Endocrine & Metabolic

**Advances in male hormonal contraception**

Maria Cristina Meriggiola† & Giuseppe Pelusi
†I Clinic of Obstetrics and Gynecology, University of Bologna, Bologna, Italy

There is a need to develop new contraceptives, particularly for men whose current choices are suboptimal in terms of effectiveness and ease of reversibility. Recent surveys indicate that men and their partners would be willing to rely on male hormonal contraceptives. Male hormonal contraception works by reversibly suppressing sperm production. Testosterone in combination with progestins or gonadotropin-releasing hormone antagonists induces profound and consistent sperm suppression. Asian men are more susceptible to the suppressive effects of testosterone given alone, even if they may benefit from the addition of an adjunctive agent to obtain optimal contraceptive protection. The aim of this review is to comment on the recent relevant achievements in the field.

Keywords: male contraception, progestins, spermatogenesis, testosterone

*Expert Opin. Investig. Drugs (2006) 15(4):389-397*

1. Introduction

Although the advent of female hormonal contraception has greatly contributed to decreasing the world’s fertility rate, the world population is still growing at a rapid pace. Curbing this overwhelming increase is of utmost importance for guaranteeing a high quality of life for future generations. The development of new contraceptive choices may help to slow population growth and represent an integral and important step in improving the sexual health of the greatest number of people possible.

With the development of female hormonal contraceptives, men have been left out of family planning. One of the reasons has been that the male methods available have certain drawbacks, which make them less appealing compared with new female methods. Indeed, over a century has passed since any new male contraceptives have been introduced (with the exclusion of a few technical developments and updating of existing methods, such as new techniques of vasectomy or new materials for condoms). In recent decades, a new approach for males (one that is very similar to the one that has been so successfully used in females) has shown promising results. Thanks to the tenacious work of a few independent researchers and support from the public sector, such as the WHO, CONRAD (Contraceptive Research and Development Program), NICHD (National Institute of Child and Human Development), MRC (Medical Research Council), Population Council, USAID (United States Agency for International Development) and others, a few studies have been completed and have demonstrated that hormonal regimens also provide effective contraception for males [1-3].

The introduction of this new contraceptive approach for males will certainly result in a new relationship between women and men, allowing the couple to not only share the same rights, but also same responsibilities towards family planning [4]. In fact, surveys carried out in the last decade indicate that the time is right, and that both men and their female partners would welcome the introduction of male hormonal contraception [5-7]. With expected cultural differences, men from different countries have expressed their willingness to use new male hormonal contraception if it becomes available.
The aim of this paper is to illustrate the concepts on which male hormonal contraception is based and comment on the recent developments and future prospects. For comprehensive and detailed reviews of all the studies published on male hormonal contraception, the reader is directed to the numerous reviews that have recently been published [1,8-13].

2. Mechanism of action

The mechanism by which hormones suppress fertility in men is very similar to the mechanism that suppresses female fertility. Exogenously administered hormones suppress gonadotropin-releasing hormone (GnRH) or gonadotropin secretion by acting directly at the hypothalamus–pituitary level. Switching off the gonadotropin drive to the male gonads leads to the suppression of sperm production and, thus fertility. The testis is both an endo- and exocrine organ, with the double function of producing both sperm and testosterone. This implies that when testicular function is switched off, both sperm production and testosterone secretion are blocked. Therefore, testosterone is an essential component of male hormonal contraceptive regimens because it allows for the maintenance of non-reproductive androgen-dependent physiological functions and, when given alone or in combination with other agents, it contributes to gonadotropin suppression (Figure 1).

Following hormone administration, sperm maturation is arrested at the spermatogonial level [14]. This mechanism of action and unique physiology of the human spermatogenetic cycle, which lasts ∼ 75 days, is responsible for two fundamental characteristics of this type of contraception: relatively slow onset of action; and complete, but slow, reversibility. The need to clear preformed sperm from the genital ducts results in a delay of the onset of contraceptive efficacy after hormone administration has stopped. Once administration is stopped and the exogenous hormones are cleared from the body, the spermatogonia resume division and spermatogenesis resumes. For the same reason (i.e., the length of the human spermatogenetic cycle), reversibility is not immediate and may take a few months [15].

