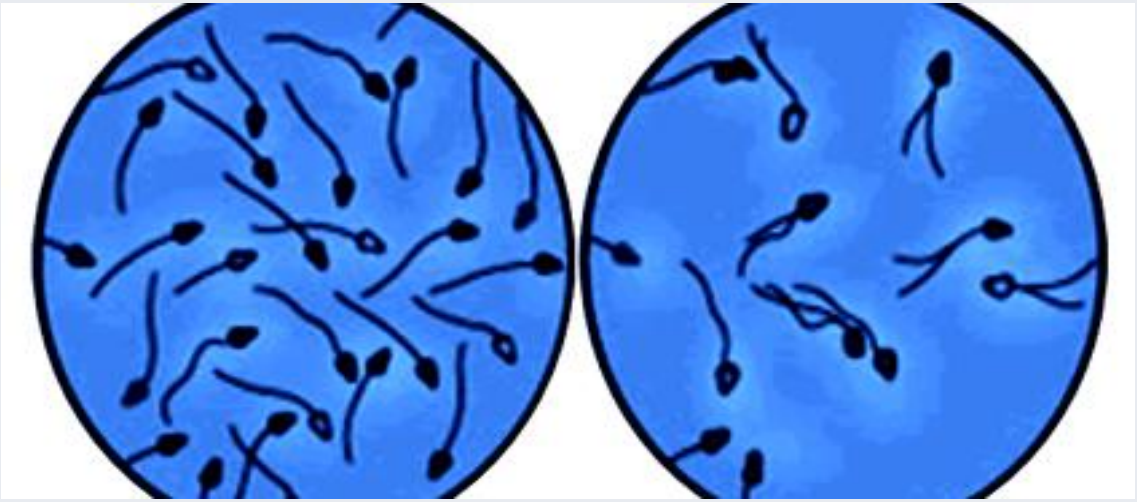
- Hypothalamic-Pituitary-Testicular Axis:
  - Suppression of LH/FSH secretion.
  - Reduction in intratesticular testosterone.
- Effect on Spermatogenesis:
  - Prevention of sperm maturation.
  - Enhanced apoptosis of spermatocytes.

Male Hormonal Contraception: How it Works



Issues in hormonal regimen choice

- How low to go?
  - Fertile ejaculate: >15 million sperm/mL
  - Severe oligozoospermia: <1 million sperm/mL, fertility= 1%/year
- Sperm rebound
  - Occurs in 2-7%
  - Ongoing monitoring?
- Reversibility
- Side effects: weight gain, lipid abnormalities, LMM, libido, mood, hepatotoxicity



Possible hormonal regimens

- Androgen alone
  - Testosterone
- Androgen + Progestin
  - More potent suppression of sperm production
  - More rapid suppression
  - Less T required
- Single agent with dual efficacy

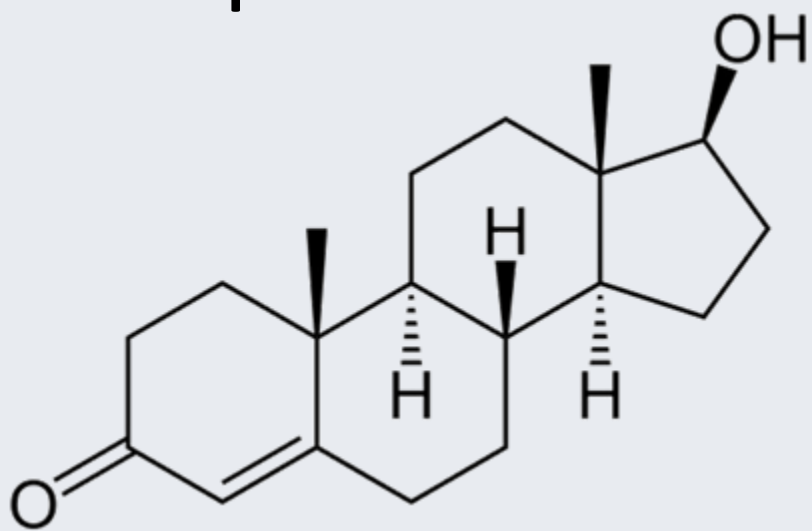
Testosterone alone

- Weekly injectable (Gu 2003, China)
  - Failure: pregnancy, failure to suppress completely, sperm rebound
  - 296 couples, **5.2% failure**
- Monthly injectable (Gu 2009, China)
  - 855 couples, **6.1% failure**
- Less effective in non-Chinese populations
- Oral formulations?
  - po methyl-T is hepatotoxic at physiologic doses
  - po T undecanoate 2-3x/day dosing
  - Lipophilic T po formulations require dosing with fatty meal

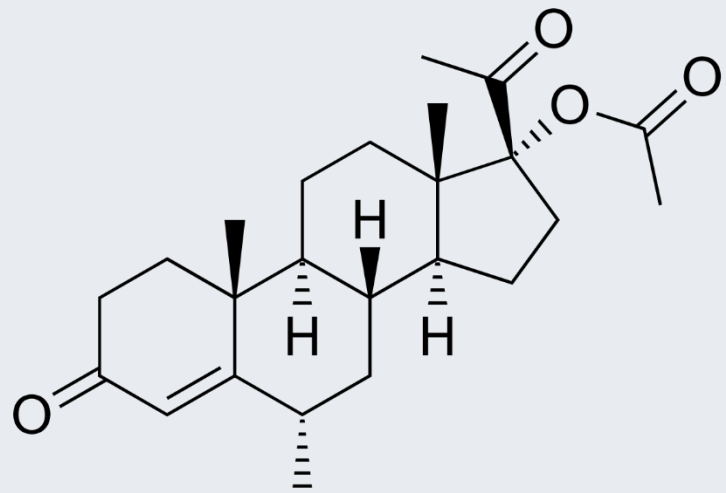
Androgen + Progestin Combinations

Androgen

- T undecanoate IM
- T enanthate IM
- T transdermal gel
- T implants

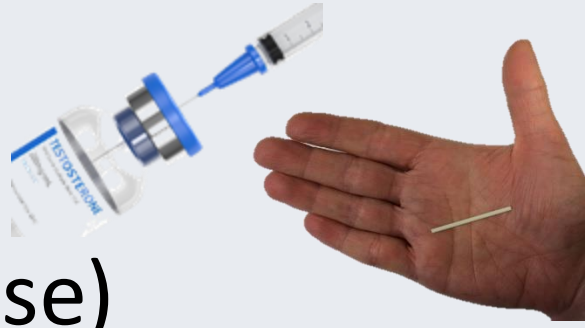


Progestin



- DMPA IM
- MPA po
- Norethistrone IM
- ENG implants
- Cyproterone acetate po
- LNG po, implant
- Segesterone gel

Example: Injection + implant



- TU (IM q 12 wks) + ENG implant (low or high dose)
  - 354 men
  - 44 weeks, 24 week F/U
  - <1 million/mL in 89% of men (94% in high TU groups)
  - Suppression maintained in 91%
  - 3% always >1 million/mL
  - Adverse events reported by 93% of men in treatment group

  …and 81% of men on placebo

Mommers E, et al. J Clin Endocrinol Metab 2008; 93: 2572–2580.

Example: Injection only

- 200-mg norethisterone enanthate (NETE) + 1000-mg testosterone undecanoate (TU), q8 weeks.
- 320 men at 10 centers, 95.9% suppressed by 6 months
- 4 pregnancies occurred: Pearl Index 2.18
- Study stopped early for “safety reasons”
  - Pain at injection site
  - Increased libido
  - Mood changes
    - 99% mild or moderate, concentrated at 1-2 sites

Behre HM, et al. Efficacy and Safety of an Injectable Combination Hormonal Contraceptive for Men. J Clin Endocrinol Metab. 2016 Dec;101(12):4779-4788.

Transdermal Gel for Male Hormonal Contraception: self-delivery

- Advantages of segesterone over other progestins:
  - No androgenic, estrogenic or glucocorticoid activity; fewer SE
  - Less androgenic within the testes
  - Shorter acting, topical formulation may accelerate recovery

Nes+Tes Gel = 6 month sperm suppression study in men: 93% effective

Ilani and Roth et al JCEM 2012

Nes-Tes Male Hormonal Contraceptive Efficacy Trial Underway

- 420 couples, UW and UCLA
  - 9 sites (Europe, USA, S. America, Africa)
- Sperm concentration monitored throughout; 12 month efficacy phase
- First user-controlled male method to reach efficacy trial
- NICHD and Population Council sponsored

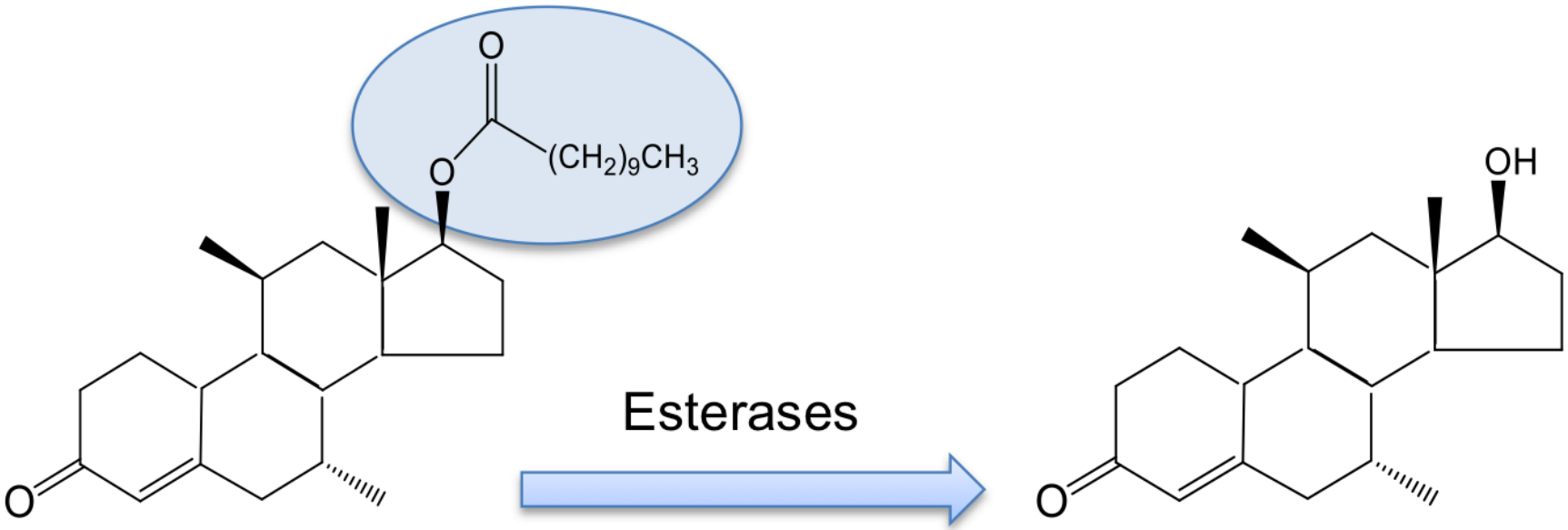
GnRH Antagonists + Androgens

- GnRH agonists
  - Downregulation of GnRH receptors
  - suppression of gonadotropins
  - reduction of intratesticular T and spermatogenesis
  - With required addback T, only weak suppression
- GnRH antagonists
  - Azoospermia achieved in high proportion of volunteers
  - Daily to weekly injections
    - Long-acting GnRH antagonist: no benefit
  - High cost
  - Orally active relugolix + orally active testosterone?

Modified Androgens

- Possible single agent 19-norT derivatives
  - Retain androgen effects of testosterone
  - Incorporate progestogenic activity
- Modified for
  - oral bioavailability
  - decreased hepatic toxicity
  - longer half-life

Dimethandronolone undecanoate (DMAU): single agent male contraceptive?



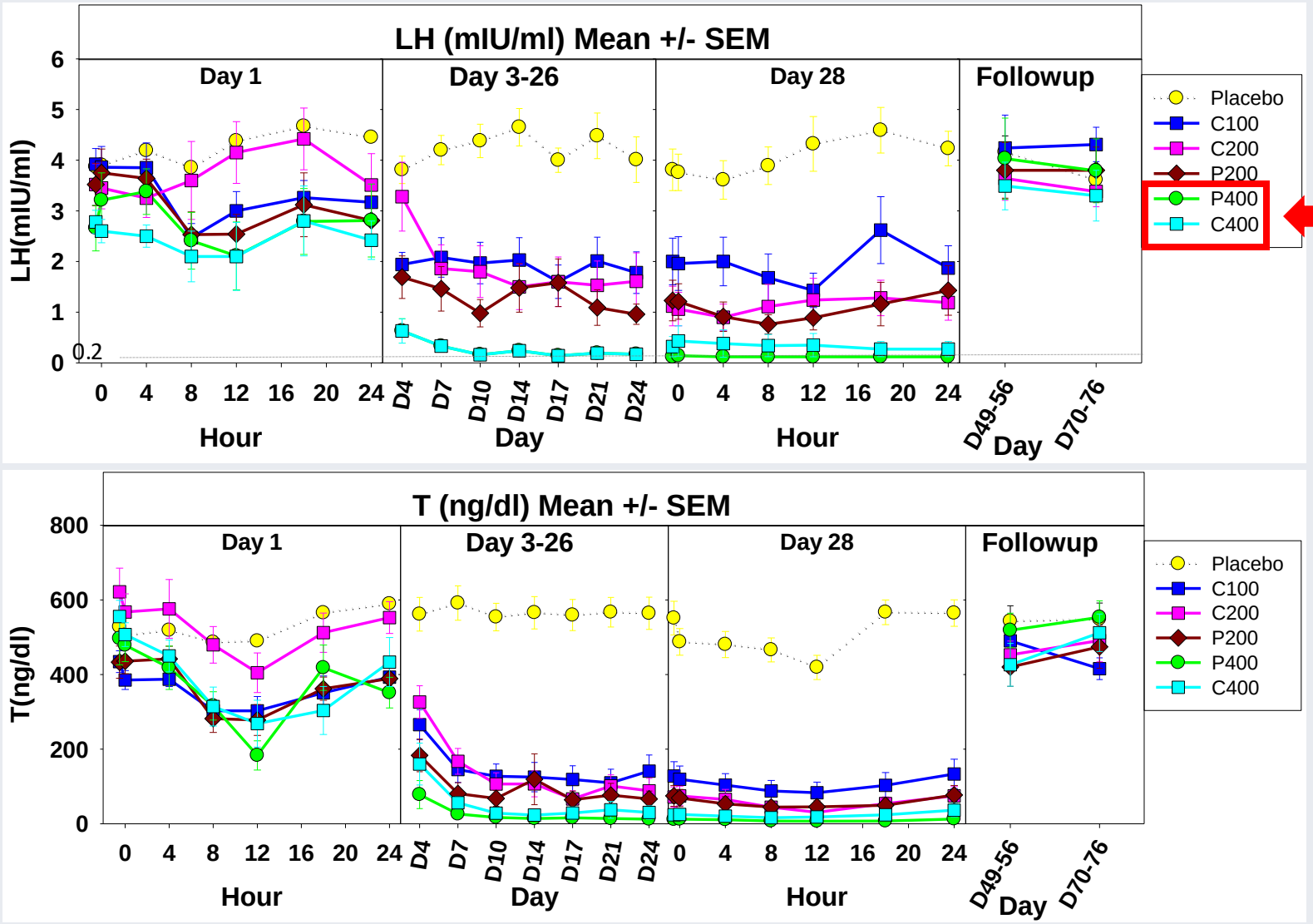
CDB-4521, DMAU
DMA undecanoate

CDB-1321, DMA
Dimethandrolone

- Oral DMAU: both progestin and androgen effects *in vitro and in vivo* without hepatic toxicity
- Reversible contraceptive in rabbits

Attardi et al Endocrinol 2006
Hild et al 2008

Oral DMAU suppresses hormones required for sperm production in men



Thirumalai et al JCEM 2018

Could DMAU become the Male Pill?

Maybe!

- Men had VERY low Testosterone, but few symptoms of **Low T**
- No significant safety concerns were identified at any dose tested.
- Mild weight gain and cholesterol changes, ?libido

Next step: Longer study (3 months) to establish safety and sperm suppression

“Depo-Provera” for Men: long-acting injectable DMAU

- DMAU given IM reversibly suppresses spermatogenesis for 1 year in non-human primates
- Phase 1 PK/PD trial underway
  - 84 subjects
  - 4 doses or placebo
  - SC or IM

Take-Home: Hormonal Contraception

- Mechanism: Suppression of gonadotropins (LH, FSH) to inhibit spermatogenesis.
- Key Approaches:
  - Testosterone and progestins (e.g., Nestorone gel).
  - GnRH antagonists.
  - Modified androgens (e.g., DMAU).
- Advantages: Reversible and effective.
- Challenges: Variability in response, side effects (e.g., mood changes, acne).

