Male Contraception

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Why Men in Family Planning?

- **International Conference on Population and Development, 1994**
- **Shared responsibility and gender equity**

Male Involvement in Fertility Regulation

- Condom
- Vasectomy
- Withdrawal
- Calendar/Rhythm

Distribution of Contraceptive Use Prevalence

World wide contraceptive use (Married Women of Reproductive age)

Contraceptive	No. of users (Millions)	Users (%)	First year failure rate (%) - Typical use
Total users	664	60.5	
Modern methods		53.6	
Female sterilization	225	20.5	0.5
IUD	149	13.6	0.8
Oral contraceptives	82	7.5	5.0
Condom	53	4.8	14.0
Male sterilization	37	4.1	0.15
Injectables	35	3.2	0.3
Vaginal barriers	4.4	0.4	20.0
Traditional methods			
Withdrawal	34	3.1	19.0
Rhythm	32	2.9	25.0

UN Population Division, 2006

Male Contraception

Research and Development

- Use of existing male methods is low, with regional and country differences
- Men are *aware* of family planning methods
- Men *approve* of the use of family planning
- Low levels of use may be related to the *negative characteristics of existing methods*
- Example: In a study conducted in Fiji, Iran, India and Korea, men considered a male pill or injection to be more acceptable than vasectomy

The Ideal Male Contraceptive

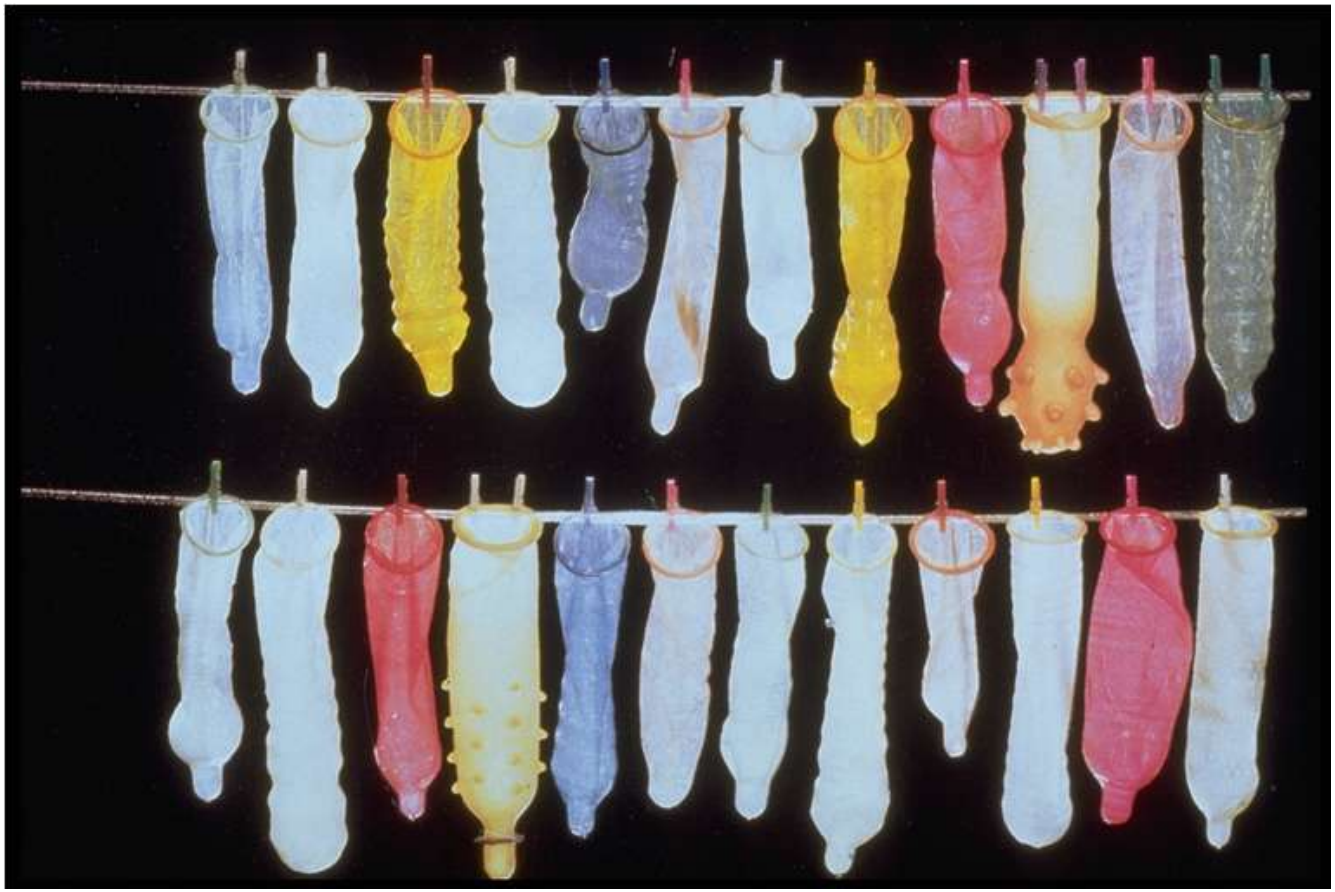
- **Safe** - *no harmful side effects*
- **Effective** - *it works!*
- **Acceptable** - *to men and their partners*
- **Affordable** - *to programs, potential users, and donors*

Approaches to Male Contraception:
Targeting the sperm

- **Block deposition**
- **Interrupt transport**
- **Inhibit production**
- **Disrupt function**
- **Prevent fertilization**

Source: Image House Medical, Copenhagen

Blocking Sperm Deposition



Blocking Sperm Deposition

Male Condoms

- Condoms are effective at preventing pregnancy and STI/ HIV
- Condom use is low even in countries with high prevalence of HIV/AIDS
- How can we increase condom use?

Blocking Sperm Deposition

Male Condoms

Condom studies

- Randomized comparative studies of "standard" and "new" condoms
  - Acceptability and preference
  - Contraceptive efficacy
  - Prevention of STI
- Reasons for use and non-use of condoms

Interrupting Sperm Transport

Vasectomy/Sterilization

World wide, about 37 million married couples rely on vasectomy

- New Zealand 18%
- United Kingdom 17%
- Canada 15.2%
- U.S. of America 13.2%
- Rep. of Korea 12.7%
- The Netherlands 10.5%
- Australia 10.4%
- Switzerland 8.3%
- Spain 8.1%
- Bhutan 8%
- China 7.7%
- Belgium 7.0%
- Nepal 6.3%
- Czech Republic 5.1%
- Denmark 5%

UN Population Division, 2001

Interrupting Sperm Transport
Vasectomy/Sterilization

- **Conventional vasectomy**
  - highly effective and safe
  - incision required
  - permanent
- **No-scalpel vasectomy**
  - highly effective
  - Somewhat more acceptable
  - lower complication rates
- **Percutaneous vas occlusion**
  - many compounds evaluated
  - lower efficacy rates
  - some additional complications

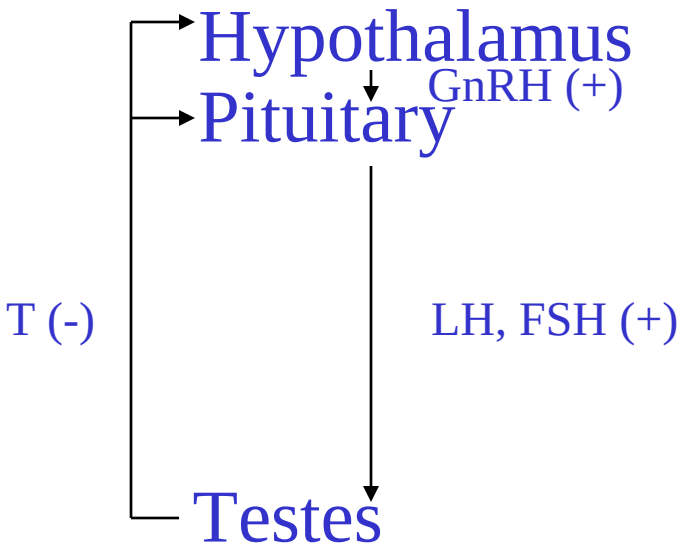
Methods of Vasectomy

Success of Reversal

Method	Follow-up (no and %)	Sperm (no and %)	Normal (no and %)	Pregnancy (no and %)
No-scalpel Vasectomy	**19/23 (82.6)**	**16/19 (84.2)**	**13/19 (68.4)**	**15/19 (78.9)**
Chemical Vas occlusion	**26/31 (83.9)**	**18/26 (69.2)**	**12/26 (46.2)**	**13/26 (50.0)**
MPU Vas occlusion	**31/34 (91.2)**	**10/31 (32.3)**	**10/31 (32.3)**	**9/31 (29.0)**