The degree of sperm suppression that should be aimed for in order to provide the public with an acceptable and attractive contraceptive is still unclear and the available data are scarce. In the late 1980s, two multi-centre trials supported by WHO and CONRAD proved that spermatogenic inhibition induced by means of hormone administration can reliably suppress fertility in men [16,17]. Indeed, the studies showed that pregnancy rate is directly related to sperm suppression. Another two trials, carried out in Australia and China [18,19], were subsequently completed and, therefore, at the time of writing, only four efficacy trials have been published. The WHO [17] and Chinese [19] studies used the 3 million/ml threshold for entering the efficacy phase, whereas the Australian study used the 1 million/ml threshold [18]. A total of 698 subjects entered the efficacy phase and the overall pregnancy rate was 0.9 (95% confidence interval [CI]; 6.4 – 11.8/100 couples/year; Tables 1, 2 and 3). Considering the pregnancy rate at each level of sperm suppression, complete sperm suppression (azoospermia) seems to be the goal that is aimed for when using hormonal contraception (Table 2). Severe oligozoospermia (< 1 million/ml) also affords optimal contraceptive protection, which is still better than condoms, the only other fully reversible contraceptive available for men. On the other hand, a lesser degree of sperm suppression (> 1 million/ml) does not seem to be associated with acceptable protection from pregnancy. Moreover, all of the studies reported the occurrence of sperm rebound in a few subjects, which seemed to be inversely related to sperm suppression. Although never systematically proven, these data may suggest that the more complete the sperm suppression, the lower the chances of an escape from spermatogenic suppression. In the Chinese study, sperm rebound was reported in six men and it was responsible for a pregnancy in one man [19].

The data available so far suggest that a contraceptive regimen that induces and maintains sperm suppression to azoospermia or severe oligozoospermia can probably provide overall acceptable contraceptive protection (Table 2) [20]. Further efficacy trials are required to provide reliable measurements of contraceptive protection and define the level of sperm suppression that should be aimed for. A large multi-centre efficacy trial is ongoing in China [101]. Testosterone undecanoate (TU) in tea seed oil is being administered to 1000 men over 2 years in 10 Chinese centres. Subjects who achieve sperm counts of < 1 million/ml will enter the efficacy phase. This study [101], which will be completed later this year (2006), will certainly provide precious additional information as to the degree of sperm suppression needed for acceptable contraceptive efficacy.

3. Testosterone monotherapy

Regimens based on testosterone administered alone have been tested as potential male contraceptives: they have the advantage of being simple because both gonadotropin suppression and peripheral testosterone replacement could be achieved with only one molecule. Short-acting testosterone esters, such as testosterone enanthate (TE), were widely used in the WHO trials [16,17]. Spermatogenesis was suppressed to azoospermia in ∼ 60% of Caucasian men and ≥ 90% of Asian men achieved azoospermia [16,17]. The major drawbacks of these formulations are: the need for frequent injections making them impractical for contraception; and side effects due to the high supraphysiological testosterone levels that result shortly after an injection.

Testosterone pellets are formulations that form a slowly dissolving subdermal depot after implantation and release testosterone with near zero-order release kinetics. Although this is not optimal for use in contraception because of the need for a minimal surgical procedure to insert them and the relatively high extrusion rate, the use of testosterone pellets provided a
good opportunity to perform initial studies on sperm suppression with long-acting testosterone formulations. These studies demonstrated the possibility of reducing the dose of testosterone without losing the effectiveness in sperm suppression and reducing the metabolic side effects at the same time [21].

Recently, new long-acting testosterone esters have been developed. TU was included in tea seed and castor oils in China and Europe, respectively, which resulted in long-acting TU formulations that maintained testosterone levels within the normal range for 8 and 12 weeks, respectively [22-24]. In China, the TU formulation at doses of 500 or 1000 mg/month induced azoospermia in 11/12 and 12/12 subjects, respectively [24]. In the larger efficacy study [19], 308 Chinese men were treated with monthly injections of TU. In 97% of the subjects, the sperm count was suppressed to < 3 million/ml, and six men had a partial return to sperm production during the efficacy phase [19]. These data open the possibility that, although more sensitive to the suppressive effects of testosterone, Chinese men may also benefit from the addition of another agent to induce or maintain more complete sperm suppression. Similar to previous testosterone formulations, TU in castor oil administered in a German population was confirmed to be effective in suppressing sperm production in ~ 50% of the subjects [25].

Another testosterone compound recently considered for male contraception is 7α-methyl-19-nortestosterone (MENT), which is a potent synthetic androgen that, unlike other synthetic testosterone molecules, has been shown to be free of hepatotoxicity. The 7-methylation of this compound prevents its 5α-reduction, but allows it to be aromatised. The lack of 5α-reduction is particularly appealing because it spares the prostate from androgen stimulation, while maintaining other androgen-dependent physiological functions. It is a potent inhibitor of gonadotropin secretion. For these characteristics, MENT looks promising for use in both hypogonadal men and as a component of male hormonal contraceptives [26]. The use of this testosterone formulation in male hormonal contraceptive regimens may improve the long-term safety of these regimens because of its favourable effects on the prostate, male-pattern baldness and acne. Administered as a single agent, its effectiveness is comparable with that of other testosterone formulations. Preliminary studies have shown that MENT induced azoospermia in 8 out of 11 subjects (73%) [27].

