23

Hormonal male contraception: the essential role of testosterone

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Contents

23.1 General prospects

23.1.1 Why male contraception at all?

The invention of the "pill" for women was undoubtedly one of the most significant medical and cultural events of the twentieth century. 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 perhaps long overdue. In addition, 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 acceptable 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.

23.1.2 Existing methods

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. 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.

Vasectomy is a safe and surgically relatively simple 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- nor long-term toxic side effects
- have no impact on eventual offspring
- be rapidly effective and fully reversible
- be as effective as comparable female methods

23.1.3 New approaches to male contraception

Despite attempts to improve the existing methods, e.g., vas occlusion instead of surgical dissection, or the introduction of new materials (e.g. polyurethane) for condoms, the inherent disadvantages of these methods preventing sperm transport into the female tract persists, and must be replaced and/or supplemented by pharmacological methods. Posttesticular approaches to male contraception are still in the preclinical phase. By investigating the molecular physiology of sperm maturation, epididymal function and fertilization, the aim is to identify processes that might be blocked by specific pharmacological agents with rapid onset of action. However, all substances investigated so far have shown toxic side effects when interfering effectively with sperm function. At the moment then, only hormonal methods fulfill most of the requirements for a male contraceptive and are currently under clinical development.

All hormonal male contraceptives clinically tested to date are based on testosterone, either on testosterone alone or on a combination of testosterone with other hormones, in particular with either gestagens or GnRH analogues. Because of the

essential role of testosterone, it is appropriate to include an overview on current hormonal approaches to male contraception in this volume.

23.2 Principle of hormonal male contraception

The testes have an endocrine and an exocrine function: the production of androgens and of male gametes. Suppression of gamete production or interference with gamete function without affecting the endocrine function is the goal of endocrine approaches to male fertility regulation. However, since the two functions of the testes are interdependent, it has remained impossible so far to suppress spermatogenesis exclusively and reversibly without significantly affecting androgen synthesis.

FSH and LH/testosterone are responsible for the maintenance of fully normal spermatogenesis (for review see Chapter 5, also Weinbauer and Nieschlag 1996). If only one of the two is eliminated, spermatogenesis will be reduced, but only in quantitative terms, i.e. fewer but normal sperm will be produced and azoospermia will not be achieved. This has been demonstrated in monkeys by the elimination of FSH by immunoneutralization, resulting in reduced sperm numbers but not in complete azoospermia (Srinath *et al.* 1983), which – at least until quite recently – was considered to be required for an effective male method. Therefore, even if new modalities for the selective suppression of FSH or FSH action should become available, it remains doubtful whether they would lead to a method for male contraception (Nieschlag 1986). However, in bonnet monkeys immunization against FSH or the FSH receptor led to an impairment of the fertilizing capacity of sperm (Moudgal *et al.* 1992; 1997a). To date it has remained equivocal whether similar effects can be obtained in humans (Moudgal *et al.* 1997b; 1997c).

Until such results become available, the concept of azoospermia remains valid as a prerequisite for effective hormonal male contraception. However, as it is very difficult to achieve azoospermia uniformly in all volunteers participating in clinical trials for hormonal contraception and the pregnancy rates appear to be acceptably low if sperm counts drop below 1 mill/ml, investigators active in the field reached a consensus that azoospermia or at least oligozoospermia <1 mill/ml sperm should be the goal for an effective hormonal method (Nieschlag 2002). To achieve this goal not only FSH must be suppressed, but also intratesticular testosterone must be drastically reduced. Since testosterone alone can maintain spermatogenesis and much lower testosterone concentrations appear to be necessary for maintenance of spermatogenesis than previously considered, intratesticular testosterone must be depleted to such an extent that peripheral serum concentrations drop into the hypogonadal range. In order to maintain androgenicity, including libido, potency, male sex characteristics, psychotropic effects, protein anabolism, bone structure and hematopoesis, testosterone levels in the general circulation have to be replaced,

while the testes themselves are depleted of testosterone. However, even testes of volunteers achieving azoospermia show measurable testosterone concentrations, although reduced to 2% of normal, and volunteers developing azoospermia have low intratesticular levels similar to those suppressing only to oligozoospermia (McLachlan *et al.* 2002). Therefore, other factors must be of additional importance. Interestingly, the macaque monkey suppressed to azoospermia shows hardly any decrease in intratesticular testosterone and elimination of FSH action appears to be more important than intratesticular testosterone (Narula *et al.* 2001; Weinbauer *et al.* 2001). For some time it was thought that the intratesticular conversion of testosterone to DHT is of importance in the maintenance of spermatogenesis and should be interfered with. However, the application of a 5α-reductase inhibitor did not additionally effect the suppression of spermatogenesis by testosterone alone (McLachlan *et al.* 2000). Recently, the number of CAG repeats in exon 1 of the androgen receptor has been found to determine the suppressibility of spermatogenesis, provided FSH and LH are well suppressed (von Eckardstein *et al.* 2002).

This leads to the general principle of hormonal male contraception, namely the suppression of FSH and LH, resulting in depletion of intratesticular testosterone and cessation of spermatogenesis, while at the same time, peripheral testosterone is substituted with an androgen preparation. This can be achieved by testosterone alone. However, since testosterone alone does not lead to azoospermia or severe oligozoospermia (<1 mill/ml) in all individuals tested, testosterone needs to be combined with other substances suppressing pituitary gonadotropin secretion. As in female hormonal contraceptives, gestagens as pituitary-suppressing agents are being tested in men in combination with androgens. GnRH agonists, as well as antagonists are also being explored as further possible combinations with androgens.

Recommendations for Regulatory Approval for Hormonal Male Contraception

(Int J Androl 25:375 (2002)

The investigators at the 6th Summit Meeting on Hormonal Male Contraception, Petersberg, Germany, held on July 7–9th, 2002 recognized the need for standardized clinical trials to develop a hormonal male method and drafted the following recommendations: The goal of hormonal male contraception is the reversible suppression of spermatogenesis to a level compatible with infertility. In principle this can be achieved by using an androgen alone or an androgen in combination with a gestagen or a GnRH-antagonist. The success of this principle in terms of lowering sperm counts in semen to azoospermia or to very low counts has been demonstrated in a multitude of trials. Some trials demonstrated the contraceptive efficacy of this approach when couples used no other method of contraception. Investigators agree that information gained from preliminary studies on male contraception have reached a stage that hormonal contraceptive products for men should now be proposed for development for general use.

In order to bring a hormonal method to the market, larger scale clinical trials are required. As no pharmacological method for male contraception is currently available, this represents a novel effort requiring new recommendations for testing.

The investigators agreed that the following criteria should be fulfilled:

1. **In phase II dose-finding studies, the suppression of spermatogenesis can be used as the main parameter.**
   As the surrogate parameter, sperm concentrations, measured according to WHO criteria, can be used and the goal should be $\leq$ 1 million/mL.
   After cessation of treatment, the return to normal values should be ascertained, i.e. $\geq$ 20 million/mL.
2. **In the efficacy trials, pregnancy rate will be the endpoint, using the efficacy rate of condoms as a reference. For contraceptive efficacy, two independent phase III trials for 1 year should be completed by 200 men/couples per trial. Alternatively, the number of subjects that can establish a significant improvement against condom use could be investigated.**
3. **For safety assurance for a new chemical entity, trials are required involving at least 300–600 men for 6 months at the intended combination and dose, 100 men exposed for 1 year and a total of 1500 men in phase I– III studies at the minimum.**
4. **Long-term safety will be monitored by post-marketing surveillance.**

The necessary laboratory investigations, especially semen analysis, need to be made under strict quality control.

