Male hormonal contraception: concept proven, product in sight?

Kati L. Matthiesson1 and Robert I. McLachlan

Department of Obstetrics and Gynaecology, Prince Henry’s Institute of Medical Research, Monash University, Monash Medical Centre, Clayton, Victoria, Australia

1To whom correspondence should be addressed at: Prince Henry’s Institute of Medical Research, PO Box 5152, Clayton, Victoria 3168, Australia. E-mail: kati.matthiesson@princehenrys.org

Current male hormonal contraceptive (MHC) regimens act at various levels within the hypothalamic pituitary testicular axis, principally to induce the withdrawal of the pituitary gonadotrophins and in turn intratesticular androgen production and spermatogenesis. Azoospermia or severe oligozoospermia result from the inhibition of spermatogonial maturation and sperm release (spermiation). All regimens include an androgen to maintain virilization, while in many the suppression of gonadotrophins/spermatogenesis is augmented by the addition of another anti-gonadotrophic agent (progestin, GnRH antagonist). The suppression of sperm concentration to $1 \times 10^6$/ml appears to provide comparable contraceptive efficacy to female hormonal methods, but the confidence intervals around these estimates remain relatively large, reflecting the limited number of exposure years reported. Also, inconsistencies in the rapidity and depth of spermatogenic suppression, potential for secondary escape of sperm into the ejaculate and onset of fertility return not readily explainable by analysis of subject serum hormone levels, germ cell number or intratesticular steroidogenesis, are apparent. As such, a better understanding of the endocrine and genetic regulation of spermatogenesis is necessary and may allow for new treatment paradigms. The development of an effective, consumer-friendly male contraceptive remains challenging, as it requires strong translational cooperation not only between basic scientists and clinicians but also between public and private sectors. At present, a prototype MHC product using a long-acting injectable testosterone and depot progestin is well advanced.

Key words: contraception/FSH/LH/spermatogenesis/testosterone

Male hormonal contraception in the global contraceptive context

The World Health Organization (WHO) has designated the provision of means by which couples can avoid childbearing when too young or too old, too quickly in succession or simply too frequently, as essential to improving the health of women (Marston and Cleland, 2004). Effective family planning has only become available within the last 50 years following the development of female hormonal contraception in the 1950s (ESHRE Capri Workshop Group, 2002). Effective family planning has only become available within the last 50 years following the development of female hormonal contraception in the 1950s (ESHRE Capri Workshop Group, 2002). However, despite this advance, unwanted pregnancy remains a significant health problem, particularly in the developing world where over half a million women die annually from the complications of pregnancy, childbearing or unsafe abortion each year (WHO, 2004a, 2004b). Furthermore, even in the developed world, a wider range of effective and convenient contraceptive choices are required to facilitate greater usage by couples for whom current options are unsuitable.

Barriers to wider contraceptive utilization include lack of financial support for services or knowledge of their availability, socio-cultural traditions and religious beliefs (Ghazal-Aswad et al., 2002). Unfortunately, these barriers are perhaps greatest in the developing world where the need for easy access to birth control is so critical. Currently, men play a major but often under-recognized role in contraceptive practices through the use of natural family planning, condoms and sterilization. Yet, these contraceptive options are restricted and not particularly attractive, for example the condom has limited acceptance and is not highly effective, whereas vasectomy is very effective but invasive, limited in availability and not readily reversible. Presently, there is no male contraceptive product that satisfies the requirements of high efficacy and reversibility whilst being inexpensive and acceptable.

Recognizing the importance of new options as a means of increasing contraceptive utilization rates, the WHO has identified the development of reversible male methods as a priority (WHO/PAHO, 2002). Male hormonal contraception (MHC) exploits the classic endocrine feedback loop to suppress spermatogenesis. Pituitary gonadotrophins are suppressed via administration of testosterone or a derivative androgen often given in combination with a second anti-gonadotrophic agent (e.g. progestin or GnRH antagonist). Emerging data indicate that MHC provides a reversible option for
men with efficacy equal to that of the female oral contraceptive pill (OCP).

The first large MHC trials in which pregnancy was an endpoint, so-called efficacy trials, were conducted under the auspices of the WHO and reported in the 1990s. These trials involved close to 700 couples and demonstrated that the suppression of sperm concentration to azoospermia (WHO Task Force on Methods for the Regulation of Male Fertility, 1990) or indeed only to severe oligozoospermia (below $3 \times 10^6$/ml) (WHO Task Force on Methods for the Regulation of Male Fertility, 1996) was highly effective in preventing pregnancy. Nonetheless, a small percentage of men fail to suppress sperm output adequately even when gonadotrophin levels are non-detectable, suggesting the possibility of gonadotrophin-independent spermatogenesis (McLachlan et al., 2004). Two more recent studies have shown that a long-acting testosterone preparation (Gu et al., 2003) and a testosterone plus progesterin combination regimen (Turner et al., 2003) also provide effective, cheap and relatively convenient contraception for wider clinical application. There have also been numerous studies [reviewed recently (Kamischke and Nieschlag, 2004; Grimes et al., 2005)] using sperm concentration as a surrogate endpoint to suggest that MHC can provide adequate suppression of spermatogenesis ($<1 \times 10^6$/ml) for acceptable efficacy based on existing data sets and the consideration of experts in the field (Sixth Summit Meeting Consensus, 2002). Together, these ‘proof of concept’ trials have fostered the first expressions of interest from the pharmaceutical industry (Bonn, 1999; Hay et al., 2005; Brady et al., 2006).

Ideally, an MHC product would provide (i) equivalent or better efficacy to the female OCP, (ii) universal spermatogenic suppression, (iii) quick onset and offset of action, (iv) easy administration, (v) good tolerability, (vi) favourable short- and long-term side-effect profiles (or even health promoting effects) and (vii) be competitively priced with existing options. Studies to date would support MHC as being likely to satisfy the first and maybe second requirements, but uncertainties remain in regard to the later demands. MHC is most clearly to be seen in the context of a stable relationship, as it does not address the issue of sexually transmitted disease (STD) and in particular HIV prevention. However, taking a more wide-ranging view, MHC may still offer advantages for personal fertility control, given that condoms may not be available and/or used and, even if used, have a reasonably high failure rate. It should also be recognized that the OCP does not address the issue of STD prevention. Future contraceptive planning strategies for men must balance the major public health role of condoms whilst bearing in mind the considerable advantages that an MHC product may offer to some men and in particular those in stable relationships.

One frequently expressed concern is whether men would/could be trusted with contraceptive responsibility and/or whether their partners would accept them taking this role. This view is particularly Western, where the burden of contraception has traditionally fallen to the women. Without a final MHC product and knowledge of the burden of its use or side-effect profile, it is difficult to perform ‘market surveys’ of consumer acceptability. However, research across different countries has shown that between 14 and 83% of men would use an MHC if available, and only a small number of women (<2%) would not trust their partners to take contraceptive responsibility (Brooks, 1998; Glasier et al., 2000; Martin et al., 2000; Weston et al., 2002a, 2002b; Heinemann et al., 2005).

In this review, we aim to (i) give an overview of the hormonal regulation of spermatogenesis, and its interruption by MHC, (ii) provide a summary of MHC trial data with particular focus on efficacy trials, (iii) explore the possible factors involved in the variable response to MHC agents, (iv) speculate on new contraceptive targets and therapies to regulate spermatogenesis and (v) consider issues of contraceptive acceptability and the barriers that must be overcome in bringing an MHC product to market.

**Physiology of spermatogenesis in relation to the MHC strategy**

The hypothalamic–pituitary–testicular (HPT) axis is a classic endocrine feedback system that allows for the precise control of circulating hormone levels and optimal sperm output. GnRH is secreted in a pulsatile fashion into the hypothalamic portal circulation, acting on the anterior pituitary to stimulate the release of the gonadotrophins, LH and FSH. In turn, these glycoprotein hormones act respectively on the testicular Leydig and Sertoli cells, of which the former provides adequate testosterone secretion for virilization and sperm production. The resulting testicular hormonal products, including testosterone, estradiol ($E_2$) and inhibin B, provide negative feedback on the hypothalamus and pituitary to regulate GnRH and gonadotrophin secretion (Finkelstein et al., 1991a, 1991b; Hayes et al., 2001). Figure 1 depicts the HPT axis and sites of trialled and potential MHC agent action.

**Gonadotrophin dependence of spermatogenesis**

The relative roles of FSH and LH in human spermatogenesis were explored in a series of studies in which men underwent both short- and long-term gonadotrophin and spermatogenic suppression via exogenous testosterone administration and then were selectively replaced with either physiological (Matsumoto et al., 1986) or supraphysiological (Bremner et al., 1981; Matsumoto and Bremner, 1985) human chorionic gonadotrophin (as an LH substitute) or FSH (Matsumoto et al., 1983). FSH and LH alone could reintegrate and maintain a degree of spermatogenesis, but normal sperm output required both gonadotrophins. Further work has shown that MHC must induce significant FSH and LH withdrawal to cause spermatogenic suppression (Buchter et al., 1999; Gonzalo et al., 2002).