Inhibiting Sperm Production

Hormonal Contraception



Inhibiting Sperm Production

Hormonal Contraception

Androgen alone	**T Enanthate**
	T Undecanoate
	T Buciclate
	Pellets
Progestin + Androgen	**Norplant**
	DMPA
	Norethisterone Enanthate
GnRH	**Agonists**
	Antagonists
	Vaccines
FSH	**Antagonists**
	Vaccines

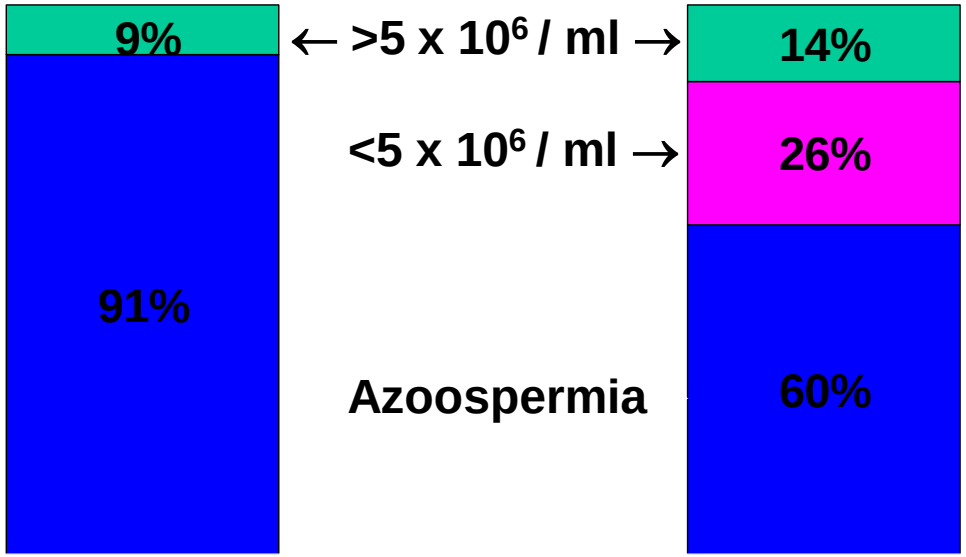
Hormonal Approaches to Male Contraception

Androgen alone

- 1990: 200 mg testosterone enanthate/week will reduce sperm production in some men
- Sperm concentrations consistently below 1 million/ml result in few or zero pregnancies
- All men do not fully suppress
- Requirement for weekly injections and high T concentrations

Hormonal Approaches to Male Contraception

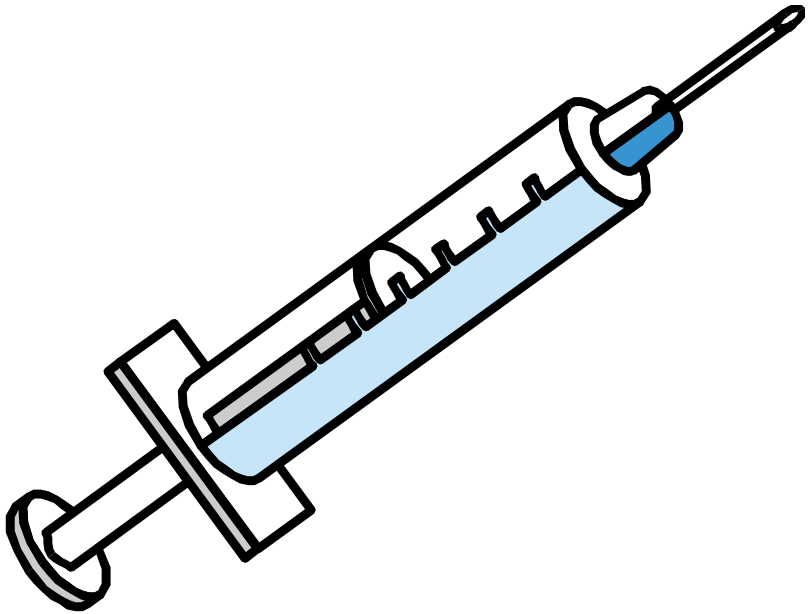
Androgen alone



Sperm concentrations following weekly inj. 200 mg T-enanthate

Hormonal Approaches to Male Contraception

Androgen alone



Testosterone Enanthate

- Extensive clinical experience
- "Burst" effect
- Short acting
- Weekly injections
- High levels testosterone

