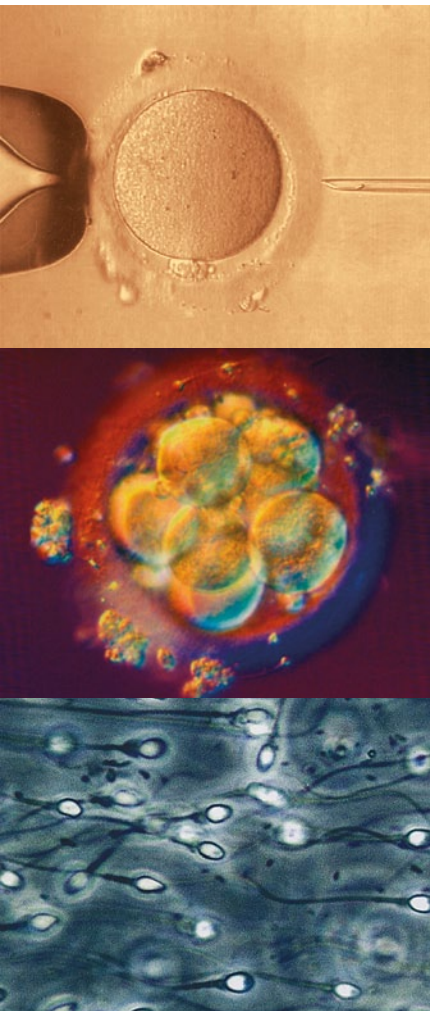


Journal für

Reproduktionsmedizin und Endokrinologie

– Journal of Reproductive Medicine and Endocrinology –

Andrologie • Embryologie & Biologie • Endokrinologie • Ethik & Recht • Genetik
Gynäkologie • Kontrazeption • Psychosomatik • Reproduktionsmedizin • Urologie



Clinical Trials in Male Hormonal Contraception

Nieschlag E

J. Reproduktionsmed. Endokrinol 2011; 8 (Sonderheft

1), 227-238

www.kup.at/repromedizin

Online-Datenbank mit Autoren- und Stichwortsuche

Offizielles Organ: AGRBM, BRZ, DVR, DGA, DGGEF, DGRM, DIR, EFA, OEGRM, SRBM/DGE

Indexed in EMBASE/Excerpta Medica/Scopus

Krause & Pachernegg GmbH, Verlag für Medizin und Wirtschaft, A-3003 Gablitz

Mitteilungen aus der Redaktion

Besuchen Sie unsere Rubrik

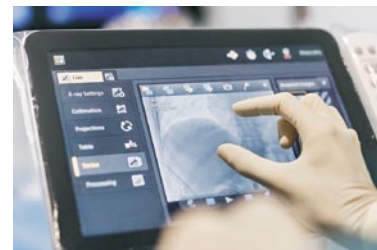
[Medizintechnik-Produkte](#)



Neues CRTD Implantat
Intica 7 HF-T QP von Biotronik



Artis pheno
Siemens Healthcare Diagnostics GmbH



Philips Azurion:
Innovative Bildgebungslösung

Aspirator 3
Labotect GmbH



InControl 1050
Labotect GmbH

e-Journal-Abo

Beziehen Sie die elektronischen Ausgaben dieser Zeitschrift hier.

Die Lieferung umfasst 4–5 Ausgaben pro Jahr zzgl. allfälliger Sonderhefte.

Unsere e-Journale stehen als PDF-Datei zur Verfügung und sind auf den meisten der marktüblichen e-Book-Readern, Tablets sowie auf iPad funktionsfähig.

[Bestellung e-Journal-Abo](#)

Haftungsausschluss

Die in unseren Webseiten publizierten Informationen richten sich **ausschließlich an geprüfte und autorisierte medizinische Berufsgruppen** und entbinden nicht von der ärztlichen Sorgfaltspflicht sowie von einer ausführlichen Patientenaufklärung über therapeutische Optionen und deren Wirkungen bzw. Nebenwirkungen. Die entsprechenden Angaben werden von den Autoren mit der größten Sorgfalt recherchiert und zusammengestellt. Die angegebenen Dosierungen sind im Einzelfall anhand der Fachinformationen zu überprüfen. Weder die Autoren, noch die tragenden Gesellschaften noch der Verlag übernehmen irgendwelche Haftungsansprüche.

Bitte beachten Sie auch diese Seiten:

[Impressum](#)

[Disclaimers & Copyright](#)

[Datenschutzerklärung](#)

Clinical Trials in Male Hormonal Contraception *

E. Nieschlag

Research has established the principle of hormonal male contraception based on suppression of gonadotropins and spermatogenesis. All hormonal male contraceptives use testosterone, but only in East Asian men can testosterone alone suppress spermatogenesis to a level compatible with contraceptive protection. In Caucasians, additional agents are required of which progestins are favored. Clinical trials concentrate on testosterone combined with norethisterone, desogestrel, etonogestrel or depot-medroxyprogesterone acetate. The first randomized, placebo-controlled clinical trial performed by the pharmaceutical industry demonstrated the effectiveness of a combination of testosterone undecanoate and etonogestrel in suppressing spermatogenesis in volunteers. **J Reproduktionsmed Endokrinol 2011; 8 (Special Issue 1): 227–38.**

Keywords: male contraception, testosterone, norethisterone, clinical trials

1. Introduction

1.1. The Rationale for Hormonal Male Contraception

The invention of the “pill” for women was undoubtedly one of the most significant medical, social and cultural events of the 20th century [1]. While nature has sweetened procreation with the pleasures of sex to guarantee human reproduction, the pill was the culmination of a millennial-long development of methods to disentangle procreation from sex and has had a substantial impact on society, e.g., on family planning, morality and demography, not to mention economic and political impact. An equivalent pharmacological male method is not yet available.

Female contraception is very effective. Nevertheless, 50% of the 1,000,000 conceptions occurring every day worldwide remain unplanned, of which 150,000 are terminated by abortion, an intervention that will end fatally for 500 of these women. Although improved distribution and utilization of female contraceptive methods might ameliorate this situation, the contribution of a male contraceptive is well worth considering. Men enjoy the pleasures of sex, but can do little to contribute to the tasks of family planning – a pharmacological male contraceptive is surely long overdue.

Moreover, the risks of contraception would also be more fairly shared between women and men. Representative surveys have shown that a pharmacological male contraceptive would be ac-

ceptable to large segments of the population in industrial nations, and would thus contribute to further stabilization of population dynamics. It might also help developing countries whose exponential population growth endangers economic, social and medical progress. Last but not least, male contraception can be considered an outstanding issue in the political field of gender equality

1.2. Choices For the Male

For the male, there are ways to eliminate both procreation and sex at the same time. Such methods have been used in the past and are still being practiced on a limited scale. Castration has been employed since ancient time to destroy enemies by abolishing their ability to reproduce and transmit their genes. Until the end of the imperial period in China (1912), men were willing to sacrifice their testicles (and often with them their lives) in return for high-ranking positions and political influence at the emperor’s court. Meanwhile, in the West, up until almost the same time, some promising boys were forced to give up their manhood for the sake of preserving their prepubertal voice and achieving fame as singers, often without success [2]. Abstinence is a less bloody means of eliminating procreation, but few men are willing to give up both sex and procreation for extended periods of time, let alone their entire lives.

Traditional male methods of contraception such as periodic abstinence or coitus interruptus are associated with a relatively high rate of unwanted pregnancy

and also cause a disturbance in sexual activity. Condoms are the oldest barrier method available. However, when using condoms, conception rates are relatively high, with 12 out of 100 couples conceiving during the first year of use (Pearl index = 12). Condom use has increased since the beginning of the AIDS epidemic, but more for protection from HIV infection and other sexually transmitted diseases than for contraceptive purposes [3]. Vasectomy is a safe and relatively simple surgical method for male contraception. The rate of unwanted pregnancies after vasectomy is less than 1%. The drawback to vasectomy is that it is not easily reversible. Achieving fatherhood after vasectomy requires either surgical reversal or sperm extraction from a testicular biopsy and intracytoplasmatic sperm injection into the ovum. Only about 50% of these men will become fathers in the end.

Given the disadvantages of these mechanical male methods, what then are the prerequisites for an ideal male contraceptive? It should

- be applied independently of the sexual act,
- be acceptable for both partners,
- not interfere with libido, potency, or sexual activity,
- have neither short- or long-term toxic side effects,
- have no impact on eventual offspring,
- be rapidly effective and fully reversible,
- be as effective as comparable female methods.

*Reprint with permission from: Contraception 2010; 82: 457–70. © 2010 Elsevier Inc. All rights reserved.

Correspondence: Prof. Eberhard Nieschlag, MD, Centre of Reproductive Medicine and Andrology of the University, WHO Collaboration Centre for Research in Male Reproduction, Domagkstr. 11, D-48149 Münster/Germany; e-mail: eberhard.nieschlag@ukmuenster.de

For the past 40 years, hormonal approaches to male contraception have been tested clinically. In the following, these developments will be reviewed taking the above prerequisites into account.

2. Principle of Hormonal Male Contraception

Of all the different experimental approaches and pharmacological methods tested so far for male contraception, hormonal methods come closest to fulfilling the criteria set out above. The endocrine feedback mechanism operating between hypothalamus, pituitary and testes is the

basis on which hormonal approaches to male contraception rest. Its goal is to suppress spermatogenesis and to reduce sperm concentration, if possible, to azoospermia or at least to a sperm concentration low enough to provide contraceptive protection ($\leq 1 \times 10^6$ sperm per mL ejaculate).

