Male Hormonal Contraceptive

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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. Condoms have high user failure rate and vasectomy is considered an irreversible method.
- Several studies have demonstrated that effective hormonal contraception that is safe, reversible, affordable and acceptable for men is feasible.
The Hypothalamus-Pituitary-Gonadal Axis

A) Normal

B) With Testosterone implants

Exogenous Testosterone (T) (-)

Apoptotic Signal

Germ cells

Leydig cells

Sertoli cells

Germ cells

Testis

LH

FSH

Inhibin (-)

Testosterone (T) (-)

GnRH

Hypothalamus

Pituitary

Leydig cells

Sertoli cells

Germ cells

Testis
Prior studies

- Two large multicenteric clinical trial using testosterone enantate 200mg IM injection weekly, produced severe oligozoospermia (< 3 million/mL) in 98% of men and provided effective and reversible contraception for 12 months with adequate short term safety.

- Weekly injection was not widely acceptable

- Pharmacokinetic profile of TE was not ideal.

WHO 1990, 1996
Prior Studies

Testosterone undecanoate (TU) in tea seed oil provides more stable, long term release of T in the circulation, one injection of 500 mg maintain serum testosterone levels in hypogonadal men for 4 weeks (Li Mh, et al 1994, Chen ZD 1991).

TU has more favorable pharmacokinetics and pharmacodynamics. One injection of 1000 mg can maintain serum testosterone levels in hypogonadal men for 12 weeks (Partsch1995, Zhang GY 1998, Nieschlag E 1999).
Prior Studies

- Dose-finding study demonstrated 500 or 1000 mg TU in tea seed oil efficiently and reversibly suppress spermatogenesis in eugonadal Chinese men without serious adverse effects (Zhang GY 1999).

- Multicenteric contraceptive efficacy study using monthly injection of TU 500mg in 308 fertile Chinese men showed high continuation rate (95%) and low contraceptive failure rate (5.2%) and 100% recovery in 12 months. (GU et al. 2003)
Multicenter Contraceptive Efficacy Trial of Injectable Testosterone Undeconoate in Chinese Men

Gu et al, Journal of Clinical Endocrinology and Metabolism

June 2009

1045 healthy, fertile Chinese male enrolled from 10 family planning service center in China

**Male subject:**
- Age 20-45 years
- Fathered at least one child in the last 2 years
- Normal medical history and physical exam
- Two normal semen analyses (> 20 m/ml)
- Normal LH, FSH, T & PSA levels
- Normal hematological, biochemical & lipid profiles

**Female partner:**
- Age 18-38 years
- Normal reproductive function
- Stable relationship with the male study participant
Study Protocol

- **Screening period:** 2 months
- **Treatment period:**
  - 30 months: **Suppression phase:** 6 months
  - **Efficacy phase:** 24 months
- **Recovery period:** 12 months
- **Total duration:** 3 years and 8 months!
Treatment Phase

- Initial IM dose of 1000mg TU was followed by monthly injection of 500 mg TU.
- Injections administered & recorded by study nurse.
- Injections outside a time window of 2 days were considered missed.

Suppression Phase

- Physical, andrological exam and semen analysis at 3rd, 5th and 6th month of suppression phase.
- Fasting blood sample collected before TU injection at 3-month intervals.
Efficacy Phase

- Entered to efficacy phase upon:
  - Two successive semen sample with \( \leq 1 \text{ m/ml} \) sperm count.
  - Negative partner’s pregnancy test.
- No other contraception was allowed
- Physical and andrological exam and semen and fasting blood sample at 3-month intervals.
- Blood sample for hormonal and PSA assays at 12 month and end of study.
Efficacy Phase

This phase ended upon:

- Completion of this phase by 24 months.
- Escape from suppression of spermatogenesis.
- Pregnancy of the partner.
- Participant withdrawal.
- Discontinuation for any reason.
Recovery Phase

- This phase started: At the end of efficacy phase
- Upon early discontinuation
- Couple were advised to use reliable contraceptive method.
- Physical exam and semen and blood sample collection at 3-month intervals for 12 months.
- Fasting blood sample at the end of this phase.
Semen Analysis

- **Azoospermia**: absence of sperm in centrifuged semen sample.
- **Severe oligozoospermia**: sperm count \( \leq 1 \text{ m/ml} \)
- **Sperm rebound**: sperm count \( >1 \text{ m/ml} \) in two successive sample during the efficacy phase.
- **Recovery of spermatogenesis**: sperm count reaching geometric mean of participant baseline values or \( > 20 \text{ m/ml} \).
Study enrollment disposition of participants