The relationship between gonadotrophin and sperm concentration suppression is linear to an extent with the inadequate withdrawal of gonadotrophins (i.e. detectable by conventional assay), resulting in failure of spermatogenic suppression (Matsumoto, 1990; Meriggiola et al., 1998; Buchter et al., 1999). However, once gonadotrophin levels are barely or non-detectable, the correlation with sperm concentration disappears suggesting the possibility of gonadotrophin-independent spermatogenesis in some individuals administered MHC agents. Data obtained using ultra-sensitive assay methods suggest that MHC treatment abolishes LH from serum (<0.4% baseline), whilst FSH levels remain at 1–2% baseline levels (Robertson et al., 2001). It is possible that despite undetectable LH some LH bioactivity remains, given that intratesticular $i\mathrm{T}$ testosterone levels remain above that in serum (i.e. 50 versus 25 nmol) (McLachlan et al., 2002b; Mattheisson et al., 2005).
Figure 1. Male hormonal contraceptive (MHC) regimens (compromising androgens alone or in combination with progestins or GnRH antagonists) act to inhibit the hypothalamic pituitary testicular axis. Exogenous testosterone (T) must be administered to maintain virilization and suppress GnRH, FSH and LH levels and thereby intratesticular androgen production (testosterone and dihydrotestosterone (DHT) (percent baseline levels following MHC administration are shown in brackets). Reduction in Sertoli cell FSH and androgen receptor (AR) activation results in marked inhibition of spermatogenesis principally, the maturation of type A pale (Ap) to type B (B) spermatogonia and of sperm release (spermiation). MHC agents that have undergone some assessment in man include progestins, GnRH antagonists, 7α-methyl-19-nortestosterone (MENT), 5α reductase inhibitors with their sites of actions marked. Potential but untried MHC agents [selective androgen responses modulators (SARMs) that target inhibition of the Sertoli cell AR, FSH-R antagonists, agents to inhibit spermiogenesis and spermiation] appear in hatched boxes. Germ cell subtypes include type A pale spermatogonia (Ap); type B spermatogonia (B); leptotene-zygotene spermatocytes (L-Z); pachytene spermatocytes (PS); steps 1–2 round spermatids (rST); steps 3–6 elongating spermatids (El), steps 7–8 elongated spermatids (Eld) and spermatozoa (S).
2005b) but more likely is that there is a low level of LH-independent androgen production (Zhang et al., 2001, 2004). Whether these residual levels of FSH and/or iT testosterone are enough to support a degree of ongoing spermatogenesis in susceptible men is a matter for discussion below.

**Gonadotrophin-independent spermatogenesis: lessons from animal models**

Animal knockout models featuring disruption of gonadotrophin and androgen action provide further evidence for the possibility of gonadotrophin-independent spermatogenesis. The hypogonadal [hpg (GnRH deficient)] mouse shows reduced testicular size, low intratesticular androgens but a degree of germ cell maturation with development arrested at pachytene spermatocytes. The administration of testosterone to these animals results in a rise of all germ cell numbers and the qualitative completion of spermatogenesis despite undetectable FSH (Singh et al., 1995).

FSH receptor knockout mice display reduced fertility, testicular size, sperm count and motility but a degree of completed spermatogenesis (Dierich et al., 1998). FSH-β knockout mice exhibit normal fertility with qualitatively normal spermatogenesis despite a 60% reduction in Sertoli cell number and a marked decline in haploid germ cell numbers (Kumar et al., 1997; Wreford et al., 2001). These models of targeted ligand and receptor disruption demonstrate that ongoing spermatogenesis, albeit at a reduced level, is still possible in the absence of FSH action. Furthermore, the reduction in sperm output appears to be a result of a lower Sertoli cell complement consequent on the lack of FSH-stimulated development (Allan et al., 2004).

Mice lacking the LH receptor are infertile and display reduced testicular size and hypoplastic accessory sex organs (Lei et al., 2001; Zhang et al., 2001); however, germ cell development nonetheless occurs but is arrested at the round spermatid (rST) stage. The administration of testosterone results in a resumption of spermatogenesis, presumably because of androgen receptor (AR) activation although sperm number is low and animals remain subfertile (Pakarainen et al., 2005). Qualitatively normal spermatogenesis is achieved in 12-month-old LH receptor knockout mice with very low iT testosterone levels (2% control), whilst the administration of the anti-androgen flutamide results in post-meiotic spermiogenic failure (Zhang et al., 2003). LH-α subunit knockout mice also show a degree of germ cell maturation in the presence of markedly reduced iT testosterone levels, but similar to LH receptor knockout animals, development is arrested at rSTs (Ma et al., 2004).

Spermatogenesis is never completed in the absence of androgen action. The role of androgens has also been explored using complete and selective AR knockout mouse models. Complete AR knockout mice are infertile displaying a feminized phenotype with small, cryptorchid testis lying in the lower abdomen, thereby confounding the interpretation of AR effects on spermatogenesis which is arrested at pachytene spermatocytes (Yeh et al., 2002). Infertility is also seen in selective Sertoli cell AR knockout mice that show normal testicular descent but again spermatogenic arrest at the pachytene spermatocyte stage with few rSTs and evidence of increased apoptosis (Chang et al., 2004; De Gendt et al., 2004). Taken together with the data from the hpg and LH ligand knockout models, a degree of germ cell development is still possible even in the absence of androgen action, but whether the second meiotic division can always be completed is unclear.

**Gonadotrophin-independent spermatogenesis in humans**

The possibility of species differences for the relative dependence of spermatogenesis on FSH and LH must be considered. To this end, the identification of patients with gonadotrophin deficiency because of congenital GnRH deficiency or mutations in either ligand or receptor genes is informative (Diemer and Desjardins, 1999). Similar to mouse models, patients with LH-β subunit mutations have shown a degree of ongoing though severely impaired spermatogenesis (Weiss et al., 1992; Valdes-Socín et al., 2004), but in contrast, a patient with an FSH-β subunit mutation displayed azoospermia (Phillip et al., 1998). Data from men with mutations of the FSH receptor show highly variable sperm densities from very severe oligozoospermia to normal (Tapanainen et al., 1997; Phillip et al., 1998). Also interesting is the description of a hypophysectomized man with an activating mutation of the FSH receptor in whom spermatogenesis and fertility was maintained despite absent FSH and LH (Gromoll et al., 1996). These data show that FSH is not essential for the completion of spermatogenesis (similar to rodents), but it is notable that four of these six men with FSH-β or receptor mutations had sperm densities below $1 \times 10^6$/ml, with one at $6 \times 10^5$/ml and one with a normal density, suggesting a relatively greater FSH-dependency of human compared with rodent spermatogenesis.

On the basis of human and animal models, the logical target for MHC development is the maximal suppression of both FSH and LH to minimize residual spermatogenesis. However, it remains unclear to what extent the gonadotrophins must be suppressed, and whether a degree of ongoing spermatogenesis is still possible even in their apparent absence. Certainly, the concept of ‘gonadotrophin independent’ spermatogenesis is worthy of further consideration, particularly in regard to new contraceptive developments not solely dependent on gonadotrophin suppression.

**Male hormonal contraceptive regimens**

**Overview of MHC regimens and efficacy**

MHC regimens require the administration of testosterone or a derivative androgen to suppress the pituitary gonadotrophins, and in turn spermatogenesis, whilst ensuring broadly physiological androgen action so as to maintain virilization and avoid excess androgenic side effects. In addition, a second agent, such as a progestin or a GnRH antagonist, is now usually added to augment spermatogenic suppression. To date, regimens have employed long- and short-acting testosterone preparations given by a variety of routes (oral, transdermal, intramuscular or implants) or derivative androgens such as 7α-methyl-19-nortestosterone (MENT) (Nieschlag et al., 2003) together with

(i) a progestin, including depot medroxyprogesterone acetate (MPA) (Brenner et al., 1977; Frick et al., 1977, 1982; Faundes et al., 1981; Knuth et al., 1989; Wu and Aitken, 1989; Pangkahila, 1991; Handelsman et al., 1996; McLachlan et al., 2002b; Turner et al., 2003; Gu et al., 2004), cyproterone acetate (Meriggiola et al., 1996, 1997, 1998, 2003), desogestrel (Wu et al., 1999; Anawalt et al., 2000; Kinniburgh et al., 2001, 2002; Anderson et al., 2002b), etonogestrel (Anderson et al., 2002a; Brady et al., 2004,
2006; Hay et al., 2005), levonorgestrel (Fogh et al., 1980; Bebb et al., 1996; Anawalt et al., 1999; Kamischke et al., 2000b; Pollanen et al., 2001; Gonzalo et al., 2002) and norethisterone (Kamischke et al., 2000a, 2001, 2002) or

(ii) a GnRH antagonist such as acyline (Matthiesson et al., 2005a), cetrorelix (Behre et al., 1992) and lebiterolix (Erb et al., 2000).

In 1990 and 1996, two WHO-sponsored trials (WHO Task Force on Methods for the Regulation of Male Fertility, 1990, 1996) were published which established the relationship between sperm concentration and contraceptive efficacy (Table I). The design of these two multi-centre studies was similar in that men were given a regimen of testosterone enanthate (TE) 200 mg IM weekly for 6 months until they achieved either azoospermia (WHO Task Force on Methods for the Regulation of Male Fertility, 1990) or azoo-oligozoospermia (<3 × 10^6/ml) (WHO Task Force on Methods for the Regulation of Male Fertility, 1996). Following this suppression phase, couples entered into the efficacy phase during which TE treatment continued but all other contraception was stopped for a period of 12 months. Results from the first study showed a conception rate of 0.8 (95% CI, 0.02–4.5) per 100 person-years (WHO Task Force on Methods for the Regulation of Male Fertility, 1990), while azoospermic men, in the second study, achieved a conception rate of 0.0 (95% CI, 0.0–1.6) and oligozoospermic men 8.1 (95% CI 2.2–20.7) per 100 person-years. Overall results from the second study showed a conception rate of 1.4 (95% CI, 0.4–3.7) per 100 person-years; however, the wide CIs in the oligozoospermic group (0.1–3 × 10^6/ml) indicated a need for more efficacy data in this subgroup. These results were encouraging in that they showed conception rates comparable with typical first-year usage of the female OCP (three per 100 person-years) and superior to that of the only available male reversible alternative, condoms (12 per 100 person-years) (Trussell and Kost, 1987). However, the high testosterone dose resulted in frequent androgenic side effects and combined with the need for weekly administration resulted in a high discontinuation rate (29–42%). More perplexing was the small number of men in both studies (primarily those of non-Asian descent), whose sperm concentration remained above 3 × 10^6/ml for unclear reasons – the so-called ‘inadequate responders’ as discussed below.