Hormonal Approaches to Male Contraception

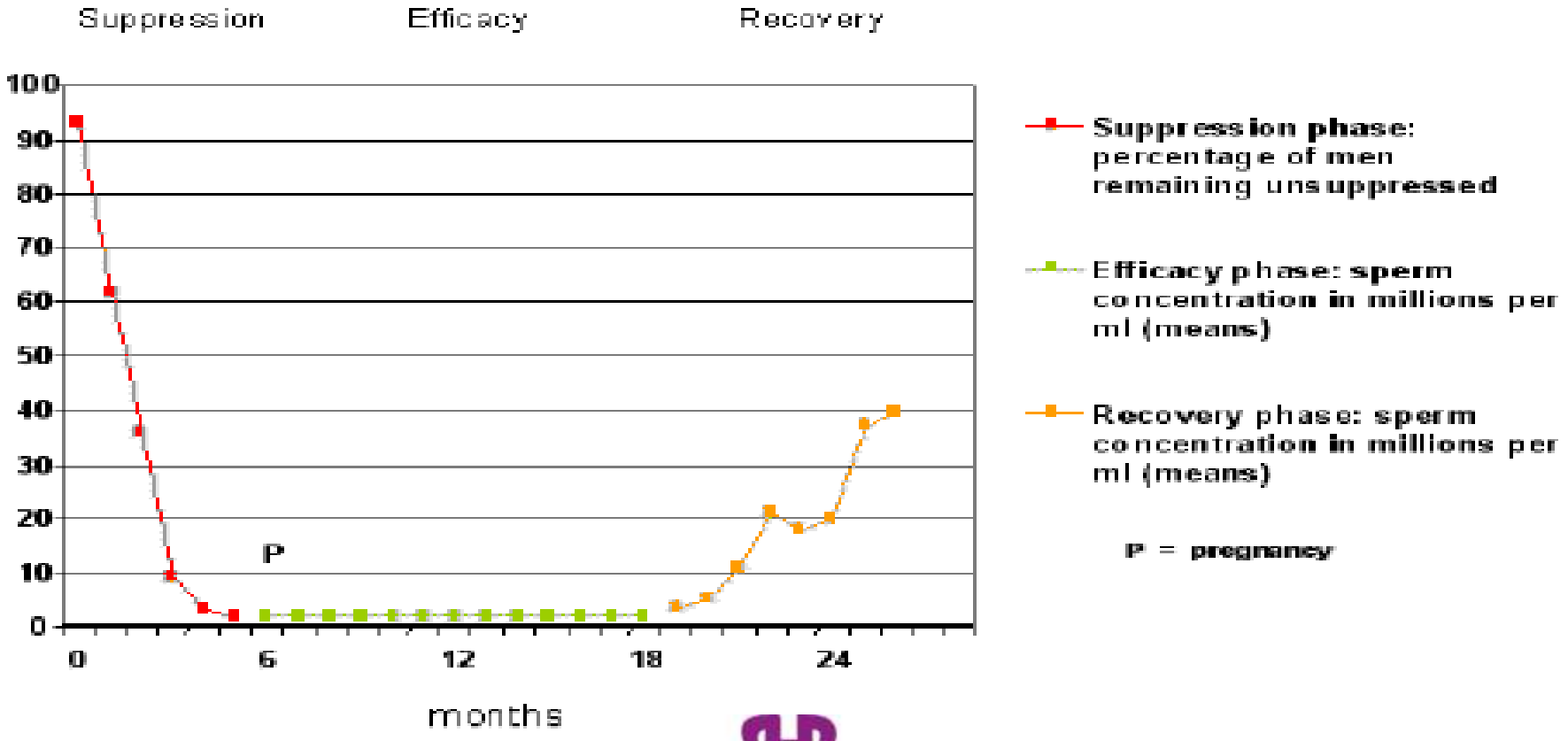
Androgen alone

Testosterone Undecanoate

- Oral or injectable
- Longer release profile
- 4-8 week injection intervals may be adequate
- Maintains testosterone in physiological range
- Large dose required

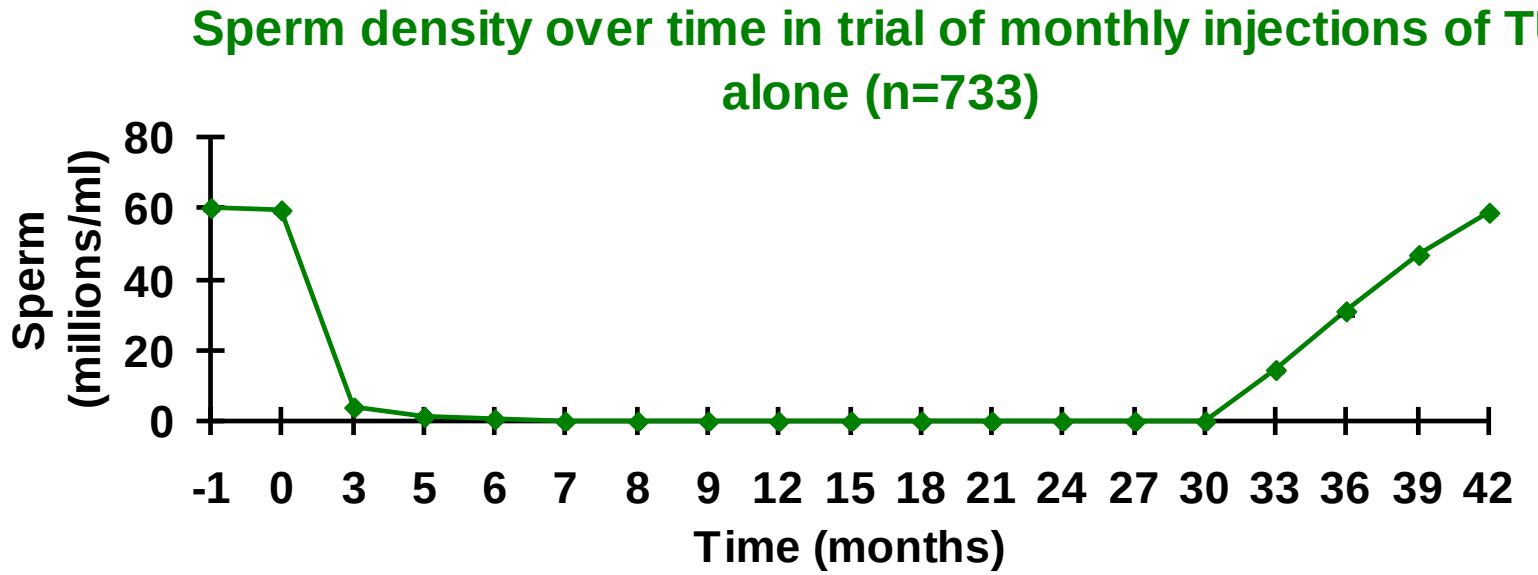
Hormonal Approaches to Male Contraception

Androgen alone



Hormonal Approaches to Male Contraception

Androgen alone



1376 Screened

331 Excluded

1045 Enrolled
Suppression phase

190 Withdrawals (18%)

855 Entered Efficacy phase

122 Withdrawals (14%)

733 Completed Efficacy

4 Withdrawals

729 Completed Recovery

312 Withdrawals
93 Lost to follow-up
43 Non-suppression
43 Change of contraceptive
40 Missed injection
36 Other reason
20 Requested withdrawal
18 Adverse event
10 Sperm rebound
9 Pregnancy

Adverse events (n=18)
5 Change of libido
5 Skin rash
3 Severe acne
2 Fear of injection
2 Increased blood pressure
1 Low fever after injection

97 Completed Recovery

Method failures
(per 100 couple years)
Non-suppression 4.69
Sperm rebound 1.26
Pregnancy 1.11
TOTAL 7.06 per 100 couple years

Hormonal Approaches to Male Contraception

Androgen with Progestin

- More rapid and effective sperm suppression
- Effective in diverse populations
- Reduced overall drug load
- Physiological testosterone levels
- Requires a 2 drug regimen
- Drugs may have different routes or frequencies of administration

Hormonal Approaches to Male Contraception

Androgen with Progestin

Progestagen	Androgen	% Azoo-spermic	% Oligozoo spermic	Reference
DMPA 250 mg every 6 weeks	**19 NT** (200 mg every week x 6/7 weeks, then 200 mg/3 or 4 weeks).	67 (W) 98 (A)	92 (W) 99 (A)	Knuth et al (1987)
	TE (200 mg(IM every week x 6/7 weeks, then 200 mg/4 weeks)	59 (W) 96 (A)	91 (W) 96 (A)	WHO (1993)
DMPA 300 mg	**T implant** (800 mg)	90 (W)	100 (W)	Handelsman et al (1996)
DMPA 300 mg, Every 3 months	**T implant** (800 mg), every 4 or 6 months		96 (W)	Turner et al (2003)

Hormonal Approaches to Male Contraception

Androgen with Progestin

Progestagen	Androgen	% Azoo-spermic	% Oligozoo-spermic	Reference
Levonorgestrel (oral)				
500 μg/day	**TE** (100 mg/week IM)	67 (W)	94 (W)	Bebb et al (1996)
250 μg/day	**TE** (100 mg/week IM)	78 (W)	89 (W)	Anawalt et al (1997)
125 μg/day	**TE** (100 mg/week IM)	61 (W)	94 (W)	
Desogestrel (oral)				
300 μg/day	**TE** (100 mg/week IM)	81 (W)	94 (W)	Wu et al (1998)
150 μg/day	**TE** (50 mg/week IM)	73 (W)	100 (W)	

W=White, A=Asian, DMPA=depotmedroxyprogesterone acetate, TE=testosterone enanthate
19 NT= 19 nortestosterone hexyloxyplenylpropionate