### 4. Androgen–progestin regimens

The addition of a progestin to long-acting injectable or depot testosterone formulations has been shown to make sperm suppression more rapid and complete [9]. Progestins have been shown to have additive effects on gonadotropin suppression. Moreover, a direct inhibitory effect at the level of the testis has been suggested for some (but not all) progestins, which may enhance spermatogenic suppression independently of gonadotropin suppression (Figure 1) [28]. The most commonly used progestins in the female have also been evaluated in male contraceptive trials (including cyproterone...
acetate [CPA], depot medroxyprogesterone acetate (DMPA), levonorgestrel [LNG], norethisterone (NET) enantate [NETE], and desogestrel (DSG) or etonogestrel [ENG]).

4.1 Cyproterone acetate
CPA is a synthetic progestin with both progestogenic and antiandrogenic activity. Given alone, it is not able to provide complete sperm suppression and induces side effects due to androgen deprivation; however, CPA induces rapid and very complete sperm suppression when given in combination with TE or injectable TU [29-32]. The high degree of spermatogenic suppression induced by CPA may be due to the fact that, in addition to its strong antigonadotropic effect, its antiandrogenic activity is likely to provide an important contribution to its suppressive ability. In fact, studies in animals and humans have shown that a certain amount of intratesticular testosterone or dihydrotestosterone (DHT) is still present and is possibly capable of maintaining sperm development in some individuals (even in the presence of complete gonadotropin suppression or no gonadotropins) [33].

Acting within the testis, CPA may block residual testosterone and DHT; therefore, providing very complete and rapid sperm suppression [31]. In small pilot studies, CPA administered in combination with TE induced complete sperm suppression, which was dependent on the doses of the progestin. Azoospermia was achieved with the administration of TE 100 mg/week plus CPA 100, 50, 25, 12.5 and 5 mg/day in 100 (5/5), 100 (5/5), 80 (4/5), 60 (3/5) and 56% (5/9) of the subjects, respectively. However, antiandrogenic effects (such as the decrease of haematocrit, haemoglobin and body weight) were still present when the highest doses of CPA were administered.

Table 2. Pregnancies and pregnancy rate for each level of sperm suppression in three efficacy studies [17-19].

| Levels of sperm suppression (million/ml) | Preganancies/exposure (couple/years) | Rate (95% CI)/100 couple years |
|----------------------------------------|--------------------------------------|-------------------------------|
| Azoospermia                            | 0/390.7                              | 0 (0 - 1.2)                   |
| 0.1 – 1                                | 2/50.4                               | 4 (0.7 – 14.9)                |
| 1.1 – 2                                | 1/10.8                               | 9.3 (0.5 – 42.9)              |
| 2.1 – 3                                | 1/6.5                                | 15.4 (0.9 – 63.5)             |

CI: Confidence interval.

4.2 Depot medroxyprogesterone acetate
DMPA has been widely used in male contraceptive trials either alone or in combination with different androgens [9]. The results in terms of sperm suppression were dependent on the doses and regimens used. DMPA 300 mg has recently been administered in combination with testosterone pellets.

To take advantage of the rapid and complete suppressive effect on spermatogenesis and simultaneously avoid the adverse effects, CPA has been administered in combination with TU only in the initial phase [32]. Thereafter, sperm suppression could be maintained by TU alone for 32 weeks. In this study [32], there was no difference in the maintenance of sperm suppression from week 12 onwards between the groups receiving CPA plus TU and group receiving TU alone.

The interesting possibility of maintaining sperm suppression with a lower hormonal dosage, once it has been induced with higher doses, has also been proven in another two studies in animals and men using different regimens [34,35]. The advantages of reducing the hormonal load for long-term administration are represented by enhanced long-term safety and cost reduction.

In spite of its potentially high efficacy, CPA has not been made available for male contraception by the pharmaceutical company that owns it. An interesting alternative to CPA could be the progestin dienogest (DNG), which has been shown to provide profound gonadotropin suppression in men [36]. It has less antiandrogenic activity compared with CPA; thus, even if it is used at high doses, side effects that are due to androgen deficiency could be avoided. This progestin has never been tested in male contraceptive trials and could represent a desirable alternative for evaluation in the future.