In the two subsequent efficacy trials (Table I), longer acting testosterone preparations have been used to provide both physiological serum testosterone levels and more acceptable dosing regimens. A study conducted in China with efficacy phase entry criteria of sperm concentration (<3 × 10^6/ml) used a loading dose of IM testosterone undecanoate (TU) 1000 mg IM (given in teesed oil) followed by a monthly 500-mg dose (Gu et al., 2003) to give a conception rate of 2.3 (95% CI, 0.5–4.2) per 100 couple-years in azo-oligozoospermic men. Only 3% of men failed to achieve azo-oligozoospermia demonstrating the propensity of Asian men to achieve adequate spermatogenic suppression with testosterone-alone preparations. The second efficacy trial in Australian men used testosterone implants 800 mg 4 monthly together with depot MPA 300 IM 3 monthly and an entry criteria of severe oligozoospermia (<1 × 10^6/ml) (Turner et al., 2003). This study reported no pregnancies (95% CI 0–8.0/annum) in 35.5 person-years of exposure. This was the first efficacy trial of a long-acting androgen/progestin combination and featured an equivalent efficacy to the previous large testosterone-alone regimens, an acceptable dosing schedule and a 3.6% failure rate of spermatogenic suppression in a predominantly Caucasian population.

### Table I. Summary of MHC efficacy studies

<table>
<thead>
<tr>
<th>Regimen</th>
<th>n</th>
<th>Ethnicity</th>
<th>Azoospermia (%)*</th>
<th>Oligozoospermia (%)*</th>
<th>Person-years of exposure</th>
<th>Conception Failure Rate (per 100 person-years)</th>
</tr>
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<tbody>
<tr>
<td>TE 200 mg IM weekly</td>
<td>271</td>
<td>Mixed</td>
<td>65</td>
<td>NA</td>
<td>123.8</td>
<td>0.8 (0.02–4.5)</td>
</tr>
<tr>
<td>TE 200 mg IM weekly</td>
<td>399</td>
<td>Mixed</td>
<td>74</td>
<td>( &lt;3 million)</td>
<td>279.9</td>
<td>1.4 (0.4–3.7)</td>
</tr>
<tr>
<td>TU 500 mg IM monthly</td>
<td>308</td>
<td>Asian</td>
<td>97</td>
<td>( &lt;3 million)</td>
<td>143</td>
<td>2.3 (0.5–4.2)</td>
</tr>
<tr>
<td>Testosterone implants 800 mg (4–6 monthly) plus DMPA 300 mg IM (3 monthly)</td>
<td>55</td>
<td>Caucasian</td>
<td>96</td>
<td>(&lt;1 million)</td>
<td>35.5</td>
<td>0 (0–8.0)</td>
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*At efficacy phase entry. †Secondary failure rate due to sperm concentration rebound. ‡Per annum.

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However, it should be recognized that in all these studies the differentiation of azoo-oligozoosperma from extreme oligozoosperma is difficult because of the considerations of counting error and the volume of semen (undiluted or concentrated) actually inspected during evaluation. The detection limit for sperm concentration is about 11 000 per milliliter when derived from analysis of a centrifuged pellet obtained using WHO methods (T Cooper, personal communication), and thus, like other laboratory parameters, the term ‘undetectable’ is more applicable. More sensitive methods to detect extremely low sperm number will inevitably reduce the reported azoospermia rate, but from a contraceptive viewpoint this distinction appears unimportant.

It is apparent that there have only been a small number of contraceptive efficacy studies that must be viewed in the context of the difficulties associated with conducting such trials, primarily their high cost (especially relative to the limited public sector funds available), the demanding nature of the studies for participants and concerns about the consequences of contraceptive failure. There has been a much greater number of studies employing various MHC agent combinations using sperm concentration as a surrogate endpoint with a number of excellent recent reviews published (Anderson and Baird, 2002; Kamischke and Nieschlag, 2004; Grimes et al., 2005). Whilst it is tempting to draw conclusions about the relative efficacy of one agent over another, this must be done cautiously. Most of the reported MHC trials have involved small subject numbers of variable ethnicity, different treatment lengths and assorted MHC agents, dosages and combinations. That being said, it is still possible to make some general statements in regard to MHC treatment.

**Androgen preparations: importance of dose, route of administration and duration of action**

Testosterone delivery systems must provide an adequate and constant serum testosterone level to ensure virilization while, in conjunction with another anti-gonadotrophic agent, being able to suppress gonadotrophin levels in a sustained fashion as is essential in achieving contraceptive efficacy. Excessive testosterone administration needs to be avoided to minimize side effects and, given the possibility of testosterone back diffusion into the testis and subsequent AR activation, to avoid androgenic support for residual spermatogenesis (Meriggiola et al., 2002; McLachlan et al., 2004). While this latter effect is less clear than is seen in rodent models (Awoniyi et al., 1990), it does indicate the prudence of using minimum androgen.

To date, studies employing oral (Nieschlag et al., 1978) or transdermal (Buchter et al., 1999; Hair et al., 2001; Gonzalo et al., 2002) testosterone preparations illustrate that these routes provide inadequate testosterone delivery for this purpose. Alternatively, parental testosterone preparations deliver a sufficient androgen dose with long-acting testosterone preparations such as TU (Kamischke et al., 2000b, 2001; Gu et al., 2003, 2004; Meriggiola et al., 2003), testosterone implants (Handelsman et al., 1992, 1996) and MENT implants (von Eckardstein et al., 2003), providing equivalent or greater efficacy to short-acting IM TE (WHO Task Force on Methods for the Regulation of Male Fertility, 1990, 1996; Handelsman et al., 1992). Long-acting testosterone preparations also have the added benefit of greater patient acceptability.

**Additional agents for suppression of gonadotrophins and spermatogenesis**

The failure to induce universal azoospermia [70% of Caucasian men (WHO Task Force on Methods for the Regulation of Male Fertility, 1990, 1996)] over the usual 6-month suppression phase of most MHC studies with testosterone-alone preparations has led to the use of additional agents such as progestins (synthetic progestosterone derivatives) and GnRH antagonists in an effort to maximize gonadotrophin and spermatogenic suppression. Importantly, these agents also allow for the use of physiological testosterone doses, thereby reducing androgenic side effects that were prominent in the initial WHO studies using TE.

**Progestins**

Whether progesterone has a physiological role in normal men is unknown, as is whether additional effects beyond those of feedback on the HPT axis exist. Male progesterone levels (0.25–0.58 nmol/l) are similar to those of mean follicular phase female levels but much lower than those of luteal phase levels (Zumoff et al., 1990; Meneyyirici-Delale et al., 1999) that see reductions in LH pulse frequency and amplitude because of modulation in GnRH secretion (Filicori et al., 1986). Presumably, progestins also act at the hypothalamic level in men but may also act through progestosterone receptors in the pituitary (Heikinheimo et al., 1995), although the presence of this receptor in humans is yet to be confirmed. Further evidence for possible hypothalamic and pituitary sites of progestin action is also provided by a recent study of normal men administered progesterone, resulting in reduced LH pulse amplitude and frequency together with a reduced LH response to GnRH administration (Brady et al., 2003).

Progestins can be administered via a variety of routes (oral, injection or implant) and have both short (hours) and long durations of action (months/years). Multiple studies using androgen/progestin combinations have been reported, which show that progestins (i) augment the induction of gonadotrophin and spermatogenic suppression (Bebb et al., 1996; Handelsman et al., 1996; Anawalt et al., 1999, 2000; Kamischke et al., 2001; Robertson et al., 2001; Gu et al., 2004), (ii) maintain suppression of spermatogenesis (Meriggiola et al., 2003, 2005; Gu et al., 2004) and (iii) allow for a lower dose of delivered androgen (Handelsman et al., 1992, 1996). Overall, these agents are well tolerated with relatively few side effects, the details of which will be discussed in a later section of this review.

**GnRH analogues**

GnRH agonist and antagonist analogues have been incorporated in MHC regimens, but thus far, only antagonists have shown acceptable suppression of sperm concentration. GnRH antagonists act at the level of the pituitary GnRH receptor, blocking the pulsatile action of the ten amino acid hypothalamic peptide GnRH. Unlike their agonist counterparts, antagonists do not result in a flare of LH and FSH secretion prior to suppression. The addition of GnRH agonists to testosterone treatment has not resulted in improved spermatogenic suppression to azoospermia (Rabin et al., 1984; Bhaisin et al., 1985) and may even potentially blunt the spermatogenic response to androgens (Behre et al., 1997), as such their incorporation into MHC regimens has not been actively pursued.
There have only been a few studies that have reported effects on sperm concentration, the majority using daily administration of the nal-glu antagonist combined with IM TE resulting in an azoospermia rate between 67 and 93% between 6 and 16 weeks (Pavlou et al., 1991; Tom et al., 1992; Bagatell et al., 1993; Swerdloff et al., 1998). A more recent study reported that daily cetrorelix combined with 19-nortestosterone hexyloxyphenylpropionate achieved azoospermia in 100% of subjects by 12 weeks; however, this could not be maintained with androgen-alone administration (Behre et al., 2001). This rate of azoospermia induction is comparable with that achieved in trials using progestins. However, GnRH antagonists have the problem of needing daily subcutaneous administration and are expensive. Recently, a new long-acting GnRH antagonist (acyline) given at twice weekly intervals has shown promise in a small number of subjects producing an azoospermia rate of 67% at 8 weeks (Matthiesson et al., 2005a) and as such is worthy of further consideration. However, there are continued problems with local injection site reactions including erythema and induration (Herbst et al., 2002; Matthiesson et al., 2005a).

