

'No sperm wanted'
Current status of contraception in the male

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Men make 1000 sperm per heartbeat

- 100 x 10⁶ acts of intercourse daily
- 1 x 10⁶ conceptions daily
- 500.000 unplanned conceptions daily
- 250.000 unwanted conceptions daily
- 150.000 abortions daily
- 55.000 unsafe abortions daily
- 500 end lethally for the woman



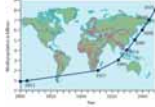
» J.K. Amory, Endocrine Society 2005
» E Nieschlag, A. Kamische, H.M. Behre, in Testosterone 3rd ed.

Male Contraception

- Prior to 1960s most common methods were male-directed
- Currently accounts for 1/3 of all current contraception in U.S., despite only two real options (vasectomy and condoms)
- 4 decades after the introduction of female OC there is still no comparable pharmacological method for men

Why male contraception at all?

- Female partner is unable to take OC
- Failure rates when 1 form used
- Vasectomy is often not reversible/available
- Global population is continuing to increase despite current family planning efforts (8 billion by 2020).
- Exponential population growth in developing countries endangers economic, social, medical progress
- Outstanding issue in the political field of gender equality



Would men use a male contraceptive?

- Definitely • 20%
 - Probably • 28%
 - Maybe • 28%
 - Probably Not • 12%
 - Definitely Not • 13%
- 75% of men

Will Australian men use hormonal contraception?
Weston et al. MJA 2002 208-210.

Cross-Cultural Impact

- ❖ Multi-center survey in UK, South Africa and China: (Martin *et al.*, 2000)
- Surveys indicate 44-83% of men willing to use such a contraceptive² (Edinburgh, Cape Town, Shanghai, Hong Kong)
- Women surveyed would trust men to use such a contraceptive³
 - ❖ Males ranked implant as *least* popular in UK, South Africa and Hong Kong; *most* popular in Shanghai
 - Males in UK and South Africa felt a pill would be convenient; China perceived it **as inconvenient**
 - Females agreed that 'male pill' would be a good idea, but were concerned that their partner would forget

Results of cross-cultural questionnaire-based interviews:
"Yes, I would use a male method".

| | Male Pill | | Injection |
|-----------|-----------|----|-----------|
| | Yes | No | |
| Cape Town | 100 | 0 | 100 |
| Black | 100 | 0 | 100 |
| White | 100 | 0 | 100 |
| Coloured | 100 | 0 | 100 |
| Hong Kong | 44 | 56 | 52 |
| Shanghai | 83 | 17 | 35 |
| Edinburgh | 66 | 34 | 17 |

Martin et al. *Sex Reprod*. 37 (2000) 457-462

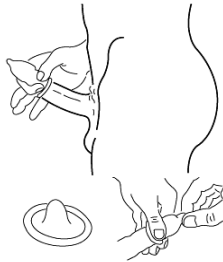
Existing methods

- 1. Castration
- 2. Abstinence
- 3. Periodic abstinence
- 4. Coitus interruptus
- 5. Condoms
- 6. Vasectomy



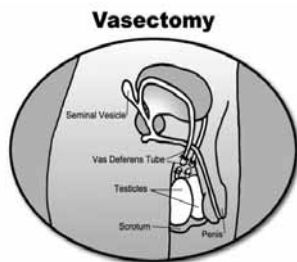
Condoms

- Reversible
- Sexually transmitted disease protection
- Fairly effective
 - But 12/100 couples conceiving in 1st yr! (vs. 85% unprotected intercourse, vs. 3% female OC)
- Obtrusive
- Proper, faithful usage a must
- Latex allergies (rare)



Vasectomy

- Very effective
 - Failure rate <1%
- Drawbacks:
 - Difficult to reverse
 - Delay in onset of azoospermia (2-3 mnd)
 - Testicular discomfort 1/3 of men
- Safe with regards to long term health



