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Reversible Contraceptive Method for Men

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Introduction

- Unintended pregnancy remains a major problem for the United States as well as globally.
- Most effective contraceptives for women are hormonal agents; however, many women are unable or unwilling to take hormones at some point during the three to four decades of reproductive age in their lives.
- Methods of male contraception are limited to condoms and vasectomy.
- Couples may want to share family planning responsibilities
Our goal is to develop a contraceptive method for men that proves effective, safe, reversible, self delivered, user friendly and affordable.
The Hypothalamus-Pituitary-Gonadal Axis

A) Normal

1. Hypothalamus
   - GnRH

2. Pituitary
   - LH
   - FSH
   - Inhibin

3. Leydig cells
   - Testosterone (T)
   - LH

4. Sertoli cells
   - Testosterone (T)
   - FSH

5. Germ cells

6. Testis

B) With Testosterone or with Progestins

1. Hypothalamus
   - GnRH

2. Pituitary
   - LH
   - FSH
   - Inhibin

3. Leydig cells
   - Testosterone (T)
   - LH

4. Sertoli cells
   - Testosterone (T)

5. Germ cells

6. Testis

7. Exogenous Testosterone (T) or + Progestins

8. Apoptotic Signal

9. Inhibin (-)
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
Efficacy of Hormonally Induced Azoospermia and Severe Oligozoospermia

- Testosterone weekly injections (a prototype) were used as the only contraceptive agent in two multicenter studies in over 700 couples.
- When azoospermia was achieved, there was 1 pregnancy during 1486 months of efficacy phase.
- When severe oligozoospermia (< 3 Million/ml ejaculate) was attained there were 4 pregnancies in 279.9 person years of exposure, Pearl rate of 1.4 (0.4 to 3.7) per 100 person years.

Androgens and Progestins

- Azoospermia however does not occur in more than 70% of non Asian men
- Addition of a progestin increase the efficacy of suppression of spermatogenesis to very low sperm concentration
- Contraceptive efficacy study of T pellets 800 mg once every 4 months plus Depo-medroxyprogesterone acetate 300 mg IM every 3 months
- Two center study in Australia
- Azoospermia in 94% of men
- No pregnancy in 36.4 person years
- Prolonged suppression of spermatogenesis with DMPA

Turner et al 2002
Male Hormonal Contraception

- Phase 3 multicenter study in China
- 1045 men (age 20-45 yr)
- TU 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
Male Hormonal Contraception

- 43 men failed to suppress (4.8%) to sperm count < 1 million/mL
- 10 men showed sperm rebound to >1 million/mL (1.3%)
Method failure 6.1%

- 9 pregnancies (6 in those who showed sperm rebound) in 1554 person years
Contraceptive failure rate 1.1 /100 men
- No serious adverse events

Gu et al, JCEM 2009
Male Hormonal Contraception

- Male hormonal contraceptives are as effective as female oral birth control pills in preventing pregnancies.
- Clinical trials in male hormonal contraception have progressed to where it is possible to suppress sperm counts to or near zero in most men with androgens alone (Phase 3 studies in China) or in combination with progestins.
- Current studies aim to find the best combination of androgens and progestins.
Recovery to Different Sperm Thresholds (Kaplan-Meier Plots)  

Liu et al 2006

Months to threshold

Proportion recovered (%)

Median (95% CI)

- 3 M/ mL: 2.5 (2.4-2.7)
- 10 M/ mL: 3.0 (2.9-3.1)
- 20 M/ mL: 3.4 (3.2-3.5)
- Baseline: 5.4 (5.1-5.8)

n
- 3 M/ mL: 790, 136
- 10 M/ mL: 1054, 228
- 20 M/ mL: 1234, 308
- Baseline: 1400, 600

n
Why study transdermal Testosterone & Nestorone?

- Transdermal steroid preparations form a reservoir in the subdermal tissues. The steroids are released gradually resulting in a relatively steady serum steroid levels.

- Transdermal Testosterone is the most user friendly method of testosterone delivery available. Studies showed dose-proportional steady serum testosterone levels after daily application.

- Nestorone is a pure progestin without androgenic or estrogenic activities and may have less adverse effects compared with other progestins. Transdermal Nestorone has been tested in females.
Our prior study showed that a high percent of subjects had suppressed LH or FSH after application of Nestorone and Testosterone gels for 3 weeks