Issues in the transition of MHC from clinical research to market

With the intention for the general use of MHC by young healthy men for extended periods, numerous issues require further consideration including the need for better definitions of efficacy and safety. In parallel, there are issues of practicality and acceptability that must be considered, given different societal backgrounds and patterns of health behaviours. For MHC delivery, an ideal system would maintain virilization and provide adequate spermatogenic suppression with relatively few side effects and would provide rapid, profound and universal spermatogenic suppression. Modern testosterone depot plus progestin regimens already approach these goals with 95% of men achieving probably adequate suppression, and often within 3 months. Existing MHC studies provide information on the kinetics of spermatogenic suppression and recovery, but because of their limited subject number and short duration do not accurately delineate the potential long term adverse (or perhaps beneficial) effects on cardiovascular, prostate and bone health. The deficiencies in the current data sets point to the need for vigilance in future MHC studies.

Maintaining eugonadism

In combination with a progestin to ensure LH suppression, the subject depends upon exogenous testosterone delivery to ensure eugonadism. The maintenance of physiological testosterone levels is important to avoid androgen deprivation (fatigue, loss of muscle, low libido, mood changes, anaemia, adverse lipid profile changes and bone loss) or excess androgenic effects (acne, fluid retention, weight gain, raised haematocrit, mood changes, gynaecomastia, adverse lipid profile and perhaps prostate enlargement). The administration of oral, transdermal and low dose IM TE has resulted in significant decreases in testosterone levels during treatment, sometimes with symptomatic androgen deficiency and, importantly, may fail to provide the synergistic suppression of gonadotrophins needed for contraceptive action (Nieschlag et al., 1978; Meriggiola et al., 1997; Wu et al., 1999; Anawalt et al., 2000; Hair et al., 2001; Gonzalo et al., 2002). Conversely, high dose IM testosterone (WHO Task Force on Methods for the Regulation of Male Fertility, 1990, 1996) and higher dose testosterone implants have resulted in significant elevations of levels in some instances to well outside the normal range (Handelsman et al., 1992; McLachlan et al., 2002b).

Relatively low doses of testosterone appear able to maintain virilization and contraceptive effectiveness, provided attention is paid to continuous uninterrupted delivery (Anderson et al., 2002a). Long-acting testosterone preparations that can maintain physiological testosterone levels are available and ideal for this purpose. The current depot testosterone preparations, TU IM or testosterone implants, provide the best serum testosterone profiles and require administration every 8 (Meriggiola et al., 2003, 2005) or 16 weeks (Turner et al., 2003), respectively. Testosterone implants require some expertise to administer, and extrusions (10%), infection, bruising and haematoma (Handelsman et al., 1990) limit their widespread usage. On the contrary, TU IM is a promising approach undergoing current evaluation (Kamischke et al., 2000b, 2001; Gu et al., 2003, 2004; Meriggiola et al., 2005).

Cardiovascular and haematological effects

A major issue in chronic treatment of male populations is the potential for adverse cardiovascular effects. The administration of combined MHC regimens containing progestins has resulted in a 12–28% reduction in high-density lipoprotein (HDL) cholesterol levels (Bebb et al., 1996; Wu et al., 1999; Anawalt et al., 2000; Kamischke et al., 2001, 2002; Gu et al., 2003; Hay et al., 2005). HDL is thought to protect against atherosclerosis via antioxidant and anti-inflammatory properties and to promote the removal of cholesterol from atherosclerotic lesions. In prospective studies, low HDL has been linked to increased cardiovascular risk; however, subjects often displayed concomitant raised triglycerides and small low-density lipoproteins (Adult Treatment Panel, 2002). Thus, given that much of the data pertain to this triad of lipid abnormalities, it is not clear that the isolated lowering of HDL cholesterol with MHC treatment in healthy young men will be predictably deleterious. Also reassuring is the reduction in time to myocardial ischaemia seen in older men with chronic stable angina with short-term transdermal testosterone administration (English et al., 2000). However, as MHC trials to date have been of short-term duration and the pathogenesis of coronary disease is long term, this highlights the need for careful ongoing surveillance.

MHC treatment also affects the haemostatic system with administration of TE resulting in initial activation returning to baseline with continued treatment (Anderson et al., 1995) and TU alone resulting in anti-thrombotic effects but the addition of a progestin ameliorating this potential benefit (Zitzmann et al., 2002). More recently, medroxyprogesterone acetate (MPA) has been shown to increase cardiovascular hyperactivity in male monkeys probably via an increase in thromboxane prostanoïd receptor expression in the vasculature with a proposed predisposition to cardiovascular hyperactivity-mediated myocardial ischaemia (Mishra et al., 2005). The significance of this finding for MHC users is unclear but cannot be disregarded, given the recently reported results of the HERS (Grady et al., 2002) and WHI trials (Rossouw et al., 2002) in menopausal women using MPA. Decreases in haemoglobin,
haematocrit and red blood cells have been reported with cyproterone acetate administration, presumably because of its anti-androgenic action on the bone marrow (Meriggiola et al., 1996, 1998, 2003).

Prostate effects

Reassuringly, there appears to be little prostatic effect in the short term with MHC administration. A number of trials using both testosterone alone and combined with a progestin or GnRH antagonist have shown no effect of treatment on either prostate specific antigen or prostate volume (Wallace et al., 1993b; Kamischke et al., 2000b, 2001, 2002; Behre et al., 2001; Meriggiola et al., 2005). While these results are encouraging, they must be interpreted cautiously given the small number of young, healthy study participants treated for relatively short periods of time. At present, the effect of MHC administration on intraprostatic steroi dogenesis and in particular the relative ratios of testosterone metabolites, dihydrotestosterone (DHT) and E₂ remain to be tested. Initial data from the Prostate Cancer Prevention Trial in which older men received the 5α reductase inhibitor, finasteride (5 mg daily) or placebo for 7 years showed that finasteride reduced the occurrence of prostate cancer but increased the risk (6.4 compared with 5.1%) of high-grade tumours (Gleason grades 7, 8, 9 or 10) (Thompson et al., 2003). However, a more recent analysis has raised the questions of excess risk assignment and over-detection bias in the finasteride-treated group (Klein et al., 2005). Taken together, these analyses indicate that a chemo-preventative role for 5α reductase inhibitors and their place in MHC regimens will need to be carefully considered.

Mood and behavioural effects

Also worthy of further consideration, although not well characterized, are the potential adverse changes in mood with MHC treatment. Results from the two WHO efficacy trials using high-dose testosterone showed relatively little effect of treatment on mood and behaviour with only 2% of men discontinuing because of a change in libido, increased aggression or depression (WHO Task Force on Methods for the Regulation of Male Fertility, 1990, 1996). A less troubling effect noted in combination regimens using progestins has been that of increased sweating (Kamischke et al., 2000b, 2001; Hay et al., 2005). In women, it is recognized that the OCP generally stabilized mood across the menstrual cycle but that there are a small subset of women who experience negative effects on mood (Oinonen and Mazmanian, 2002). It is likely that with wider clinical application of MHC, there will be a small number of men who also experience deleterious mood effects.

Body compositional changes

MHC regimens using androgens alone or in combination with progestins have in general shown a small increase in body weight of less than 5% (WHO Task Force on Methods for the Regulation of Male Fertility, 1990, 1996; Kamischke et al., 2000b, 2001, 2002). However, there are relatively few studies looking at the effects of MHC or levels of androgen exposure on body compositional changes in healthy young men. In a 20-week study of eugonadal men, administered TE (25–600 mg IM weekly), a dose-dependent increase in fat-free mass together with a negative correlation between serum testosterone and fat mass was found (Bhasin et al., 2001). Another study (Herbst et al., 2003) showed no change in abdominal fat mass and an increase in lean mass in men given 8 weeks of TE and LNG, whilst men given TE alone had a decrease in abdominal fat mass (at 8 weeks) and trended towards an increase in lean mass (at 4 weeks). Men given levonorgestrel (LNG) alone had an increase in abdominal fat mass and no change in lean mass. These results suggest that in the shorter term, LNG may negate the effect of testosterone on fat mass and be additive to its effect on lean mass. However, a second longer term study of men given testosterone implants and etonogestrel for 48 weeks saw no changes in body compositional data from baseline (Brady et al., 2004). Thus, whether there are significant changes in body composition and potential cardiovascular risk with long-term MHC treatment remains unclear, as does the impact of variable androgen exposure.

Kinetics of spermato genic suppression and recovery

Given the kinetics of spermatogenesis and sperm transport, it is not surprising that the ‘on and off’ rates of MHC are measured for weeks and months. There is clear variability between individuals in regard to patterns of spermatogenic suppression and recovery. Defining these time frames is difficult, as studies have used different MHC regimens, thresholds of response (azoo-o oligozoospermia versus oligozoospermia) and statistical analyses (median versus mean). It is recognized that the initial decline in sperm concentration (seen at around 15–18 days) is consistent with a rapid disruption in spermiation (Garrett et al., 2005). Most men then appear to take somewhere between 6 and 12 weeks to achieve sufficiently suppressed sperm concentrations (<1×10⁹/ml) to afford likely contraceptive efficacy (Kamischke et al., 2000b; Kinniburgh et al., 2001; Anderson et al., 2002a; Brady et al., 2004; Ly et al., 2005; Meriggiola et al., 2005). However, even at this point, there remain some men with the potential to suppress given more time (i.e. beyond 6 months) (WHO Task Force on Methods for the Regulation of Male Fertility, 1990, 1996). This raises a key practical question whether and how frequently sperm concentration should be monitored during suppression. It must also be contrasted with female hormonal methods that are rapid (one month) and do not require confirmatory testing.