The Ideal Contraceptive

- ❖ The ideal male contraceptive should:
 - be rapidly effective and fully reversible
 - be of acceptable modality (compliance)
 - not interfere with other testosterone-dependent processes (libido, sex activity)
 - have no short or long-term side effects
 - have no impact on eventual offspring
 - be more effective than current methods
 - be acceptable for both partners
 - be applied independently of the sexual act
 - be easily available and financially affordable

Gossypol

Constituent of cottonseed oil
 Suppression of spermatogenesis to a various degree
 Side effects: nausea, hypokalemia, possible irreversibility

Countinho et al. 2000 15 mg / d in 151 men for 16 weeks,
Contraception "Suppression of spermatogenesis" in 81 men.
 Recovery phase:
 21 men did not reach sperm counts > 20 x 10⁶ / ml,
 8 remained azoospermic after 1 year of cessation.

Gu et al. 2000 10 mg / d to 12.5 mg / d in 55 men for 6 months,
Asian J Androl Sperm count < 4 x 10⁶ / ml in ca. 70 % of
 subjects.
 Recovery phase: not reported.

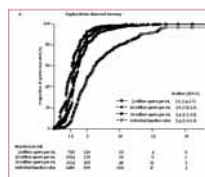
In the late 1990s, the WHO's Research Group on Methods for the Regulation of Male Fertility reviewed the studies to date on gossypol and concluded that contraceptive research should be abandoned (Waites 1998).

Waites, GMH, C Wang and PD Griffin (1998) "Gossypol: reasons for its failure to be accepted as a safe, reversible male antifertility drug." *International Journal of Andrology* 21: 8-12.

Hormonal Male Contraceptives

- Highly predictable recovery to fertility¹ (n = 1549)
- Slow on/off (on up to 2-4 months/ off 4-5 months)

¹Liu et al. *The Lancet* 2006;367:1412-1420

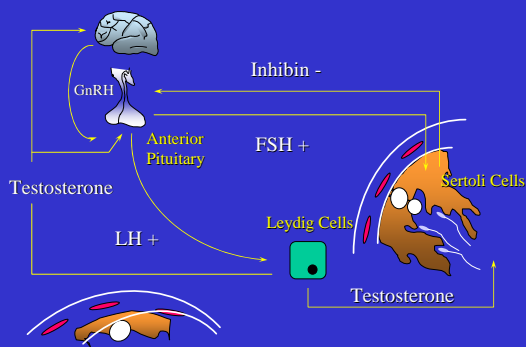


Approaches to the Development of Male Hormonal Contraceptives

1. Testosterone alone
2. Newer Androgens
2. Testosterone + Progestins
3. Testosterone + GnRH antagonists



Endocrinology of spermatogenesis



1. Testosterone alone: effective?

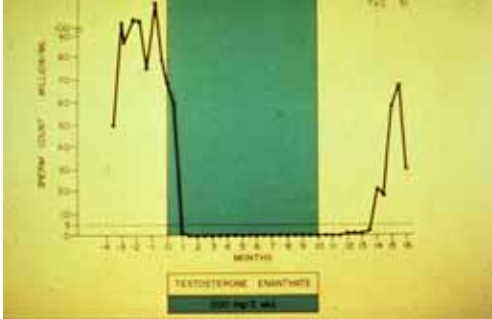
- ❖ The WHO (1990-96) conducted two studies; proof of concept for testosterone alone regimen
- ❖ *Weekly* intramuscular injections of testosterone enanthate 200 mg for 6 months
- ❖ Those who achieved a threshold entered the efficacy phase (1 yr) - no other contraceptive methods

Contraceptive efficacy of testosterone-induced azoospermia in normal men. World Health Organization Task Force on methods for the regulation of male fertility. *Lancet* 1990; 336: 956.

WHO. *Fert Steril* 1996;65:821.