Sperm production and secretion of testicular testosterone are so closely interwoven that it has remained impossible to interrupt spermatogenesis by hormonal means without inhibiting androgen production. Inhibition of follicle-stimulating hormone (FSH) alone, e.g., by antibodies, leads to reduction of sperm concentration but not to azoospermia, as monkey studies have shown. Suppression of both FSH and luteinizing hormone (LH) would indeed lead to azoospermia, but would also induce symptoms of androgen deficiency which affects libido, potency, male role behavior and general metabolic processes (erythropoiesis, protein, mineral and bone metabolism). For this reason inhibition of gonadotropins will always necessitate androgen administration.

Thus, the principle of hormonal male contraception is based on

- (1) suppression of LH and FSH,
- (2) depletion of intratesticular testosterone and atrophy of spermatogenesis, and
- (3) substitution of peripheral testosterone to maintain androgenicity.

At first sight, testosterone itself would be the steroid of choice as it simultaneously suppresses the gonadotropins and maintains androgenicity. However, studies showed that by administration of testosterone alone, azoospermia could only be achieved in two-thirds of Caucasian men, so that another gonadotropin-suppressing agent must be added to interrupt spermatogenesis as completely as possible. Gonadotropin-releasing hormone (GnRH) analogues and several different steroid combinations and delivery systems such as oral, transdermal, subcutaneous and intramuscular (im) have been examined. Each has its respective merits and drawbacks (Fig. 1B and C).

Table 1 provides an overview of clinical trials for male hormonal contraception based on steroids. At the outset of this

summary, it should be noted that in all these many clinical trials, only very few untoward side effects were reported, including mild acne and moderate weight gain as a more frequent symptom, the latter due to the anabolic effect of testosterone. A recently performed placebo-controlled clinical trial for male contraception demonstrated that several symptoms previously ascribed to the steroid regimen used, also occur in the placebo group [55]. Minimal serious adverse events were registered in this multitude of trials. In all studies, sperm counts returned to normal levels as a review of major studies also revealed [61] so that one of the prime goals of male hormonal contraception, i.e., reversibility, is met. However, long-term studies extending over three or more years have not yet been performed. Incidentally, it is worth mentioning that results from animal studies have contributed little to the development of male hormonal contraception, except in the case of GnRH analogues using non-human primates. On the contrary, humans have provided models for fertility control in wildlife [62].

3. Clinical Trials to Date

3.1. Androgens Alone

3.1.1. Testosterone Enanthate

Soon after testosterone was synthesized and became available for clinical use in the late 1930s, its spermatogenesis-suppressing effect was recognized [63], but not until the 1970s did investigations start to exploit this phenomenon for male contraception. As in most hormonal male contraceptive studies to date, in the early studies, sperm concentrations and counts were used as surrogate parameters for efficacy.

The first efficacy study of testosterone-based hormonal male contraception was sponsored by the World Health Organization (WHO) [5] and included 10 centers on four continents. Healthy fertile participants were given 200 mg of the longer-acting testosterone enanthate weekly by im injection. One hundred fifty-seven men (70%) reached azoospermia after 6 months of treatment and entered the efficacy phase for a further year, during which no other contraceptive was used by the couple. Only one pregnancy was reported in this first proof-of-principle study. Although the

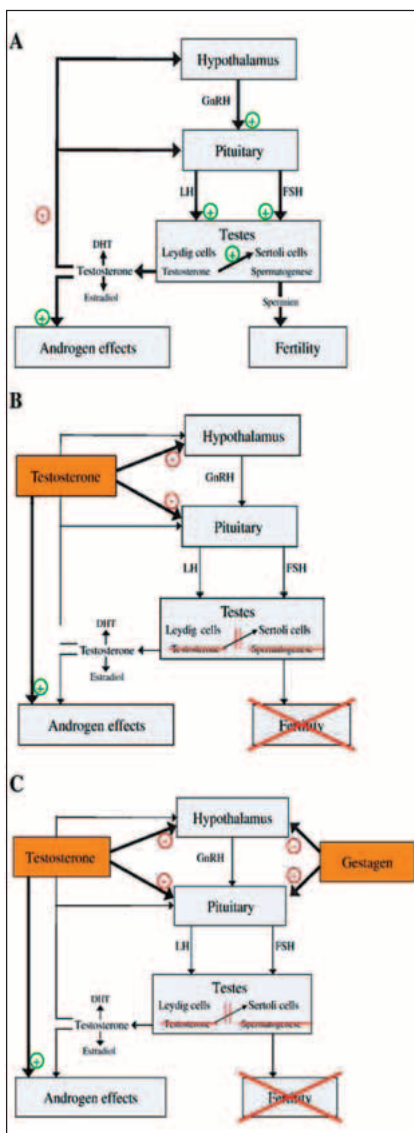


Figure 1. Schematic representation of the endocrine mechanism controlling testicular function (A). (B) the principle of hormonal male contraception using testosterone. (C) the principle of hormonal male contraception using testosterone plus a gestagen (adapted from [2]).

Table 1. Overview of studies on hormonal male contraception using either testosterone alone or in combination with progestins (updated from [4])

Reference, year	Ref. no.	Number of subjects	Ethnic origin	Androgen dose	Progestin dose	Azoospermia (n)	Severe Oligozoospermia (< 1 Mio/ml [n])	Oligozoospermia (< 3 Mio/ml [n])
Testosterone alone								
WHO, 1990	[5]	271	Mixed	TE 200 mg im/week	None	157	??	??
Behre et al., 1995	[6]	8	Caucasian	TB 1000 mg im one	None	3	-	-
Handelsman et al., 1992	[7]	9	Unknown	T-Pellets 1200 mg	None	5	4	0
Handelsman et al., 1996	[8]	10	Unknown	T-Pellets 400 mg	None	0	0	0
Handelsman et al., 1996	[8]	10	Unknown	T-Pellets 800 mg	None	4	0	0
Meriggola et al., 1996	[9]	5	Caucasian	TE 100 mg im/week	None	5	0	0
Bebb et al., 1996	[10]	18	Caucasian	TE 100 mg im/week	None	6	4	1
WHO, 1996	[11]	225	Mixed	TE 200 mg im/week	None	157	29	8
Zhang et al., 1999	[12]	12	Chinese	TU*500 mg im/4 weeks	None	11	1	0
Zhang et al., 1999	[12]	12	Chinese	TU*1000 mg im/4 weeks	None	12	0	0
Kamischke et al., 2000	[13]	14	Caucasian	TU 1000 mg im/6 weeks	None	7	4	1
McLachlan et al., 2002	[14]	5	Not stated	TE 200 mg im/week	None	4	4	0
						4 ≤ 0.1 or azoospermia		
von Eckardstein et al., 2003	[15]	35	Caucasian	MENT implants, 3 doses	None	10	-	3
Gu et al., 2003	[16]	305	Chinese	TU*500 mg im/4 weeks	None	284	6	6
Gu et al., 2009	[17]	898	Chinese	TU*500 mg im/4 weeks	None	855	-	43
DMPA								
Alvarez-Sanchez et al., 1977	[18]	8	Dominican Republic	TE 250 mg im/week	DMPA 150 mg/4 weeks	4	3	1
Alvarez-Sanchez et al., 1977	[18]	10	Dominican Republic	TE 250 mg im/week	DMPA 3000 mg/4 weeks	7	2	0
Brenner et al., 1977	[19]	6	Caucasian	TE 200 mg im/week	DMPA 100 mg/4 weeks	1	2	1
Brenner et al., 1977	[19]	3	Caucasian	TE 200 mg im/week	DMPA 150 mg/4 weeks	1	0	0
Frick et al., 1977	[20]	12	Caucasian	TE 250 mg im/week	DMPA 100 mg im/4 weeks	6	4	0
Frick et al., 1977	[20]	6	Caucasian	T-Propionate 4 rods	DMPA 100 mg im/4 weeks	2	0	0
Melo and Coutinho, 1977	[21]	11	Brasilian	TE 200 mg im/week	DMPA 100-150 mg im/4 weeks	11 ≤ 0.1 or azoospermia	0	???
Faundes et al., 1981	[22]	10	Dominican Republic	TE 500 mg im/week	DMPA 150 mg/ 4weeks	8	1	0
Frick et al., 1982	[23]	4	Caucasian	TE 500 mg/4 weeks	150 mg/4 weeks	4	0	0
Frick et al., 1982	[23]	5	Caucasian	TE 250 mg/2 weeks	75 mg/2 weeks	5	0	0
WHO, 1993	[24]	45	Indonesian	19-Nortestosterone 200 mg im/3 weeks	DMPA 250 mg im/6 weeks	44	1	0
WHO, 1993	[24]	45	Indonesian	TE 200 mg im/3 weeks	DMPA 250 mg im/6 weeks	43	2	0
Knuth et al., 1989	[25]	12	Caucasian	19-Nortestosterone 200 mg im/3 weeks	DMPA 250 mg im/6 weeks	6	4	2
Wu and Aitken, 1989	[26]	10	Caucasian	TE 250 mg im/week	DMPA 200 mg/4 weeks	6	0	4
Pangkahila, 1991	[27]	10	Indonesian	TE 100 mg im/week	DMPA 100 mg/4 weeks	10	0	0
Pangkahila, 1991	[27]	10	Indonesian	TE 250 mg im/week	DMPA 200 mg/4 weeks	10	0	0
Handelsman et al., 1996	[8]	10	Not stated	T-Pellets 800 mg	DMPA once 300 mg im	9	0	1
McLachlan et al., 2002	[14]	5	Not stated	TE 200 mg im/week	DMPA once 300 mg im	5 ≤ 0.1 or azoospermia	5	0
Turner et al., 2003	[28]	53	Unknown	T-Pellets 800 mg/16 weeks	DMPA 300 mg im/12 weeks	49	2	0
Gu et al., 2004	[29]	30	Chinese	TU* 1000 mg/weeks	DMPA 150 or 300 mg/8 weeks	28	1	1
Page et al., 2006	[30]	38	Not stated	T gel 100 mg/day	DMPA 300 mg/12 weeks ± GnRH antagonist	31	2	3

