The development of hormonal contraception for men

Gap or abyss?

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UK contraceptive use
National statistics survey 2006, women aged 16-49

Total: 74%
Male methods 36%

Preferred method: men

Unreliable methods

How many women will fall pregnant in 1 year?
How many women will still be using it after 1 year?

Women attending for abortion:
• 2/3rds are using condoms
• Very few continue with afterwards

Women’s attitudes to novel male contraceptives

Glasier et al 2000 Hum Reprod 15:646-649
So, gap or abyss?

Gap: we could do it, but don’t

Abyss: it can’t be done

Charles-Eduard Brown-Séquard
1817-1894

‘Increased physical strength, mental abilities and appetite’
Lancet 1889, 2, 105

David et al 1935: crystallisation of testosterone
Butenandt 1935: synthesis of testosterone

Testosterone suppresses spermatogenesis


Potential of testosterone for contraception

Landmark WHO efficacy studies

• To determine contraceptive efficacy
• Azoospermia’ study:
  – 170 couples (70% of subjects), 1 pregnancy
• Oligospermia’ study:
  – Testing efficacy at <3M/ml
  – 357 men achieved adequate suppression (92%)

Reddy and Rao, 1972

How low is safe?

<table>
<thead>
<tr>
<th>Pregnancy (%)</th>
<th>0 ≤ 1.0</th>
<th>1.0 ≤ 2.0</th>
<th>2.0 ≤ 3.0</th>
<th>3.0 ≤ 4.0</th>
<th>4.0 ≤ 5.0</th>
<th>5.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>All (&lt;3)</td>
<td>1.4 (0.4-4.7)</td>
<td>8.1 (2.3-30.7)</td>
<td>2.2 (0.4-10.7)</td>
<td>3.1 (2.1-20.1)</td>
<td>2.2 (0.2-20.7)</td>
<td>1.4 (0.4-10.7)</td>
</tr>
<tr>
<td>Oligo (0.1-3)</td>
<td>0.5</td>
<td>2.3</td>
<td>2.2</td>
<td>3.4</td>
<td>2.3</td>
<td>1.4</td>
</tr>
</tbody>
</table>

WHO Efficacy studies, 200mg TE per week

Why isn’t everyone azoospermic?

Ethnicity
Diet
Androgen receptor structure
Androgen metabolism (5alpha reductase)
Continuing low T production

A wealth of combinations.....

Limited range of testosterone preparations

Longest acting
Best pharmacokinetics

Etonogestrel dose-response

LARC for men
Effective progestogenic dose
Physiological T replacement
Oral vs Implant doses

Etonogestrel (µg/ml)

- 300µg oral DSG
- 250µg oral DSG (COC dose)

Weeks

0 4 8 12 16 20 24 28 32 36 40 44 48

Implanon

Depo MPA + T pellets
- Efficacy study (<1 x10^6/ml)
- n=55, 1 year treatment
- No pregnancies
- 3.5 person years exposure
- Confidence interval 0-8%

New testosterone preparations

TU 750mg/12 weeks
TU 1000mg/12 weeks
TU+Eto: new WHO approach

What are the side effects, doc?

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Treated (%)</th>
<th>Placebo (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acne</td>
<td>77 (26)</td>
<td>5 (10)</td>
</tr>
<tr>
<td>Body weight increase</td>
<td>72 (24)</td>
<td>5 (10)</td>
</tr>
<tr>
<td>Libido change</td>
<td>38 (13)</td>
<td>0</td>
</tr>
<tr>
<td>Mood changes</td>
<td>55 (19)</td>
<td>5 (10)</td>
</tr>
<tr>
<td>(Night) sweating</td>
<td>79 (27)</td>
<td>4 (8)</td>
</tr>
</tbody>
</table>

Combination of androgenic and progestogenic?
- Norethisterone enanthate
  - Strong progestogen
  - Long history in contraception
  - 200mg in 1 ml
- Testosterone undecanoate (TU)
  - Long-acting testosterone ester
  - 1000mg in 4ml
- Target: 400 couples
- Efficacy when sperm conc $\leq 1$M/ml, for 52 weeks

Is it an effective contraceptive?

255 men in efficacy phase
4 pregnancies, all within 16 weeks

Contraceptive efficacy ✓

Overall: 1.59% (95% CI 0.6 - 4.2)

T/NES gel: efficacy study

MENT: potent androgen aromatised not 5$\alpha$-reduced health benefits?
MENT implants for male contraception

Sperm concentrations in New Zealand white rabbits treated with 200 mg/kg WIN 18,446 orally for 16 weeks

Small molecule, reversible inhibition of spermatogenesis

So, gap or abyss?

So why isn’t a male pill available?

Industry aren’t convinced/involved
Is there really a market?
Regulatory issues: one person takes a drug to prevent a condition in someone else
Takes time to work (similar to vasectomy)
Not all men are “responders”
Non-hormonal methods are largely pre-clinical