Sperm Suppression by Exogenous Testosterone



The WHO Studies

- ❖ Volunteers in 10 centers on 4 continents (7 countries) participated
- ❖ **Study 1 (1990): Azoospermia**
 - 65% (2/3) of subjects developed azoospermia (n = 137)
 - 1 pregnancy
- ❖ **Study 2 (1996): Severe oligozoospermia (<3 million sperm/mL)**
 - 98% of subjects
 - 4 pregnancies, better than condoms
 - If > 3 million sp/ml (2%): higher pregnancy rates than when using condoms (N=571)
- ❖ Azoospermia: 'gold standard', realistic < 1 million sp/ml

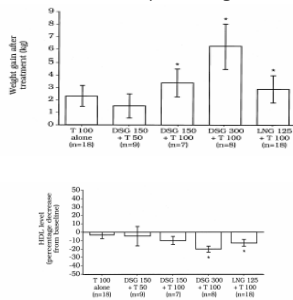
Ethnic differences in the WHO multicenter studies.

- ❖ 91% of East Asian males reached azoospermia, compared to 60% Caucasian.
- ❖ Reason for dichotomy is unclear
 - ↑ feedback sensitivity to exogenous testosterone
 - ↑ germ cell apoptosis rate in Asian men
 - diet and lower androgen production rate in Asian men living in Asia
 - 5α-reductase activity higher in non-responders
- ❖ It is necessary to investigate other methods, weekly intramuscular injections are not acceptable for broad use + higher dosage T side effects:

Higher dosage T-side effects

- Increased muscle mass and weight (but decrease in fat mass)
- Increased in oily skin and acne
- ~10% decrease in serum HDL cholesterol
- No change in libido, aggression or prostate size
- ~25% decrease in testicular size (reversible)
- Dose-related increase in hematocrit and hemoglobin

Weight and HDL levels in male hormonal contraceptive regimens



Anawalt et al. Fertil Steril 2000 74:707-714

Male Hormonal Contraceptive Regimens Increase Lean Body Mass

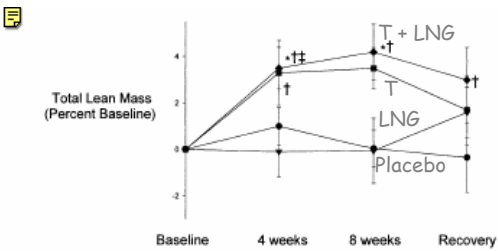


FIG. 3. Change in total lean mass. † Increases total lean mass in 4 wk in healthy young men. Data are the percentage of baseline \pm SEM. •, Placebo; †, LNG alone; ‡, T alone; ††, T + LNG. * $P < 0.05$ vs. baseline; † $P < 0.05$ vs. placebo; ‡ $P < 0.05$ vs. LNG alone.

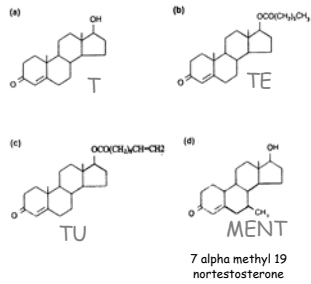
Herbst et al. JCEM (2003) 88:1167-73

Testosterone Alone as a Male Contraceptive: conclusion

- Rates of azoospermia 60% (Caucasian) to 90 % (Asian) men
- ~ 95% overall contraceptive efficacy
- 1-3 month delay in onset
- Requires weekly intramuscular injections (impractical!)
- Short-term side effects mild
- Long-term side effects/benefits unknown

2. Newer Androgens for Male Contraception

- Testosterone undecanoate can be given by IM injection every 4- 8-12 weeks
- MENT -not 5 α -reduced to DHT, may limit acne, baldness, BPH (subdermal silastic implants) (4 implants of MENT were more effective than 2)



MENT

7 α -Methyl-19-Nortestosterone (MENT) vs Testosterone in Combination With Etonogestrel Implants for Spermatogenic Suppression in Healthy Men

MELANIE J. WALTON*, NARENDER KUMAR*, DAVID T. BAIRD*, HELEN LUDLOW,† AND RICHARD A. ANDERSON*

Sperm concentrations fell rapidly to less than 1x10⁶/ml at 12 weeks in 8 of 10 subjects in the MENT group and 13 of 16 subjects in the testosterone group with equally suppressed gonadotropins. Thereafter, suppression was not maintained in the MENT group, and 6 men noted loss of libido.