4.3 Norethisterone enantate
NETE is another synthetic progestin with both progestogenic and antiandrogenic activity. Given alone, it is not able to provide complete sperm suppression; however, NETE induces rapid and very complete sperm suppression when given in combination with TE or injectable TU [29-32]. The high degree of spermatogenic suppression induced by NETE may be due to the fact that, in addition to its strong antigonadotropic effect, its antiandrogenic activity is likely to provide an important contribution to its suppressive ability. In fact, studies in animals and humans have shown that a certain amount of intratesticular testosterone or dihydrotestosterone (DHT) is still present and is possibly capable of maintaining sperm development in some individuals (even in the presence of complete gonadotropin suppression or no gonadotropins) [33].

Acting within the testis, NETE may block residual testosterone and DHT; therefore, providing very complete and rapid sperm suppression [31]. In small pilot studies, NETE administered in combination with TE induced complete sperm suppression, which was dependent on the doses of the progestin. Azoospermia was achieved with the administration of TE 100 mg/week plus NETE 100, 50, 25, 12.5 and 5 mg/day in 100 (5/5), 100 (5/5), 80 (4/5), 60 (3/5) and 56% (5/9) of the subjects, respectively. However, antiandrogenic effects (such as the decrease of haematocrit, haemoglobin and body weight) were still present when the highest doses of NETE were administered.

Table 3. Cumulative pregnancies and pregnancy rate for different thresholds of sperm suppression in three efficacy studies [17-19].

| Thresholds of sperm suppression (million/ml) | Preganancies/exposure (couple/years) | Rate (95% CI)/100 couple years |
|--------------------------------------------|--------------------------------------|-------------------------------|
| Azoospermia                                | 0/390.7                              | 0 (0 - 1.2)                   |
| ≤ 1                                        | 2/441.1                              | 0.5 (0.1 – 1.8)               |
| ≤ 2                                        | 3/451.9                              | 0.7 (0.2 – 2.1)               |
| ≤ 3                                        | 4/458.4                              | 0.9 (6.4 – 11.8)              |

CI: Confidence interval.
800 mg [18]. This combination has been proven to be very effective, and 9 out of 10 men became azoospermic. This combination was also proven to be very effective in a contraceptive efficacy trial. In China, this progestin was given in combination with TU in tea seed oil and azoospermia was subsequently achieved in all volunteers [37]. Even though it may look attractive because of its high effectiveness in sperm suppression, the major drawbacks of this progestin include a relatively high extrusion rate (5 – 7%), as reported in most of the studies, in addition to the fact that it accumulates, thus requiring a lengthy period to clear it from the body once administration is stopped. Consequently, a long time is required for spermatogenesis to resume.

4.3 Levonorgestrel
LNG has been administered in doses ranging from 50 to 500 µg/day in combination with TE 100 mg/day [38-41]. Sperm suppression induced by this hormonal combination was quite profound, and azoospermia or severe oligozoospermia was achieved in 89 – 94% of the subjects with the highest doses. Reduction of the LNG dose minimised side effects, such as a decrease in HDL cholesterol or weight gain, without reducing sperm suppression. LNG 250 µg in combination with the long-acting TU induced similar sperm suppression to that obtained in previous studies with TE [41]. LNG implants have been shown to provide a steady-state delivery of LNG compared with the fluctuating levels provided by the administration. They have been shown to enhance the effect of testosterone pellets on sperm suppression in both Chinese and non-Chinese men [42]. In another study [43], the combination of LNG implants with TU 1000 mg every 8 weeks suppressed the sperm count to severe oligozoospermia (< 3 million/ml) in 95 – 100% of the Chinese men.

4.4 Norethisterone
NET has been used in male contraceptive trials, both in its orally active (norethisterone acetate [NETA]) and injectable (long-acting NETE) formulations. Of interest are the results obtained with NETE 200 mg in combination with TU 1000 mg every 6 or 8 weeks, which induced profound sperm suppression [44-46]. In these studies, 93 – 100% of the subjects achieved either azoospermia or severe oligozoospermia. Although the compounds were injected separately in these studies, they could potentially be included in a single injection and represent a convenient formulation. Therefore, this certainly represents one of the most promising combinations that will be investigated in depth in the future.