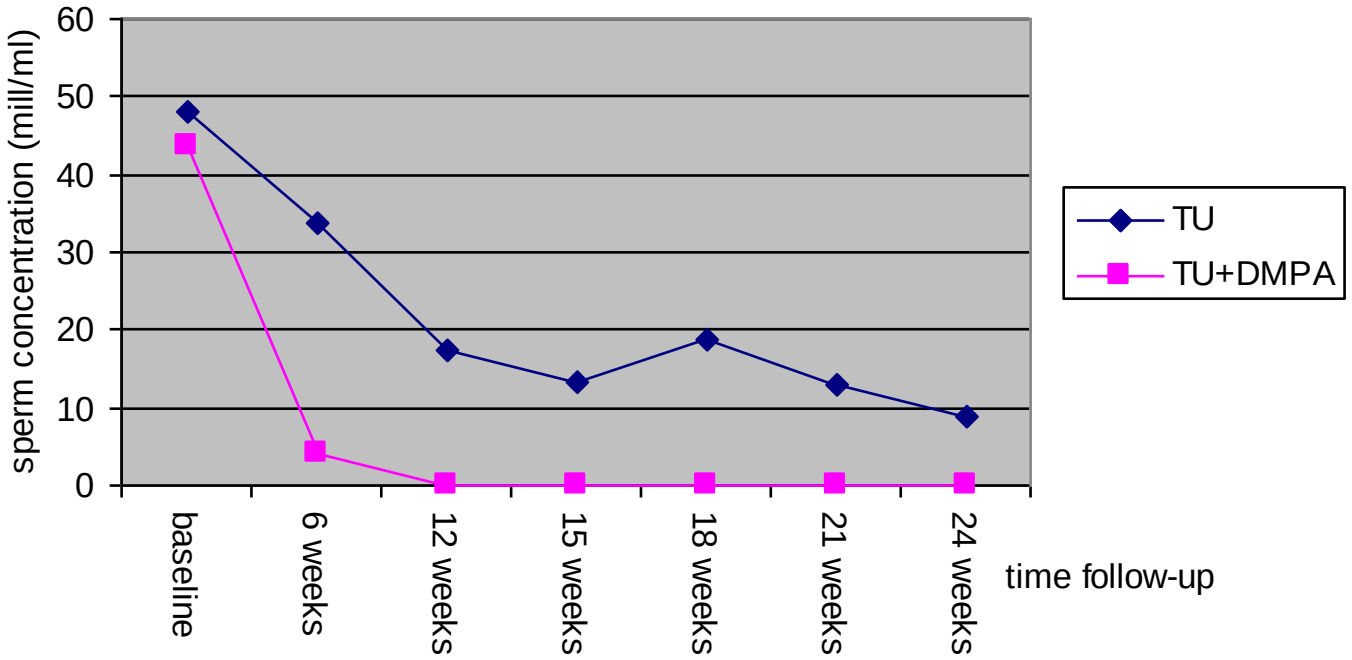
Hormonal Approaches to Male Contraception

Androgen with Progestin

Progestagen	Androgen	% Azoospermic	% Oligozoospermic (< 1 million/ml at week 16)	Reference
Etonogestrel implant (Implanon)				Mommers et al 2008
178 mg/implant (low release)	TU 750 mg every 12 weeks IM		90	
	TU 750 mg every 10 weeks IM		83	
	TU 1000 mg every 12 weeks IM		89	
144 mg/implant (high release)	TU 750 mg every 12 weeks IM		89	
	TU 750 mg every 10 weeks IM		93	
	TU 1000 mg every 12 weeks IM		95	

Hormonal Approaches to Male Contraception

Androgen with Progestin



Sperm suppression and contraceptive protection provided by norethisterone enantate (Net-En) combined with testosterone undecanoate (TU) in healthy men

A WHO and CONRAD Multicentre Phase IIb clinical trial

- Norethisterone enantate (Net-En)
  - Strong progestational activity
  - Androgenic activity
- Testosterone Undecanoate (TU)
  - Long-acting testosterone ester; well-tolerated

Norethisterone enantate (Net-En) + testosterone undecanoate (TU)

Initial study: Net-En 200 mg/6 weeks + TU 1000 mg/6 weeks (Kamischke et al 2001)

- 13/14 men azoospermic
- Reversible weight gain
- Decrease HDL
- Increase LDL
- Well-tolerated

Norethisterone enantate (Net-En) + testosterone undecanoate (TU)

Follow-up study: A) Net-En 200 mg/6 weeks + TU 1000 mg/6 weeks; B) Net-En 400 mg/6 weeks + TU 1000 mg/6 weeks (Kamischke et al 2002)

- Net-En alone first 2 weeks (Group A)
- 24/26 men azoospermic (13/14, 11/12)
- 2/26 men < 1 million sperm/mL
- Reversible weight gain
- Decrease HDL
- Well-tolerated

Norethisterone enantate (Net-En) + testosterone undecanoate (TU)

Net-En 200 mg + TU 1000 mg/8 weeks (Meriggiola et al 2005)

- 9/10 men azoospermic (median time 16 ± 3 weeks)
- 1/10 men severely oligozoospermic
- Median time to recovery 27 ± 1.1 weeks
- Nadir serum T higher than baseline, in normal range

Net-En 200 mg + TU 1000 mg/8 weeks (Quobaitary et al 2006)

- 10/10 men severely oligozoospermic by 24 weeks
- Testosterone profiles within normal range following 3 injections

Norethisterone enantate (Net-En) + testosterone undecanoate (TU)