The recovery of baseline sperm concentrations is also slow with the majority of men needing 9–16 weeks to recover sperm concentrations to baseline or >20×10⁶/ml (WHO Task Force on Methods for the Regulation of Male Fertility, 1990, 1996; Meriggiola et al., 1995; Anawalt et al., 2000; Anderson et al., 2002b; Turner et al., 2003; Brady et al., 2004; Hay et al., 2005; Ly et al., 2005). It is interesting to note that this problem of delayed recovery (up to 1 year) in some men is particularly seen with the use of TU, depot MPA and norethisterone enanthate (Turner et al., 2003; Meriggiola et al., 2005). This may in part relate to the relatively large volume of distribution of these long-acting agents such that the actual time of recovery phase onset cannot be well defined and may vary between men. Other possible reasons for delayed recovery include unrecognized spermatogenic disorders (despite a sperm concentration of greater than 20×10⁶/ml), and the effects of prolonged suppression as supported by the observation that serum inhibin, a marker of seminiferous tubule function, continues to fall through the second 6 months of MHC treatment and shows minimal recovery by 4 months (Brady et al., 2004).
While there is currently no reason for concern, future studies will need to establish whether there is any reduction in fertility following MHC administration through the careful definition of recovery sperm concentration (baseline versus an arbitrary threshold such as $>20 \times 10^6$/ml) and prolonged subject follow-up. Clinically, men interested in using MHC will need to be informed of the potential for a protracted delay in fertility return. However, it should also be remembered that pregnancies have occurred in the recovery phase of MHC trials despite low sperm densities, reflecting the relative fecundity of the populations involved and in keeping with the experience of fertility treatment in hypogonadotropic men (Burris et al., 1988).

Despite the relatively slow ‘on and off’ rates, it is still likely that MHC will provide considerable advantages to some couples. It would seem that those men in a stable relationship, where quick changes in fertility status may be less important, would be ideal candidates for these products (e.g. post-natal). It must also be remembered that no contraceptive is perfect for all couples and that any new option will be welcomed given that currently available male options are so limited.

**Inadequate spermatogenic suppression**

The non-uniform induction and maintenance of azoo-oligozoospermia or severe oligozoospermia is a significant issue in MHC development. This is particularly true of androgen-alone preparations that induce azoospermia in 70% of Caucasian men compared with near-universal response in Asian men (WHO Task Force on Methods for the Regulation of Male Fertility, 1990, 1996). Undoubtedly, the prospective identification of contraceptive response would be helpful in tailoring treatment for patients. However, previous work exploring baseline and treatment characteristics in MHC trial subjects with heterogenous spermatogenic suppression has only identified a small number of differences (Table II). In combined MHC studies, the ‘non-suppression’ issue (about 3–5% of subjects) makes testing to establish the presence of severe oligozoospermia or azoospermia mandatory during the next phase of MHC development as, without this approach, the inclusion of such men will introduce a predictable and substantial background failure rate that is unlikely to be accepted.

**Persistent spermatogenesis despite fully suppressed gonadotrophin levels**

MHC treatment seeks to achieve maximal gonadotrophin suppression and thereby spermatogenic suppression. While the data broadly support this simple proposition, it is perplexing that many studies have found individuals who display ongoing spermatogenesis despite FSH and LH withdrawal and conversely others with spermatogenic suppression in the presence of detectable FSH and LH.

The comparison of treatment phase gonadotrophin levels in azoospermic and oligozoospermic men has provided conflicting results with a number of studies failing to show differences (Wallace et al., 1993a; Handelsman et al., 1995; Anderson and Wu, 1996; Amory et al., 2001) but two more recent reports (Anderson et al., 2002a; Mergioli et al., 2002) finding higher treatment gonadotrophin levels in oligozoospermic men. A more consistent finding has been that of higher pre- and post-treatment gonadotrophin levels (Wallace et al., 1993a; Handelsman et al., 1995; Handelsman, 1995; Amory et al., 2001) in men becoming azoospermic with MHC treatment. While it is necessary to markedly suppress gonadotrophins to arrest spermatogenesis, once below this threshold, the relationship between gonadotrophins and spermatogenesis becomes less straightforward. As discussed above, this raises the concept of gonadotrophin-independent residual spermatogenesis in some men because of unexplained mechanisms and suggests that focusing on new and better ways to suppress gonadotrophins is unlikely to yield dividends in the ‘non-suppressed’ minority.

**Intratesticular testosterone and spermatogenesis: human and animal models**

No differences in baseline or treatment levels of serum or seminal plasma testosterone levels have been reported between men achieving azoospermia or oligozoospermia (Wallace et al., 1993a; Handelsman et al., 1995; Anderson and Wu, 1996; Anderson et al., 1997; Amory et al., 2001). Intuitively, the fall in iT androgen action consequent on LH suppression would seem key to MHC action, but the iT testosterone level is not readily assessed. A high level of testosterone in the order of 1000–2000 nmol/l is maintained in human testis under physiological conditions, some 40- to 100-fold higher than circulating serum levels (Morse et al., 1973; Huhtaniemi et al., 1987; McLachlan et al., 2002b; Coviello et al., 2004, 2005; Matthiesson et al., 2005b). This same high testicular to serum gradient also exists for the androgenic metabolites of testosterone [DHT 26 versus 4.7 nmol/l, 3α-adiol (81 versus 8.1 nmol/l) and 3α-adiol (158 versus 4.8 nmol/l)] and for E2 (11000 versus 27 pmol/l) (Matthiesson et al., 2005b). The administration of MHC results in a marked suppression of urinary epitestosterone (10% baseline) (Brady et al., 2004) and iT testosterone levels (2% baseline) (Morse et al., 1973; McLachlan et al., 2002b; Coviello et al., 2004; Matthiesson et al., 2005b) with the androgenic metabolites (DHT, 3α- and 3β-adiol) and E2 falling to a much lesser extent (Matthiesson et al., 2005b).

Previous work in rodents and monkeys has examined the relationship between iT steroids and spermatogenesis. Given testosterone or DHT implants, the hpg mouse shows completion of meiosis.

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**Table II. Potential factors involved in inadequate spermatogenic suppression**

<table>
<thead>
<tr>
<th>Contributing factor to inadequate spermatogenic suppression</th>
<th>Possible MHC strategies</th>
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</thead>
<tbody>
<tr>
<td>Incomplete suppression of FSH and LH</td>
<td>FSH receptor antagonists, i.e. substituted 6-amino-4-phenyl-tetrahydroquinoline derivatives</td>
</tr>
<tr>
<td>Persistent FSH action</td>
<td>Testis-specific androgen antagonists i.e. SARMS</td>
</tr>
<tr>
<td>Incomplete iT testosterone withdrawal</td>
<td>Non-gonadotrophin-dependent MHC agents, i.e. alkylated imino sugars</td>
</tr>
<tr>
<td>Persistent androgen action</td>
<td>Spermigenesis and spermatogenesis inhibitors</td>
</tr>
<tr>
<td>Gonadotrophin independent spermatogenesis and spermatiation</td>
<td>Improved 5α reductase inhibitors</td>
</tr>
<tr>
<td>Increased 5α reductase activity with preserved intratesticular DHT</td>
<td>Non-5α reducible androgens</td>
</tr>
<tr>
<td>Genetic factors, i.e. increased CAG repeat length</td>
<td>Pharmacogenetic approaches</td>
</tr>
</tbody>
</table>

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and initiation of qualitatively normal spermatogenesis (Singh et al., 1995). Following testosterone implant removal, elongated spermatids are lost by 3 weeks and testicular weight regresses (Handelsman et al., 1999). Interestingly, subsequent replacement of the implants shows that a lower dose of testosterone is required for restoration of spermatogenesis than that required for initiation, suggesting different androgen-dependent genetic switches for these two processes (Handelsman et al., 1999). In rats, the administration of testosterone/E₂ implants results in selective LH/IT testosterone withdrawal with relative preservation of FSH. Examination of the testis in this model shows a marked reduction in the progression of round through to elongated spermatids, reflecting a spermiogenic lesion (Awoniyi et al., 1990; McLachlan et al., 1994). Spermiogenesis is returned to normal levels by high-dose testosterone that results in supraphysiological serum levels but iT testosterone levels 10–40% of normal (Awoniyi et al., 1989, 1990; McLachlan et al., 1994; O’Donnell et al., 1994), thus reflecting the androgen dependence of the later stages of spermatogenesis to iT testosterone restoration and the fact that high testicular levels of testosterone are likely to be a consequence of local production, rather than a necessity for normal spermatogenesis.

In contrast, monkeys administered exogenous testosterone show marked reductions in gonadotrophin levels, yet a less marked reduction in iT testosterone levels (15% baseline) (Narula et al., 2002). Stereological evaluation of germ cell development shows a general fall in all germ cell subtypes but predominantly two lesions: (i) maturation of type A to B spermatogonia and (ii) spermiation (the process of sperm release from the seminiferous epithelium) (O’Donnell et al., 2001a). This is very similar to the pattern seen in men given an MHC regimen of androgen alone or in combination with a progestin but in whom profound falls in iT testosterone (2% baseline) are seen (Zhengwei et al., 1998; McLachlan et al., 2002b; Matthiesson et al., 2005b).