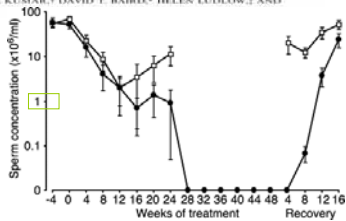


Figure 2. Sperm concentrations during treatment and recovery phases. 7-Methyl-19-nortestosterone (MENT) group (open squares), n = 13; testosterone group (filled circles), n = 19; mean \pm SEM. The MENT group received drug treatment for 24 weeks and the testosterone group for 48 weeks.

TU in Chinese men: pilot dose-finding study

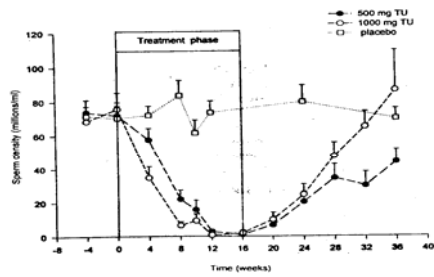


FIG. 1. Mean spermatozoal concentrations (mean \pm SEM) in each group during baseline, treatment, and recovery periods.

Zhang et al. JCEM 84:3642, 1999

TU alone in Chinese men-Efficacy

- Loading injection of 1000 mg, then monthly injections of 500 mg of TU
- 308 men, 299 (97%) achieve azoospermia or counts < 3 million sperm/ml
- 1 pregnancy among 296 men using TU as sole means of contraception for one year
- No serious side effects
- > Phase III trial: 1000 couples 2 years ? 1st registered hormonal male contraceptive in China
- Gu et al. JCEM 88:562-568, 2003

TU alone in Caucasian men-Efficacy

- TU 1000 mg IM/6 weeks
- Azoospermia 57%
- Oligozoospermia 86%

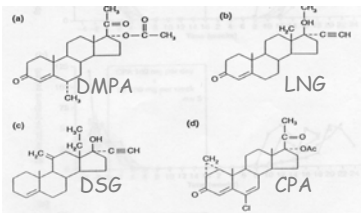
Kamischke A, Pflager D, Venharm S, von Eckardstein S, von Eckardstein A, Nieschlag E. Intramuscular testosterone undecanoate with or without oral levonorgestrel: a randomized placebo-controlled feasibility study for male contraception. Clin Endocrinol (Oxf). 2000 Jul;53(1):43-52.

Newer Agents for Hormonal Contraception in the Male

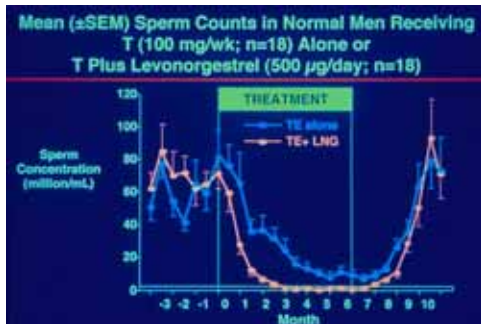
- Longer-acting and non-traditional androgens
- **Addition** of Progestins (27 studies) or GnRH antagonists (4 studies) to improve efficacy
- ⇒ Possibility to reduce dosage of androgens

3. Progestins in Male Contraceptive Research

- Suppress FSH and LH production
- May interfere with steroidogenesis in testicle (esp. CPA)
- Associated with additive increases in weight