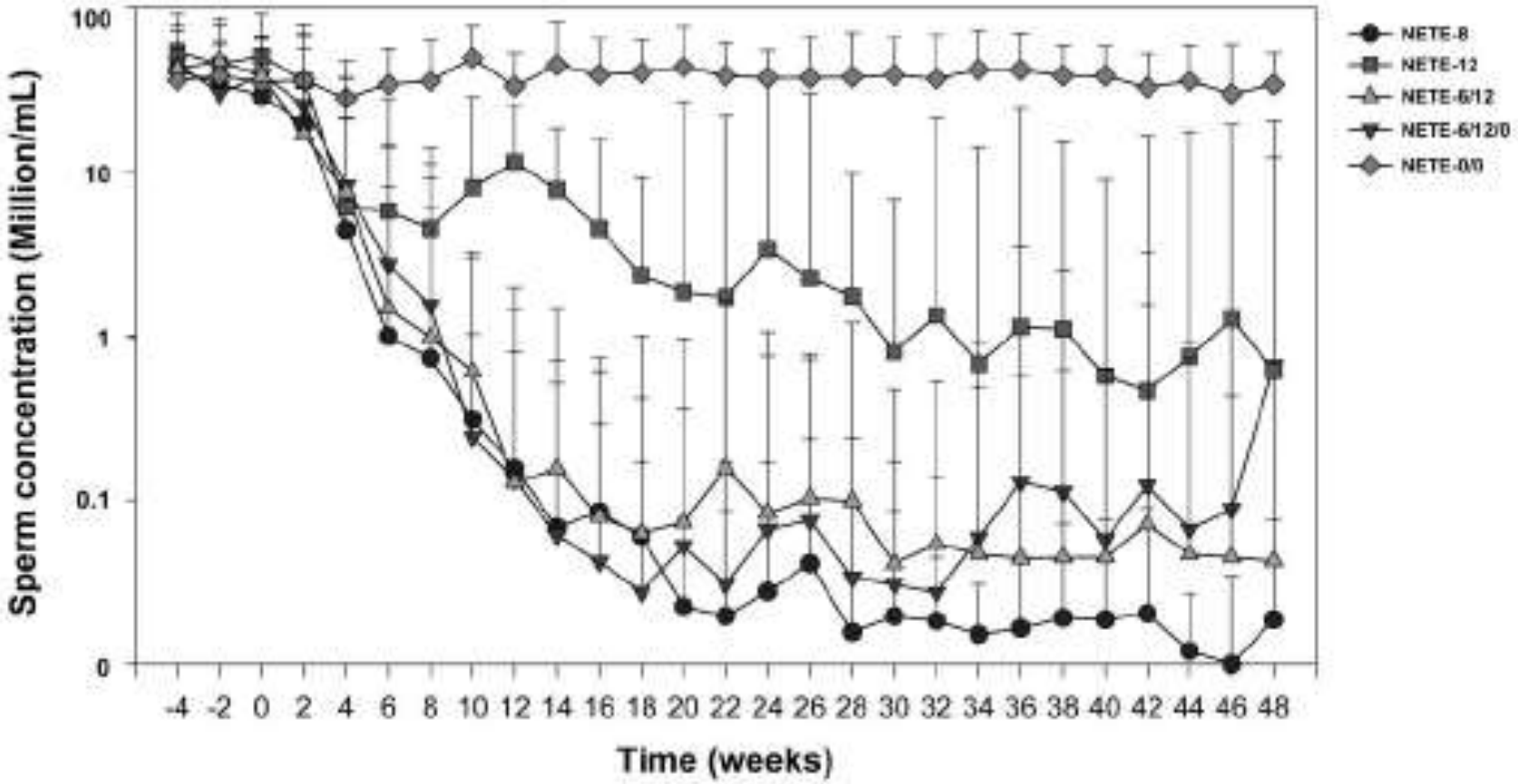
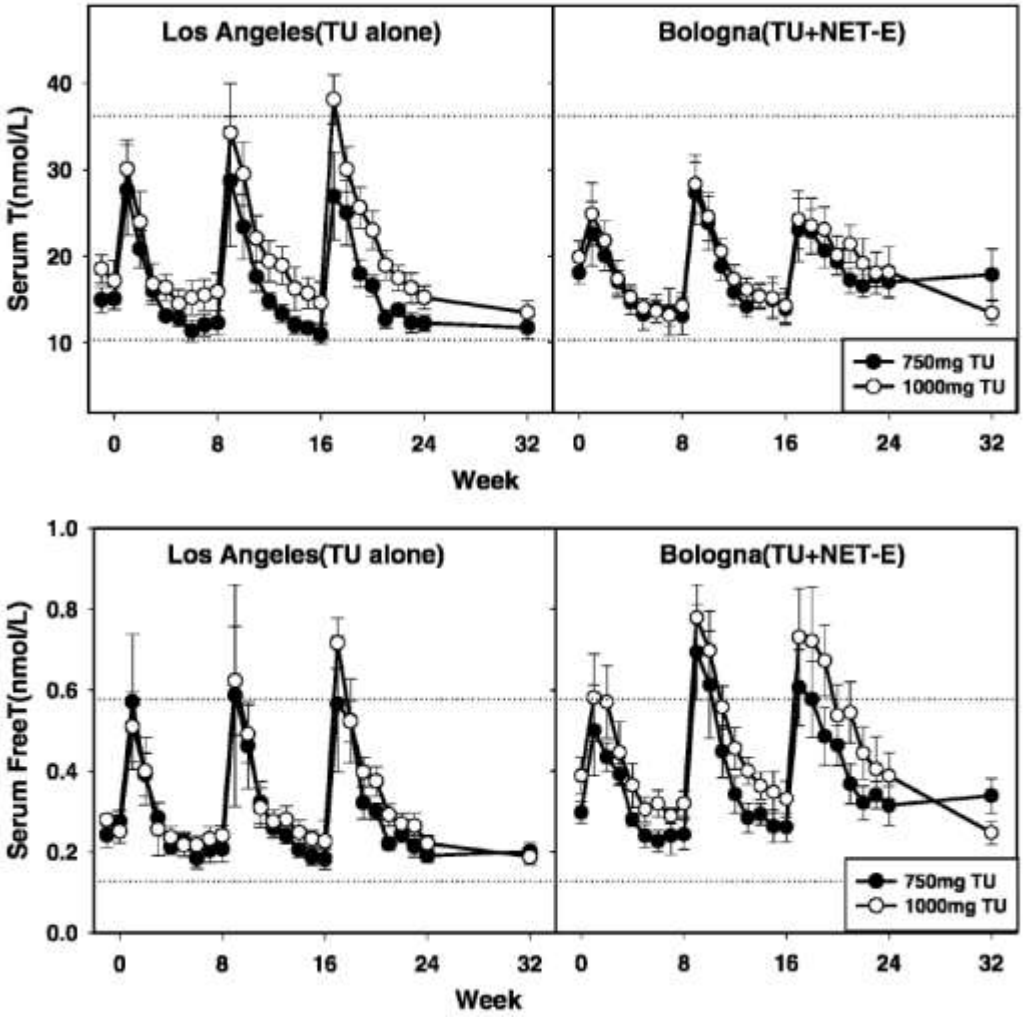


FIG. 1. Mean (± SD) sperm concentrations in the five groups during baseline and treatment phases.

Meriggiola et al 2005

Norethisterone enantate (Net-En) + testosterone undecanoate (TU) (Quobaitary et al 2006)



Norethisterone enantate (Net-En) + testosterone undecanoate (TU) (Quobaitary et al 2006)

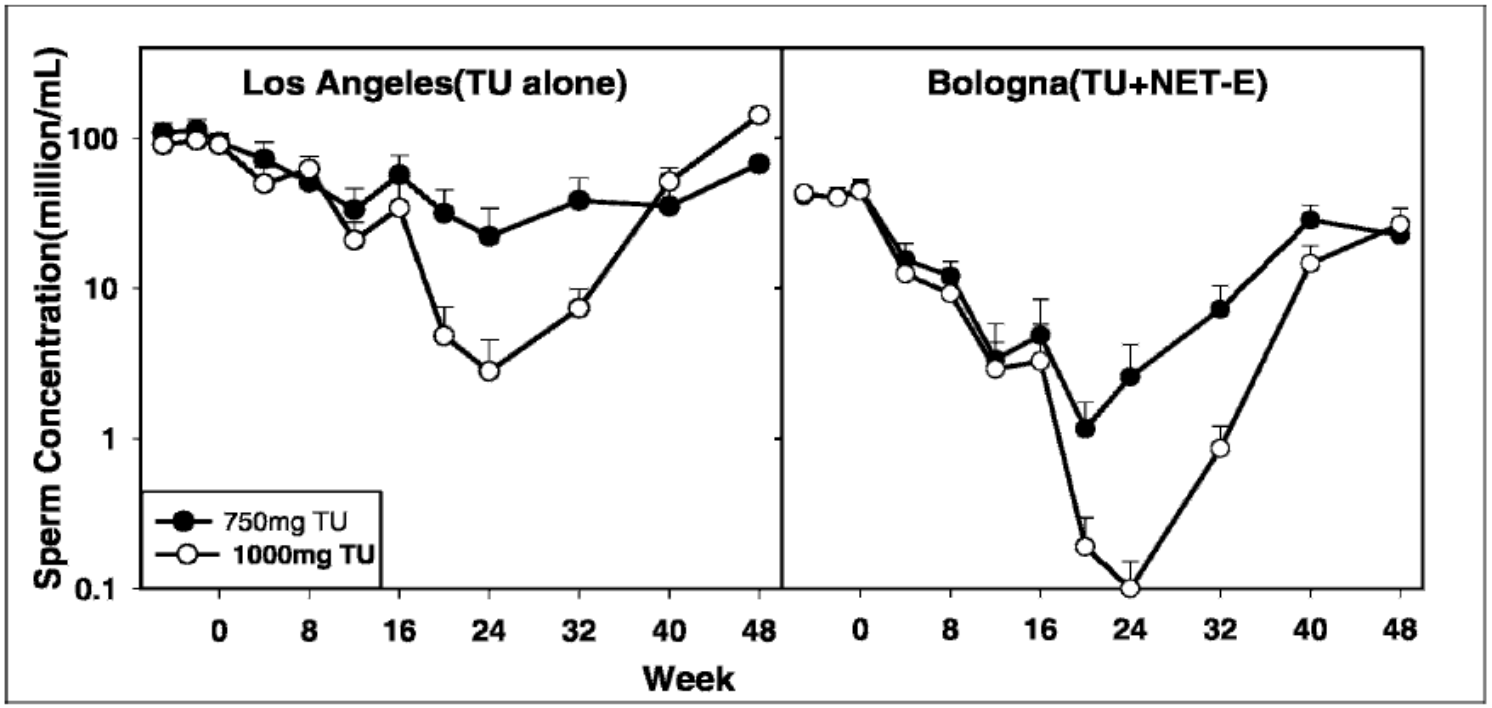


Figure 5. Sperm concentrations in subjects administered TU alone or TU with NETE.

