**Hormonal Male Contraception: Endocrine Concepts**

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**Disclosures**

- National Institutes of Child Health and Human Development  
- Clarus Therapeutics, TesoRX, Antares

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**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 while a number of new leads (testicular and post-testicular) are being investigated

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**MALE HORMONAL METHODS**

**Target Population**

- Stable monogamous union  
- Spacing and delay of family  
- Desire of male partner to share family planning responsibilities  
- Female methods unacceptable  
- Gender Equity

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**WHO Studies to Assess the Contraceptive Efficacy of Hormonally Induced Azoospermia & Oligozoospermia (Proof of Concept)**

Study 1: Will hormonally induced azoospermia by testosterone injections provide continuing protection as a male contraceptive? WHO 1990

Study 2: Will hormonally induced oligozoospermia be efficacious as a male contraceptive? WHO 1996

U.S. centers supported by CONRAD
Contraceptive Efficacy Of Injectable Testosterone-induced Oligozoospermia

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Pregnancy Rate</th>
<th>Pregnancy Rates per 100 person years (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe Oligozoospermia (0.1 to 3 M/ml)</td>
<td>49.5</td>
<td>4</td>
</tr>
<tr>
<td>Azoospermia</td>
<td>230.4</td>
<td>0</td>
</tr>
<tr>
<td>Both Groups</td>
<td>279.9</td>
<td>4</td>
</tr>
</tbody>
</table>

US Centers supported by CONRAD WHO, 1996

Male Hormonal Contraception

- Phase 3 multicenter study in China
- 1045 men (age 20-45 yr)
- Testosterone Undecanoate 1000 mg loading followed by 500 mg IM every 4 weeks for 30 months
- 855 men entered efficacy, 733 completed 30 months of TU injections

Gu et al, JCEM, 2009

Male Hormonal Contraception

- 43 men failed to suppress (4.7/100 couple yr) to sperm count < 1 million/mL
- 10 men showed sperm rebound to >1 million/mL (1.3/100 couple yr)
Method failure 6/100 couple yr
- 9 pregnancies (6 in those who showed sperm rebound)
Contraceptive failure rate 1.1 /100 couples yr

Gu et al, JCEM, 2009

Efficacy of Injectable Combined Hormonal Contraception for Men

- Suppression: 95.9/100 users (95% CI 92.8 to 97.9) suppress to sperm count < 1 million/mL by 24 weeks
- Contraceptive Efficacy: 4 pregnancies in 266 couples, 1.57/100 users (95% CI 0.59 to 4.14). Pearl Index 2.19/100 person years (95% CI 0.82-5.80)
- Maintenance: 3 men sperm counts rebound within 3 months.
- Recovery: 94.6/100 users (95% CI 91.5-97.1) by 52 weeks.

Behre et al, JCEM 2016

Androgens and Progestins for Male Contraception

Pros
- Addition of a progestin increases the rate extent of spermatogenesis suppression (Liu et al JCEM 2008)
- Combination of androgens and progestins may reduce the dose of androgen required to achieve contraceptive efficacy

Cons
- Combination may have more adverse effects than androgens alone
- Combination regimens are more complex and the optimal steroid combinations, formulations and doses have to determined.
Recovery to Different Sperm Thresholds (Kaplan-Meier Plots)
Percent Men With Sperm Concentrations Suppressed to 0, ≤ 1, ≤ 3, > 3 million/ml

Week
0 4 8 12 16 20 24 28 32 36 40

% Subjects
0 20 40 60 80 100

Azoospermic
≤1 million/ml
≤3 million/ml
>3 million/ml

Treatment
Recovery

Nestorone + Testosterone Gel Study

• No serious adverse event
• No skin irritability at application site
• Acne in 21% and weight gain in 7% of men
• Changes in mood and sexual function were similar in the testosterone versus the testosterone + nestorone groups

Transdermal Nestorone and Testosterone: Issue

• Possible transfer of both hormones from men to another persona on close skin contact
• Must wear protective clothing or shower before close contact with women or children
• We studied the transference of both hormones from men to women upon skin contact under direct version

Testosterone and Nestorone Contraceptive Efficacy Study

• Contraceptive Efficacy Study with combined testosterone and nestorone gel
• 4 months suppression phase and 12 months efficacy with 350 couples to assess pregnancy in partner
• Assessment of adherence to treatment
• Safety and tolerability and acceptability
• 9 centers in 4 continents, supported by NICHD to start in 2nd quarter 2018

Average Serum T (ng/dl) Levels after T/NES Gel Application with male wearing a T shirt, after a shower and no intervention

Average Serum Nestorone (pg/ml) Levels after T/NES Gel Application with male wearing a T shirt, after a shower and no intervention

Average Serum T (ng/dl) Levels after T/NES Gel Application with male wearing a T shirt, after a shower and no intervention

Average Serum Nestorone (pg/ml) Levels after T/NES Gel Application with male wearing a T shirt, after a shower and no intervention
Clinical Evaluation of Nestorone® (NES) and Testosterone (T) Combination Gel for Male Contraception (Phase 2b)

**Primary Endpoint**

- Twelve-month (365 days) cumulative contraceptive efficacy (during the efficacy portion of the study)
- Kaplan-Meier methods to estimate the twelve-month cumulative pregnancy probability (and 95% CI) in the typical use population.

Androgens with progestational activities:

- Dimethandrolone Undecanoate
- 11-Beta methyl 19-Nortestosterone 17-β dodecylcarbonate

DMAU for male contraception, a new option for contraception?

- DMA is more potent than testosterone, thus DMAU at a low dose may have the same efficacy as testosterone
- DMA has both androgenic and progestational activity, then DMA may be used as a single agent for male hormonal contraception

Conversion of DMAU to DMA

- DMA has enhanced androgen receptor binding activity compared to testosterone (Cook et al, 2005) and has same binding activity to progesterone activity
- DMA is not aromatized and 5 alpha reduction is not necessary for its activity (Attardi et al, 2008)

Tolerability and Safety of DMAU

Phase 1 study

- Three formulations,
- Single dose
- Dose ranging from 100 to 800 mg dose
- No serious adverse events (AE)
- Acne in 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
Next Steps for DMAU

- Completed 28 days repeat dose study for safety and tolerability, pharmacokinetics and suppression of gonadotropins
- Preliminary data showed marked suppression of LH, FSH and T
Suppression of Serum T after 28 days dosing of oral DMAU

Adverse Events after Oral Dosing of DMAU
- No Serious Adverse Event
- No changes in mood, some men had changes in libido
- As anticipated decreases in SHBG and HDL-cholesterol were observed

Next Steps for DMAU and other SARM
- Completed longer term primate toxicology studies
- Started Single IM/SC injection of DMAU dose escalating study in castor oil with benzyl benzoate
- Spermatogenesis suppression study in 2018
- Single dose, dose-esc17-β dodecylcarbonate alating of second novel androgen 11β-methyl-19-nortestosterone

Are Men Willing to Use New Male Contraception Method?
Yes, the time as come for male to have a reversible user friendly effective, safe contraceptive