1376 Screened
- 331 Excluded
  - 1045 Enrolled into suppression phase
    - 43 Non-suppressors
    - 58 Lost to follow-up
    - 24 Change of contraceptive
    - 8 Adverse events
    - 24 Missed injections
    - 10 Requested withdrawals
    - 23 Other reasons
    - 2 Fear of injection
      - 5 Skin rashes
    - 1 Low fever after TU injections
  - 190 Withdrawals
  - 855 Entered efficacy phase
    - 122 Withdrawals
      - 10 Sperm rebound
      - 9 Pregnancies
      - 35 Lost to follow-up
      - 19 Change of contraceptive
      - 10 Adverse events
      - 16 Missed injections
      - 10 Requested withdrawals
      - 13 Other reasons
      - 3 Severe acnes
      - 5 Libido change
      - 2 Increased blood pressures
  - 733 Completed efficacy phase
    - 4 Withdrawals
  - 729 Completed recovery period
- 97 Completed recovery period
Results

- **Primary method failure 4.8%**. 43 of 898 men failed to suppress sperm count adequately.
- 19 pregnancies occurred during suppression (failure or nonuse of a barrier contraceptive).
- **Secondary method failure 1.3%**. 10 of 743 men exhibited sperm rebound during 24 months of efficacy phase.
- **Combined method failure 6.1%**.
Results

Nine pregnancies during efficacy period (6 were attributed to sperm rebound to 2-8 m/ml).

Cumulative contraceptive failure rate 1.0 and 1.1 per 100 men by 12 and 24 months respectively

This contraceptive failure rate is comparable to female injectable contraceptives or intrauterine devices
No serious adverse event reported during the study

- Tenderness or discomfort at the injection site for 1-2 days. (didn’t lead to discontinuation)
- **Acne** (n=77)
- **Severe cough lasting minutes after injection** (n=22)
- **Change in mood and behavior** (n=8)
- **Facial swelling or skin rash** (n=8)
- **Change in libido** (predominantly increased)
- Increase body weight 0.4-1.6 kg
- **Decrease of testicular size by 4% in 28% of participants.**
### Clinical features and serum parameters in each phase for men who completed all phases of the study

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Suppression</th>
<th>Efficacy</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>BW (kg)</td>
<td>64.5 ± 0.29</td>
<td>64.9 ± 0.29</td>
<td>65.5 ± 0.27</td>
<td>64.9 ± 0.28</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22.7 ± 0.09</td>
<td>22.8 ± 0.08</td>
<td>23.0 ± 0.08</td>
<td>22.8 ± 0.08</td>
</tr>
<tr>
<td>TTV (ml)</td>
<td>35.5 ± 0.20</td>
<td>33.6 ± 0.22</td>
<td>30.3 ± 0.24</td>
<td>34.0 ± 0.18</td>
</tr>
<tr>
<td>SV (ml)</td>
<td>2.7 ± 0.04</td>
<td>2.5 ± 0.03</td>
<td>2.3 ± 0.03</td>
<td>2.8 ± 0.04</td>
</tr>
<tr>
<td>NSM (%)</td>
<td>51.9 ± 0.54</td>
<td>Not measured</td>
<td>Not measured</td>
<td>56.5 ± 0.65</td>
</tr>
<tr>
<td>TC (mmol/liter)</td>
<td>4.7 ± 0.05</td>
<td>4.2 ± 0.04</td>
<td>3.7 ± 0.03</td>
<td>4.0 ± 0.04</td>
</tr>
<tr>
<td>HDL-C (mmol/liter)</td>
<td>1.3 ± 0.02</td>
<td>1.2 ± 0.01</td>
<td>1.0 ± 0.02</td>
<td>1.1 ± 0.01</td>
</tr>
<tr>
<td>LDL-C (mmol/liter)</td>
<td>2.7 ± 0.05</td>
<td>2.4 ± 0.04</td>
<td>1.9 ± 0.03</td>
<td>2.3 ± 0.03</td>
</tr>
<tr>
<td>LDL-C/HDL-C</td>
<td>2.2 ± 0.04</td>
<td>2.2 ± 0.04</td>
<td>1.9 ± 0.05</td>
<td>2.2 ± 0.04</td>
</tr>
<tr>
<td>Hb (g/liter)</td>
<td>132.0 ± 0.49</td>
<td>136.6 ± 0.47</td>
<td>141.4 ± 0.47</td>
<td>138.9 ± 0.43</td>
</tr>
<tr>
<td>T (nmol/liter)</td>
<td>17.6 ± 0.23</td>
<td>23.6 ± 0.36</td>
<td>21.1 ± 0.25</td>
<td>17.6 ± 0.22</td>
</tr>
<tr>
<td>LH (IU/liter)</td>
<td>3.9 ± 0.07</td>
<td>0.2 ± 0.01</td>
<td>0.1 ± 0.01</td>
<td>5.5 ± 0.12</td>
</tr>
<tr>
<td>FSH (IU/liter)</td>
<td>5.1 ± 0.11</td>
<td>0.3 ± 0.02</td>
<td>0.3 ± 0.01</td>
<td>7.2 ± 0.16</td>
</tr>
<tr>
<td>PSA (ng/ml)</td>
<td>0.8 ± 0.03</td>
<td>0.8 ± 0.03</td>
<td>0.7 ± 0.03</td>
<td>1.3 ± 0.03</td>
</tr>
</tbody>
</table>