Table 1 (continued). Overview of studies on hormonal male contraception using either testosterone alone or in combination with progestins (updated from [4])

Reference, year	Ref. no.	Number of subjects	Ethnic origin	Androgen dose	Progestin dose	Azoospermia (n)	Severe oligozoospermia (< 1 Mio/ml [n])	Oligozoospermia (< 3 Mio/ml [n])
Levonorgestrel (LNG)								
Fogh et al., 1980	[31]	5	Caucasian	TE 200 mg/4 weeks	LNG 250 mcg p.o./day	1	?	1
Fogh et al., 1980	[31]	5	Caucasian	TE 200 mg im/4 weeks	LNG 500 mcg p.o./day	2	?	?
Bebb et al., 1996	[10]	18	Caucasian	TE 100 mg im/week	LNG 500 mcg p.o./day	12	2	3
Anawalt et al., 1999	[32]	18	Caucasian	TE 100 mg im/week	LNG 125 mcg p.o./day	11	5	1
Anawalt et al., 1999	[32]	18	Caucasian	TE 100 mg im/week	LNG 250 mcg p.o./day	14	2	0
Ersheng et al., 1999	[33]	16	Chinese	TU 250 mg im/4 weeks	Sino-Implant 2 rods	6	0	1
Kamischke et al., 2000	[13]	14	Caucasian	TU 1000 mg im/6 weeks	LNG 250 mcg p.o./day	8	4	2
Gaw Gonzalo et al., 2002	[34]	20	Mixed	Testoderm TTS 2 patches/day	Norplant II 4 rods	7	5	2
Gaw Gonzalo et al., 2002	[34]	15	Mixed	Testoderm TTS 2 patches/day	LNG 125 mcg p.o./day	5	1	1
Gaw Gonzalo et al., 2002	[34]	14	Mixed	TE 100 mg im/week	Norplant II 4 rods	13	1	0
Pölänen et al., 2001	[35]	5	Caucasian	DHT-Gel 250 mg/day	LNG 30 mcg p.o./day	0	0	1
Pölänen et al., 2001	[35]	5	Caucasian	DHT-Gel 250 mg/day	Jardelle (LNG) 1 rod	0	0	0
Pölänen et al., 2001	[35]	8	Caucasian	DHT-Gel 500 mg/day	Jardelle (LNG) 2 rods	0	0	0
Pölänen et al., 2001	[35]	7	Caucasian	DHT-Gel 250 mg/day	Jardelle (LNG) 4 rods	0	0	0
Gui et al., 2004	[36]	41	Chinese	TU*500 or 1000 mg/8 weeks	LNG 4 implants	31	5	4
Anawalt et al., 2005	[37]	41	Mixed	TE 100 mg/week	LNG 31 mcg or 62 mcg/day	25	13	2
Wang et al., 2006	[38]	19	Caucasian	T implants/15-18 weeks	LNG 4 implants	13	-	-
Wang et al., 2006	[38]	21	Chinese	TU*500 mg/6 weeks	LNG 250 mg p.o./day	19	-	-
Wang et al., 2007	[39]	18	Chinese	TU*500 mg/6 weeks	LNG 250 mg p.o./day	17	-	1
Norethisterone enanthate (NETE)								
Kamischke et al., 2001	[40]	14	Caucasian	TU 1000 mg im/6 weeks	NETE 200 mg/6 weeks	13	0	0
Kamischke et al., 2002	[41]	14	Caucasian	TU 1000 mg im/6 weeks	NETE 200 mg/6 weeks	13	1	0
Kamischke et al., 2002	[41]	14	Caucasian	TU 1000 mg im/6 weeks	NETE 400 mg/6 weeks	13	1	0
Kamischke et al., 2002	[41]	14	Caucasian	TU 1000 mg im/6 weeks	NETA 10 mg p.o./day	12	2	0
Meriggiola et al., 2005	[42]	10	Caucasian	TU 1000 mg/8 weeks	NETE 200 mg/6 weeks	9	0	0
Meriggiola et al., 2005	[42]	8	Caucasian	TU 1000 mg/12 weeks	NETE 200 mg/12 weeks	3	0	1
Oubaitry et al., 2006	[43]	10	Mixed	TU 750 mg/8 weeks	NETE 250 mg/8 weeks	5	2	1
Oubaitry et al., 2006	[43]	10	Mixed	TU 1000 mg/8 weeks	NETE 250 mg/8 weeks	10	2	1
Cyproterone acetate								
Meriggiola et al., 1996	[9]	5	Caucasian	TE 100 mg im/week	CPA 50 mg p.o./day	3	0	1
Meriggiola et al., 1996	[9]	5	Caucasian	TE 100 mg im/week	CPA 100 mg p.o./day	5	0	0
Meriggiola et al., 1998	[44]	5	Caucasian	TE 100 mg im/week	CPA 12.5 mg p.o./day	3	2	0
Meriggiola et al., 1998	[44]	5	Caucasian	TE 100 mg im/week	CPA 25 mg p.o./day	5	0	0
Meriggiola et al., 2002	[45]	9	Caucasian	TE 100 mg im/week	CPA 5 mg p.o./day	6	3	0
Meriggiola et al., 2002	[45]	7	Caucasian	TE 200 mg im/week	CPA 5 mg p.o./day	0	4	2
Meriggiola et al., 2003	[46]	24	Caucasian	TU 1000 mg/6 weeks	CPA 20 and 2 mg p.o./day	13	11	-

Table 1 (continued). Overview of studies on hormonal male contraception using either testosterone alone or in combination with progestins (updated from [4])

Reference, year	Ref. no.	Number of subjects	Ethnic origin	Androgen dose	Progestin dose	Azoospermia (n)	Severe oligozoospermia (< 1 Mio/ml [n])	Oligozoospermia (< 3 Mio/ml [n])
Desogestrel (DSG) or etonogestrel								
Wu et al., 1999	[47]	8	Caucasian	TE 50 mg im/week	DSG 300 mcg p.o./day	8	0	0
Wu et al., 1999	[47]	7	Caucasian	TE 100 mg im/week	DSG 150 mcg p.o./day	4	3	0
Wu et al., 1999	[47]	8	Caucasian	TE 100 mg im/week	DSG 300 mcg p.o./day	6	0	1
Anawalt et al., 2000	[48]	7	Caucasian	TE 50 mg im/week	DSG 150 mcg p.o./day	4	1	0
Anawalt et al., 2000	[48]	8	Caucasian	TE 100 mg im/week	DSG 150 mcg p.o./day	8	0	0
Anawalt et al., 2000	[48]	8	Caucasian	TE 100 mg im/week	DSG 300 mcg p.o./day	7	1	0
Kinniburgh et al., 2001	[49]	8	Caucasian	T-Pellets 400 mg/12 weeks	DSG 150 mcg p.o./day	6	2	0
Kinniburgh et al., 2001	[49]	7	Caucasian	T-Pellets 400 mg/12 weeks	DSG 150 mcg p.o./day	5	1	0
Anderson et al., 2002	[50]	9	Black	T-Pellets 400 mg/12 weeks	DSG 150 mcg p.o./day	9	0	0
Anderson et al., 2002	[50]	11	Mixed	T-Pellets 400 mg/12 weeks	DSG 150 mcg p.o./day	9	0	1
Anderson et al., 2002	[50]	8	Black	T-Pellets 400 mg/12 weeks	DSG 300 mcg p.o./day	8	0	0
Anderson et al., 2002	[50]	12	Mixed	T-Pellets 400 mg/12 weeks	DSG 300 mcg p.o./day	8	0	0
Anderson et al., 2002	[51]	14	Caucasian	T-Pellets 400 mg/12 weeks	Implanon (ENG) 1 rod	9	1	3
Anderson et al., 2002	[51]	14	Caucasian	T-Pellets 400 mg/12 weeks	Implanon (ENG) 2 rods	9	4	0
Kinniburgh et al., 2002	[52]	15	Caucasian	T-Pellets 400 mg/12 weeks	DSG 300 mcg p.o./day	15	0	0
Kinniburgh et al., 2002	[52]	18	Chinese	T-Pellets 400 mg/12 weeks	DSG 300 mcg p.o./day	18	0	0
Kinniburgh et al., 2002	[52]	18	Chinese	T-Pellets 400 mg/12 weeks	DSG 150 mcg p.o./day	11	2	2
Kinniburgh et al., 2002	[52]	13	Caucasian	T-Pellets 400 mg/12 weeks	DSG 150 mcg p.o./day	11	2	0
Brady et al., 2004	[53]	9	Not stated	T pellets 400 mg/12 weeks	Etonogestrel implants	9	2	-
Walton et al., 2007	[54]	16	Caucasian	T pellets 600 mg/12 weeks	Etonogestrel implants	11	2	-
		10	Caucasian	MENT implants	Etonogestrel implants	3	5	-
Mommers et al., 2008	[55]	134	Caucasian	TU 750 mg/12 weeks	Etonogestrel implants high dose	-	≈125	-
		112	Caucasian	TU 750 mg/10 weeks	Etonogestrel implants low dose	-	≈100	-
				TU 1000 mg/12 weeks				
Self applicable								
Nieschlag et al., 1978	[56]	7	Caucasian	Andriol 240 mg p.o./day	None	1	0	0
Guerin and Rollet, 1988	[57]	13	Caucasian	Andriol 160 mg p.o./day	NETA 10 mg p.o./day	7	2	3
Guerin and Rollet, 1988	[57]	5	Caucasian	T gel 250 mg/day	NETA 5 mg p.o./day	4	1	0
Guerin and Rollet, 1988	[57]	5	Caucasian	T gel 250 mg/day	NETA 10 mg p.o./day	5	0	0
Guerin and Rollet, 1988	[57]	8	Caucasian	T gel 250 mg/day	MPA 20 mg p.o./day	5	0	1
Moriggiola et al., 1997	[58]	8	Caucasian	Andriol 80 mg p.o./day	CPA 12,5 mg p.o./day	1	3	2
Hair et al., 1999	[59]	4	Caucasian	Andropatch 2 patches/day	DSG 75 mcg p.o./day	0	1	0
Hair et al., 1999	[59]	6	Caucasian	Andropatch 2 patches/day	DSG 150 mcg p.o./day	3	0	0
Hair et al., 1999	[59]	7	Caucasian	Andropatch 2 patches/day	DSG 300 mcg p.o./day	4	1	0
Büchter et al., 1999	[60]	12	Caucasian	Testoderm TTS 2 patches/day	LNG 250 mcg p.o. later 500 mcg	2	3	0
Gaw Gonzalo et al., 2002	[34]	19	Mixed	Testoderm TTS 2 patches/day	None	5	0	1
Pölänen et al., 2001	[35]	2	Caucasian	DHT-Gel 250 mg/day	None	0	0	0