4.5 Desogestrel and etonogestrel
DSG is a potent progestin that is widely used in female contraception. Its active metabolite (ENG) has been included in a subdermal implant and was recently introduced for use in female contraception. Initial trials have shown that DSG 150 or 300 µg/day p.o. in combination with an injection of TE 100 mg/week induces profound suppression of spermatogenesis [47,48]. In the search for a more practical route of administration, later trials tested the combination of ENG implants with testosterone pellets and testosterone decanoate [49-52]. Both of these combinations represent a more practical and effective approach. Azoospermia or severe oligozoospermia were induced in > 90% of the subjects with the use of higher doses of ENG (204 mg) [50,52]. A multi-centre trial with ENG implants and TU injections that is cosponsored by Organon and Schering has almost been completed and the results will soon be available. If the data are promising, it is possible that this combination will be the first male hormonal contraceptive to hit the market in the foreseeable future.

5. Regimens including non-injectable testosterone formulations
In recent decades, numerous non-injectable, short-acting testosterone formulations have been developed, such as transdermal, sublingual, buccal or spray, for use in hypogonadic men. Some of these formulations have favourable characteristics; namely, they can be self administered and induce physiological testosterone levels. With the purpose of developing contraceptive formulations that do not require injections or surgical procedures, but can be easily self administered, some of the old and new non-injectable formulations, such as oral and transdermal (patches and gels), have been tested in male contraceptive trials, either alone or in combination with progestins. The old formulation of oral TU administered either alone [53] or in combination with CPA induced variable and inconsistent suppression of gonadotropins and, thus spermatogenesis [54]. In the same way, the use of recent formulations, such as testosterone patches or testosterone/DHT gels in combination with progestins (such as oral LNG or implants, and DSG), were unable to induce and maintain reliable sperm suppression [55-58]. The low efficacy of these formulations in sperm suppression is probably due to their inability to induce stable and complete gonadotropin suppression. Many surveys have pointed out that some men may prefer non-injectable formulations [4]; therefore, this line of research is an important one to pursue in the future for the development of new, non-injectable formulations.

6. GnRH antagonists plus testosterone
GnRH antagonists act by inducing a potent and rapid inhibition of gonadotropin secretion. For this reason, they have been tested in combination with TE for use in male hormonal contraception. The few human clinical trials that have used GnRH antagonists (such as Nal-Glu, cetrorelix or acyline) have produced very promising results in terms of gonadotropins and/or sperm suppression [59-63]. Overall, azoospermia and severe oligozoospermia was achieved in 39 and 40 out of 47 men, respectively [59-62].
7. Expert opinion

Only a few scattered studies on male hormonal contraception have been carried out since the introduction of female hormonal contraception. It is only in recent decades that more systematic trials have been completed, thus leading to promising regimens in terms of potential effectiveness and acceptability. Although they are often small in size and short in duration [13], these preliminary trials deserve credit for having demonstrated the feasibility of male hormonal contraception and have generated significant interest in the field to the point that two major drug companies that are heavily involved in female hormonal contraception have decided to collaborate for the development of a hormonal product for men. This involvement will allow for larger studies and will certainly improve the chances of having a valid product on the market in the near future.

Testosterone is an important component of all male hormonal contraceptives, because of its contribution to gonadotropin suppression and the need to maintain androgen-dependent physiological functions. For many years, the lack of favourable testosterone formulations in terms of pharmacokinetics and of convenience of administration has interfered with the development of male hormonal contraceptives. The recent development of new testosterone formulations, such as injectable TU, represents a turning point regarding progress in the development of male hormonal contraceptives. Preliminary studies using oral progestins with short-acting testosterone formulations can be credited with demonstrating that the concept of combining two steroids (progestin and an androgen) may lead to a safe and more effective hormonal contraceptive compared with testosterone alone regimens. Recent studies using implants or long-acting testosterone and progestin formulations have not only provided more acceptable products, but have also shown that, with the use of these improved formulations, consistent reduction of the daily dosage can be obtained alongside maintaining (or even improving) the suppression of spermatogenesis.

Some preliminary studies have suggested an interesting theory that the complete sperm suppression that is achieved with higher hormonal doses can be maintained by lower dosages. A range of regimens, such as high-dose GnRH antagonists or high-dose antiandrogenic progestin combined with testosterone (although probably contraindicated for long-term use) may be very effective and useful for initial rapid and complete sperm suppression. Whether this initial ‘enhancement’ effect of high-dose regimens represents a real advantage, the maintenance effect on sperm suppression is indefinite or a suppressive dose has to be readministered after a certain period of time remains unknown and worth exploring.

Alongside aiming at formulations that suppress sperm production to azoospermia in all men is a goal to be pursued in future research, the currently available formulations that suppress spermatogenesis to < 1 million/ml in most men already provide a very good option for many men who are looking for an alternative to condoms or the definitive contraceptive effect of vasectomy. In this respect, the most promising combinations tested so far, such as ENG implants or NETE in combination with long-acting testosterone formulations, will soon undergo large efficacy trials in order to confirm the results of previous smaller studies and prove their real contraceptive effectiveness.