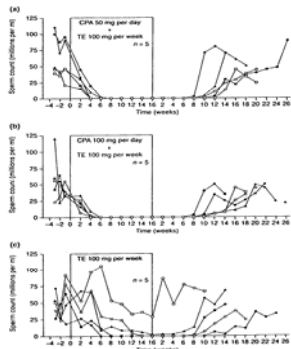


Testosterone combined with progestins for male contraception



Bebb et al. JCEM 1996 81:747-762

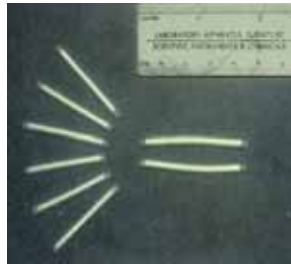
T + CPA for Male Contraception



Meriggiola et al. 1996 81:3018-3023

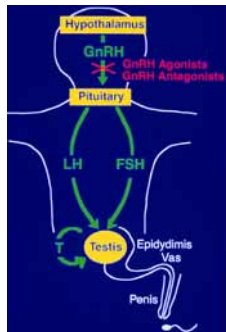
Implant Contraception

- Silastic capsules implanted in subcutaneous tissue
- Steady systemic levels of a progestin
- Requires procedure to implant and remove



4. GnRH Antagonists for Male Contraception

- GnRH agonist
- GnRH receptor desensitisation
- Ineffective! (only 30% sp conc < 5 10⁶/ml)
 - ?better constant infusion
 - ?Diminution of effects when combined with T
- Remain partial agonists
- GnRH antagonists
- Block FSH and LH release from the pituitary
- Expensive



GnRH Antagonists to initiate azoospermia



Swerdloff et al. JCEM 1998 83:3527-3533

The Effect of 5 α -Reductase Inhibition with Dutasteride and Finasteride on Semen Parameters and Serum Hormones in Healthy Men

John S. Alpert, Christian Wang, Ronald S. Swerdloff, Bradley D. Assari, John H. Matsumoto, William J. Broecker, James B. Walker, Linda J. Gillman, and Richard F. Clark

| | Finasteride | | Dutasteride | |
|---|-----------------------------|----------------------|-----------------------------|----------------------|
| | Percent change ¹ | P value ² | Percent change ¹ | P value ² |
| Sperm count (millions) | | | | |
| wk 26 | -34.3 | 0.004 | -28.6 | 0.013 |
| wk 52 | -16.2 | 0.175 | -24.9 | 0.051 |
| Follow-up | -6.2 | 0.361 | -23.3 | 0.050 |
| Semen volume (ml) | | | | |
| wk 26 | -21.1 | 0.010 | -24.0 | 0.003 |
| wk 52 | -14.5 | 0.117 | -29.7 | 0.003 |
| Follow-up | -4.5 | 0.319 | -16.8 | 0.021 |
| Sperm concentration (million/ml) | | | | |
| wk 26 | -21.5 | 0.032 | -12.9 | 0.140 |
| wk 52 | -7.4 | 0.285 | -3.2 | 0.399 |
| Follow-up | -4.3 | 0.383 | -10.4 | 0.205 |
| Sperm motility | | | | |
| wk 26 | -10.5 | 0.006 | -10.1 | 0.006 |
| wk 52 | -10.5 | 0.012 | -11.8 | 0.003 |
| Follow-up | -9.7 | 0.006 | -6.3 | 0.033 |
| Sperm morphology | | | | |

TABLE 3. Percentage change in semen parameters from baseline during treatment

A mild negative impact on spermatogenesis.

Cochrane Database of Systematic Reviews

- **OBJECTIVES:** To summarize all randomized controlled trials of male hormonal contraception.
- **DATA COLLECTION AND ANALYSIS:** Azoospermia (absence of spermatozoa on semen examination) was the primary outcome measure. Data were insufficient to examine pregnancy rates and side effects.
- **CONCLUSIONS:**
 - No male hormonal contraceptive is ready for clinical use.
 - Most trials were small exploratory studies. As a result, their power to detect important differences was limited and their results imprecise.
 - The definition of oligozoospermia has been imprecise or inconsistent.