TE, testosterone enanthate; TB, testosterone bucciate; TU*, testosterone undecanoate in tea seed oil; TU, testosterone undecanoate in castor oil; MENT, 7α-methyl-19-nortestosterone.

efficacy of this study was very high, it cannot be used to determine the overall efficacy of testosterone alone as a contraceptive because only men who became azoospermic could enter the efficacy phase while the others were excluded.

In order to clarify the question whether men developing oligozoospermia can be considered infertile, a second worldwide multicenter efficacy study involving 357 couples followed [11]. In this study, azoospermia again proved to be a most effective prerequisite for contraception. If sperm concentration, however, failed to drop below $3 \times 10^6/\text{mL}$ ejaculate, resulting pregnancy rates were higher than when using condoms. When sperm concentrations decreased below $3 \times 10^6/\text{mL}$, which was the case in 98% of the participants, then protection was not as effective as for azoospermic men, but was better than that offered by condoms (Fig. 2).

Even if these WHO studies represented a breakthrough by confirming the principle of action, they did not offer a practicable method. For a method requiring weekly im injections is not acceptable for broad use. Moreover, several months, often up to one year, are required before sperm production reaches significant suppression. For this reason, current research is concentrating on the development of long-acting testosterone preparations and on methods to hasten the onset of effectiveness.

3.1.2. Testosterone Buciclate

As long-acting testosterone preparations appeared more promising in terms of practicability and acceptability, WHO and the NIH initiated a synthesis program for such preparations [64] through which the long-acting testosterone ester testosterone buciclate was identified. This molecule showed a half-life of 29.5 days when tested in hypogonadal men, much longer than the 4.5 days of testosterone enanthate [65]. Suppression of spermatogenesis was comparable to that of weekly testosterone enanthate injections, reaching azoospermia in three out of eight volunteers after a single injection of 1200 mg of testosterone buciclate [6]. Despite its promising pharmacokinetic profile, no industrial partner could be found to undertake development of this preparation.

3.1.3. Testosterone Undecanoate

Initially, testosterone undecanoate was studied as an oral preparation in volunteers of Caucasian origin [56]. Subjects were given a daily dose of 240 mg over a period of 12 weeks, but only one out of seven volunteers reduced sperm output sufficiently for contraception. This low effectiveness is probably due to the short half-life of testosterone undecanoate when given orally. Even if administered four times a day, the peaks are not sufficient to suppress gonadotropins consistently and thereby to achieve azoospermia.

While testosterone undecanoate had been developed as an oral preparation in Europe, it was turned into an injection in China, using tea seed oil as a vehicle and is used as such in China for hypogonadism and in trials for male contraception. Back in Europe, the half-life of this Chinese preparation could be extended even further when dissolved in castor oil and is now available for clinical use in 1000 mg depot injections [66].

In the clinical trials in China, testosterone undecanoate alone administered every 4 weeks resulted in azoospermia in all Chinese men who received a dose of 1000 mg and in azoospermia or severe oligozoospermia in 95% of Chinese men who received a dose of 500 mg during a 4–6-month suppression phase [12]. In the ensuing phase III study involving 305 couples, an efficacy phase followed the suppression phase, and no pregnancies were initiated by men exhibiting azoospermia or severe oligozoospermia

[16]. However, reappearance of sperm occurred in six men during the efficacy phase; one pregnancy was attributed to “sperm rebound”. Side effects observed in subjects were all typical of elevated testosterone serum levels. The largest efficacy study to date was also performed in China, based on a loading dose of 1000 mg followed by monthly injections of 500 mg testosterone undecanoate. Eight-hundred ninety-eight men entered the efficacy phase during which only 9 pregnancies were recorded. This represents a pregnancy rate of 1.1 per 100 person-years [17]. Thus, in China, testosterone undecanoate provides better protection against pregnancy than condom use. Although injection intervals of four weeks appeared to be an achievement over the weekly injections of testosterone enanthate, the participants in a Chinese study considered the frequency of injections the most inconvenient part of this regimen [67]. Would testosterone undecanoate in castor oil also be used in China, this complaint could certainly be overcome.

In a first contraceptive trial of testosterone undecanoate in castor oil, 1000 mg was injected into 14 Caucasian volunteers at 6-week intervals. Eight of 14 men achieved azoospermia [13]. Although this rate of azoospermia is not different from that achieved with testosterone enanthate alone, the longer injection interval represents a significant advantage. A later pharmacokinetic study concluded that 8-week intervals of 1000-mg injections would be sufficient for contraceptive purposes [43].

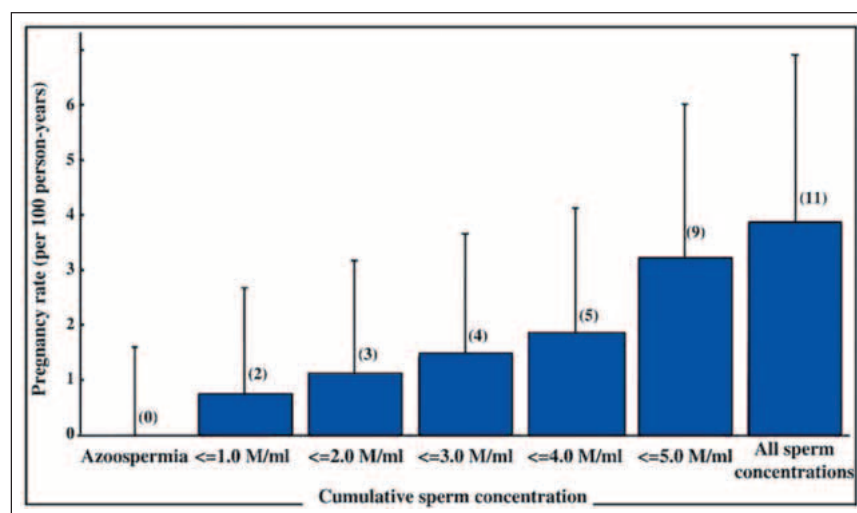


Figure 2. Contraceptive efficacy of testosterone enanthate (250 mg/weekly) in 364 volunteers: pregnancy rates per 100 person-years in relation to sperm concentration (adapted from [11]).

Considering that 10- to 14-week intervals of 1000 mg testosterone undecanoate are required for substitution of hypogonadal men, about one third more testosterone is required for contraception in normal volunteers.

3.1.4. Testosterone Pellets

Pellets consisting of pure testosterone are used for substitution in hypogonadism in some countries. In male contraceptive studies, the sperm suppressing effect was comparable to weekly testosterone enanthate injections [68]. The disadvantage of minor surgery required for insertion under the abdominal skin is compensated for by their low price. Spontaneous extrusion may be a disadvantage.

3.1.5. 19-Nortestosterone

When searching for preparations with longer lasting effectiveness, 19-nortestosterone-hexoxyphenylpropionate was tested. Its spectrum of effects is very similar to that of testosterone and it has been used as an anabolic steroid since the 1960s. The 19-nortestosterone ester injected every 3 weeks enabled azoospermia to be reached by as many men as by testosterone enanthate. Thus, the 19-nortestosterone ester is as effective as testosterone enanthate but allows a longer interval between injections [69].