Interestingly, these human studies show that despite significant gonadotrophin and iT testosterone withdrawal, spermatogenesis continues, albeit at markedly reduced levels (Zhengwei et al., 1998; McLachlan et al., 2002b; Matthiesson et al., 2005b). The establishment of relationships between specific events in germ cell development and iT testosterone levels has thus far not been demonstrated (Matthiesson et al., 2005b). Much like the gonadotrophins, the relationship between iT testosterone and spermatogenesis at the extreme of suppression is less than clear. The germ cell response to MHC-induced iT testosterone withdrawal (2% baseline) appears variable, but whether this represents testosterone-independent spermatogenesis or more probably a very low threshold for its action in some individuals is unclear.

**Increased 5α-reductase activity and preserved intratesticular DHT**

Higher 5α-reductase activity has been suggested as a potential cause of heterogenous MHC response (Anderson et al., 1997). Testosterone is converted to DHT through the action of the type 1 and type 2 5α-reductase isoenzymes (Jenkins et al., 1992) with the former being more highly expressed in the testis (Mahony et al., 1998). DHT, in turn, is reversibly metabolized to 5α-androstane-3α,17β-diol (3α-adiol) and 5α-androstane-3β,17β-diol (3β-adiol) by the action of 3α and β hydroxy-steroid dehydrogenase.

Previous work comparing azoospermic and oligozoospermic responders, given 16 weeks of TE treatment, has shown that oligozoospermic men had higher seminal plasma DHT levels, suggesting a relatively higher 5α-reductase activity in their reproductive tracts (Anderson et al., 1997). On the basis of rat and human data, it has been postulated that in response to the lowering of iT testosterone levels, 5α-reductase activity may be up-regulated and may serve to maintain iT levels of the more potent androgen, DHT, thereby supporting ongoing spermatogenesis (O’Donnell et al., 1996b, 1999; McLachlan et al., 2002b; Fratis et al., 2003).

Consequently, finasteride, a type 2 5α-reductase inhibitor, was incorporated into MHC regimens (McLachlan et al., 2000; Kinniburgh et al., 2001) in an attempt to improve efficacy. Both studies were negative, possibly because of this drug’s lack of activity against the testicular type 1 5α reductase. More recently, the dual type 1 and type 2 5α reductase inhibitor, dutasteride, combined with an MHC regimen has been used in a small group of men (Matthiesson et al., 2005a, 2005b). While dutasteride was effective in significantly lowering iTDHT levels, this did not translate to significant additional reductions in sperm concentrations nor germ cell numbers, nor was there any correlation between any germ cell subtype and iTDHT levels (Matthiesson et al., 2005b). Thus, there is currently no interventional evidence to support residual DHT-promoting spermatogenesis when iT testosterone levels are dramatically lowered by MHC.

**Other testosterone metabolites: intratesticular adiol and oestrogen**

The role of the other testosterone metabolites, E₂, 3α-adiol and 3β-adiol in spermatogenesis during MHC treatment is even less well characterized. Despite being abundant in human testis (Matthiesson et al., 2005b), nothing is known about the possible roles of 3α- and 3β-adiol. Conventionally, 3α-adiol has not been viewed as exerting significant androgenic action despite its high local iT concentration due to its low affinity for the AR, which is five orders of magnitude lower than DHT (Penning, 1997). However, in some species (marsupials), 3α-adiol is a key androgen in sexual differentiation with its action probably mediated through DHT (Wilson et al., 2003). 3β-Adiol interacts with oestrogen receptor-β (ER-β) but has no known role in the testis.

The metabolism of testosterone to E₂ in the testis is mediated through the action of the CYP19 aromatase gene using a PII tissue-specific promoter (Lanzino et al., 2001). In rodents, aromatase expression in Leydig, Sertoli and germ cells is induced by FSH, LH, testosterone and DHT (Bourgiba et al., 2003), but its regulation and that of E₂ production in the human testis is unknown. It has recently been found that iTE₂ levels remain at 30% of baseline during MHC treatment despite a 98% fall in iT testosterone substrate levels (Matthiesson et al., 2005b). However, it is unknown whether this relative maintenance of iTE₂ relates to up-regulation of the aromatase gene or to residual iT testosterone levels remaining at or above the Km of aromatase for testosterone (40 nmol) (Yoshida and Osawa, 1991).

More pertinent is whether E₂ has any role in adult spermatogenesis and thus MHC (see review, O’Donnell et al., 2001b). ER-β has been localized to human germ and Sertoli cells (Pentikainen et al., 2000; Taylor and Al-Azzawi, 2000; Saunders et al., 2001) with ER-α (ER-α) identified less consistently in human germ and Leydig cells (Pelletier and El-Alfy, 2000; Pentikainen et al., 2000; Saunders et al., 2001) but certainly found in rodent. Data from the aromatase knockout mouse show normal spermatogenic develop-
ment followed by the mid-life onset of spermiogenic disruption (Robertson et al., 1999). The ER-α mouse shows an earlier degeneration because of impairment of epididymal fluid reabsorption (Hess et al., 1997), whilst the ER-α mouse displays a normal reproductively phenotypic, fertility and epididymal sperm counts (Krege et al., 1998; Couse et al., 1999). Taken together, these data provide little support for E₂ acting directly on Sertoli or germ cells or being involved in the establishment of spermatogenesis but rather that effects are mediated indirectly by disruption of post-testicular ductal structures (O’Donnell et al., 2001b; Hess, 2003).

**Ethnic and genetic factors in the variable response to MHC**

In response to testosterone-alone treatment, almost all Asian men become azoospermic compared with only 70% of Caucasian men (WHO Task Force on Methods for the Regulation of Male Fertility, 1990, 1996; Handelsman et al., 1992; Zhang et al., 1999; Kamischke et al., 2000b, 2001; Gu et al., 2003). This heterogeneity of response maybe because of differences in testicular structure (Johnson et al., 1998), a greater propensity for apoptosis (Hikim et al., 1998), earlier and greater sensitivity in LH response to testosterone administration (Wang et al., 1998) and/or potentially lower spermatogenic reserve (Wang et al., 1998) in Asian men. As proposed above, reduced levels of 5α-reductase activity in Asian men (Lookingbill et al., 1991; Ross et al., 1992), as evidenced by decreased serum 3α-diol glucuronide and androsterone glucuronide levels, may increase their sensitivity to MHC treatment. As yet, there is no unifying hypothesis to explain the ethnic difference in susceptibility.

AR CAG repeat length modulates signal transduction, varies within populations and may account for the variability of androgen action seen within the testis and other tissues (Zitzmann M et al., 2005). Two previous studies examining the relationship between CAG repeat length and contraceptive response have provided differing results. The first study of seventy-five MHC-treated men found no association (Yu and Handelsman, 2001), while the second study reported that a CAG repeat length of greater than 22 in a subset of men with incomplete gonadotrophin suppression was associated with a 2.5 higher chance of achieving azoospermia (Eckardstein et al., 2002). Analysis of polymorphic variation in the CYP3A4, ER-α and FSH receptor genes was shown to differ between responders and inadequate responders (Yu and Handelsman, 2001; Eckardstein et al., 2002). Interestingly, Asian men display longer CAG repeat lengths (0.91–1.66) compared with Caucasian men (Mifsud et al., 2001), which may in part explain observed ethnic diversity but would seem to small a difference to account entirely for the greater susceptibility to MHC treatment seen in this population.

**New approaches identifying intrinsic differences in MHC response**

Given the lack of difference in any known clinical, endocrine or therapeutic factors in explaining non-suppression, ‘intrinsic differences’ in the sensitivity of spermatogenesis has been proposed (Handelsman et al., 1995). It is therefore necessary to stand back and understand the process by which germ cell progression is impaired by MHC to begin to identify such factors.

**Stereological approaches to study spermatogenesis in MHC**

The effects of MHC treatment on germ cell development can be assessed by estimating the numbers of individual cell populations, using stereological methods. Sections are carefully handled to avoid artefacts, fixed in methacrylate, cut into thick (25 μm) sections and germ/Sertoli cells identified based primarily on nuclear morphology and location using the optical dissector (sic) technique in combination with a random sampling scheme (Wreford, 1995; McLachlan et al., 2002b). The germ cell data are expressed as number per Sertoli cell, a denominator presumed to be constant within the MHC paradigm (Zhengwei et al., 1998).

Testicular tissue has been obtained from normal men at the time of a previously planned vasectomy but with preceding MHC treatment and used for stereological analysis of germ cell number and steroid content (Zhengwei et al., 1998; McLachlan et al., 2002b; Matthiesson et al., 2005b). Importantly, these biopsy studies illustrate a range of patterns and severity of inhibition in germ cell development that show little correlation with sperm concentration (Matthiesson et al., 2005b). Understanding the basis for these variable patterns and the determinants of final sperm output is important for a more targeted future approach to MHC development.

The effects of MHC can be seen at each of the four major stages in normal spermatogenesis, which include (i) mitosis of type A spermatogonia with renewal of stem cell population and commitment of type B forms to differentiation, (ii) meiosis wherein the maturation of a series of spermatocytes involves DNA synthesis, condensation, then pairing of homologous chromosomes with exchange of genetic material followed by two meiotic divisions to yield haploid rSTs, (iii) spermiogenesis whereby the rST, without further division, is transformed into a motile spermatozoon that involves formation of the acrosome, nuclear condensation, sperm tail development and extensive reorganization of the cytoplasm and cell organelles (de Kretser, 2002) and (iv) spermiogenesis involving interactions between elongated spermatid and Sertoli in which there is removal and phagocytosis of spermatid cytoplasm by the Sertoli cell, then release of the mature sperm into the tubule lumen (Russell and Clermont, 1976; de Kretser, 2002).