These recommendations were drafted and approved by:

Prof. Dr. Eberhard Nieschlag (Organizer of the Summit Meeting) (University of Muenster, Germany), Dr. Richard A. Anderson (University of Edinburgh, Scotland), Dr. Dan Apter (Family Federation of Finland, Helsinki, Finland), Dr. Kiagus M. Arsyad (University of Sriwijaya, Palembang, Indonesia), Prof. Dr. David Baird (University of Edinburgh, Scotland), Prof. Dr. Hermann M. Behre (University of Halle, Germany), Prof. Dr. William J. Bremner (University of Washington, Seattle, WA, USA), Doug Colvard (CONRAD, Arlington, VA, USA), Dr. T. G. Cooper (University of Muenster, Germany), Dr. Gu Yi-Qun (National Research Institute for Family Planning, Beijing, China), Prof. Dr. Mike Harper (CONRAD, Arlington, VA, USA), Prof. Dr. Ilpo Huhtaniemi (University of Turku, Finland), Dr. Axel Kamischke (University of Muenster, Germany), Dr. Peter Liu (University of Sydney, Australia), Dr. Robert McLachlan (Monash University, Melbourne, Australia), Dr. M. Cristina Meriggiola (University of Bologna, Italy), Prof. Dr. Dr. Nukman Moeloek (University of Indonesia, Jakarta, Indonesia), Prof. Dr. Somnath Roy (National Institute of Health and Family Welfare, New Delhi, India), Dr. Régine Sitruk-Ware (Population Council, New York, NY, USA), Dr. Kalyan Sundaram (Population Council, New York, NY, USA), Prof. Dr. Ronald S. Swerdloff (University of California, Torrance, CA, USA), Prof. Dr. Geoffrey M. H. Waites (St. Jean de Gonville, France), Prof. Dr. Christina C. L. Wang (University of California, Torrance, CA, USA), Dr. Xing-Hai Wang (Jiangsu Family Planning Research Institute, Nanjing, China), Prof. Dr. Frederick C. W. Wu (University of Manchester, UK), Dr. Michael Zitzmann (University of Muenster, Germany).

Present at the Summit Meeting were also representatives of Schering/Jenapharm (Dr. Ulrich Gottwald, Dr. Doris Huebler, Dr. Albert Radlmaier, Dr. Farid Saad, Dr. Rolf Schuermann) and Organon (Dr. Thom

Dieben, Dr. AJ Grootenhuis, Dr. Wendy Kersemaekers, Dr. Mirjam L. P. J. Mol-Arts, Dr. Gerrit Voortman), Dr. Robert Spirtas (National Institutes of Health, Bethesda, MD, USA), Dr. Judy Manning (USAID, Washington, DC, USA), and WHO-HRP Dr. Michael T. Mbizvo (WHO, Geneva, Switzerland), and Dr. Kirsten Vogelsong (WHO, Geneva, Switzerland).

23.3 Testosterone alone

23.3.1 Testosterone enanthate

According to the principle outlined above, testosterone should be the first choice for hormonal male contraception since it not only suppresses pituitary LH and FSH secretion, but also replaces testosterone. Indeed, since the 1970s various investigations have been undertaken to suppress spermatogenesis with testosterone alone (Reddy and Rao 1972; Patanelli 1978) (Table 23.1). Not until 1990 was an initial study testing this form of male contraception published by the WHO, the first study ever performed on the efficacy of hormonal male contraception (WHO 1990). Volunteers in ten centers on four continents participated and received 200 mg testosterone enanthate intramuscularly per week. Those volunteers developing azoospermia within the first six months continued to receive injections for a further year. In this period (efficacy phase) couples refrained from using any further contraceptive methods. A total of 137 men reached the efficacy phase. During this period only one pregnancy occurred. This high rate of efficacy is well comparable to that of established female methods. This was a very encouraging result. However, only about two-thirds of all participants developed azoospermia. The other volunteers showed strong suppression of spermatogenesis, as evidenced by oligozoospermia (Waites 2003).

In order to answer the question of whether men developing oligozoospermia can be considered infertile, a second worldwide multicenter study followed (WHO 1996). In this study azoospermia again proved to be a most effective prerequisite for contraception. If sperm concentrations, however, failed to drop below 3×10^6/ml, resulting pregnancy rates were higher than when using condoms. When sperm concentrations decreased below 3×10^6/ml, which was the case in 98% of the participants, protection was not as effective as for azoospermic men, but was better than that offered by condoms.

Even if these WHO studies represented a breakthrough by confirming a principle of action (Waites 2003), they did not offer a practicable method. For a method requiring weekly intramuscular injections is not acceptable for broad use. Moreover, several months (on average four) were required before sperm production reached significant suppression. For this reason current research is concentrating

on the development of long-acting testosterone preparations and on substances to improve overall effectiveness.

The WHO multicenter studies revealed an interesting phenomenon: the rate of azoospermia was greater in East Asian than in Caucasian men (WHO 1990; 1996). This finding was also confirmed by independent studies using testosterone enanthate injections in men in Indonesia (Arysad 1993), Thailand (Aribarg *et al.* 1996) and China (Cao *et al.* 1996).

23.3.2 Testosterone buciclate

Under the auspices of WHO a synthesis program identified testosterone buciclate as a testosterone ester with long-lasting effectiveness. First tested in monkeys and then in hypogonadal patients, it showed a long effective phase of 3–4 months after a single injection (see Chapter 11). A single injection of 1200 mg in a contraceptive study resulted in suppression of spermatogenesis comparable to that of weekly enanthate injections (Behre *et al.* 1995). Unfortunately, WHO and the NIH, which jointly hold the patent on testosterone buciclate, were unable to find an industrial partner to further develop this promising ester for general use, so that its potential for male contraception has never been fully explored.

23.3.3 Testosterone undecanoate

If testosterone is suited for contraception, the orally effective testosterone undecanoate should provide the male contraceptive "pill". This possibility was tested in the early phase of development. However, even when high doses of 3×80 mg were taken daily for 12 weeks, only one of seven volunteers developed azoospermia (Nieschlag *et al.* 1978). Although this result was disappointing, the study demonstrated that stable levels of testosterone in serum are important to suppress pituitary gonadotropins.

While testosterone undecanoate was used as an oral preparation solely in the West, in China it has been marketed as an intramuscular preparation for use in hypogonadism (see Chapter 14) and has more recently also been tested for male contraception. In a large multicenter efficacy study – the first completed since the WHO studies – involving 308 Chinese men given monthly injections of 500 mg testosterone undecanoate after a loading dose of 1,000 mg, only 3% of the subjects did not suppress to azoospermia or severe oligozoospermia, and the remaining 97% induced no pregnancy (Gu *et al.* 2003). This highly successful trial encouraged the Chinese investigators to undertake a phase III trial involving 1,000 couples for an efficacy phase of two years which is currently underway (Handelsman 2003). If successful, testosterone undecanoate may become the first registered hormonal male contraceptive – in China.