The dose-sparing effect provided by long-acting formulations should also provide advantages in terms of an improvement in long-term safety. To date, the short-term trials that have been carried out have not demonstrated the balance between the potential adverse effects and benefits that hormonal contraception may offer to men. If potential side effects could be minimised by adjusting the dosage and type of compound (a more androgenic progestin versus a less androgenic one), health benefits could increase. The maintenance of testosterone levels within the normal range over a long period of time could provide men with positive effects on the muscle, bone, and haematopoietic and metabolic systems, and the prostate could also benefit from some of the non-5α-reducible testosterone formulations.
Bibliography
Papers of special note have been highlighted as either of interest (*) or of considerable interest (***) to readers.

1. KAMISCHKE A, NIESCHLAG E: Progress towards hormonal male contraception. *Trends Pharmacol. Sci.* (2004) 25:49-57.

• A detailed review of the field.

2. NIESCHLAG E, HENKE A: Hopes for male contraception. *Lancet* (2005) 365:554-556.

3. WAITES GM: Development of methods of male contraception: impact of the World Health Organization Task Force. *Fertil. Steril.* (2003) 80:1-15.

4. MARTIN CW, ANDERSON RA, CHENG L et al.: Potential impact of hormonal male contraception: cross-cultural implications for development of novel male preparations. *Hum. Reprod.* (2000) 15:637-645.

5. 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.* (2000) 15:805-809.

6. HEINEMANN K, SAAD F, WIESEMES M, HEINEMANN L: Expectations toward a novel male fertility control method and potential user types: results of a multinational survey. *J. Androl.* (2005) 26:155-162.

7. GLASIER AF, ANAKWE R, EVERINGTON D et al.: Would women trust their partners to use a male pill? *Hum. Reprod.* (2000) 15:646-649.

8. MERIGGIOLA MC, COSTANTINO A, CERPOLINI S: Recent advances in hormonal male contraception. *Contraception* (2002) 65:269-272.

9. MERIGGIOLA MC, FARLEY TM, MBIZVO MT: A review of androgen–progestin regimens for male contraception. *J. Androl.* (2003) 24:466-483.

• A detailed review of the field.

10. ANAWALT BD, AMORY JK: Advances in male hormonal contraception. *Ann. Med.* (2001) 33:587-595.

• A detailed review of the field.

11. ANDERSON RA, BAIRD DT: Male contraception. *Endocr. Rev.* (2002) 23:735-762.

• A detailed review of the field.

12. WANG C, SWERDLOFF RS: Male contraception. *Best Pract. Res. Clin. Obstet. Gynaecol.* (2002) 16:193-203.

• A detailed review of the field.

13. GRIMES D, GALLO M, GRIGORIEVA V, NANDA K, SCHULZ K: Steroid hormones for contraception in men. *Cochrane Database Syst. Rev.* (2004) 3:CD004316.

14. 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) 87:546-556.

15. LI YP, LIU PY, HANDELSMAN DJ: Rates of suppression and recovery of human sperm output in testosterone-based hormonal contraceptive regimens. *Hum. Reprod.* (2005) 20:1733-1740.

16. WHO TASK FORCE ON METHODS FOR THE REGULATION OF MALE FERTILITY CONTRACEPTIVE: Efficacy of testosterone-induced azoospermia in normal men. *Lancet* (1990) 336:955-959.

• First efficacy study with a male hormonal contraceptive.

17. WHO TASK FORCE ON METHODS FOR THE REGULATION OF MALE FERTILITY CONTRACEPTIVE: Efficacy of testosterone-induced azoospermia and oligozoospermia in normal men. *Fertil. Steril.* (1996) 65:821-829.

• Follow-up efficacy study to [15] including azooospermic and oligozoospermic men.

18. TURNER L, CONWAY AJ, JIMENEZ M et al.: Contraceptive efficacy of a depot progesterin and androgen combination in men. *J. Clin. Endocrinol. Metab.* (2003) 88:4659-4667.

• Efficacy study that uses an androgen–progestin regimen.

19. 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) 88:562-568.

• Large efficacy study with a long-acting testosterone formulation.

20. NIESCHLAG E, ANDERSON RA, APTER D et al.: Sixth Summit Meeting Consensus: recommendations for regulatory approval for hormonal male contraception. *Int. J. Androl.* (2002) 25:375-395.