Although effective in suppressing spermatogenesis and without any notable side effects in the studies, it could not be determined whether this synthetic androgen would have any unwanted effects with long-term use. The lack of negative reports from widespread use of 19-nortestosterone in athletes cannot be taken as evidence for its clinical application as systematic evaluations in athletes have not been published.

3.1.6. 7 α -Methyl-19-Nortestosterone

The synthetic androgen 7 α -methyl-19-nortestosterone (MENT) offers an approximately 10-fold higher potency to suppress pituitary gonadotropins than does testosterone. In contrast to testosterone, there is no 5 α -reduction so that effects on the prostate could be minimal. A first dose-finding study showed that MENT administered in subcutaneous implants was as effective as testosterone given alone [15]. The potential of these implants either alone or in combination

with gestagen implants is currently being investigated by the Population Council.

3.2. Androgens Combined With GnRH Analogues

3.2.1. GnRH Agonists

The pituitary-inhibiting effects of GnRH agonists are well known from their use in females and in the therapy of prostate cancer. After an initial phase of gonadotropin stimulation, they suppress gonadotropins and, consequentially, intratesticular testosterone by GnRH receptor down-regulation. However, trials for hormonal male contraception in which mostly testosterone was added showed that sperm numbers were only insufficiently reduced, thus rendering these agonists unsuitable as male contraceptives [70].

3.2.2. GnRH Antagonists

GnRH antagonists lack the effect of initial gonadotropin release as they competitively inhibit pituitary GnRH receptors, thus leading to a more immediate onset of azoospermia. This could be demonstrated by small clinical studies using various GnRH antagonists in addition to a testosterone preparation [71]. Out of 47 volunteers participating in various clinical trials with different GnRH-antagonists, azoospermia was achieved in 39 subjects and oligozoospermia $\leq 1 \times 10^6$ sperm per mL ejaculate occurred in one additional volunteer, while only three men maintained sperm concentrations above 3×10^6 /mL ejaculate. Of the more recently developed GnRH antagonists, acyline has been tested in male contraceptive trials. Although acyline given alone had a potent gonadotropin-suppressing effect [72], the addition of acyline to a combination of testosterone gel plus depot medroxyprogesterone acetate (DMPA) did not increase the suppression of sperm achieved by the steroids alone [30].

Despite these encouraging results, the requirement for daily or weekly injections and the high costs of the available preparations have hindered the further development of GnRH antagonists for hormonal male contraception. Promising attempts to use the GnRH antagonists only to initiate azoospermia and then maintain this by androgens alone were not pursued further [73, 74].

3.3. Androgens Plus Gestagens

The potency of gestagens to suppress gonadotropins is well known from female contraceptives where gestagens effectively supplement estrogens. Numerous studies combining androgens (mainly testosterone) with various gestagens have been performed over the past 4 decades in order to identify a regimen suited for male contraception (Fig. 3).

Unfortunately, a systematic comparison of the different gestagens with regard to their contraceptive potency in males has never been performed. Even worse, a Cochrane Review analyzing 45 clinical trials came to the conclusion that the studies comprised too small numbers of volunteers so that significant differences between the various steroid combinations could not be detected [75]. Moreover, not all studies observe strict criteria for randomized controlled trials. However, it should be kept in mind that many of these trials were performed as proof of principle and not necessarily as trials for registration with the regulatory authorities. In addition, single centers are financially and logistically unable to cope with the numbers of volunteers and criteria demanded by regulatory agencies. Stimulated by researchers and by public demand, the pharmaceutical industry finally performed a trial fulfilling the Cochrane criteria – and left the field! [55] In the following, important studies are briefly summarized to highlight the cumbersome and often frustrating development (Table 1).

The gestagens used in these studies derive either from 19-nortestosterone or from 17-hydroxyprogesterone and are all being used in female contraceptives (Fig. 3).

3.3.1. Depot Medoxyprogesterone Acetate

From early studies in the 1970s initiated by the WHO and the Population Council, DMPA emerged as a gestagen with great potential in male contraception [76]. The combination of DMPA with 19-nortestosterone in 3-week intervals first tested in Caucasians [25] was especially promising in Indonesian men [24].

One of the very few efficacy studies aiming at pregnancy rates also used DMPA, however, in combination with testosterone pellets [28]. In this Australian study,

53 of 55 volunteers suppressed to azoospermia and during the 1-year efficacy phase, no pregnancy occurred. However, the discontinuation rate in this study was high and onset of and recovery from azoospermia took several months.

In order to test whether one of the two steroid entities could be self-administered, the addition of a testosterone transdermal gel to the DMPA injections (300 mg/3 months) was tested [30]. The results were comparable to those from trials where DMPA was combined with injectable testosterone.

3.3.2. Levonorgestrel

Oral levonorgestrel, when combined with testosterone enanthate im slightly enhanced the effect of testosterone enanthate alone [10]. Similarly, when combined with testosterone undecanoate im the additional effect of oral levonorgestrel remained marginal in Caucasian men [13] but seemed to increase effectiveness in Chinese men [39].

In a comparative study, when levonorgestrel implants were combined with testosterone pellets, an additive effect of levonorgestrel was seen in Caucasian men, but not in Chinese men who re-

sponded equally well to testosterone pellets alone [38].

When MENT implants were combined with levonorgestrel implants in different doses, a clear dose-dependent effect could be observed, but it remains undetermined whether implants with sufficiently long duration can be manufactured; non-biodegradable implants that have to be removed surgically from the implantation site when contraceptive protection is no longer required appear impractical for widespread use unless they can be left in situ for long periods [77].

3.3.3. Norethisterone

The injectable depot preparation norethisterone enanthate (NETE) and the orally effective norethisterone acetate (NETA) are hydrolyzed to release the active compound norethisterone, which can be 5 α -reduced to 5 α -norethisterone and aromatized to ethinyl estradiol. While norethisterone has strong androgenic activity (~ 10% of testosterone), 5 α -norethisterone also shows antiandrogenic properties.

Of 14 men who received 200 mg NETE combined with 1000 mg testosterone undecanoate every 6 weeks, 13 achieved azoospermia [40]. Further investigations showed that the injection intervals could be extended to 8 weeks [42] or that testosterone undecanoate could be combined with oral NETA without loss of effectiveness [41]. Based on these findings, together with CONRAD, WHO is planning a phase II efficacy study involving 400 couples in 8 centers worldwide [78].

3.3.4. Cyproterone Acetate

The orally effective antiandrogen cyproterone acetate (CPA) has strong gestagenic properties. In early studies combining oral CPA with testosterone enanthate injections, the sperm-suppressing effects were considerable, but the antiandrogenic effects (e.g., reflected by decreased hematocrit) were undesirable. However, when combining 1000 mg testosterone undecanoate every 6 weeks with 20 mg CPA daily initially, followed by only 2 mg CPA/day, the initial suppression of spermatogenesis could be maintained and antiandrogenic effects prevented [46].

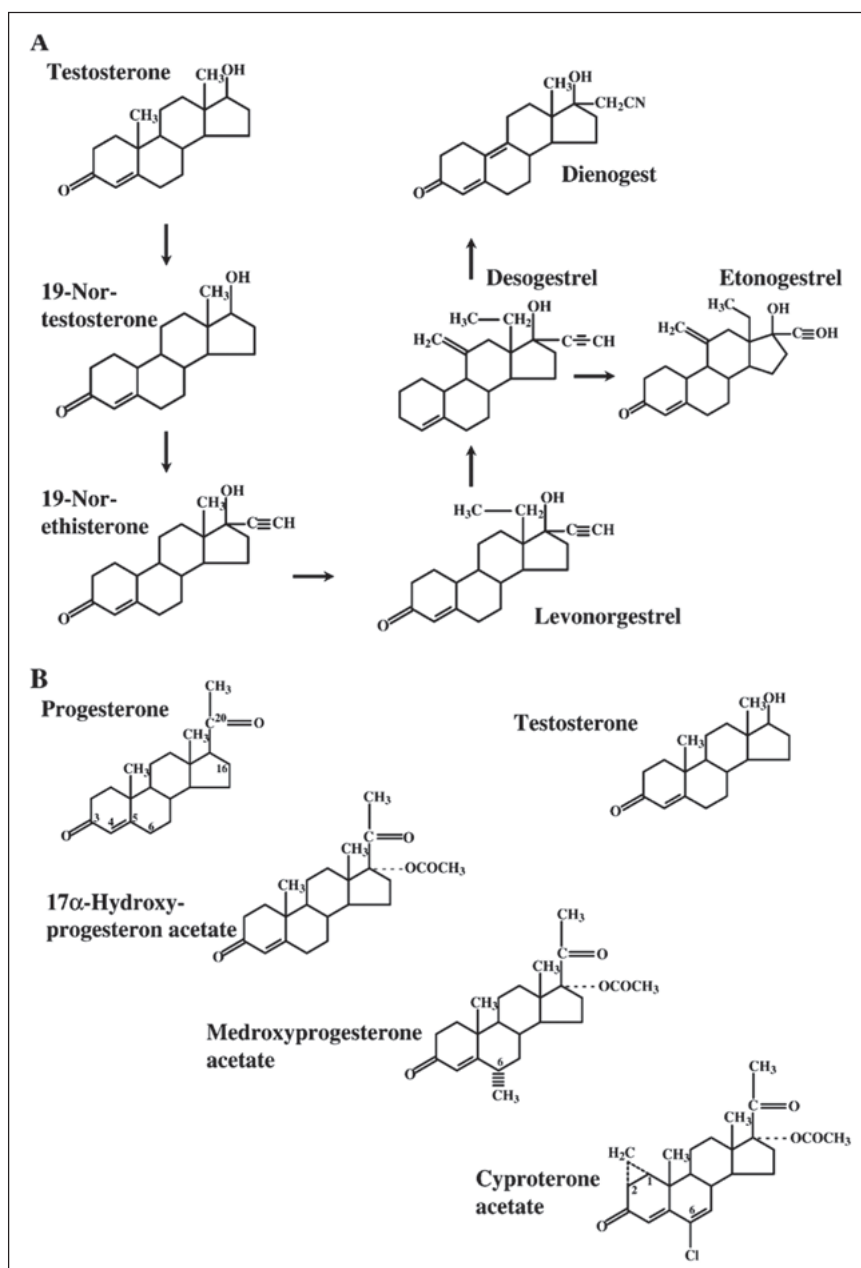


Figure 3. Gestagens derived from either testosterone (A) or progesterone (B) in trials for male hormonal contraception.