Norethisterone enantate (Net-En) + testosterone undecanoate (TU)

Net-En 200 mg + TU 1000 mg

- 8 week injection intervals
- 2 baseline/control visits
- 6 month suppression period
- 12 month efficacy period (≤1 million sperm/ml)
- 6-12 month recovery period, as required
- Recruitment target: 400 couples/12 months
- 8 centres in 7 countries: Australia, Chile, Germany, India, Indonesia, Italy, the United Kingdom
- Central lab for hormone analyses
- Electronic data capture

Norethisterone enantate (Net-En) + testosterone undecanoate (TU)

Primary outcomes

- Contraceptive efficacy
- Suppression of spermatogenesis – degree and timing

Secondary outcomes

- Maintenance of spermatogenic suppression
- Reversibility
- Changes in circulating hormone concentrations
- Safety parameters
- Acceptability

Hormonal Approaches to Male Contraception

Other Approaches

- Androgen with anti-androgen (*cyproterone acetate*)
  - Progestin with anti-androgen properties
  - May block the activity of any residual T in the testis
- Androgen with GnRH Analogue
  - Effective suppression of gonadotrophins
  - High cost; frequent application

Disrupting Sperm Function and Preventing Fertilization

- Targeted basic science research on testicular, epididymal or vas approaches

  Some promising targets:

  – functional development, i.e. motility
  – structural development, i.e. organelles
  – structure and function, i.e. membrane integrity and intracellular pathways

Male Reproductive Health Agenda

- Contraceptive research and development
- Targeted basic science -physiology and fertility
- Social & behavioral sciences
- Men's roles in reproductive health
- Building networks

Acceptability/Sociobehavioral Studies

- Current use of male methods
- Preferences for new methods
- Characteristics of new methods
- Continuation and discontinuation of trial
- Effects on mood
- Effects on behavior
- Effects on cognition
- Partner's views on mood and behavior

Acceptability/Sociobehavioral Studies

Reports from 25 Swedish men participating in TE trial

Expectations

- Freedom and security
- Problems with female methods
- Desire for more satisfying sex life
- Need for male control
- Fear of negative side effects

Satisfaction

- Greater freedom
- More ease in sex life
- Would recommend method to others
- Trouble with injections
- Fear of problems with aggressiveness
- Dermatological problems

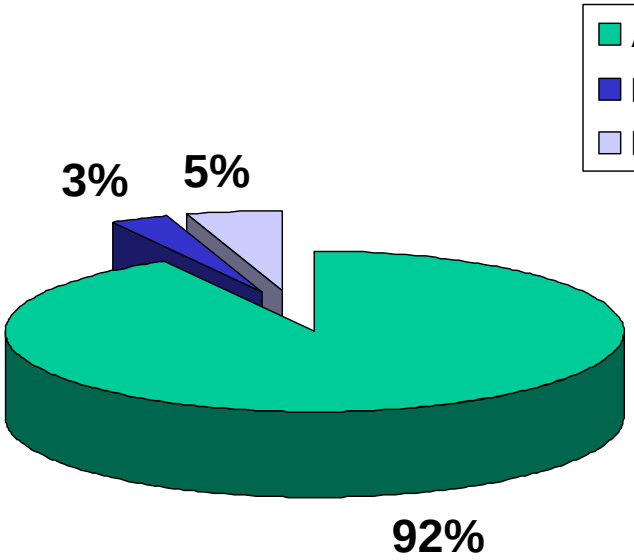
Acceptability/Sociobehavioral Studies

	Very important	*Somewhat important*	*Not important*
Men should share responsibility for contraception	41.2	51.0	7.8
Contributing to solving the population problem	41.6	48.7	9.7
I felt I was doing a good thing for my country	36.7	52.9	7.9
I like to be involved in new things	25.0	56.8	18.2
I felt pride in contributing to scientific advancement	26.9	51.6	21.4
Pioneer of a new method of contraception	24.4	46.1	29.5
My wife wanted me to take responsibility	23.1	44.8	32.1
I joined for getting the financial compensation	12.7	28.6	58.8

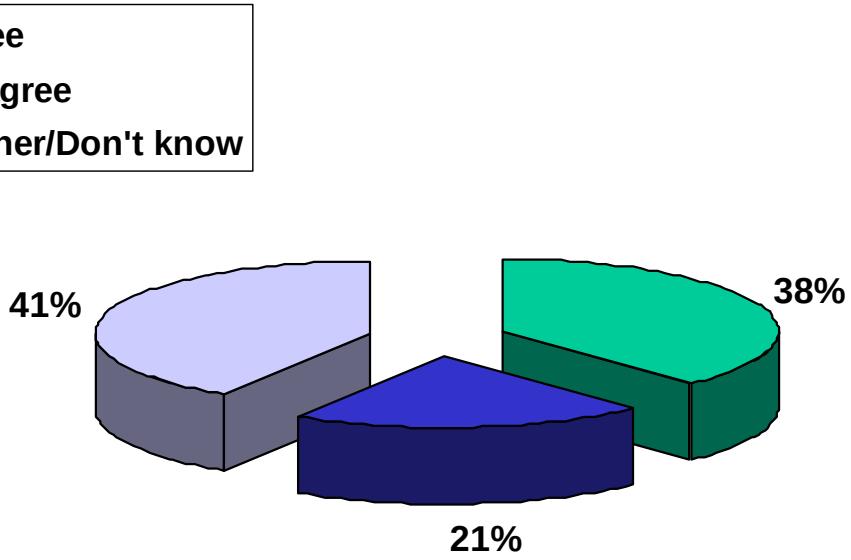
Acceptability/Sociobehavioral Studies

	Month 4 %	Month 8 %
Reasons for perceived inconvenience	(n = 78)	(n = 117)
Have to come to clinic	23.1	9.3
Once a month too frequent	70.5	76.3
Wait at the clinic	1.3	5.1
Other	5.1	9.3
Total	100.0	100.0
Reasons for dissatisfaction	(n = 87)	(n = 117)
Side effect	11.5	6.0
Inconvenience	54.0	48.7
Injection pain	21.8	12.0
Others	12.6	33.3
Total	100.0	100.0

Acceptability of TU + NetEn
(Meriggiola et al 2006)

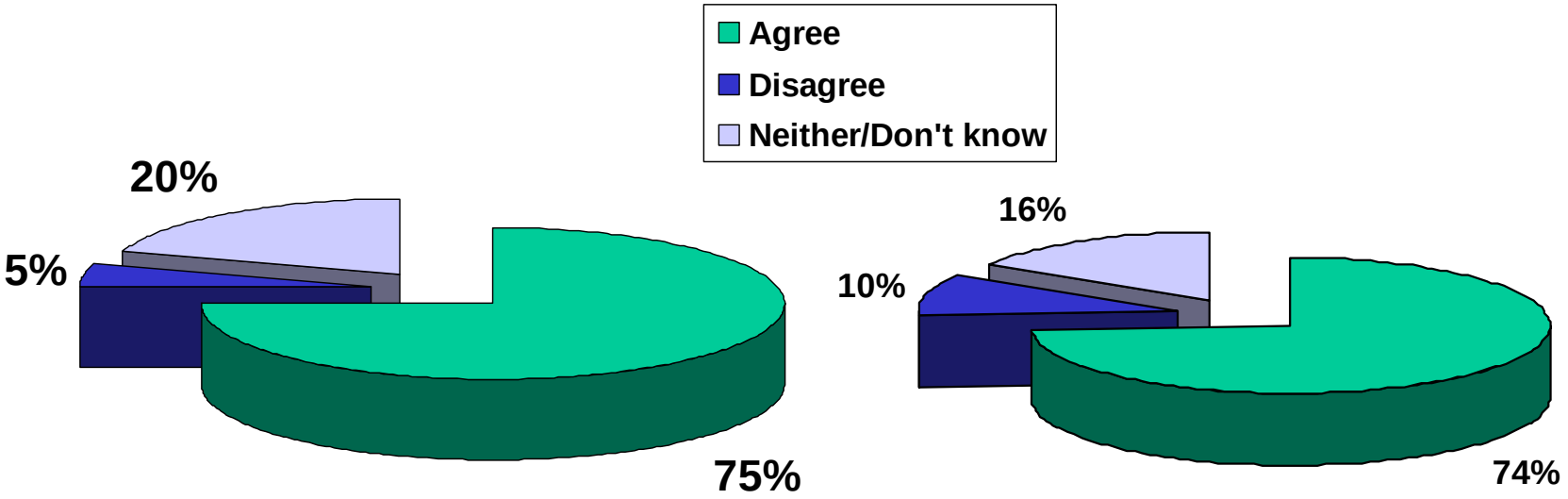


Men and women should share the responsibility for contraception equally (n=122)