In Caucasian men intramuscular testosterone undecanoate has not only been tested successfully for the treatment of male hypogonadism (von Eckardstein and Nieschlag 2002), but also for male contraception. Applying an improved galenic preparation of testosterone undecanoate (using castor oil instead of Chinese tea seed oil as vehicle) injection intervals could be spaced to six weeks, but, as with testosterone enanthate in weekly injections, only 2/3 of the volunteers achieved azoospermia (Kamischke *et al.* 2000b). Extrapolating from the kinetic profiles it appears that the injection intervals might be further extended, but the rate of sperm suppression remains in the range of other testosterone preparations so that other substances need to be added to achieve higher success in Caucasians.

23.3.4 Testosterone pellets

Pellets consisting of pure testosterone are used for substitution in hypogonadism in some countries (see Chapter 14). In male contraceptive studies a one-time application showed efficacy comparable to weekly testosterone enanthate injections (Handelsman *et al.* 1992). The disadvantage of minor surgery required for insertion under the abdominal skin is compensated by their low price and long duration of action. In further studies testosterone pellets have only been used in combination with other substances (see below).

23.3.5 19-Nortestosterone

When searching for preparations with longer-lasting effectiveness, 19-nortestosterone-hexoxyphenylpropionate was tested whose spectrum of effects is very similar to that of testosterone, and which has been used as an anabolic since the 1960s (molecular structure in Fig. 23.1). This 19-nortestosterone ester injected every three 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 injection interval (Behre *et al.* 2001; Knuth *et al.* 1985; Schürmeyer *et al.* 1984). However, 19-nortestosterone is not fully equivalent to testosterone as it is converted to estrogens to a lesser degree than testosterone. Although no side effects were detected in the trials using 19-nortestosterone, long-term untoward effects, e.g. on bones, cannot be excluded. In the light of newer long-acting testosterone preparations, 19-nortestosterone appears less attractive for contraception.

23.3.6 7α-Methyl-19-nortestosterone (MENT)

Another synthetic androgen with possible application in hypogonadism (see Chapter 13) and in male contraception is 7α-methyl-19-nortestosterone (MENT). It has been tested in three doses of subdermal silastic implants in a multicenter study by the Population Council. In a dose-dependent fashion azoospermia can be

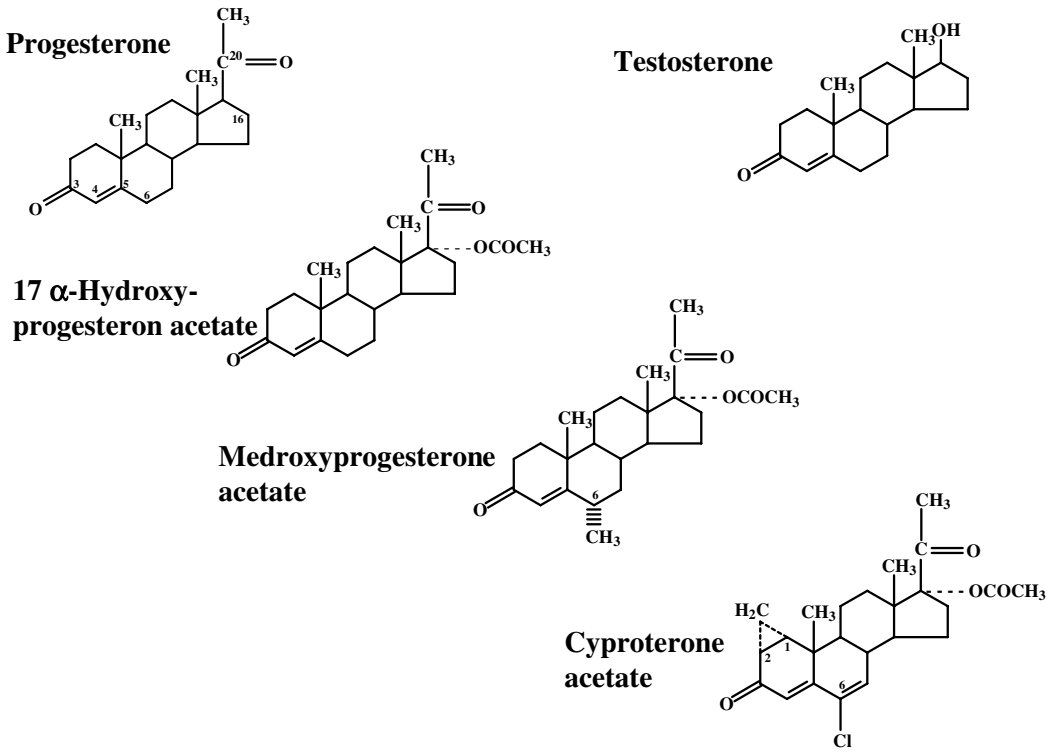

Fig. 23.1 Progestins derived from 17-hydroxyprogesterone tested in hormonal male contraception.

achieved at the same rate as other testosterone preparations alone, i.e. in about 2/3 of the tested subjects, the advantage being that the effect of one set of implants may last for as long as one year (von Eckardstein *et al.* 2003).

23.4 Testosterone combined with progestins

An overview of all studies using testosterone in combination with a progestin performed to date is given in Table 23.1.

23.4.1 Testosterone or 19-nortestosterone plus DMPA

19-Norethisterone (norethindrone), medroxyprogesterone acetate (MPA), depot-MPA (DMPA), 17-hydroxyprogesterone capronate and megestrol acetate have been used in clinical trials initiated by the WHO (1972–1983) and the Population Council (Schearer *et al.* 1978) (molecular structures in Figs. 23.1 and 23.2). The most favorable combination was the monthly intramuscular injection of 200 mg DMPA plus 200 mg testosterone enanthate or testosterone cypionate; this combination gave the best results in suppressing spermatogenesis and the incidence of untoward side

Table 23.1 Overview of studies on hormonal male contraception using testosterone either alone or in combination with progestins

Reference	Number of subjects	Ethnic origin	Androgen dose	Progestin dose	Azoospermia (n)	Severe oligozoospermia below 1 mill/ml (n)	Oligozoo-spermia below 3 mill/ml (n)
Testosterone alone							
WHO 1990	271	mixed	TE 200 mg. i.m. / week	None	157	??	??
Handelsman *et al.* 1992	9	unknown	T-Pellets 1200 mg	None	5	4	0
Handelsman *et al.* 1996	10	unknown	T-Pellets 400 mg	None	0	0	0
Handelsman *et al.* 1996	10	unknown	T-Pellets 800 mg	None	4	0	0
Meriggiola *et al.* 1996	5	Caucasian	TE 100 mg. i.m. / week	None	5	0	0
Bebb *et al.* 1996	18	Caucasian	TE 100 mg. i.m. / week	None	6	4	1
WHO 1996	225	mixed	TE 200 mg. i.m. / week	None	157	29	8
Zhang *et al.* 1999	12	Chinese	TU 500 mg i.m./ 4 weeks	None	11	1	0
Zhang *et al.* 1999	12	Chinese	TU 1000 mg i.m./ 4 weeks	None	12	0	0
Kamischke *et al.* 2000b	14	Caucasian	TU 1000 mg i.m. / 6 weeks	None	7	4	1
McLachlan *et al.* 2002	5	unknown	TE 200 mg. i.m. / week	None	4= < 0.1 or azoospermia	4	0
Gu *et al.* 2003	305	Chinese	TU 500 mg i.m./ 4 weeks	None	284	6	6
Depot medroyprogesterone acetate							
Alvarez-Sanchez *et al.* 1977	8	Dominican Republic	TE 250 mg. i.m. / week	DMPA 150 mg/4 weeks	4	3	1
Alvarez-Sanchez *et al.* 1977	10	Dominican Republic	TE 250 mg. i.m. / week	DMPA 300 mg/4 weeks	7	2	0
Brenner *et al.* 1977	6	Caucasian	TE 200 mg. i.m. / week	DMPA 100 mg / 4 weeks	1	2	1
Brenner *et al.* 1977	3	Caucasian	TE 200 mg. i.m. / week	DMPA 150 mg / 4 weeks	1	0	0
Frick *et al.* 1977	12	Caucasian	TE 250 mg. i.m. / week	DMPA 100 mg i.m. / 4 weeks	6	4	0
Frick *et al.* 1977	6	Caucasian	T-Propionate 4 rods	DMPA 100 mg i.m./4 weeks	2	0	0
Melo and Coutinho 1977	11	Brasilian	TE 200 mg. i.m. / week	DMPA 100–150 mg i.m/ 4 weeks	11= < 0.1 or azoospermia	0	?

(*cont.*)

Table 23.1 (*cont.*)

Reference	Number of subjects	Ethnic origin	Androgen dose	Progestin dose	Azoospermia (n)	Severe oligozoospermia below 1 mill/ml (n)	Oligozoo-spermia below 3 mill/ml (n)
Faundes *et al.* 1981	10	Dominican Republic	TE 500 mg i.m. / week	DMPA 150 mg/4 weeks	8	1	0
Frick *et al.* 1982	4	Caucasian	TE 500 mg/4 weeks	150 mg/4 weeks	4	0	0
Frick *et al.* 1982	5	Caucasian	TE 250 mg/2 weeks	75 mg/2 weeks	5	0	0
WHO 1993	45	Indonesian	19-Nortestosterone 200 mg i.m. / 3 weeks	DMPA 250 mg i.m./ 6 weeks	44	1	0
WHO 1993	45	Indonesian	TE 200 mg i.m. / 3 weeks	DMPA 250 mg i.m./ 6 weeks	43	2	0
Knuth *et al.* 1989	12	Caucasian	19-Nortestosterone 200 mg i.m. / 3 weeks	DMPA 250 mg i.m./ 6 weeks	8	3	1
Wu and Aitken 1989	10	Caucasian	TE 250 mg i.m. / week	DMPA 200 mg/4 weeks	6	0	4
Pangkahila 1991	10	Indonesian	TE 100 mg i.m. / week	DMPA 100 mg / 4 weeks	10	0	0
Pangkahila 1991	10	Indonesian	TE 250 mg i.m. / week	DMPA 200 mg/4 weeks	10	0	0
Handelsman *et al.* 1996	10	unknown	T-Pellets 800 mg	DMPA once 300 mg i.m.	9	0	1
McLachlan *et al.* 2002	5	unknown	TE 200 mg i.m. / week	DMPA once 300 mg i.m.	5 = < 0,1 or azoospermia	5	0
Turner *et al.* 2003	53	unknown	T-Pellets 800 mg/ 16 weeks	DMPA 300 mg i.m. /12 weeks	49	2	0
Levonorgestrel							
Fogh *et al.* 1980	5	Caucasian	TE 200 mg / 4 weeks	LNG 250 µg p.o. / day	1	?	1
Fogh *et al.* 1980	5	Caucasian	TE 200 mg i.m. / 4 weeks	LNG 500 µg p.o. / day	2	?	?
Bebb *et al.* 1996	18	Caucasian	TE 100 mg i.m. / week	LNG 500 µg p.o. / day	12	2	3
Anawalt *et al.* 1999	18	Caucasian	TE 100 mg i.m. / week	LNG 125 µg p.o. / day	11	5	1
Anawalt *et al.* 1999	18	Caucasian	TE 100 mg i.m. / week	LNG 250 µg p.o. / day	14	2	0
Ersheng *et al.* 1999	16	Chinese	TU 250 mg i.m./ 4 weeks	Sino-Implant 2 rods	6	0	1
Kamischke *et al.* 2000b	14	Caucasian	TU 1000 mg i.m. / 6 weeks	LNG 250 µg p.o. / day	8	4	2
Gaw Gonzalo *et al.* 2002	20	Mixed	Testoderm TTS 2 patches / day	Norplant II 4 rods	7	5	2

Gaw Gonzalo *et al.* 2002	15	Mixed	Testoderm TTS 2 patches / day	LNG 125 μg p.o. / day	5	1	1
Gaw Gonzalo *et al.* 2002	14	Mixed	TE 100 mg i.m. / week	Norplant II 4 rods	13	1	0
Pöllänen *et al.* 2001	5	Caucasian	DHT-Gel 250 mg / day	LNG 30 μg p.o./day	0	0	1
Pöllänen *et al.* 2001	5	Caucasian	DHT-Gel 250 mg / day	Jardelle (LNG) 1 rod	0	0	0
Pöllänen *et al.* 2001	8	Caucasian	DHT-Gel 500 mg / day	Jardelle (LNG) 2 rods	0	0	0
Pöllänen *et al.* 2001	7	Caucasian	DHT-Gel 250 mg / day	Jardelle (LNG) 4 rods	0	0	0
Norethisterone							
Kamischke *et al.* 2001	14	Caucasian	TU 1000 mg i.m. / 6 weeks	NETE 200 mg / 6 weeks	13	0	0
Kamischke *et al.* 2002	14	Caucasian	TU 1000 mg i.m. / 6 weeks	NETE 200 mg / 6 weeks	13	1	0
Kamischke *et al.* 2002	14	Caucasian	TU 1000 mg i.m. / 6 weeks	NETE 400 mg / 6 weeks	13	1	0
Kamischke *et al.* 2002	14	Caucasian	TU 1000 mg i.m. / 6 weeks	NETA 10 mg p.o. / day	12	2	0
Cyproterone acetate							
Meriggiola *et al.* 1996	5	Caucasian	TE 100 mg i.m. / week	CPA 50 mg p.o/day	3	0	1
Meriggiola *et al.* 1996	5	Caucasian	TE 100 mg i.m. / week	CPA 100 mg p.o/day	5	0	0
Meriggiola *et al.* 1998	5	Caucasian	TE 100 mg i.m. / week	CPA 12.5 mg p.o/day	3	2	0
Meriggiola *et al.* 1998	5	Caucasian	TE 100 mg i.m. / week	CPA 25 mg p.o/day	5	0	0
Meriggiola *et al.* 2002b	9	Caucasian	TE 100 mg i.m. / week	CPA 5 mg p.o/day	6	3	0
Meriggiola *et al.* 2002b	7	Caucasian	TE 200 mg i.m. / week	CPA 5 mg p.o/day	0	4	2
Desogestrel or etonorgestrel							
Wu *et al.* 1999	8	Caucasian	TE 50 mg i.m. / week	DSG 300 μg p.o. / day	8	0	0
Wu *et al.* 1999	7	Caucasian	TE 100 mg i.m. / week	DSG 150 μg p.o. / day	4	3	0
Wu *et al.* 1999	8	Caucasian	TE 100 mg i.m. / week	DSG 300 μg p.o. / day	6	0	1
Anawalt *et al.* 2000	7	Caucasian	TE 50 mg i.m. / week	DSG 150 μg p.o. / day	4	1	0
Anawalt *et al.* 2000	8	Caucasian	TE 100 mg i.m. / week	DSG 150 μg p.o. / day	8	0	0
Anawalt *et al.* 2000	8	Caucasian	TE 100 mg i.m. / week	DSG 300 μg p.o. / day	7	1	0
Kinniburgh *et al.* 2001	8	Caucasian	T-Pellets 400 mg / 12 weeks	DSG 150 μg p.o. / day	6	2	0
Kinniburgh *et al.* 2001	7	Caucasian	T-Pellets 400 mg / 12 weeks	DSG 150 μg p.o. / day	5	1	0
Anderson *et al.* 2002b	9	Black	T-Pellets 400 mg / 12 weeks	DSG 150 μg p.o. / day	9	0	0

