Rising to the challenge of male hormonal contraception

MARK GREENER

Despite decades of research, and surveys showing that the majority of men are willing to try it, a reversible male hormonal contraceptive (MHC) has not yet reached the market. There have been many scientific and regulatory barriers to development but recent advances indicate that MHC is at last a realistic prospect.

More than a quarter of couples worldwide depend on male contraception.¹ Yet, vasectomy aside, male contraceptives are not very reliable. The unintended pregnancy rate with condoms, for example, is 15% to 20% a year.² This unreliability probably helps explain why more than half of men might try a male hormonal contraceptive (MHC).³ Indeed, new male contraceptives seem to be popular across all races, religions and ethnic backgrounds.¹

Nevertheless, despite promising results in clinical studies dating back to the 1970s,¹ a reversible MHC has not yet reached the market. “There are many challenges with MHC development,” says Stephanie Page, Robert G McMillen professor in lipid research at the University of Washington, Seattle. In particular, MHCs are not universally effective – for reasons no one really understands. There are lingering concerns over safety, and MHCs do not seem to be priorities for pharmaceutical companies or regulatory agencies.

How MHC works
In healthy men, the hypothalamus releases gonadotropin-releasing hormone (GnRH). The pulses of GnRH trigger, in turn, the pituitary gland to release pulses of the gonadotropins luteinising hormone (LH) and follicle stimulating hormone (FSH). LH stimulates testosterone production in the testes, while testosterone and FSH trigger spermatogenesis. Testosterone from the testes is released into the circulation and feeds back on the hypothalamus and pituitary gland, reducing production of GnRH, FSH and LH (see Figure 1).¹,⁴

Clinical trials to develop a MHC based on testosterone began in the 1970s.¹ The liver metabolises testosterone rapidly, particularly when the hormone is taken orally. So, most studies since the 1970s used longer-acting analogues, such as testosterone undecanoate, which can be administered by injection or implant.

Initially, researchers developing MHCs aimed to totally suppress

---

spermatogenesis (azoospermia). But clinical trials suggested that this was unattainable for many men.¹ Today, researchers aim to reduce spermatogenesis to about one million sperm per ml of ejaculate or less. This ‘severe oligozoospermia’ seems to be associated with failure rates of about 0.6% to 1.0% per year.¹⁵ Professor Page notes that, in clinical trials, 95% of men achieve reductions in sperm counts that are sufficient for effective contraception. “In clinical trials, many MHCs are as effective as the female pill, perhaps even better, and we have tools to determine which men have not achieved adequate sperm suppression,” she explains.

For example, a phase 3 trial found that over six months, monthly injections of testosterone undecanoate produced azoospermia or severe oligozoospermia in 95% of 1045 Chinese men. (A sperm’s development takes about 72 days. So, most men need to take a MHC for two or three months before the full contraceptive effect emerges.) The overall efficacy rate in men whose sperm levels fell below one million sperm per ml of ejaculate was 94%.⁶ Other MHCs have produced similar results.

“What makes the other 5% of men relatively ‘resistant’ to MHC is not known and remains the major final scientific challenge,” Professor Page says. However, in some men, the dose of the testosterone analogue might not have been sufficient high to suppress gonadotropin release. In other men, the concentrations of testosterone might have been high enough to cross the blood-testes barrier and trigger sperm production (see Figure 2). This raises the prospects of a two-dose approach: initially, using high doses of testosterone to rapidly suppress sperm output. A lower maintenance dose could then maintain severe oligozoospermia, but further studies assessing this approach are needed.⁵

Furthermore, the effectiveness of MHC might depend on the man’s racial background. Overall, 90% to 100% of Asian men achieve azoospermia and severe oligozoospermia with testosterone. This compares with just 60% to 80% of Caucasian men receiving the same regimen.² Again, the reason for the discordance is not clear, but might arise from differences in sensitivity of androgen receptors or the metabolism of the hormone, or variations in testicular structure.⁶ Nevertheless, the difference between races can complicate interpretation of MHC trials performed in different parts of the world.²

The need to inject testosterone analogues poses another hurdle. Indeed, John Amory, professor of medicine at the University of Washington, believes that new methods of reversible male contraception will become available “in the not too distant future”.¹ But he admits that the “delivery of steroids is challenging”. Testosterone analogues are usually given by injections and implants. However, in one study, 12% of men receiving weekly intramuscular injections discontinued because of the injection schedule.² Moreover, combination regimens (see below) might mean administering androgens and progestins through different routes and at different times.¹ So, an oral or transdermal formulation might be needed to persuade some men to use MHC.

Combination male hormonal contraceptives
Combination MHC might overcome some of the development challenges. Adding a progestin (synthetic progestogen) to testosterone suppresses spermatogenesis more rapidly and persistently than either alone. Indeed, adding progestins and GnRH analogues to testosterone produces severe oligozoospermia in more than 90% of men.³ Moreover, the combination might contain lower testosterone doses than using the analogue alone, which could reduce the risk of certain adverse events. A progestin’s exact mechanism of action is another aspect of MHC that awaits clarification.¹ However, progestins are pharmacologically diverse. Some progestins suppress LH production. Others seem to directly suppress spermatogenesis.⁸

The ideal combination for MHC is currently being investigated. For instance, a mix of two transdermal gels, one containing Nestorone – a potent progestin that profoundly suppresses gonadotropins, but shows little oestrogenic or androgenic actions – and the other testoster-
one achieved severe oligozoospermia in 89% of men. This compared with 23% using the testosterone gel alone. