Male Hormonal Contraception: New Options

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Disclosures

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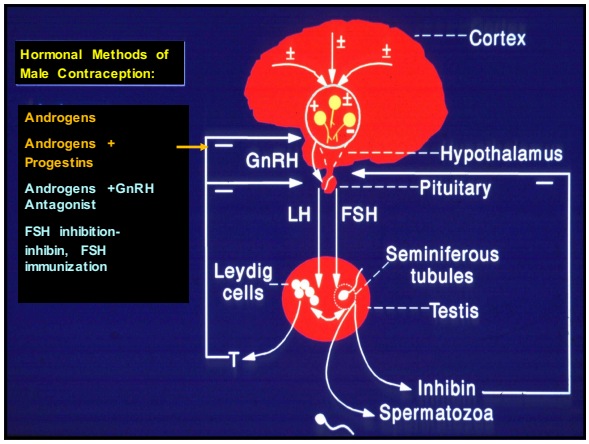
- Lipocine, TesoRX (Temporary advisor)

Male Hormonal Contraception

- Currently available methods include condom (high user failure rate) and vasectomy (considered irreversible)
- A variety of male contraceptive methods should be available to men to meet the needs of different cultural and ethnic backgrounds
- Focus on hormonal male contraception though a number of new leads (testicular and post-testicular) are being investigated



Older Steroidal Molecules/Esters/Formulations for Male Contraception

Androgen

- Testosterone esters enanthate and undecanoate
- Testosterone pellets

Progestin

- Depo-Medroxyprogesterone injections
- Levonorgestrel Oral and Implants
- Desogestrel Oral, Etonogestrel Implants

Efficacy of Male Hormonal Contraception

(adapted from Wang, Festin, Swerdloff 2016)

Study	Sperm Conc. Threshold million/ml	# Enrolled/ # completing suppression	# Reaching Threshold	Pregnancy/ Failure Rate (Pearl Index)
WHO 1990	0	271/225	157 (70%)	0.8 (0.0-4.5)
WHO 1996	< 3	399/357	349 (98%)	1.4 (0.4-3.7)
Turner 2003	<1	55/55	53 (94%)	0 (0-8)
Gu 2003	<1	308/308	299 (97%)	2.3 (0.5-4.2)
Gu 2009	<1	1045/898	855 (95%)	1.1 (0.4-1.8)
WHO/Conrad	<1	320/283	274(96%)	2.2(0.8-5.8)

WHO - T enanthate 200 mg/week IM
Gu - T undecanoate 1000mg loading , 500 mg/month IM
Turner - T implants 800 mg/4-6 month + DMAP 300mg/3 month IM
WHO/CONRAD - T undecanoate 1000mg +Net-EN 200mg/8 weeks IM

Efficacy of Male Hormonal Contraception

(adapted from Wang, Festin, Swerdloff 2016)

- Male hormonal contraceptive efficacy studies indicate that the method is as effective as many female hormonal contraceptives with comparable failure rates
- Will hormonally suppressed spermatogenesis recover?

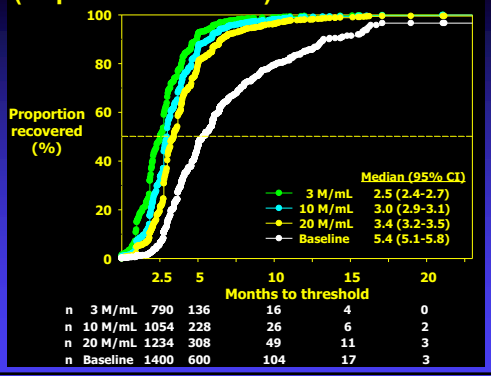
Suppression and Recovery of Spermatogenesis in Male Contraceptive Clinical Trials

- De-identified individual subject data provided by investigators of 30 studies published/submitted for publication between 1990-2006
- 1756 healthy (by physical, blood and semen exam) men aged 18-51 years of predominately Caucasian (two-thirds) or Asian (one-third) descent. This represents about 85% of all the published data.

Liu et al, 2006, 2008

Recovery to Different Sperm Thresholds (Kaplan-Meier Plots)

Liu et al 2006



New Steroidal Molecules/Esters/Formulations for Male Contraception

Androgen

- MENT Acetate (7α-methyl-19-nortestosterone)
- Dimethandrolone Undecanoate (7α, 11β-dimethyl-19-nortestosterone 17β undecanoate)
- Oral nanomilled testosterone
- New testosterone undecanoate in SEDDS
- 11 beta-methyl-19-nortestosterone