(*cont.*)

Table 23.1 (*cont.*)

Reference	Number of subjects	Ethnic origin	Androgen dose	Progestin dose	Azoospermia (n)	Severe oligozoospermia below 1 mill/ml (n)	Oligozoo-spermia below 3 mill/ml (n)
Anderson *et al.* 2002b	11	Mixed	T-Pellets 400 mg / 12 weeks	DSG 150 μg p.o. / day	9	0	1
Anderson *et al.* 2002b	8	Black	T-Pellets 400 mg / 12 weeks	DSG 300 μg p.o. / day	8	0	0
Anderson *et al.* 2002b	12	Mixed	T-Pellets 400 mg / 12 weeks	DSG 300 μg p.o. / day	8	0	0
Anderson *et al.* 2002a	14	Caucasian	T-Pellets 400 mg / 12 weeks	Implanon (ENG) 1 rod	9	1	3
Anderson *et al.* 2002a	14	Caucasian	T-Pellets 400 mg / 12 weeks	Implanon (ENG) 2 rods	9	4	0
Kinniburgh *et al.* 2002b	15	Caucasian	T-Pellets 400 mg / 12 weeks	DSG 300 μg p.o. / day	15	0	0
Kinniburgh *et al.* 2002b	18	Asian	T-Pellets 400 mg / 12 weeks	DSG 300 μg p.o/day	18	0	0
Kinniburgh *et al.* 2002b	18	Asian	T-Pellets 400 mg / 12 weeks	DSG 150 μg p.o. / day	11	2	2
Kinniburgh *et al.* 2002b	13	Caucasian	T-Pellets 400 mg / 12 weeks	DSG 150 μg p.o. / day	11	2	0
Self-applicable							
Nieschlag *et al.* 1978	7	Caucasian	Andriol 240 mg p.o. / day	None	1	0	0
Guerin and Rollet. 1988	13	Caucasian	Andriol 160 mg p.o. / day	NETA 10 mg p.o./day	7	2	3
Guerin and Rollet. 1988	5	Caucasian	T gel 250 mg / day	NETA 5 mg p.o. / day	4	1	0
Guerin and Rollet. 1988	5	Caucasian	T gel 250 mg / day	NETA 10 mg p.o. / day	5	0	0
Guerin and Rollet. 1988	8	Caucasian	T gel 250 mg / day	MPA 20 mg p.o. / day	5	0	1
Meriggiola *et al.* 1997	8	Caucasian	Andriol 80 mg p.o. /day	CPA 12.5 mg p.o./ day	1	3	2
Hair *et al.* 1999	4	Caucasian	Andropatch 2 patches / day	DSG 75 μg p.o / day	0	1	0
Hair *et al.* 1999	6	Caucasian	Andropatch 2 patches / day	DSG 150 μg p.o,/ day	3	0	0
Hair *et al.* 1999	7	Caucasian	Andropatch 2 patches / day	DSG 300 μg p.o. / day	4	1	0
Büchter *et al.* 2000	12	Caucasian	Testoderm TTS 2 patches / day	LNG 250 μg p.o. later 500 μg	2	3	0
Gaw Gonzalo *et al.* 2002	19	Mixed	Testoderm TTS 2 patches / day	None	5	0	1
Pöllänen *et al.* 2002	2	Caucasian	DHT-Gel 250 mg / day	None	0	0	0

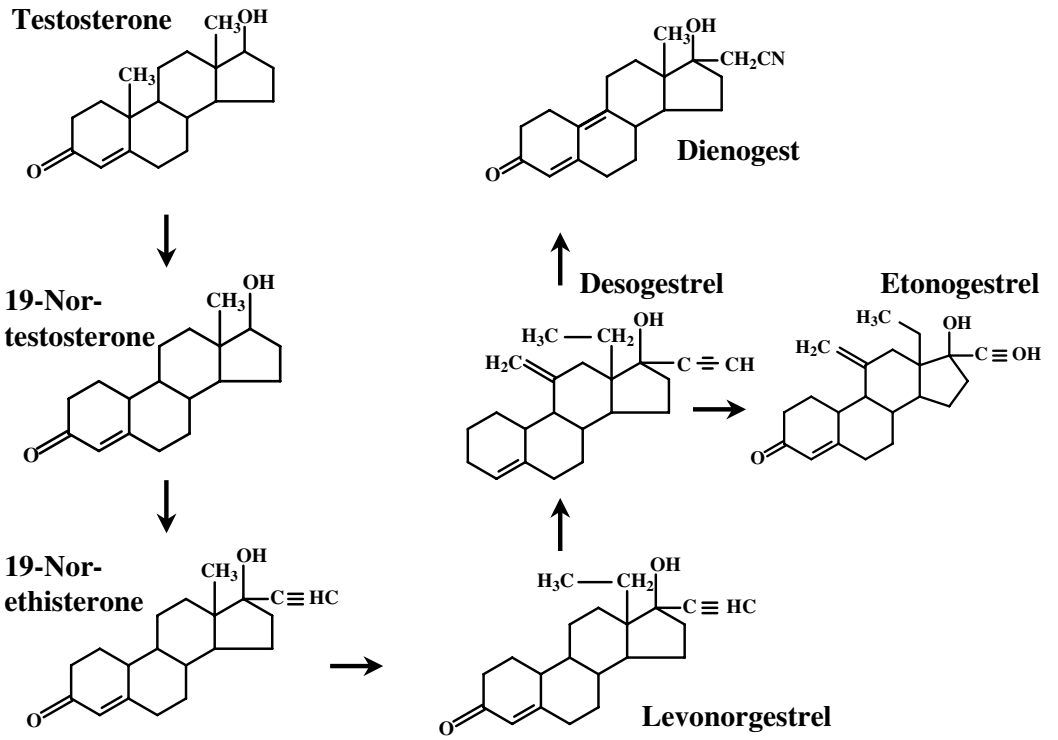

Fig. 23.2 Progestins derived from 19-nortestosterone tested in hormonal male contraception.

effects was low. However, this combination did not produce azoospermia uniformly and its possible efficacy remained uncertain.

Since monotherapy with the long-acting androgen ester 19-nortestosterone-hexoxyphenylproprionate injected every three weeks resulted in effective suppression of spermatogenesis to azoospermia in about 70% of the volunteers (Schürmeyer *et al.* 1984) the possibility of even more complete suppression of spermatogenesis was tested (Knuth *et al.* 1989). Twelve volunteers were injected weekly with 200 mg 19-nortestosterone hexoxyphenylpropionate, followed by injections with the same dose every three weeks up to week 15. In addition, the volunteers were injected with 250 mg DMPA in weeks 0, 6 and 9. Azoospermia was achieved in eight of twelve volunteers during the study course, while in three of the remaining four volunteers, spermatogenesis was suppressed to single sperm, and, in one volunteer, to a sperm concentration of 1.4 mill/ml.