<table>
<thead>
<tr>
<th>Percent subject with suppressed LH &amp; FSH</th>
<th>&lt; 0.5 IU/L No.</th>
<th>&lt;0.5 IU/L %</th>
<th>&lt; 1.0 IU/L No.</th>
<th>&lt;0.1 IU/L %</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-10 g (18)</td>
<td>4</td>
<td>21.1</td>
<td>6</td>
<td>31.6</td>
</tr>
<tr>
<td>Nestorone 2 mg (16)</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
<td>6.3</td>
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<tr>
<td>Nestorone 4 mg (16)</td>
<td>0</td>
<td>0.0</td>
<td>2</td>
<td>12.5</td>
</tr>
<tr>
<td>T-10g Nestorone 2mg (19)</td>
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<td>36.8</td>
<td>11</td>
<td>57.9</td>
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<tr>
<td>T-10g Nestorone 4mg (15)</td>
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<td>40.0</td>
<td>8</td>
<td>53.5</td>
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<tr>
<td>T-10g Nestorone 6mg (18)</td>
<td>11</td>
<td>61.1</td>
<td>13</td>
<td>72.2</td>
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<tr>
<td>T-10g Nestorone 8mg (16)</td>
<td>11</td>
<td>68.8</td>
<td>13</td>
<td>81.3</td>
</tr>
</tbody>
</table>

Mahabadi et al, 2009
Nestorone alone has some gonadotropin suppression activity, T gel alone or in combination with Nestorone gel suppresses gonadotropin more than Nestorone gel alone.

This suggests that Nestorone +T gel may be effective in suppressing spermatogenesis.

No clinically significant changes in body weight, total LDL cholesterol, hemoglobin or hematocrit levels with any of the treatment groups. HDL decreased in all T treated groups.

Mahabadi et al, 2009
A Multicenter, Randomized, Double-Blind Comparator Trial of the Safety and Sperm and Gonadotropin Suppression Resulting from Combined Use of Nestorone Gel (0, 8 or 12 mg NES) and Testosterone Gel (10 g)

Supported by NIH, NICHD as part of the Male Contraceptive Clinical Trials Network Center at Harbor-UCLA/LA BioMed and University of Washington
Study Design

- 120 healthy men (age 18-50) with sperm concentration above 15 million/ml will be randomized to one of three groups:
  - Group 1: T Gel 10 g and NES 0 mg (placebo gel) per day
  - Group 2: T Gel 10 g and NES 8 mg per day
  - Group 3: T Gel 10 g and NES 12 mg per day

- Three phases:
  - Pretreatment screening phase (2-10 weeks)
  - Treatment 24 weeks
  - Recovery phase 12 weeks or till sperm concentration > 15 million/ml

- 18 visits: Semen samples, blood for hormones and safety labs, psychosexual questionnaire, acceptability of gels
Principal Outcomes

Primary outcome:
- Suppression of sperm production ≤1 million/mL at the end of treatment phase.

Secondary outcome:
- Suppression of sperm production ≤ 3 million/mL or azoospermia
- Suppression of gonadotropins (FSH and LH) and correlation of gonadotropin suppression with sperm suppression.
- Sperm morphology and motility in men who are not azoospermic.
- Safety monitoring
Hormonal Male Contraception: Importance of Tight Junctions in the Blood-Testis Barrier
Suppression of Spermatogenesis in Male Hormonal Contraception

- Our group has previously shown that increase apoptosis is the major cause of decrease in sperm output after hormonal male contraception in rodents, monkeys and men.
  

- We have not investigated changes in BTB in experimental male hormonal contraception.
Background

- Blood Testis Barrier (BTB) is created by tight junctions between Sertoli cells near basal lamina.
- BTB restricts diffusion of solutes to adluminal compartment and provides immunological barrier.
- During spermatogenesis spermatocytes must migrate through the BTB while undergoing meiosis and differentiation into haploid spermatids.
- BTB composed of several critical proteins:
  - Occludin-present in mouse Sertoli cell but not in humans
  - Claudins (1,3,4,5,7,8 &11)
  - JAM-A
  - ZO-1.
Tight Junctions forming BTB

C. YAN CHENG AND DOLORES D. MRUK 2002
Background-Prior Studies

- Claudin 3 encodes a transient component of newly formed tight junctions.
- Sertoli cell-specific ablation of androgen receptor in mice results in a significant decrease of claudin 3 mRNA, increased permeability of the BTB.
- Claudin 3 regulates the movement of small molecules across the Sertoli cell tight junctions.
- Androgen action in Sertoli cells regulates germ cell differentiation, in part by controlling the tight junctions of the BTB.
- Hormonal strategies for male contraception using androgens may interfere with the BTB, resulting in the disturbance of movement of germ cells or increased permeability of the BTB.

Meng et al, PNAS, Nov 2005
Sertoli Cell Androgen Receptor Ablation caused loss of claudin 3

Meng et al, PNAS, Nov 2005
Objective

- Investigate the effect of exogenous administration of Testosterone (T) and Levonorgestrel (LNG) administration as experimental male contraceptives on tight junctions in human testicular biopsies.
Study Design

- Healthy male volunteers (age between 35-48 years) with proven fertility were randomized to 2 treatment groups (n=18 per group) for 18 weeks:
  - 1) T undecanoate (TU) (1000 mg IM injection of TU followed by 500 mg injection every 6 weeks
  - 2) TU + LNG 250 mcg orally daily.