21. HANDELSMAN DJ, CONWAY AJ, HOWE CJ, TURNER L, MACKEY MA: Establishing the minimum effective dose and additive effects of depot progesterin in suppression of human spermatogenesis by a testosterone depot. *J. Clin. Endocrinol. Metab.* (1996) 81:4113-4121.

22. VON ECKARDSTEIN S, NIESCHLAG E: Treatment of male hypogonadism with testosterone undecanoate injected at extended intervals of 12 weeks: a Phase II study. *J. Androl.* (2002) 23:419-425.

23. ZHANG GY, GU YQ, WANG XH, CUI YG, BREMNER WJ: A pharmacokinetic study of injectable testosterone undecanoate in hypogonadal men. *J. Androl.* (1998) 19:761-768.

24. 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) 84:3642-3647.

25. KAMISCHKE A, PLOGER 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.

26. CUMMINGS DE, KUMAR N, BARDIN CW, SUNDARAM K, BREMNER WJ: Prostate-sparing effects in primates of the potent androgen 7α-methyl-19-nortestosterone: a potential alternative to testosterone for androgen replacement and male contraception. *J. Clin. Endocrinol. Metab.* (1998) 83:4212-4219.

• Investigation of a synthetic androgen with tissue selectivity.

27. VON ECKARDSTEIN S, NOE G, BRACHE V et al.: A clinical trial of 7α-methyl-19-nortestosterone implants for possible use as a long-acting contraceptive for men. *J. Clin. Endocrinol. Metab.* (2003) 88:5232-5239.

28. MCLACHLAN RI, ROBERTSON DM, PRUYERS E et al.: Relationship between serum gonadotropins and spermatogenic suppression in men undergoing steroidal contraceptive treatment. *J. Clin. Endocrinol. Metab.* (2004) 89:142-149.

29. MERIGGIOLA MC, BREMNER WJ, PAULSEN AC et al.: A combined regimen...
of cyproterone acetate and testosterone enanthate as a potentially highly effective male contraceptive. J. Clin. Endocrinol. Metab. (1996) 81:3018-3023.

- High-efficacy regimen with oral CPA.

30. 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) 13:1225-1229.

31. 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) 23:684-690.

32. 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) 88:5818-5826.

- Demonstration that lower hormonal dose can maintain sperm suppression.

33. ZHANG FP, PAKARAINEN T, POUTANEN M, TOPPARI J, HUHTANENMI I: The low gonadotropin-independent constitutive production of testicular testosterone is sufficient to maintain spermatogenesis. Proc. Natl. Acad. Sci. USA (2003) 100:13692-13697.

34. WEINBAUER GF, GOCKELER E, NIESCHLAG E: Testosterone prevents the complete suppression of spermatogenesis in the gonadotropin-releasing hormone antagonist-treated non-human primate (Macaca Fascicularis). J. Clin. Endocrinol. Metab. (1987) 67:284-290.

35. 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. Endocrinol. Metab. (1998) 83:3527-3533.

36. MERIGGIOLA MC, BREMNER WJ, COSTANTINO A et al.: Twenty-one day administration of dienogest reversibly suppresses gonadotropins and testosterone in normal men. J. Clin. Endocrinol. Metab. (2002) 87(5):2107-2113.

37. 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) 89:2254-2262.

38. 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 contraceptive approach. J. Clin. Endocrinol. Metab. (1996) 81:757-762.

39. ANAWALT BD, BEBB RA, BREMNER WJ, MATSUMOTO AM: A lower dosage levonorgestrel and testosterone combination effectively suppresses spermatogenesis and circulating gonadotropin levels with fewer metabolic effects than higher dosage combinations. J. Androl. (1999) 20:407-414.

40. 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 randomised clinical trial. J. Androl. (2005) 26:405-413.

41. KAMISCHKE A, PLOGER 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. (Oxf.) (2000) 53(1):43-52.

42. WANG C, WANG HH, NELSON AL et al.: Levonorgestrel implants enhanced the suppression of spermatogenesis by testosterone implants: comparison between Chinese and non-Chinese Men. J. Clin. Endocrinol. Metab. (2005) In Press.

43. 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) 25:720-727.

44. KAMISCHKE A, VENHERM S, PLOGER D, VON ECKARDSTEIN S, NIESCHLAG E: Intramuscular testosterone undecanoate and norethisterone enanthate in a clinical trial for male contraception. J. Clin. Endocrinol. Metab. (2001) 86:303-309.

- A promising androgen–progestin combination.

45. KAMISCHKE A, HEUERMANN T, KRUGER K et al.: An effective hormonal male contraceptive using testosterone undecanoate with oral or injectable norethisterone preparations. J. Clin. Endocrinol. Metab. (2002) 87:530-539.