I would like to relieve my partner of the responsibility for contraception (n=122)

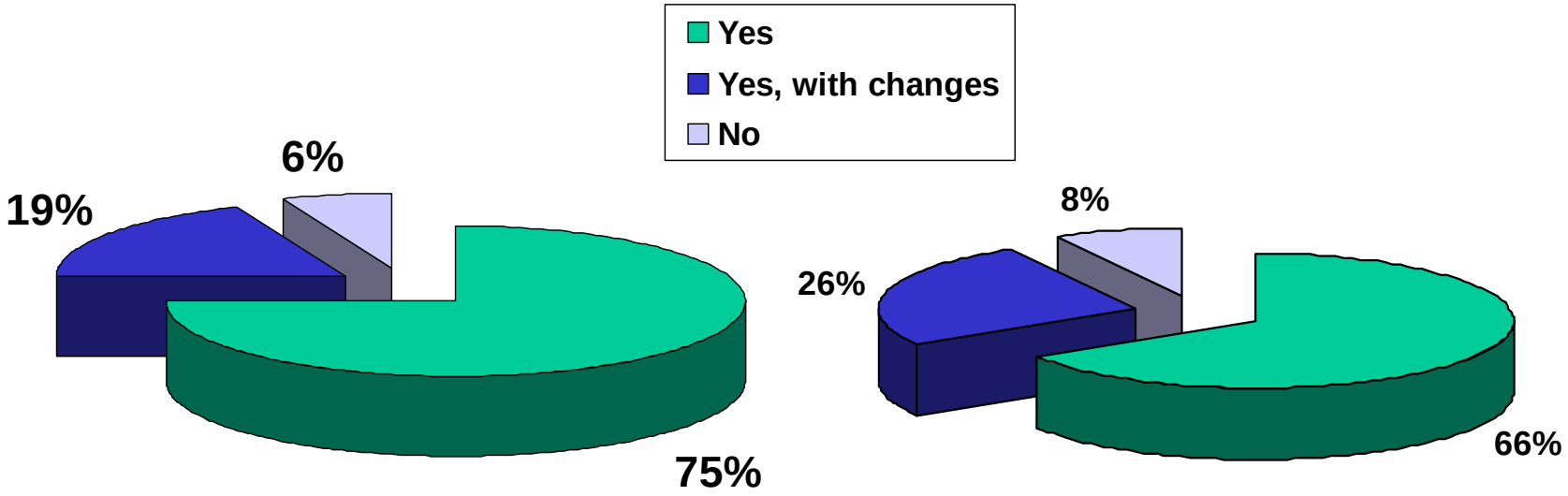
Acceptability of TU + NetEn
(Meriggiola et al 2006)



If a new contraceptive for men were available, I would try it (n=122)

Women would welcome the idea of a new contraceptive for men (n=122)

Acceptability of TU + NetEn
(Meriggiola et al 2006)



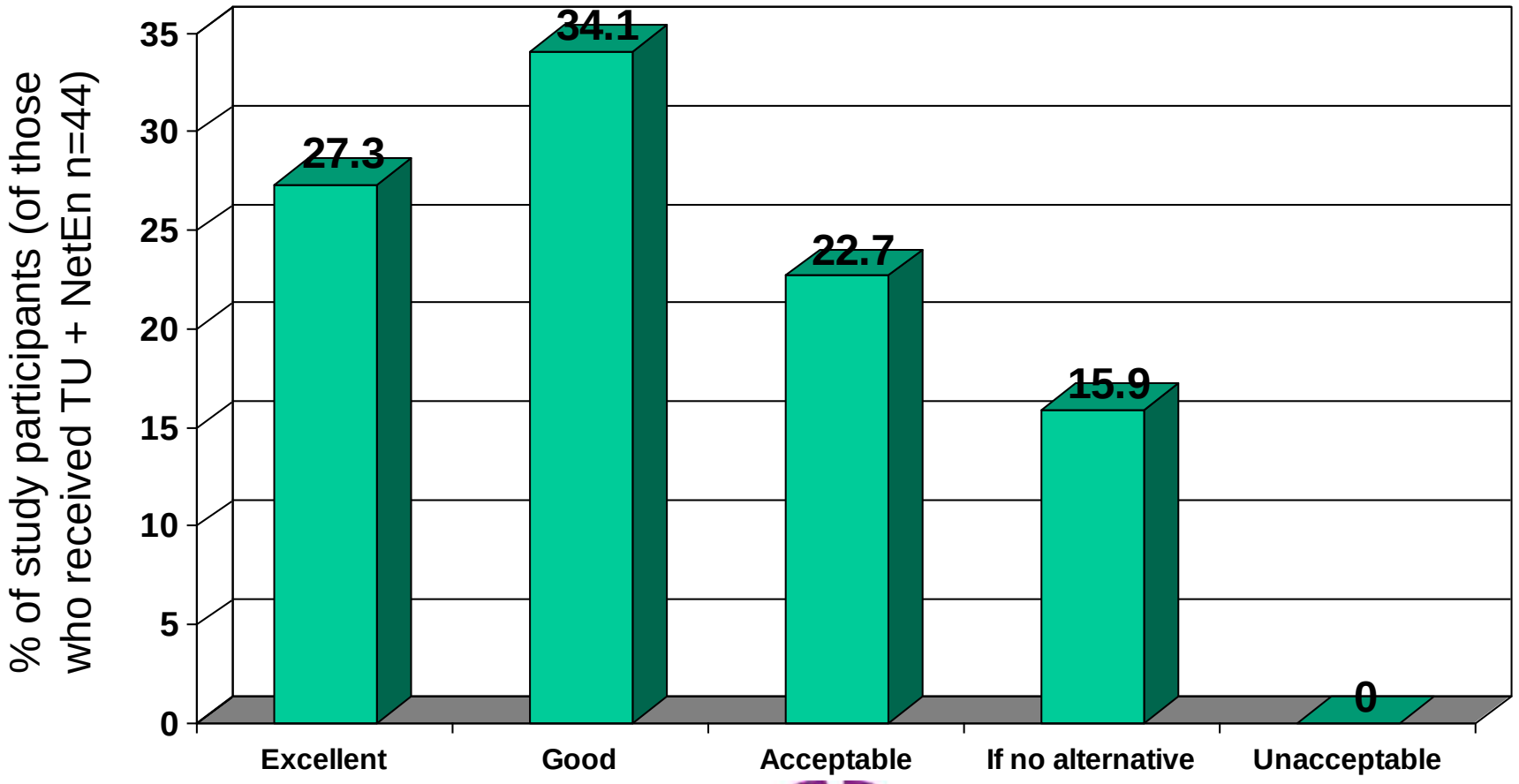
Beginning of study (n=48)

End of study (n=47)

If a male hormonal method of fertility regulation with the same schedule as this one were available, would you use it for contraception?