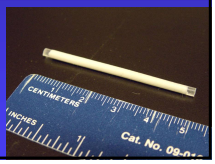
Progestin

- Nestorone
- Levonorgestrel Butanoate

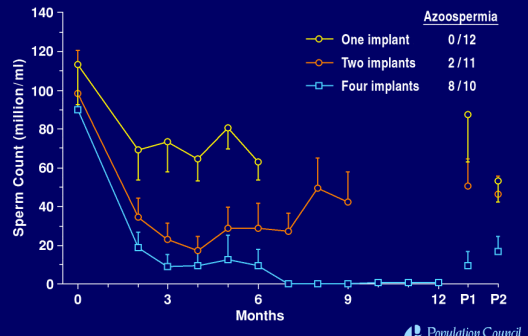
7 α - Methyl - 19 - Nortestosterone (MENT)

- MENT does not undergo 5 α reduction but is aromatized to 7 α - methyl estradiol
- About 10 to 12 times more potent than T in suppression of gonadotropins and only 3-4 times more potent in stimulating prostate growth in castrated animals (rats, monkeys)

(Agarwal et al, 1988; Kumar et al, 1992; Sundaram, 1995)



Effect of MENT Ac Implants on Sperm Count



Von Eckardstein S et al JCEM 2003

Population Council

NES+ T Gels Study Rationale

- Develop a provider independent, user friendly male contraceptive
- Gels applied to skin deliver relatively stable levels of both Testosterone (T) and Nestorone (NES)
- NES has no estrogenic, androgenic or glucocorticoid activity and very potent
- Pilot study with NES + T gels showed significant and effective suppression of gonadotropina

Nestorone and Testosterone Gels for Male Contraception

NICHD, NIH: Contraceptive Clinical Trials Network Centers (Male area), Contraceptive Research Centers
Program Director: Diana Blithe, PhD
Medical Monitor: Alicia Christy, MD

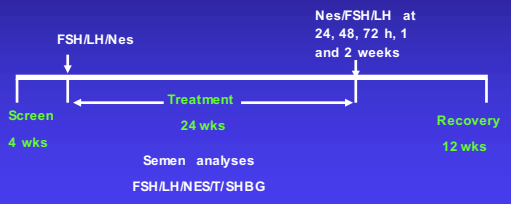
Population Council :
Investigators: Regine Sitruk-Ware, MD
Narender Kumar, PhD

Los Angeles Biomedical Research Institute at Harbor-UCLA
Investigators: Ronald S. Swerdloff, MD (Center Director)
Christina Wang, MD (PI CCN 005, 005A, 007)
Peter Liu, MD, PhD

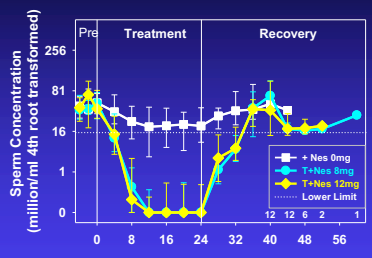
University of Washington
Investigators: William J. Bremner, MD, PhD (Center Director)
John Amory, MD (PI CCN005/007)
Stephanie Page, MD, PhD
Mara Roth, MD (PI CCN005A)

NES + T Gels Study Design

3 groups: T gel 10 g/day + Nes 0 mg/day
T gel 10 g/day + Nes 8 mg/day
T gel 10 g/day +Nes 12 mg/day

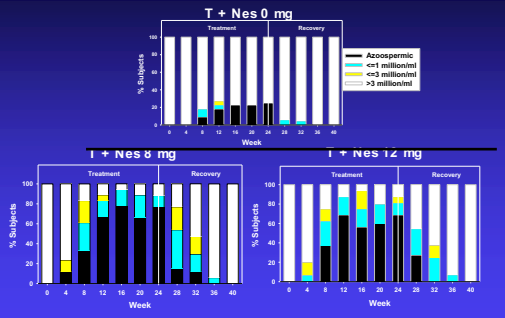


Sperm Concentration (million/mL) In Efficacy Eligible subjects (Median, 25 and 75 percentile)



Ilani et al, JCEM 2012

Percent Men With Sperm Concentrations Suppressed to 0, ≤1, ≤3, > 3 million/ml



Ilani et al, JCEM 2012

What are next steps?

- Nes gel very effective in suppressing spermatogenesis together with T gel with few adverse events
- Transdermal preparation may have less adverse effects than other modalities of delivery of steroids
- Combined T and NES gel showed equivalent suppression of gonadotropins
- Adherence issues with user friendly but non-provider dependent methods

NES+ T Gel Phase 2b study

- Contraceptive Efficacy Study with combined testosterone and nestorone gel to start in 2017
- Nine centers in US, Europe (UK, Sweden, Italy), South America (Chile) and Africa Kenya)
- 4 months suppression phase and 12 months efficacy
- 350 couples to be enrolled, expecting a bout 210 couples completing this 18 months study
- Primary end point pregnancy in partner
- Need accurate assessment of adherence to treatment
- Safety and tolerability (mood changes)
- Acceptability in male and female partners

Evaluation of Nestorone® (NES) and Testosterone (T) Combination Gel for Male Contraception (Phase 2b)