The promising results prompted the WHO Task Force on the Regulation of Male Fertility to launch a large-scale multicenter trial in five centers in Indonesia, comparing the effectiveness of testosterone enanthate, or 19-nortestosterone hexyoxyphenylpropionate, in combination with DMPA (WHO 1993). Surprisingly,

43/45 and 44/45 subjects in the testosterone and the 19-nortestosterone groups respectively suppressed to azoospermia. Unfortunately, this study had failed to include groups treated with the androgens alone, so that it remained unclear whether the azoospermia rates of 97% and 98% were due to the combined treatment or could also be achieved by the androgens alone.

The latter possibility appears likely in the light of the ethnic differences between Caucasian and East Asian men described above. Although ultimately effective, the disadvantage remains that it took almost 20 weeks to reach azoospermia or the lowest sperm counts in these volunteers. Thus, more rapid onset of sperm suppression is required.

A recent study using either 200 mg testosterone enanthate given alone in weekly intramuscular injections or in combination with an injection of 300 mg DMPA showed that the suppression rate was not greater when DMPA was added (McLachlan *et al.* 2002). However, when subcutaneous testosterone implants of 200 mg were applied every 4 or 6 months in combination with 300 mg DMPA given every three months, 51/53 men achieved azoospermia or suppression below 1×10^6 sperm/ml. During a twelve-month efficacy phase with otherwise unprotected intercourse no pregnancy occurred (35.5 person years) (Turner *et al.* 2003). The differences between the studies highlight the fact that obviously the kinetics of testosterone are very important, since the implants produce very stable serum levels and the testosterone enanthate injections cause high peaks and troughs. Although the combination of an implant with an injection every three months may not be ideal, this study is the first to demonstrate the contraceptive efficacy of a testosterone + progestin combination.

Recovery to baseline semen parameters appears to be rather slow in studies employing DMPA. This may be due to secondary depots of this progestin formed in the subcutaneous and abdominal fat and requires special attention should studies be extended over several years.

23.4.2 Testosterone plus levonorgestrel

Levonorgestrel has been widely used for contraception in females either orally or as an implant and has proved safe and effective. Although early studies combining 0.5 mg levonorgestrel given orally with testosterone enanthate were not very encouraging (Fogh *et al.* 1980), more recent trials comparing testosterone enanthate (100 mg/week) alone with testosterone enanthate in combination with 0.5 mg levonorgestrel given orally showed that the combination resulted in more pronounced suppression of spermatogenesis than testosterone enanthate alone (Bebb *et al.* 1996).

Encouraged by the renewed interest in levonorgestrel we conducted a trial combining oral levonorgestrel with a transdermal testosterone patch applied to the trunk

(Büchter *et al.* 1999). The advantage of such a combination is that it is completely self-administered and thus independent of medical personnel. Unfortunately the results were disappointing, as suppression of spermatogenesis was insufficient. We presume that the testosterone dose absorbed from the transdermal systems was too low and often impeded by inadequate adhesiveness to the skin of the systems (Büchter *et al.* 1999). The study again emphasizes the need for steady serum testosterone levels to suppress gonadotropins, even when co-administered with a potent gestagen.

Similarly it was shown that the combination of 0.5 mg levonorgestrel given orally with transdermal DHT was quite ineffective, nor did the combination of transdermal DHT with levonorgestrel implants lead to sufficient suppression of spermatogenesis (Pöllänen *et al.* 2001).

Finally, when the long-acting testosterone preparation testosterone undecanoate (in castor oil) given at six weeks intervals was combined with oral levonorgestrel, the progestin did not enhance the effect of testosterone undecanoate alone (Kamischke *et al.* 2000). However, when levonorgestrel was administered in 4 capsules delivering about 160 μg levonorgestrel (Norplant II = Jadelle)/per day together with weekly injections of 100 mg testosterone enanthate, 93% of the subjects achieved azoospermia and all suppressed to oligozoospermia below 1×10^6/ml sperm (Gaw Gonzalo *et al.* 2002). As effective as this combination may be, it brings us back to weekly testosterone injections, making the approach impractical for general use. The combination of levonorgestrel implants with long-acting testosterone preparations (ideally also implants) might be a solution and requires investigation.

23.4.3 Testosterone plus cyproterone acetate

Animal studies and studies in sexual delinquents have shown that the antiandrogen cyproterone acetate, which can be considered a potent progestin, suppresses spermatogenesis, an effect exerted through suppression of pituitary gonadotropin secretion. In clinical trials using 5 to 20 mg cyproterone acetate per day for up to 16 weeks, sperm counts and motility were reduced markedly (Fogh *et al.* 1979; Moltz *et al.* 1980; Wang and Yeung 1980). Thus, cyproterone acetate appeared to be a possibility for male fertility control. However, decreases in serum testosterone levels to below normal were also observed. Some of the volunteers complained of fatigue, lassitude and decrease in libido and potency attributable to the diminished testosterone levels.

When later cyproterone acetate was combined with testosterone enanthate injections at even higher doses of 50 and 100 mg, it effectively suppressed spermatogenesis (Meriggiola *et al.* 1996), but even when lower doses of cyproterone acetate were administered, antiandrogenic effects prevailed and the volunteers showed decreased red blood, preventing this antiandrogenic gestagen from being an attractive

combination for male contraception (Meriggiola *et al.* 1998). Although the attempt to create a male pill by co-administration of oral testosterone undecanoate with oral cyproterone acetate led to suppression of spermatogenesis, it had to be discontinued because of a decrease in hemoglobin and hematocrit caused by the antiandrogen (Meriggiola *et al.* 1997).

23.4.4 Testosterone plus 19-norethisterone

19-noresthisterone, one of the earliest progestins derived from testosterone (Djerassi *et al.* 1954), is characterized by some undesirable androgenicity when given to women, but might be of advantage when administered to men. An early study with only few volunteers using a combination of orally effective 19-norethisterone acetate with either a transdermal testosterone gel or oral testosterone undecanoate led to azoospermia in all volunteers (Guerin and Rollet 1988). Considering its properties and these promising results, it was surprising that it took another ten years to investigate the use of 19-norethisterone more systematically.

In a pharmacokinetic study single injections of 200 mg 19-norethisterone enanthate led to a marked suppression of the gonadotropins (FSH for 29 days), testosterone, SHBG and sperm (Kamischke *et al.* 2000a). When testosterone undecanoate became available in the form of intramuscular depot injections it was combined with noresthisterone enanthate and volunteers achieved azoospermia or severe oligozoospermia in all but one. The additive effect to testosterone undecanoate alone was striking. An injected dose of 200 mg 19-norethisterone enanthate every 6 weeks was as effective as 400 mg, so that 200 mg appears to be a useful dose. Although 19-noresthisterone acetate 10 mg given orally daily in combination with intramuscular testosterone undecanoate is as effective as injected noresthisterone enanthate, the combination of the two steroids in one injection appears quite attractive (Kamischke *et al.* 2000b; 2001; 2002b). The effectiveness of various combinations is shown in Figure 23.3. Larger-scale trials should now be performed in order to test the contraceptive efficacy of this combination.