Why non-hormonal male contraception

- Avoids impact on T concentration, sexual function
- No sports disqualification
- Several tested in small mammals or non-human primates
  - none yet tested in men

Approach to Non-Hormonal contraception

- Methods that target sperm function or production without hormonal pathways.

- **Development Approaches:**
  - Target-based chemical screening.
  - Identification of testis-specific proteins (e.g., GAPDHS).
  - Innovative drug delivery systems.

Mechanisms of Non-Hormonal Action

- **Spermatogenesis Inhibitors**
  - Small molecules disrupting meiosis.
- **On-Demand Options**
  - Rapid-acting agents like triptonide.

Sperm Function Inhibitors

- Soluble adenylyl cyclase (sAC) inhibitors to reduce motility.
- Ion channel blockers (e.g., CatSper, Slo3).

Examples of Non-Hormonal Methods

- **Pre-Clinical Candidates:**
  - GAPDHS inhibitors disrupting energy metabolism.
  - sAC inhibitors for reversible, on-demand contraception.
- **Clinical Trials:**
  - YCT-529 targeting retinoic acid receptors.
  - Triptonide: Non-hormonal reversible agent.

Non-hormonal male targets

- Adjudin: antisperm--disrupts adhesion of spermatids to Sertoli cells
  - High cost, possible anti-FSH antibodies
- H2-gamendazole: antisperm, impairs apical ectoplasmic specialization
  - 43% of rats remained infertile
- Immunization against semen protein Eppin produces reversible sterility in non-human primates
  - Small molecular inhibitors of Eppin binding
- Blockade of retinoic acid function or biosynthesis
  - Retinoic acid receptor antagonists successful in rats

Non-hormonal agents in development

AGENT	MECHANISM OF ACTION	SURROGATE MARKER OF EFFICACY
Retinoic acid receptor antagonists or synthesis inhibitors[23]	Inhibition of retinoic acid signaling leads to a block in spermatogonial differentiation, spermiogenesis, and spermiation	Absence of, or very few sperm on semen analysis
YCT-529[†]	*Inhibitor of retinoic acid receptor-alpha (RAR-alpha).*	*First safety study ongoing NCT06094283*
Testis-specific Bromodomain inhibitors[24]	Blockade of chromatin remodeling leading to a cessation of spermatogenesis	Absence of, or very few sperm on semen analysis
EPPIN (Epididymal Peptidase Inhibitor)[18]	Blockade of Eppin-semenogelin interaction in semen	Inhibition of sperm liquefaction and motility on semen analysis
Ion channel targets (Catsper, SLO3)[25]	Inhibition of calcium or potassium influx into sperm	Reduction in sperm motility on semen analysis
Soluble adenylate cyclase[26]	Inhibition of cAMP production in sperm	Reduction in sperm motility and capacitation markers on semen analysis
Testis Specific Serine/Threonine Kinases[27]	Inhibition of post-meiotic spermiogenesis	Absence of sperm with normal morphology on semen analysis
Triptonide (SPEM1)[28]	Inhibition of SPEM1 interactions	Absence of sperm with normal morphology on semen analysis

Devices

- Reversible vas occlusive polymers
  - Vasogel
  - ADAM
- Implantable valve
  - Bimek SLV
- Thermal devices
  - Androswitch

Regulatory challenges

- Mechanism of action
- Efficacy thresholds
- Potential adverse effects
- Phase III studies
- Reversibility

Special considerations for side-effects

- What is acceptable when risks and benefits accrue to different patients?
- Maternal medication withheld or changed during pregnancy to protect a fetus
  - Seizure meds
  - Psychiatric meds
  - Anticoagulation
- Major surgery on well women to repair structure of fetus
- Transplant

- **Key Takeaways:**
  - Male contraception is advancing with diverse options.
  - Hormonal methods are effective and nearing market readiness.
  - Non-hormonal methods show promising pre-clinical and clinical results.
- **Call to Action:**
  - Physicians' role in patient education and advocacy.
  - Support for ongoing research and funding.

Conclusions

- For social, medical, economic, and planetary well-being, there is room to improve contraception!
- Safer
- Greener
- Combining with HIV and STI prevention
- Involving men
- **Requires investment in basic and translational research**

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Questions?

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