Grimes DA et al. Steroid hormones for contraception in men. Cochrane Database Syst Rev. 2007 Apr 18;(2)

A few important differences:

- LNG implants (160 µg/d) combined with **IM** TE > LNG 125 µg daily combined with testosterone **patches**;
- LNG 500 µg daily improved the effectiveness of TE 100 mg **IM** weekly;
- desogestrel 150 µg < desogestrel 300 µg (with testosterone pellets);
- TU 500 mg was less likely to produce azoospermia than TU 1000 mg (with LNG implants);
- norethisterone enanthate 200 mg with TU 1000 mg led to more azoospermia when given every 8 weeks versus 12 weeks;
- 4 implants of MENT were more effective than 2 MENT implants

• Big pharma not interested in 'male pill'

22 June 2007

- Ned Stafford/Hamburg, Germany
German drug giant Bayer has officially stopped research and development of a hormonal male contraceptive
- Bayer had previously indicated it would stop the programme, but company officials confirmed the decision this week at a meeting in Leverkusen, Germany. The male contraceptive research had been carried out as a joint project between German pharma firm Schering and US-based Organon. However, Bayer last year acquired Schering for 17 billion (£11 billion) and the cooperation with Organon was ended.
- the administration route investigated in the trial, which combined an annual implant with three-monthly injections, would unlikely result in a product that would be acceptable for widespread everyday use.
- Bayer felt market demand for such a complicated process would be limited. 'It is not as convenient as a woman taking a pill once a day.'
 - 'Treating healthy young people is a risky business to be in'

Male Hormonal Contraceptives- Summary

- Reversible inhibition of spermatogenesis in most, but not all men
- Safe, with minimal side effects
- Would be widely accepted by men and partners
- Needs final "pharmaceutical company push" to get to market



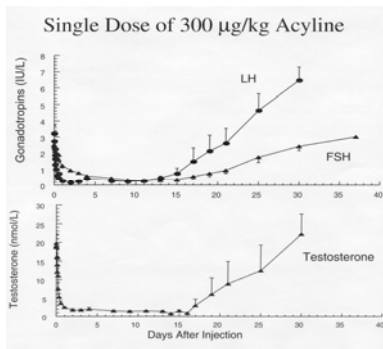
Future Goals for Male Contraception

- Short-term (5-10 years)
 - Phase III in China (androgens alone)
 - Phase II in Europe (androgen-progestagen): STOPPED
 - Oral/Implant PG and 2-3 monthly injections TU
- Longer-term
 - New methodologies emerging from basic science
 - Sperm maturation
 - Spermatogenesis
 - Epididymal function (Eppin, epididymal protease inhib)
 - Designer hormones (SARMs)

A birth control pill for men, that's fair. It makes more sense to take the bullets out of the gun than to wear a bulletproof vest.

~Author Unknown

Acyline: Single Dose Pharmacodynamics



Herbst et al, JCEM 2004

GnRH Agonists/Antagonists

| Amino-Acid | | | | | | | | | | | |
|---------------------|-------------|-----------|----------|-------|-----|------------|-----------|-----|----------|---------------------|-------|
| Position: | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | |
| <u>GnRH</u> | pGlu | His | Trp | Ser | Tyr | Gly | Leu | Arg | Pro | Gly-NH ₂ | |
| <u>Agonists:</u> | | | | | | | | | | | |
| Leuprolide | | | | | | D-asn(2) | | | | Pro-NH ₂ | |
| Buserelin | | | | | | D-ser(tBu) | | | | Pro-NH ₂ | |
| <u>Antagonists:</u> | | | | | | | | | | | |
| Cetrorelix | Ac-D-Nal(2) | D-Phe(4C) | D-pal(3) | | | | D-Cis | | | | D-Ala |
| Acyline | Ac-D-Nal(2) | D-Cpa | | D-pal | | Asp(As) | D-Asp(As) | | Lys(3pr) | | D-Ala |

Preferred Mode of Male Contraceptive

- Oral pill (daily) • 33%
- Injection every 3 months • 23%
- Injection every 2 years • 18%
- Injection every month • 13%
- Skin Patch • 3%
- Weekly Injection • 1%

Medical J Austral (2002) 176:208-210