23.4.5 Testosterone plus desogestrel or etonogestrel

Orally administered desogestrel, a levonorgestrel derivative, was evaluated in clinical trials using 300 μg/day combined with weekly injections of 50 or 100 mg testosterone enanthate for 24 weeks. A third group received 150 μg/day desogestrel and 100 mg testosterone enanthate per week intramuscularly. While the group receiving 50 mg testosterone enanthate showed complete suppression of spermatogenesis i.e. azoospermia, the other groups achieved only incomplete suppression. In the most effective group, total serum testosterone levels were found in the range of the lower limit of normal men and this may explain the volunteers complaints of decreased sex drive, depression, fatigue and nocturnal sweating (Wu *et al.* 1999).

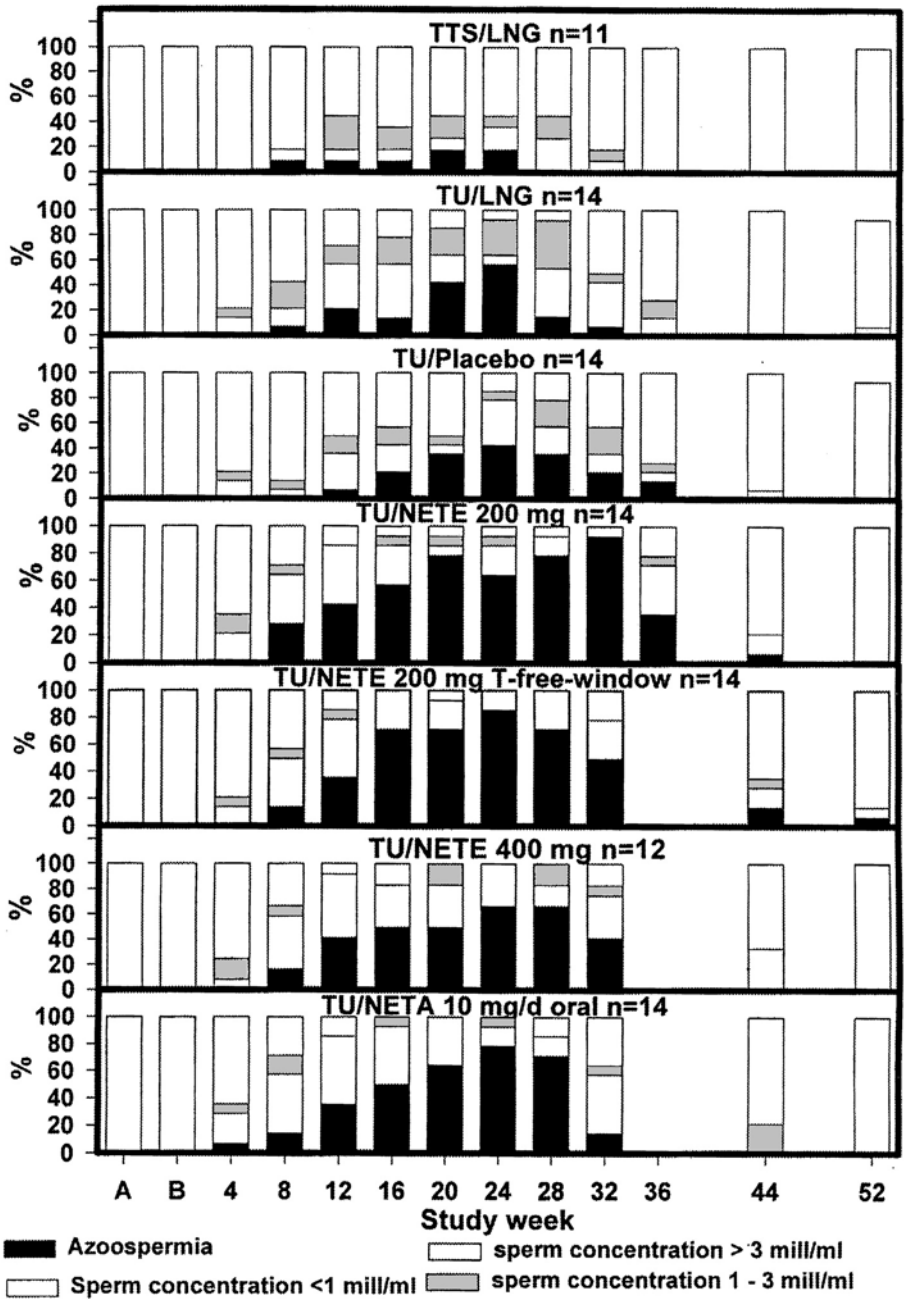

Fig. 23.3 Effectiveness of various testosterone (T) and progestin combinations in terms of suppression of spermatogenesis (data from Büchter *et al*. 1999; Kamischke *et al*. 2000; 2001; 2002b). TTS = transdermal T, LNG = Levonorgestrel, TU = T undecanoate intramuscular, NETE = norethisterone enanthate intramuscular, NETA = norethisterone acetate.

In a two-center study in Edinburgh and Shanghai testosterone pellets (400 mg every 3 months) were combined with either 150 or 300 μg desogestrel/day orally (Kinniburgh *et al.* 2002a). Azoospermia was achieved in all 33/33 men receiving the 300 μg desogestrel dose. Disregarding the fact that a combination of an implant with an oral pill might not offer a highly attractive option, these results are quite promising.

This group continued their investigations using etonogestrel, the active metabolite of orally active desogestrel, as an implant which was recently licensed for use as a female contraceptive (Implanon). 28 men received one or two etonogestrel implants which provide contraceptive protection in females for three years, but the implants were removed from the volunteers after six months. In addition, they received 400 mg testosterone pellets at the beginning of the study and after three months. Nine men in each group achieved azoospermia and in the group with 2 implants sperm counts fell to 0.1×10^6/ml in 13/14 men (Anderson *et al.* 2002).

23.4.6 Testosterone plus dienogest

The latest progestin to be tested for male contraceptive purposes is the orally effective dienogest. This is another 19-norprogestin in which position 17 is not substituted by the common ethinyl group, but by a cyanomethyl group and a double bond is introduced in ring B. When given at 2, 5 or 10 mg doses over 21 days, 10 mg resulted in a suppression of gonadotropins comparable to 10 mg of cyproterone acetate. Semen parameters were not affected, as one would expect with this short application period (Meriggiola *et al.* 2002a). As dienogest displays only mild antiandrogenic activity, this substance may be a possible candidate for future trials.

23.5 Testosterone plus GnRH analogues

23.5.1 Testosterone plus GnRH agonists

In contrast to naturally occurring GnRH, GnRH agonists – after producing an initial stimulation of gonadotropin release for approximately two weeks – lead to GnRH receptor down-regulation and thereby to suppression of LH and FSH synthesis and secretion.

Between 1979 and 1992, 12 trials for hormonal male contraception using GnRH agonists, mostly in combination with testosterone were published (for review Nieschlag *et al.* 1992). Altogether 106 volunteers participated in these trials. The GnRH agonists decapeptyl, buserelin and nafarelin were administered at daily doses of 5–500 μg/volunteer for periods of 10–30 weeks. In about 30% of men, sperm production could be suppressed below 5×10^6/ml and azoospermia occurred in 21 men, while in the remaining volunteers, sperm numbers were only slightly reduced or remained unaffected. One explanation for the ineffectiveness of GnRH

agonist plus androgen is the escape of FSH suppression after several weeks of GnRH agonist treatment (Behre *et al.* 1992; Bhasin *et al.* 1994).

Altogether, GnRH agonists in combination with testosterone did not prove useful in male contraception. At times it has been suggested that higher doses of the GnRH agonists should be used, but currently no further clinical studies appear to be under way.