Data were expressed as means ± SE. Data from the control phase were two measurements combined, and data representing other phases were collected from the last follow-up of each phase and calculated. BW, Body weight; BMI, body mass index; TTV, total testis volume; SV, semen volume; NSM, normal sperm morphology; TC, total cholesterol; HDL-C, HDL cholesterol; LDL-C, LDL cholesterol; Hb, hemoglobin.
Median time to onset of azoospermia or severe oligozoospermia was 108 ± 1 days.

**Sperm rebound in 16 subjects**

7 Azoospermic 9 Oligozoospermic

on their most recent semen analysis
Recovery of Spermatogenesis

- **Median time of recovery 196 days**
- All subject except 17 recovered to normal reference levels, during 12 months recovery phase
- 15 of 17 subjects recovered to normal reference levels in additional 3-month follow up
- One subject reached 13 m/ml sperm count and the other remained nearly azoospermic by end of 18 months of recovery follow up (this patient had bilateral painful nodes (epididymitis) by palpation at 9th month of the recovery follow up and presumptive tubule obstruction).
The changes in sperm concentration with log scale during the study period. Values were expressed as the mean ± SEM. C, S, E, and R indicate the control, suppression, efficacy, and recovery phases, respectively.
Reproductive Hormones

At the end of the treatment:

- $T$ increased by 34%
- LH suppressed by 97%
- FSH suppressed by 94%

Significant Difference in mean serum FSH levels:

- Azosspermia or severe oligozoospermia $0.25\pm0.01$ IU/L
- In sperm rebound or pregnancy $0.61\pm0.31$ IU/L
Hematology and Biochemistry

At the end of the efficacy phase:

- Hemoglobin increased by 7%
- Mean total cholesterol decreased by 21%, HDL by 23% and LDL by 29%
- PSA remained in normal range
Strengths

- **Proof of concept** (effective, reversible, acceptable)
- Largest clinical trial in this field
- General satisfaction; high Retention rate: > 85% of men over 30-month.
- Higher sperm suppression to azoospermia
- Excellent efficacy and less failure rate in first year use in comparison to condom (17%), withdrawal (18%) and OCP (8%) methods.
Limitations

Long term safety not known
- Cardiovascular, prostate, behavioral,…
- Long term safety mandates epidemiological studies, if the product become available.

Monthly injection
- Injections every 4 weeks may not be acceptable by all men on long term basis.
- Injection volume is high (250mg/2ml).
- Injections are not self administered.
- New vehicle for testosterone undecanoate namely castor oil may extend the injection intervals to 8-12 weeks.
Limitations

Ethnicity

- Only about 60-70% of non-Asian men will show such high suppression rate with testosterone alone.
- May be related to different body fat mass.
- Combination of testosterone and progestin may solve this concern by increasing the suppression to sever oligozoospermia in most men.

Are men willing to use contraceptive?

- In USA vasectomy rose from 8 to 12% from 1975 to 2008.
- Great Britain and New Zealand rate of vasectomy is as high as 20%
- World wide survey: 60-70% of men with partners of reproductive age in Spain, Germany, Brazil, Mexico and 50% in USA would be willing to apply such method.
Thank you