The endocrine regulation of these processes has been extensively studied in animal and human models but remains unclear (McLachlan et al., 2002a). In rodent and monkey models, spermatogenic maturation is largely dependent on FSH, while LH and testosterone are thought not to play a significant role (Weinbauer et al., 1991; Meachem et al., 1997, 2005; Haywood et al., 2003). The regulation of the two meiotic divisions is poorly understood, although it is recognized that the cyclins and cyclin-dependent kinases may play a major role (Wolgemuth et al., 2002). Spermiogenesis in rodents is testosterone dependent (O’Donnell et al., 1994, 1996a), while spermiogenesis is reliant on both FSH and testosterone (Saito et al., 2000). Beyond the clinical studies indicating dual gonadotrophic control described above, the differential gonadotrophic regulation of these processes in man remains unclear and the relevance of animal data to the human is unproven (McLachlan et al., 2002a).

**Key sites of germ cell maturation sensitive to MHC**

Whatever the relative roles of FSH and LH/T, both are profoundly suppressed by MHC with affects on spermatogenesis that are striking on the sites, extent and variability of the impairment.
Overall data in rodent, monkey and human models indicate that the spermatogenic process is particularly vulnerable at two sites; (i) type A to type B spermatogonia maturation and (ii) spermiation (Zhengwei et al., 1998; McLachlan et al., 2002b; Matthiesson et al., 2005b). Following just 2 weeks of MHC-induced gonadotrophin withdrawal, type B spermatogonial numbers fall together with a concomitant increase in Adark numbers (McLachlan et al., 2002b), suggesting abnormal Apale to B maturation and a transition of Apale spermatogonia to the presumed ‘resting’ Adark subtype. This pattern continues after 6 weeks of gonadotrophin withdrawal (McLachlan et al., 2002b), but by 8 weeks, the increase in Adark numbers is lost (Matthiesson et al., 2005b), suggesting that the number of Apale spermatogonia reverting to Adark may be reduced. At 12 weeks, the number of Apale spermatogonia also begins to fall with the testis relatively able to maintain Adark numbers (McLachlan et al., 2002b).

Impairment of spermiation may in fact be the major determinant of sperm output in both the short and the long terms. The molecular mechanisms involved in sperm release from the Sertoli cell are unclear, although various adhesion and signalling molecules have been localized to the Sertoli–spermatid junction (Chapin et al., 2001). In particular, integrins may be an important mediator of sperm release, because β-1 integrin is apparent between spermatids and Sertoli cells just prior to release, and remains on spermatids that fail to spermiate in a rat model of exogenous androgen administration (Beardsley and O’Donnell, 2003).

Evidence for failure of spermiation, which because of the dynamic nature of the process can only be circumstantial, includes (i) the rapid decline in sperm concentration that cannot be explained by an interruption in spermatogonial maturation, i.e. before 70 days (Meriggiola et al., 1996). Indeed, extremely low sperm output can be seen as early as 4 weeks, which in view of the duration of epididymal transit, indicates a lesion in spermiogenesis and (ii) the presence of elongated spermatids (13–40% control) in testicular biopsy specimens at a time when very few or no sperm are seen in a concurrent ejaculate (0–0.05 × 10⁷/ml) (McLachlan et al., 2002b; Matthiesson et al., 2005b). Figure 2 shows a striking example of the key role for spermiation inhibition in determining sperm output.

Other sites of MHC affect include haploid germ cell survival with particular sensitivity of elongated spermatids and failure of entry into meiosis I with relative preservation of the first meiotic prophase once initiated (Matthiesson et al., 2005b). A recent study using a range of effective MHC regimens found marked interindividual variation in the pattern of germ cell suppression within all treatment groups (Matthiesson et al., 2005b). Analysis of physical, biochemical and seminal parameters showed no significant differences, and yet, the response to MHC treatment as assessed using germ cell number was highly inconsistent. Germ cell subtypes did not correlate with sperm concentration, indicating that this parameter is not a suitable endpoint in understanding treatment effects on germ cell maturation.

**Application of new technologies to the issue of heterogeneous or non-suppression**

The heterogeneity of testicular response to MHC treatment irrespective of baseline characteristics, germ cell subtype, testicular steroids or contraceptive regimen suggests that there are inherent differences between individuals that have yet to be identified. It is unlikely that current treatment regimens will further lower FSH and testosterone levels, and thus, a heterogenous germ cell response with a percentage of non-responsive men will remain. It is possible that these distinctive patterns of germ cell suppression may be because of underlying genetic or post-receptor differences. Given this possibility, technologies such as microarray analysis and proteomics may offer new insights as they have in other fields such as oncology pharmacogenomics (Burczynski et al., 2005). The collection of testicular tissue from otherwise healthy subjects is difficult, particularly repeated sampling, and not without risk (bleeding and infection). The human testis, because of its complex helical arrangement of stages, does not lend itself so easily to techniques such as laser microdissection with pressure catapulting as applied to rodent models (Sluka et al., 2002). However, the effect of treatment on single cell types (e.g. Sertoli, type A spermatogonia) using PALM microdissection, although labour intensive, is likely to be applicable to human tissue.

**Novel therapeutic approaches**

Efficacy studies suggest that MHC regimens may provide acceptable contraceptive efficacy at sperm concentrations below 1 × 10⁹/ml,
but the induction and maintenance of universal azoospermia would avoid any concern about the need for confirmatory testing of spermatogenic suppression and thus markedly enhance MHC viability in the marketplace. Novel contraceptive agents and MHC combinations may be possible based on a detailed understanding of the HPT axis and the intratesticular milieu.

Gonadotrophin suppression or antagonism

Using ultra-sensitive assay methods, serum FSH levels often remain detectable at 1–2% baseline (Robertson et al., 2001). Combined MHC regimens using a progestin, a GnRH antagonist or both appear unable to eliminate FSH from serum in all individuals (Matthiessen et al., 2005a). This raises two questions: firstly, could such low levels of FSH support ongoing spermatogenesis, and if so, could this be eliminated? It is unlikely that inhibit B, a negative feedback inhibitor of FSH in the male (Hayes et al., 2001), will offer a solution, given the potential generalized effects of this peptide. A more targeted alternative may be the development of an FSH receptor antagonist such as the substituted 6-amino-4-phenyl-tetrahydroquinoline derivatives that have shown efficacy in a CHO cell line expressing the human FSH receptor, a rat granulosa cell assay and an ex vivo mouse model (van Straten et al., 2005). However, it should be noted that even complete FSH blockade may fail to provide substantial contraceptive efficacy (Nieschlag, 1986).

Modified androgens with reduced 5α-reduced metabolites

It remains possible that DHT may support ongoing spermatogenesis in the absence of LH and the iT testosterone-depleted MHC environment. There has been considerable interest in modified androgens such as MENT, a long-acting synthetic androgen which is not available for 5α reduction (Sundaram et al., 1993) and thereby avoids unwanted tissue-specific (prostate and skin) amplification which may be of potential benefit.

Previous work in monkeys has shown MENT to adequately suppress spermatogenesis (Ramachandra et al., 2002) with ten times greater potency than testosterone on gonadotrophin suppression and anabolism and comparatively less stimulatory affect on the prostate (Cummings et al., 1998). Human application of MENT has been limited with only one published contraceptive trial using 1–4 MENT acetate implants reporting promising rates of azoospermia in the four implant group over a 12-month period (von Eckardstein et al., 2003). Side effects commonly reported with testosterone use such as raised haemoglobin, haematocrit and decreased sex hormone-binding globulin were also seen.

However, of concern is a more recently published study using 1–2 MENT implants in hpg men over a 6-month period (Anderson et al., 2003). While a number of androgen-dependent parameters such as haemoglobin, haematocrit and to an extent sexual function were maintained, bone mineral density at the lumbar spine fell. This study illustrates that all testosterone effects, including (i) direct via AR activation (muscle), (ii) amplified via 5α reduction (prostate and skin) and (iii) diversified via aromatization (bone and brain) (Handelsman, 2004), need to be considered when designing and dosing with synthetic androgen derivatives. MENT continues to be an attractive androgen in MHC development, but further work is needed on its delivery and dosing, and in delineation of its long-term tissue-specific effects on prostate and bone in particular.

Selective AR modulators and targeting androgen action

Selective AR modulators (SARMs) may hold promise. The unbound AR, a member of the nuclear receptor superfamily, is normally a cytoplasmic protein that upon binding of its ligand transfers to the nucleus where in conjunction with other factors it regulates target gene transcription (Roy et al., 2001). The structure of the SARM-bound AR is the basis by which selective promoter interactions and tissue-specific gene transcription are attempted (Chen et al., 2002). Whilst the potential of tissue targeting is beyond the scope of this review, it is possible to envisage a ‘contraceptive ideal SARM’ that would avoid adverse anabolic effects on the testis (on potential direct stimulatory effects on spermatogenesis), prostate, skin and lipids whilst suppressing gonadotrophins and maintaining bone and muscle health.

Progestins and non-steroidal agents acting on the seminiferous epithelium

The development of agents that directly affects the seminiferous epithelium and germ cell development may provide a mechanism for improving spermatogenic suppression. It is recognized that progestins inhibit 5α reductase activity (Rabe et al., 2000) with an analysis of MHC studies postulating this and other direct progestin effects within the testis (McLachlan et al., 2004); however, direct experimental evidence is lacking. The recent discovery of a membrane-bound progesterone receptor (PR) protein and intracellular PR-A and PR-B mRNA in human germ, Sertoli and less commonly Leydig cells (Shah et al., 2005) is yet to be confirmed. Thus, there is a need for a more in-depth exploration of progestin affect on germ cell maturation, iT steroidogenesis and gene expression, in addition to assessing its effects on non-testicular sites.