46. MERIGGIOLA MC, COSTANTINO A, SAAD FE 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) 90:2005-2014.

- A promising androgen–progestin combination.

47. WU FC, BALASUBRAMANIAN R, MULDERS TM, COELINGH-BENNINK HJ: 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) 84:112-122.

48. 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) 74:707-714.

49. ANDERSON RA, KINNIBURGH D, BAIRD DT: Suppression of spermatogenesis by etonogestrel implants with depot testosterone: potential for long-term acting male contraception. J. Clin. Endocrinol. Metab. (2002) 87:3640-3649.

50. 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) 19:2658-2667.

- A promising androgen–progestin combination.

51. HAY CJ, BRADY DM, ZITTMANN M et al.: A multicentre Phase Ib study of a novel combination of intramuscular androgen (testosterone decanoate) and oral progestogen (etonogestrel) for male hormonal contraception. J. Clin. Endocrinol. Metab. (2005) 90:2042-2049.
52. BRADY BM, AMORY JK, PERHEENTUPA A et al.: A multicentre study investigating subcutaneous etonogestrel implants with injectable testosterone decanoate as a potential long-acting male contraceptive. *Hum. Reprod.* (2006) **21:**285-294.

53. NIESCHLAG E, HOOGEN H, BOLK M, SCHUSTER H, WICKINGS EJ: Clinical trial with testosterone undecanoate for male fertility control. *Contraception* (1978) **18:**607-614.

54. 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:**844-850.

55. BUCHTER D, VON ECKARDSTEIN S, VON ECKARDSTEIN A et al.: Clinical trial of transdermal testosterone and oral levonorgestrel for male contraception. *J. Clin. Endocrinol. Metab.* (1999) **84:**1244-1249.

56. GONZALO IT, SWERDLOFF RS, NELSON AL 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.

57. HAIR WM, KITTERIDGE K, O’CONNOR DB, WU FC: A novel male contraceptive pill-patch combination: oral desogestrel and transdermal testosterone in the suppression of spermatogenesis in normal men. *J. Clin. Endocrinol. Metab.* (2001) **86:**5201-5209.

58. POLLANEN P, NIKKANEN V, HUHTANIEMI I: Combination of subcutaneous levonorgestrel implants and transdermal dihydrotestosterone gel for male hormonal contraception. *Int. J. Androl.* (2001) **24:**369-380.

59. PAVLOU SN, BREWER K, FARLEY MG et al.: Combined administration of a gonadotropin-releasing hormone antagonist and testosterone in men induces reversible azoospermia without loss of libido. *J. Clin. Endocrinol. Metab.* (2001) **86:**5201-5209.

60. TOM L, BHASIN S, SALAMEH W et al.: Induction of azoospermia in normal men with combined Nal-Glu gonadotropin-releasing hormone antagonist and testosterone enanthate. *J. Clin. Endocrinol. Metab.* (1992) **75:**476-483.

61. BAGATELL C, MATSUMOTO AM, CHRESTENSENB, RIVIER JE, BREMNER WJ: Comparison of a gonadotropin releasing-hormone antagonist plus testosterone (T) versus T alone as potential male contraceptive regimens. *J. Clin. Endocrinol. Metab.* (1993) **77:**427-432.

62. NIESCHLAG E, BEHRE HM: Hormonal male contraception: suppression of spermatogenesis with GnRH antagonists and testosterone. In: Treatment with GnRH analogs: controversies and perspectives. Filicori M, Flamigni C (Eds), Parthenon Publishing Group, Italy (1995):243-248.

63. HERBST KL, COVIELLO AD, PAGE ST, AMORY JK, ANAWALT BD, BREMNER WJ: A single dose of the potent gonadotropin-releasing hormone antagonist acyline suppresses gonadotropins and testosterone for 2 weeks in healthy young men. *J. Clin. Endocrinol. Metab.* (2004) **89:**5959-5965.

**Website**

101. [http://www.futureofmalecontraception.com/FMCabstracts/Individual%20Speakers/Vogelsong,%20K;%20Gu,%20YQ.doc](http://www.futureofmalecontraception.com/FMCabstracts/Individual%20Speakers/Vogelsong,%20K;%20Gu,%20YQ.doc)

**Affiliation**

Maria Cristina Meriggiola†, Professor of obstetrics and gynecology & Giuseppe Pelusi

†Author for correspondence

††I Clinic of Obstetrics and Gynecology, University of Bologna, Bologna, Italy

Tel: +39 051 636 3716; Fax: +39 051 636 3716; E-mail: cristina.meriggiola@unibo.it