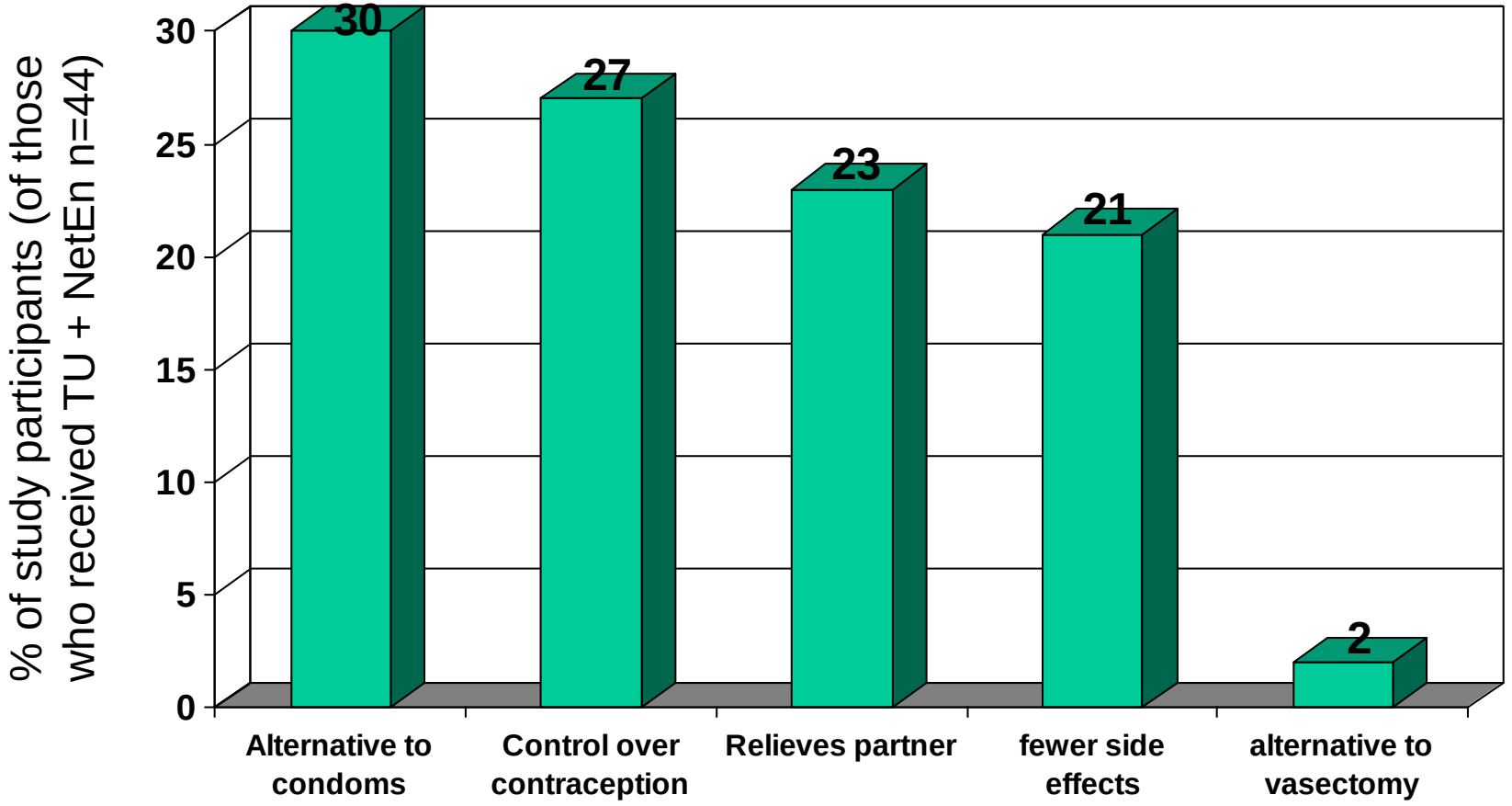
Acceptability of TU + NetEn
(Meriggiola et al 2006)

How would you rate the method in this study as a contraceptive method for men?



Acceptability of TU + NetEn
(Meriggiola et al 2006)

What are the biggest advantages of a hormonal contraceptive method for men?



Acceptability of TU + NetEn
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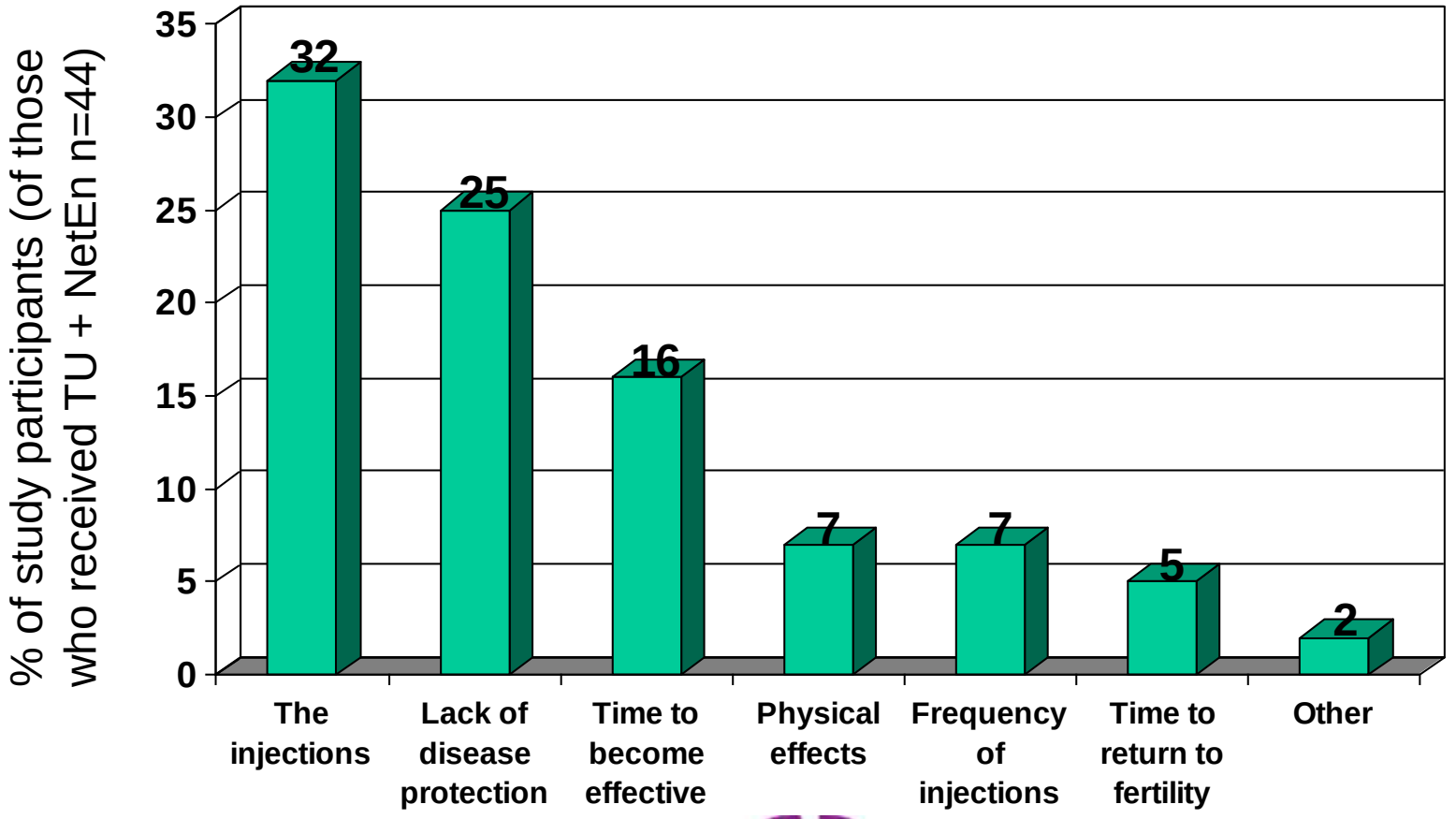
What are the biggest disadvantages of a hormonal contraceptive method for men?



Men's Roles in Reproductive Health

Men can:

- **Inhibit access to and use of FP**

OR

- **Facilitate & support use of contraception**

- **Expose women and themselves to disease including HIV**

OR

- **Protect themselves and their partners from infection**

- **Act as barriers to women's reproductive health**

OR

- **Act as partners in promoting reproductive rights and care for all**

Providing FP Services to Men

- How can FP service facilities address men's needs?
- How to create and then address an increase in demand for FP services for men?
- Who will provide FP services to men?