3.3.5. Desogestrel and Etonogestrel

Desogestrel is an orally effective gestagen which becomes active after conversion to etonogestrel. Etonogestrel can be administered directly as an implant (Implanon). In combination with testosterone enanthate or testosterone pellets, desogestrel showed good suppression of spermatogenesis [47, 49]. Etonogestrel implants combined with testosterone pellets s.c. resulted in a high azoospermia rate, although it took up to 28 weeks to reach this goal in some individuals [53].

In the first (and so far last) industry-sponsored trial, Organon and Schering decided to test etonogestrel implants with testosterone undecanoate injections in various combinations [55]. This study involved 354 volunteers in seven treatment groups receiving either placebo or 750–1000 mg testosterone undecanoate every 10–12 weeks with two doses of etonogestrel for 42–44 weeks. Ninety percent of treated men suppressed spermatogenesis to $\leq 1 \times 10^6/\text{mL}$ ejaculate.

Although the combination of an implant with injections may not appear too attractive for practical use, the study had a high success rate and could have formed the basis for a phase III efficacy study. Unfortunately, both companies discontinued their male contraception programs when they were taken over by other firms who were at that stage not interested in male contraception.

4. Acceptability of Male Contraception

One of the reasons why the pharmaceutical industry has not continued to further develop a male contraceptive at this stage may be doubts about the possible acceptability of such a pharmacological method. However, recently, public interest in male methods for contraception has notably grown. It is increasingly expected that men share with their partners not only the advantages but also the risks of family planning. As risks tend to increase with duration of use, sharing contraception between men and women would reduce dangers for each partner. Population conferences and women's world forums have explicitly called for new male contraceptive methods.

Worldwide, one quarter of all couples practicing contraception rely on male methods, albeit with varying preferences and the proportion of men practicing contraception is increasing. Thus, in the Netherlands, the percentage of vasectomized men whose wives were of reproductive age rose from 2% to 10.5% from 1975 to 2008 and from 8% to 12.2% in the USA; the highest rates of vasectomized men are found in the United Kingdom and in New Zealand. Worldwide, however, only 2.7% of men are vasectomized.

Similarly, the use of condoms for contraception varies from country to country with a worldwide average of 5.7%. It is to be expected that the percentage of men willing to practice contraception varies between cultures and with methods available. According to a survey in Hongkong and Shanghai 10 years ago, half the men interviewed were willing to take a daily contraceptive pill; in Edinburgh and Capetown two thirds were willing to do so [79, 80]. After almost 50 years of female oral contraception, the attitude of men towards new methods of male contraception has changed. Worldwide, surveys showed men willing to use pharmacological contraceptive methods [81] (Fig. 4).

5. Responsibility For the Development of Contraceptives

The world population has tripled in the last 50 years and is approaching 7 bil-

lion. Less developed countries bear the onus of this enormous population growth while the population in industrialized nations is largely stable – due to use of contraceptive methods. The population explosion creates minimal surmountable ecologic and economic problems. Medical progress has decisively lowered mortality, particularly of children, so that life expectancy worldwide is currently 64.2 years for men and 68.6 years for women. Ever more people reach reproductive age. If medical progress allows increasing number of people to achieve reproductive age, causing overpopulation, then medicine must also provide contraceptive methods in order to maintain or restore a balance between reproduction and death. It has become clear that the Millennium Development Goals cannot be achieved with the current level of population growth [82]. It goes without saying that a newly developed male contraceptive would not suddenly resolve population problems, but a male method could contribute to the resolution, especially as research into female methods for contraception is similarly on the decline [83]. In addition, women increasingly demand that men share the responsibility and risks of family planning and men, on the other hand, want to regain some of the reproductive power they surrendered to women since the advent of modern female contraceptives [84, 85]. This should be reason enough for the pharmaceutical industry to actively develop male contraceptives. While a large proportion of clinical research is driven by the pharmaceutical

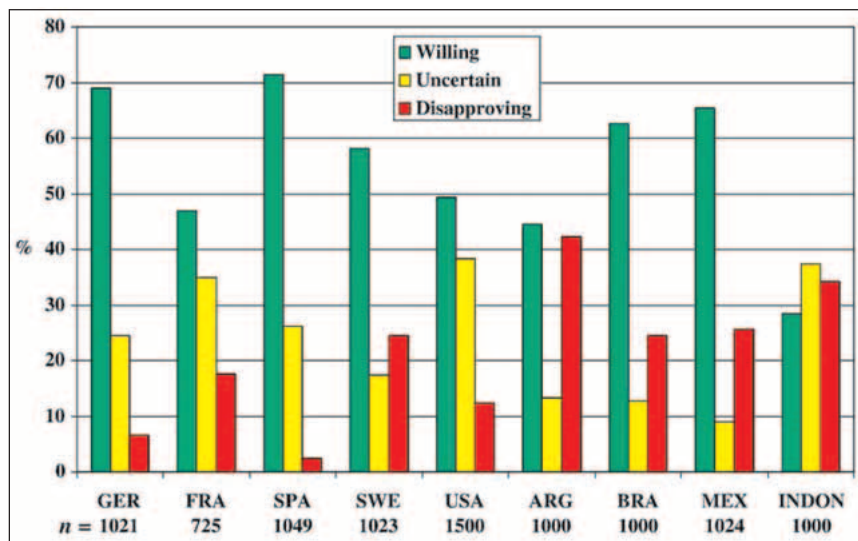


Figure 4. Multinational male fertility control survey among 9342 men who were asked the question: „If available, would you be willing to use the new male fertility control method?“ (adapted from [81]).

industry, in the case of male contraception, industry fails. Without the long-range perspective and endurance of institutions and organizations such as NICHD, CONRAD, Population Council, WHO, some medical research councils and few foundations, male contraception would long have been abandoned. The principle and effectiveness of hormonal male contraception has been demonstrated in many studies. The fact that the majority of clinical trials on hormonal male contraception have been published in high-ranking journals is important. This emphasizes the high priority the scientific community attributes to these endeavors. Investigators are so convinced of the validity of the concept of hormonal male contraception that they drafted recommendations for regulatory approval for male hormonal contraception at their annual summit meetings (since 1997) [86]. Little more is required to convince industry to bring this development to fruition.

Comparing the situation with the development of the female pill, the lack of public advocacy for male contraception is striking. Male contraception lacks prominent advocates as the development of female contraception benefited from personalities such as Margaret Sanger (1879–1966) and Katherine McCormick (1875–1967). Hormonal male contraception requires similar advocacy to finally result in a marketable product.

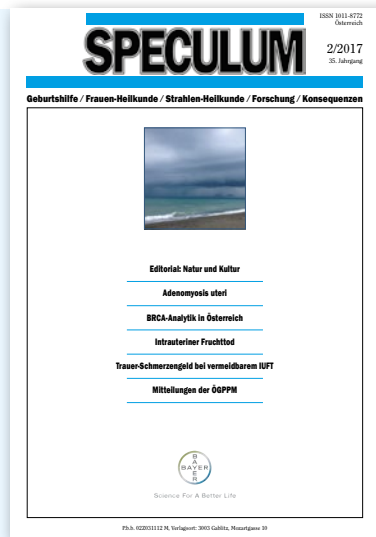
References:

- Benagiano G, Bastianello C, Farris M. Contraception: a social revolution. *Europ Contracept Reprod Health Care* 2007; 12: 3–12.
- Nieschlag E, Behre HM, Wieacker P, Meschede D, Kamischke A, Kliesch S. Disorders at the testicular level. In: Nieschlag E, Behre HM, Nieschlag S, editors. *Andrology: male reproductive health and dysfunction*, 3rd ed. Springer, Heidelberg, 2009; 194–238, chap. 13.
- April K, Köster R, Schreiner W. Wie effektiv schützen Kondome vor einer HIV-Übertragung? *Med Klinik* 1993; 88: 304–11.
- Kamischke A, Nieschlag E. Progress towards hormonal male contraception. *Trends Pharmacol Sci* 2004; 25: 49–57.
- World Health Organization Task Force on Methods for the Regulation of Male Fertility. Contraceptive efficacy of testosterone-induced azoospermia in normal men. *Lancet* 1990; 336: 955–9.
- Behre HM, Baus S, Kliesch S, Keck C, Simoni M, Nieschlag E. Potential of testosterone buccinate for male contraception: endocrine differences between responders and nonresponders. *J Clin Endocrinol Metab* 1995; 80: 2394–403.
- Handelsman DJ, Conway AJ, Boylan LM. Suppression of human spermatogenesis by testosterone implants. *J Clin Endocrinol Metab* 1992; 75: 1326–32.
- Handelsman DJ, Conway AJ, Howe CJ, Turner L, Mackey MA. Establishing the minimum effective dose and additive effects of depot progestin in suppression of human spermatogenesis by a testosterone depot. *J Clin Endocrinol Metab* 1996; 81: 4113–21.
- Meriggiola MC, Bremner WJ, Paulsen, et al. A combined regimen of cyproterone acetate and testosterone enanthate as a potentially highly effective male contraceptive. *J Clin Endocrinol Metab* 1996; 81: 3018–23.
- Bebb RA, Anawalt BD, Christensen RB, Paulsen CA, Bremner WJ, Matsumoto AM. Combined administration of levonorgestrel and testosterone induces more rapid and effective suppression of spermatogenesis than testosterone alone: a promising male contraceptive approach. *J Clin Endocrinol Metab* 1996; 81: 757–62.
- World Health Organization Task Force on Methods for the Regulation of Male Fertility. Contraceptive efficacy of testosterone-induced azoospermia and oligozoospermia in normal men. *Fertil Steril* 1996; 65: 821–9.
- Zhang GY, Gu YQ, Wang XH, Cui YG, Bremner WJ. A clinical trial of injectable testosterone undecanoate as a potential male contraceptive in normal Chinese men. *J Clin Endocrinol Metab* 1999; 84: 3642–7.
- Kamischke A, Plöger D, Venherm 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* 2000; 53: 43–52.
- McLachlan RI, O'Donnell L, Stanton PG, et al. Effects of testosterone plus medroxyprogesterone acetate on semen quality, reproductive hormones and germ cell populations in normal young men. *J Clin Endocrinol Metab* 2002; 87: 546–56.
- von Eckardstein S, Noe G, Brache V, et al. International Committee for Contraception Research, The Population Council. A clinical trial of 7 alpha-methyl-19-nortestosterone implants for possible use as a long-acting contraceptive for men. *J Clin Endocrinol Metab* 2003; 88: 5232–9.
- Gu YQ, Wang XH, Xu D, et al. A multicenter contraceptive efficacy study of injectable testosterone undecanoate in healthy Chinese men. *J Clin Endocrinol Metab* 2003; 88: 562–8.
- Gu Y, Liang X, Wu W, et al. Multicenter contraceptive efficacy trial of injectable testosterone undecanoate in Chinese men. *J Clin Endocrinol Metab* 2009; 94: 1910–5.
- Alvarez-Sanchez F, Faundes A, Brache V, Leon P. Attainment and maintenance of azoospermia with combined monthly injections of depot medroxyprogesterone acetate and testosterone enanthate. *Contraception* 1977; 15: 635–48.
- Brenner PF, Mishell Jr DR, Bernstein GS, et al. Study of medroxyprogesterone acetate and testosterone enanthate as a male contraceptive. *Contraception* 1977; 15: 679–91.
- Frick J, Bartsch G, Weiske WH. The effect of monthly depot medroxyprogesterone acetate and testosterone enanthate on spermatozoa. II. High initial dose. *Contraception* 1977; 15: 669–77.
- Melo JF, Coutinho EM. Inhibition of spermatogenesis in men with monthly injections of medroxyprogesterone acetate and testosterone enanthate. *Contraception* 1977; 15: 627–34.
- Faundes A, Brache V, Leon P, Schmidt F, Alvarez-Sanchez F. Sperm suppression with monthly injections of medroxyprogesterone acetate combined with testosterone enanthate at a high dose (500 mg). *Int J Androl* 1981; 4: 235–45.
- Frick J, Danner C, Kunit G, Joos H, Kohle R. Spermatogenesis in men treated with injections of medroxyprogesterone acetate combined with testosterone enanthate. *Int J Androl* 1982; 5: 246–52.
- World Health Organization Task Force on Methods for the Regulation of Male Fertility. Comparison of two androgens plus depot-medroxyprogesterone acetate for suppression to azoospermia in Indonesian men. *Fertil Steril* 1993; 60: 1062–8.
- Knuth UA, Yeung CH, Nieschlag E. Combination of 19-nortestosterone-hexoxyphenylpropionate (Anadur) and depot-medroxyprogesterone-one-acetate (Clinovir) for male contraception. *Fertil Steril* 1989; 51: 1011–8.
- Wu FC, Aitken RJ. Suppression of sperm function by depot-medroxyprogesterone acetate and testosterone enanthate in steroid male contraception. *Fertil Steril* 1989; 51: 691–8.
- Pangkahila W. Reversible azoospermia induced by an androgen-progestin combination regimen in Indonesian men. *Int J Androl* 1991; 14: 248–56.
- Turner L, Conway AJ, Jimenez M, et al. Contraceptive efficacy of a depot progestin and androgen combination in men. *J Clin Endocrinol Metab* 2003; 88: 4659–67.
- Gu YQ, Tong JS, Ma DZ, et al. Male hormonal contraception: effects of injections of testosterone undecanoate and depot medroxyprogesterone acetate at eight-week intervals in Chinese men. *J Clin Endocrinol Metab* 2004; 89: 2254–62.
- Page ST, Amory JK, Anawalt BD, et al. Testosterone gel combined with depot-medroxyprogesterone acetate is an effective male hormonal contraceptive regimen and is not enhanced by the addition of a GnRH antagonist. *J Clin Endocrinol Metab* 2006; 91: 4374–80.
- Fogh M, Corker CS, McLean H. Clinical trial with levonorgestrel and testosterone enanthate for male fertility control. *Acta Endocrinol* 1980; 95: 251–7.
- Anawalt BD, Bebb RA, Bremner WJ, Matsumoto AM. A lower dosage levonorgestrel and testosterone combination effectively suppresses spermatogenesis and circulating gonadotrophin levels with fewer metabolic effects than higher dosage combinations. *J Androl* 1999; 20: 407–14.
- Ersheng G, Cuihong L, Youlun G, Lamei L, Changhai H. Inhibiting effects of Sino-implant plus testosterone undecanoate on spermatogenesis in Chinese men. *Reprod Contraception* 1999; 10: 98–105.
- Gaw Gonzalo IT, Swerdloff RS, et al. Levonorgestrel implants (Norplant II) for male contraception clinical trials: combination with transdermal and injectable testosterone. *J Clin Endocrinol Metab* 2002; 87: 3562–72.
- Pöllänen P, Nikkanen V, Huhtaniemi I. Combination of subcutaneous levonorgestrel implants and transdermal dihydrotestosterone gel for male hormonal contraception. *Int J Androl* 2001; 24: 369–80.
- Gui YL, He CH, Amory JK, et al. Male hormonal contraception: suppression of spermatogenesis by injectable testosterone undecanoate alone or with levonorgestrel implants in Chinese men. *J Androl* 2004; 25: 720–7.
- Anawalt BD, Amory JK, Herbst KL, et al. Intramuscular testosterone enanthate plus very low dosage oral levonorgestrel suppresses spermatogenesis without causing weight gain in normal young men: a randomized clinical trial. *J Androl* 2005; 26: 405–13.
- Wang C, Wang XH, Nelson AL. Levonorgestrel implants enhanced the suppression of spermatogenesis by testosterone implants: comparison between Chinese and non-Chinese men. *J Clin Endocrinol Metab* 2006; 91: 460–70.
- Wang C, Cui YG, Wang XH, et al. Transient scrotal hyperthermia and levonorgestrel enhance testosterone-induced spermatogenesis suppression in men through increased germ cell apoptosis. *J Clin Endocrinol Metab* 2007; 92: 3292–304.
- Kamischke A, Venherm S, Plöger D, von Eckardstein S, Nieschlag E. Intramuscular testosterone undecanoate and norethisterone enanthate in a clinical trial for male contraception. *J Clin Endocrinol Metab* 2001; 86: 303–9.
- Kamischke A, Heuermann T, Krüger K, et al. An effective hormonal male contraceptive using testosterone undecanoate with oral or injectable norethisterone preparations. *J Clin Endocrinol Metab* 2002; 87: 530–9.
- Meriggiola MC, Costantino A, Saad F, et al. Norethisterone enanthate plus testosterone undecanoate for male contraception: effects of various injection intervals on spermatogenesis, reproductive hormones, testis, and prostate. *J Clin Endocrinol Metab* 2005; 90: 2005–14.
- Qoubaitary A, Meriggiola C, Ng CM, et al. Pharmacokinetics of testosterone undecanoate injected alone or in combination with norethisterone enanthate in healthy men. *J Androl* 2006; 27: 853–67.
- Meriggiola MC, Bremner WJ, Costantino A, Di Cintio G, Flamigni C. Low dose of cyproterone acetate and testosterone enanthate for contraception in men. *Hum Reprod* 1998; 13: 1225–9.
- Meriggiola MC, Costantino A, Bremner WJ, Morselli-Labate AM. Higher testosterone dose impairs sperm suppression induced by a combined androgen-progestin regimen. *J Androl* 2002; 23: 684–90.
- Meriggiola MC, Costantino A, Cerpolini S, et al. Testosterone undecanoate maintains spermatogenic suppression induced by cyproterone acetate plus testosterone undecanoate in normal men. *J Clin Endocrinol Metab* 2003; 88: 5818–26.
- Wu FCW, Balasubramanian R, Mulders TMT, Coelingh-Bennink HJT. Oral progestogen combined with testosterone as a potential male contraceptive: additive effects between desogestrel and testosterone enanthate in suppression of spermatogenesis, pituitary-testicular axis, and lipid metabolism. *J Clin Endocrinol Metab* 1999; 84: 112–22.
- Anawalt BD, Herbst KL, Matsumoto AM, Mulders TM, Coelingh-Bennink HJ, Bremner WJ. Desogestrel plus testosterone effectively suppresses spermatogenesis but also causes modest weight gain and high-density lipoprotein suppression. *Fertil Steril* 2000; 74: 707–14.
- Kinniburgh D, Anderson RA, Baird DT. Suppression of spermatogenesis with desogestrel and testosterone pellets is not enhanced by addition of finasteride. *J Androl* 2001; 22: 88–95.