- Open testicular biopsy was performed on four volunteers at baseline, and four participants from each group at 2 and 9 weeks after T alone or T + LNG treatment.
TU +LNG was more effective than TU alone in Suppression of Spermatogenesis

Wang et al 2007
Testicular sections from biopsies before and at 2 and 9 weeks after treatment subjected to Immunohistochemistry to study tight junction proteins:
ZO-1
JAM-A
Claudin 3 and 11
Occludin
Results
Vasa stains Pachytene Spermatocytes and Round Spermatids in Human Testes

Pachytene Spermatocytes and Spermatids are most susceptible cells to apoptosis induced by exogenous administration of androgens and progestins.
Number of Pachytene Spermatocytes and Round Spermatids Decreased Significantly in Human Testes after T and LNG treatment for 9 weeks
Claudin 11 showed intact BTB after T and T + LNG treatment

Control | T 9 Wks | T + LNG 9 Wks
JAM-A showed intact BTB after T and T+ LNG administration
ZO-1 showed intact BTB after T and T+LBG treatment

Control   T 9 Wks   T+LNG 9 Wks
Claudin 3 was present after T and T+LNG Treatment

Note Claudin 3 is only present in newly formed tight junctions. Thus not all the junctions are stained.
Conclusion

- Based on immunohistochemistry of tight junction proteins, BTB remains structurally intact 2 (data not shown) and 9 weeks after TU or TU+LNG treatment in men despite significant decreases in sperm concentration (decrease of spermatocytes and round spermatids) after 9 weeks treatment with T or T + LNG.
Limitations

- The longer term effect of TU alone or TU+LNG treatment on the blood testis barrier’s structural and functional integrity remains to be determined.
Acknowledgment

- Christina Wang, M.D.
- Yan-He Lue, M.D
- Ronald S. Swerdloff, M.D.
- Amiya Sinha Hikim, Phd
- Vince Atienza
- Sima Baravarian
- Alex Adler
- Christina Tsang
- Yu-Gui Cui
- Xing-Hai Wang
- Zuo-Min Zhou
- Jia-Hao Sha,
Thank You
Testosterone Undecanoate as a Potential Male Contraceptive

- Efficacy study in 208 men from 6 centers in China showed that TU administered as a loading dose of 1000 mg IM followed by 500 mg monthly injections to men was effective in inducing severe oligozoospermia in 296 (97.1%).
- This TU alone treatment prevented pregnancies in their partners for 6 months.
- TU dose administered was probably supraphysiological.

Gu et al, 2003
TU Study in China: Suppression Phase

Gu et al., 2003
TU Study in China: Efficacy Phase

Gu et al., 2003
Factors Affecting Suppression of Spermatogenesis

Hazard Ratio

Race (NonAsian vs Asian)
Progestin Use (Yes vs No)
MENT (Referent)
T pellet
T undecanoate
T decanoate
T enanthate
T pill/patch
Baseline Sperm Concentration (M/mL)
Baseline Blood T (nmol/L)
Age (years)

Liu et al, 2008
Male Hormonal Contraceptive Methods

**Advantages**

- Fully reversible
- Agents used for other clinical conditions
- Potential adverse effects known
- Toxicology of some of the agents are well defined
Male Hormonal Methods

**Disadvantages**

- Failure to achieve azoospermia in a small proportion of men
- Until recently, lack of method of providing stable, physiologic androgen substitution
- Absence of long-acting (in US) or orally active testosterone
- Requirement of a waiting period (12 weeks) before onset of efficacy
- **No protection against sexually transmitted infections**
HORMONAL MALE CONTRACEPTION
ANDROGENS & PROGESTINS

- Do androgens and progestins have additive effect on the suppression of gonadotropins?
- Which combination and at what dose will result in optimal suppression of spermatogenesis and have least adverse effects?
- Do progestins have additional direct effects on the testis?
- What other adverse/beneficial effects do progestins have to men in addition to weight gain and alterations in lipid profile?
Loss of androgen signaling in Sertoli cells increases the permeability of the BTB.
Sub-studies

- SpermCheck® sub-study to validate the use of a dipstick with a threshold detection of 1 million/mL by the lab and by the participants.

- Text message sub-study to verify (and improve) compliance (text or voice mail to remind subjects to apply gels and to send response to center, coordinators will be notified if subject not responding).
Testicular sections from biopsies before and at 2 and 9 weeks after treatment.

Immunohistochemistry:
A) Use VASA as a marker to count pachytene spermatocytes and round spermatids, cells most susceptible to apoptosis
B) to study tight junction proteins:
   ZO-1
   JAM-A
   Claudin 3 and 11
   Occludin