23.5.2 Testosterone plus GnRH antagonists

In contrast to GnRH agonists, GnRH antagonists produce a precipitous and prolonged fall of LH and FSH serum levels in men (e.g. Behre *et al.* 1994; Pavlou *et al.* 1989). It took much longer to develop GnRH antagonists that were suitable for clinical application than it did for GnRH agonists, and clinical trials using GnRH antagonists for male contraception started some 12 years later than those using agonists. To date, results have become available from five clinical trials using GnRH antagonists for male contraception (for review Nieschlag and Behre 1996; Swerdloff *et al.* 1998; Behre *et al.* 2001).

Overall, 35 of the 40 volunteers (88%) who took part in these studies became azoospermic, most within three months. This is a much better rate of complete suppression than that produced by the administration of testosterone enanthate alone. Although studies in monkeys had suggested that delayed testosterone administration would increase the effectiveness of GnRH antagonists (Weinbauer *et al.* 1987; 1989) – in men GnRH administration followed by delayed testosterone administration (azoospermia in 20/22 men) offered little advantage over concomitant GnRH and testosterone administration (azoospermia in 15/18 men). It should also be noted that, in the later studies with concomitant administration, all 14 volunteers became azoospermic (Behre *et al.* 2001; Pavlou *et al.* 1994). The major advantage of using GnRH antagonists is the short time required to achieve azoospermia, i.e., within 6–8 weeks, which is considerably shorter than the mean of 17 weeks that is required in Caucasian men when testosterone alone was used (WHO 1995).

These results are promising. However, the antagonists and regimen tested to date require daily injections which makes them unacceptable for contraceptive purposes. The development of depot formulations is therefore anticipated with great interest, but such development appears to be much more difficult than it had been for GnRH agonists. Furthermore, it could be argued that the high price of GnRH antagonists may preclude their development as male contraceptives which need to be affordable and in the same price range as comparable female methods. In order to shorten the period of use of GnRH antagonists, two studies have investigated the possibility of applying GnRH antagonists only in an initial suppression phase, and then continuing with the androgen alone (Swerdloff *et al.* 1998; Behre *et al.*

2001). Although successful in the monkey model (Weinbauer *et al.* 1994) studies in men produced contradicting results so that this approach requires further experimentation.

23.6 Side effects and acceptability

Possible side effects of hormonal male contraception might be caused by too high or too low testosterone levels or by additional substances. Decreased testicular volumes reflecting suppression of spermatogenesis is inherent to all hormonal methods, but is not considered a serious effect by the volunteers as long as sexual function remains unaltered. Weight gain is most likely an anabolic effect of testosterone. Due to the high peak serum testosterone levels caused by testosterone enanthate in the earlier studies, acne and mild gynecomastia could be observed in individual cases. Except for local skin reactions, side effects of GnRH analogues are mainly attributable to decreased testosterone levels, not sufficiently compensated for by testosterone supplementation. Sweating and in particular, nocturnal sweating is a feature of some added progestins (see Table 23.2).

Depending on the type and doses of progestin, significant decreases are observed in sex hormone binding globulin. This indicates the influence of progestins on liver function and may enhance the androgenicity of the testosterone preparation, since the unbound free fraction of testosterone in circulation may increase. Some of the effects seen when progestins are added may be due to this phenomenon. When adding levonorgestrel or 19-noresthisterone acetate or enanthate an increase in prolactin is seen, which remains without biological significance. An increase in red blood was more pronounced when progestins were added to testosterone than when testosterone was given alone. Hemostasis is affected by testosterone alone (down-regulation) and by progestin (in this case norethisterone) alone (up-regulation), but given in combination, the effects appear to be neutralized (Zitzmann *et al.* 2002).

Overall, very few subjects left the trials due to side effects, but it has to be kept in mind that all studies so far were of relatively short duration and long-term effects need to be investigated. This should best be done with a combination showing enough contraceptive efficacy to become marketed.

Similarly, the acceptability of hormonal male contraception can only be assessed when a final product becomes available. Nevertheless, interviews with volunteers in contraceptive trials and systematic opinion polls in different cultural settings indicate that a substantial proportion of men would be ready to take a hormonal male contraceptive, preferably a pill, but injections or implants would also attract users (Martin *et al.* 2000; Weston *et al.* 2002). Above all, the female partners would be quite in favour of the men using a contraceptive (Glasier *et al.* 2000).

Table 23.2 Side effects noted in three trials for male contraception using testosterone undecanoate intramuscular alone (1000 mg/6 weeks) or in combination with oral levonorgestrel (0.5 mg/day) or intramuscular norethisterone enanthate intramuscular (200 or 400 mg/6 weeks) or oral norethisterone acetate (10 mg/day)

	TU alone n = 14	TU + LNG n = 14	TU + NETE n = 40	TU + NETA n = 14
Body weight	(↑)	↑	↑	↑
Testis volume	↓	↓	↓	↓
Prostate volume	–	–	–	–
PSA	–	–	–	–
Blood pressure	–	–	–	–
Libido/sexual function	–	–	–	–
(Mild) acne	+	+	+	–
Nocturnal sweating	–	+	++	++
SHBG	(↓)	↓↓	↓↓	↓
Prolactin	(↑)	↑	↑	↑
Erys, Hb, Hk[a]	(↑)	↑	↑	(↑)
HDL cholesterol	↓	↓	↓	↓↓
LDL cholesterol	–	–	(↑)	–
Lp (a)	–	↓	↓	↓
ApoA-1	↓	↓	↓	↓
Glucose basal	–	–	–	–
Glucose tolerance	–	–		
Plasmin α_2-anti-Plasmin complex (PAP)	↓	–	–	

[a] Erys = erythrocytes, Hb = hemoglobin, Hk = hematocrit

Kamischke 2000, 2001, 2002; Zitzmann *et al.* 2002

23.7 Outlook

Initially research in hormonal male contraception was predominantly driven by the WHO Human Reproduction Programme (Waites 2003), by the Population Council, the NIH and USAID/CONRAD. While these organisations still play an important role in the development of the field, investigators initiated complementary research and tapped the national research councils and other organisations for support. When pressure from the public also increased, the pharmaceutical industry finally succumbed to the organisations' and investigators' demand for involvement, since without their input no marketable contraceptive can be developed. The

pharmaceutical industry has now become a partner in development: its pace now rests with industry – and the regulatory agencies. Cooperation as well as competition between the companies may both spur development of a hormonal male contraceptive. The prospect of China being the first country to have a hormonal male contraceptive will further accelerate efforts in the West.

23.8 Key messages

- Testosterone-induced azoospermia leads to effective, safe and reversible male contraception.
- Suppression of spermatogenesis to below 1 mill/ml sperm may still be compatible with protection from pregnancy.
- About two thirds of Caucasian and almost all East Asian men reach azoospermia when given weekly testosterone enanthate injections or 4 to 6 weekly injections of testosterone undecanoate.
- In order to speed up suppression of spermatogenesis and increase the rate of azoospermia, testosterone is combined with either progestins or GnRH antagonists.
- All effective approaches tested so far require injections or implantations. Self-administered modalities (oral or transdermal) did not yet prove to be effective.
- Side effects of hormonal contraception are rare and tolerable. Long-term effects require further investigation.
- Acceptability of a hormonal method as assessed by opinion polls is high.
- After academic research established the principle of hormonal male contraception, the pace of development is now dictated by impetus on the part of the pharmaceutical industry.

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