50. Anderson RA, Van Der Spuy ZM, Dada OA, et al. Investigation of hormonal male contraception in African men: suppression of spermatogenesis by oral desogestrel with depot testosterone. *Hum Reprod* 2002; 17: 2869–77.
51. Anderson RA, Kinniburgh D, Baird DT. Suppression of spermatogenesis by etonogestrel implants with depot testosterone: potential for long-acting male contraception. *J Clin Endocr Metab* 2002; 87: 3640–9.
52. Kinniburgh D, Zhu H, Cheng L, Kicman AT, Baird DT, Anderson RA. Oral desogestrel with testosterone pellets induces consistent suppression of spermatogenesis to azoospermia in both Caucasian and Chinese men. *Hum Reprod* 2002; 17: 1490–501.
53. Brady BM, Walton M, Hollow N, Kicman AT, Baird DT, Anderson RA. Depot testosterone with etonogestrel implants result in induction of azoospermia in all men for long-term contraception. *Hum Reprod* 2004; 19: 2658–67.
54. Walton MJ, Kumar N, Baird DT, Ludlow H, Anderson RA. 7 α -Methyl-19-nortestosterone (MENT) vs testosterone in combination with etonogestrel implants for spermatogenic suppression in healthy men. *J Androl* 2007; 28: 679–88.
55. Mommers E, Kersemaeker WM, Elliesen J, et al. Male hormonal contraception: a double-blind, placebo-controlled study. *J Clin Endocrinol Metab* 2008; 93: 2572–80.
56. Nieschlag E, Hoogen H, Bölk M, Schuster H, Wickings EJ. Clinical trial with testosterone undecanoate for male fertility control. *Contraception* 1978; 18: 607–14.
57. Guerin JF, Rollet J. Inhibition of spermatogenesis in men using various combinations of oral progestagens and percutaneous or oral androgens. *Int J Androl* 1988; 11: 187–99.
58. Meriggiola MC, Bremner WJ, Costantino A, Pavani A, Capelli M, Flamigni C. An oral regimen of cyproterone acetate and testosterone undecanoate for spermatogenic suppression in men. *Fertil Steril* 1997; 68: 844–50.
59. Hair WM, Kitteridge K, Wu FCW. A new male contraceptive pill/patch combination-oral desogestrel and transdermal testosterone: suppression of gonadotropins and spermatogenesis in men. The Endocrine Society's 81st Annual Meeting; June 12–15; San Diego, CA, USA. Poster P3-374; 1999.
60. Büchter D, von Eckardstein S, von Eckardstein A, et al. Clinical trial of a transdermal testosterone and oral levonorgestrel for male contraception. *J Clin Endocr Metab* 1999; 84: 1244–9.
61. Liu PY, Swerdloff RS, Christenson PD, Handelsman DJ, Wang C. Hormonal Male Contraception Summit Group. Rate, extent and modifiers of spermatogenic recovery after hormonal male contraception: an integrated analysis. *Lancet* 2006; 367: 1412–20.
62. Barfield JP, Nieschlag E, Cooper TG. Fertility control in wildlife: humans as a model. *Contraception* 2006; 73: 6–22.
63. Heckel M. Production of oligospermia in a man by the use of testosterone propionate. *Proc Soc Exp Biol Med* 1939; 40: 658–9.
64. Waites GMH. Development of methods of male contraception: impact of the World Health Organization Task Force. *Fertil Steril* 2003; 80: 1–15.
65. Behre HM, Wang C, Handelsman DJ, Nieschlag E. Pharmacology of testosterone preparations. In: Nieschlag E, Behre HM (eds). *Testosterone: action, deficiency, substitution*, 3rd ed. University Press, Cambridge, 2004; 405–44.
66. Nieschlag E. Testosterone treatment comes of age: new options for hypogonadal men. *Clin Endocrinol* 2006; 65: 275–81.
67. Zhang L, Shal IH, Liu Y, Vogelsong KM, Zhang L. The acceptability of an injectable, once-a-month male contraceptive in China. *Contraception* 2006; 73: 548–53.
68. McLachlan RI, McDonald J, Rushford D, Robertson DM, Garrett C, Baker HW. Efficacy and acceptability of testosterone implants, alone or in combination with a 5 α -reductase inhibitor, for male contraception. *Contraception* 2000; 62: 73–8.
69. Knuth UA, Behre HM, Belkien L, Bents H, Nieschlag E. Clinical trial of 19-nortestosterone-hexoxyphenylpropionate (Anadur) for male fertility regulation. *Fertil Steril* 1985; 44: 814–21.
70. Behre HM, Nashan D, Hubert W, Nieschlag E. Depot gonadotropin-releasing hormone agonist blunts the androgen-induced suppression of spermatogenesis in a clinical trial of male contraception. *J Clin Endocr Metab* 1992; 74: 84–90.
71. Nieschlag E, Kamischke A, Behre HM. Hormonal male contraception: the essential role of testosterone. In: Nieschlag E, Behre HM (eds). *Testosterone: action, deficiency, substitution*, 3rd ed. Cambridge University Press; 2004; 685–714.
72. Page ST, Amory JK, Bremner WJ. Advances in male contraception. *Endocr Rev* 2008; 29: 465–93.
73. Swerdloff RS, Bagatell CJ, Wang C, et al. Suppression of spermatogenesis in man induced by Nal-Glu gonadotropin-releasing hormone antagonist and testosterone enanthate (TE) is maintained by TE alone. *J Clin Endocr Metab* 1998; 83: 3527–33.
74. Behre HM, Kliesch S, Lemcke B, Nieschlag E. Suppression of spermatogenesis to azoospermia by combined administration of GnRH antagonist and 19-nortestosterone cannot be maintained by 19-nortestosterone alone in normal men. *Hum Reprod* 2001; 16: 2570–7.
75. Grimes DA, Lopez LM, Gallo MF, Halpern V, Nanda K, Schulz KF. Steroid hormones for contraception in men (review). *Cochrane Database Syst Rec* 2007; 004316.
76. Barfield A, Melo J, Coutinho E, et al. Pregnancies associated with sperm concentrations below 10 million/ml in clinical studies of a potential male contraceptive method, monthly depot medroxyprogesterone acetate and testosterone esters. *Contraception* 1979; 20: 121–7.
77. Liu PY, Swerdloff RS, Wang C. Recent methodological advances in male hormonal contraception. *Contraception* 2010; 82: 471–5.
78. WHO. Controlled trials register NET-EN plus TU as a male contraceptive (WHO-HRP ID A25165). (accessed 2005-11-29). <http://www.who.int/reproductive-health/rhl/a25165.html>
79. Anderson RA, Baird DT. Progress towards a male pill. *IPPF Med Bull* 1997; 31: 3–4.
80. Martin CW, Anderson RA, Cheng L, et al. Potential impact of hormonal male contraception: cross-cultural implications for development of novel preparations. *Hum Reprod* 2000; 15: 637–45.
81. Heinemann K, Saad F, Wiesemes M, White S, Heinemann L. Attitudes toward male fertility control: results of a multinational survey on four continents. *Hum Reprod* 2005; 20: 549–56.
82. All Party Parliamentary Group on Population. Development and Reproductive Health. Return of the population growth factor: its impact upon the Millennium Development Goals. House of Commons, London, 2007.
83. Strauss JF, Chaudhuri G. The accelerated pace of pharmaceutical abandonment of research and development in family planning and fertility: will reproductive health technology be frozen in time? *Fertil Steril* 2007; 87: 717–8.
84. Darroch JE. Male fertility control – where are the men? *Contraception* 2008; 78: S7–S17.
85. Meriggiola MC, Cerpolini S, Bremner WJ, et al. Acceptability of an injectable male contraceptive regimen of norethisterone enanthate and testosterone undecanoate for men. *Hum Reprod* 2006; 21: 2033–40.
86. Nieschlag E. 10th Summit Meeting Group. 10th Summit Meeting consensus recommendations for regulatory approval for hormonal male contraception, October 22–23, 2006. *Contraception* 2007; 75: 166–7.

Mitteilungen aus der Redaktion

Die meistgelesenen Artikel



Speculum

Journal für Reproduktionsmedizin und Endokrinologie