It is also possible that non-steroidal agents could be employed to disrupt specific sites in the spermatogenic process. Targeting either haploid germ cells (the processes of meiosis, spermiogenesis and spermatiation) or testis-specific molecules would seem sensible to minimize systemic effects. In this regard, the use of the alkylated imino sugars, N-butyldeoxynojirimycin and N-butyldeoxygalactonojirimycin in mice is of interest. These agents have been shown to reversibly disrupt spermiogenesis (van der Spoel et al., 2002) without compromising genetic integrity (Suganuma et al., 2005). Also of note is that these compounds are currently used in human subjects with inherited metabolic disorders of glycosphingolipid metabolism (Butters et al., 2005).

Acceptability and practical issues

It is unlikely that any currently available MHC treatment will fulfill all the ideals outlined in the Introduction, including offering total contraceptive efficacy. But it is important to keep in perspective that this ought not to preclude its use, as certainty is not provided by any currently available method, including the best female hormonal contraceptive methods and even surgical sterilization. Thus, if we accept less than 100% efficacy as a more reasonable goal, then the minimization of practical problems in MHC administration would seem the key to widespread adoption.

Onset and confirmation of suppression

There is no doubt that the relatively protracted and variable time course of spermatogenic suppression is a disadvantage. In some
men, the time taken to suppress sperm concentrations below a contraceptive efficacy threshold \(<1 \times 10^6/\text{ml}\) has been as little as 4–6 weeks (Meriggiola et al., 1996; Anderson et al., 2002a), but in general, a more certain time frame for the majority of men to adequately suppress would seem to be between 12 and 16 weeks (Bebb et al., 1996; Wu et al., 1999; Anawalt et al., 2000; Kinniburgh et al., 2001; Kamischke et al., 2002; Meriggiola et al., 2002, 2003; Hay et al., 2005; Ly et al., 2005). However, even after 16 weeks, some men will not have reached target threshold, and a percentage of these men may never adequately suppress. This means that there is no certain safe interval from treatment initiation to the cessation of other methods and also suggests the need to confirm semen concentrations before stopping alternative contraceptive methods, raising issues of when and how to screen for adequacy of suppression [formal semen analysis versus the convenience of home testing kits (Morroll et al., 1993) and how to counsel and care for couples in their fertility planning]. Informed consent would dictate that men be told to employ alternative forms of contraception for a period of 3–4 months with an expected failure rate occurring after this time, in a similar way to that following vasectomy.

Semen analysis testing will add a layer of medical supervision, time commitment and cost for the patient that is not inherent in many other contraceptive options. It is also likely to place a greater burden on local medical practitioners because of the high potential for non-compliance with semen analyses after the contraceptive has been administered. An alternative is to decline routine testing of the adequacy of suppression and to accept that a fraction of MHC users will have a contraceptive failure. This may be applicable in some jurisdictions but is unlikely to be acceptable in others, given the fact that perhaps 5% of Caucasian men (although few Asian men) with established prior fertility will be chronic non-suppressors. In such couples, sperm densities above 3 \(\times 10^6/\text{ml}\) will result in pregnancy. Thus, accepting all men without screening of suppression will introduce an unacceptable background failure rate that could jeopardize the early acceptance of MHC.

Secondary escape

Also problematic, following initial spermatogenic suppression, is the reappearance of sperm in the ejaculate (secondary escape) because of inadequate maintenance of gonadotrophin withdrawal. Three previous efficacy studies using androgen-alone regimens have demonstrated secondary escape in approximately 2% of subjects with only one pregnancy a directly attributable consequence (WHO Task Force on Methods for the Regulation of Male Fertility, 1990, 1996; Gu et al., 2003). A fourth efficacy study using a combined androgen and progestin regimen has shown a higher rate of spermatogenic escape (29%; CI, 10–58%) in men receiving testosterone implants 6 monthly compared with no escape in men receiving testosterone implants 4 monthly (Turner et al., 2003), thus underscoring the need for adequate and regular androgen dose.

Previous studies of women presenting with unintended pregnancy have shown a far lower rate of injectable, intrauterine or implantable contraception usage, implying an increase in efficacy with compliance-independent methods (Glasier and Shields, 2006). While ‘the Male Pill’ may be an appealing and readily marketable product, for efficacy (primary failure of suppression or secondary escape), non-oral routes of adequate androgen and progestin dose may well provide greater efficacy and allow for better monitoring of compliance.

Fertility return

For spermatogenic recovery, there is also likely to be a delay of fertility return of between 9 and 16 weeks (Hay et al., WHO Task Force on Methods for the Regulation of Male Fertility, 1990, 1996; Meriggiola et al., 1996; Anawalt et al., 2000; Anderson et al., 2002b; Turner et al., 2003; Brady et al., 2004; 2006; Ly et al., 2005) and particularly so with the use of long-acting agents and progestins. The adequacy of some sperm recovery data can be questioned, as some men who fail to meet early recovery targets may fail to continue participation and not be included in late time-point data sets. Future studies must assiduously follow all men into recovery and use consistent definitions of restoration of sperm concentration and also subsequent fertility.

MHC effects on men with sperm concentrations below \(20 \times 10^6/\text{ml}\) are not defined, as all studies have required subjects to fulfill normal semen analysis according to WHO criteria. Given that a significant percentage of men without a prior reproductive history have sperm concentrations below this threshold (up to 20%) (Andersen et al., 2000), it is essential that future MHC studies consider inclusion of men with suboptimal spermatogenesis. This is an important practical issue in the development of male contraception, as many subfertile men will have conceived children spontaneously and be unaware of their problem, yet present for temporary fertility control. Whether they will recover baseline fertility and at the same rate as men with sperm concentrations >\(20 \times 10^6/\text{ml}\) remains to be clarified.

Pre- and post-marketing surveillance

For safety and tolerability, there are no data on the long-term effects of MHC administration, with most studies reporting 6- to 12-month treatment phases. This raises the need for further phase 3 studies and for subsequent strict post-marketing surveillance of the potential adverse effects on bone, prostate and cardiovascular health induced by MHC products once bought into wider use.

Despite the apparent difficulties, it should be noted that there is much to gain by the development of an MHC. It undoubtedly relieves pressure from the female partner and gives men a greater choice for fertility regulation. Administration of MHC will probably be undertaken by general practitioners, giving them a new point of contact with the younger male population with potential for health screening. It is also possible that the development of MHC products with selective tissue effects may provide significant non-contraceptive health benefits. Direct and indirect costs will be of consideration, but it seems reasonable to expect that products will need to be similarly priced to female alternatives for their widespread adoption.

Barriers

The development of contraceptives for men has some unique problems that are not faced by other therapeutic agents. Firstly, these medications are being used for prevention of conception as
opposed to treatment of a specific disease entity in which the posi-
tive benefits are perhaps more easily quantifiable. These agents
are intended for administration to healthy and in general young
men for presumably long periods of time, and therefore, it is
imperative that their side-effect profile in both the short- and the
long term be well characterized. Also problematic is the conse-
quence of therapeutic failure, unplanned pregnancy, with its per-
sonal and societal burdens. At present, there is no defined
acceptable failure rate, although arguably equivalent efficacy to
that of the female OCP should be realized.

To bring an MHC to market, some innovative strategies that
involve a strong translational approach and close cooperation
between public sector research centres and drug companies. Cer-
tainly, there are collaborations taking place currently that hope-
fully will be productive. Also needed is liability limitation such
that the development of these agents can be seen in the broader
interests of the community. It is as yet unclear what yardstick will
be applied by regulatory agencies, such as the number of couples
and years of exposure that will be required to provide sufficiently
accurate estimates of pregnancy risk for proper product labelling.
Also, what is to be the appropriate contraceptive comparator? Is it
to be the only other reversible male method available to such cou-
ouples (the condom, PEARL index of 12) or the standard for female
contraception (hormonal methods, PEARL index of 3) for the first
year of typical couple usage (Pearl, 1933; Trussell and Kost,
1987)?

Given the success of the female OCP, which sometimes
(although not always accurately) is perceived as a highly effective
and side-effect free contraceptive option, it is likely that some edu-
cation and lowering of expectations for MHC agents will be
necessary. During the process of MHC product development, con-
sumers must be consulted to ascertain their expectations, concerns
and requirements. It must also be remembered that expectations
for MHC will vary, such as between the developed and the de-
veloping world. The former maybe prepared to pay for a more user-
friendly option, whereas the latter may not be in a position to do
so. In the development of these agents, the opportunity to make an
impact on global health must not be overlooked in the pursuit of
profit such that these agents price themselves out of use in the
developing world.

Conclusion

The development of an effective, consumer-friendly male contra-
ceptive is challenging in that it requires strong translational coop-
eration not only between basic scientists and clinicians but also
between public and private sectors. Steroidal based male contra-
ceptive regimens are clinically effective, but there is a need for
greater understanding of their action within the testis together with
further definition of their effects on the reproductive tract and
other body systems. The refinement of currently available thera-
petic options and the development of new targeted approaches
are goals for the future as is the need for MHC trials in larger num-
ers of men with less strict inclusion parameters for longer periods
of time.

Fifteen years have now elapsed since the publication of the first
WHO sponsored trial that showed the suppression of spermatogenesis
to azoospermia could provide comparable contraceptive efficacy
to the female OCP. Since that time, data have been accumulated to
confirm and extend this finding (to oligozoospermic men), and
yet, we seem little closer to bringing an MHC product to market in
the near future. As stakeholders in the reproductive choice of cou-
ouples and men in particular, it is important to critically evaluate the
MHC trials to date. In the light of the accumulating evidence for
efficacy and initial evidence for safety, a commitment is required
to develop and apply MHC in a ‘real world’ clinical setting. Simi-
lar to the evolution of the female OCP for which much informa-
tion was gathered after marketing, a promising MHC method will
become available, but its use will need to come with an acceptance
that definitive data are not available for all questions but rather
will flow from its wider adoption. A structured approach of practi-
tioner and patient education together with strict post-marketing
surveillance would seem ideal for this purpose.

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