Screening

Suppression 16 wks | Efficacy 52 weeks | Recovery 24 weeks

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Parameters to be assessed at enrollment and then :

Male: Weekly phone calls or text message

Monthly visits for semen analyses, NES and other hormone levels

Safety labs every 3 months

PHQ9, Psychosexual questionnaire and IPSS every 3 months

Male acceptability questionnaire every 6 months

Contraceptive use, sexual activity every month

Female: Every 3 months, option to attend more frequently

Monthly calls in between visits

Bleeding and coital diary

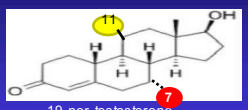
Female acceptability questionnaire every 3 months

Pregnancy test at screening, entering suppression and efficacy,

Dimethandrolone

- 7 alpha, 11beta-dimethyl-19-nortestosterone (Dimethandrolone, DMA)

DMA



19-nor-testosterone

7 alpha methyl

11 beta methyl

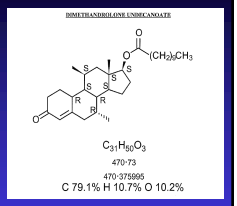
- DMA has enhanced androgen receptor binding (Cook et al, 2005)
- Not aromatized and 5 alpha reduction not necessary for its activity (Attardi et al, 2008)

Dimethandrolone Undecanoate

Preclinical Studies (rats and rabbits), DMAU

- Suppresses serum LH
- Has androgenic and progestational activity
- Suppresses sperm counts and 2.5 mg/Kg in rabbits

(Attardi et al, 2006, 2010)



Preclinical toxicology studies in rats and monkeys showed androgenic effects and no toxicity

Phase 1 Clinical Study of DMAU in Men

Primary Endpoint

- Safety and tolerability of DMAU

Secondary Endpoint

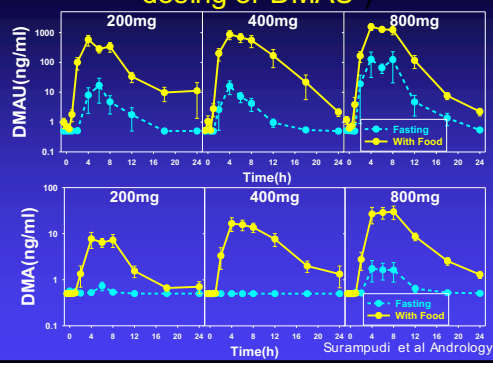
- Pharmacokinetics of DMA and DMAU
- Effect of food on the highest tolerable does of DMAU (single dose study)
- Suppression of serum LH, FSH and testosterone (28 day repeat dose study)

Tolerability and Safety of DMAU

- No serious adverse events (AE)
- Acne in 2 participants possibly related to DMAU, other AEs not related to study medications
- No clinically significant changes in blood counts, clinical chemistry and EKGs including QCT interval

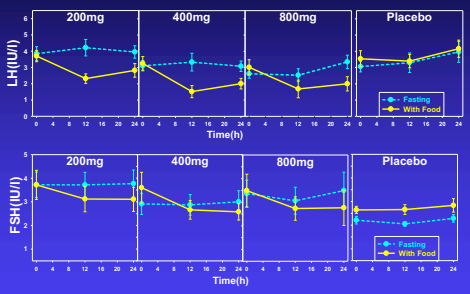
Surampudi et al Andrology 2014

Serum DMAU and DMA after oral dosing of DMAU



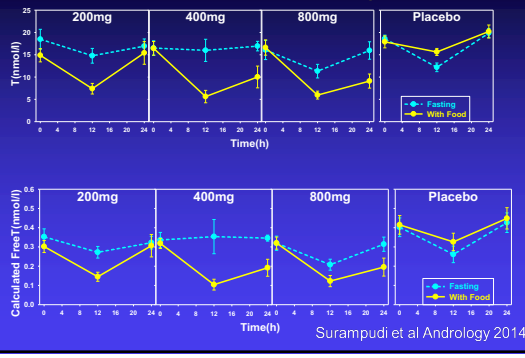
Surampudi et al Andrology 2014

Serum LH, FSH and T Levels after Single Oral DMAU dosing



Surampudi et al Andrology 2014

Serum T and Calculated Free T after Oral DMAU Dosing



Surampudi et al Andrology 2014

Next Steps for DMAU

- 28 days repeat dose study for safety and tolerability, pharmacokinetics and suppression of gonadotropins ongoing
- Single IM injection of DMAU dose escalating study in castor oil with benzyl benzoate will begin in June 2016
- Complete longer term primate toxicology and efficacy studies ongoing
- Determine dose for 6 months oral oo longer IM study

Hormonal Male Contraception

- Support from US National Institutes of Health, NICHD for male contraceptive development from pre-clinical to phase 3 clinical trials
- Collaboration with academia, industry, professional societies and advocacy groups
- Product available within 10 years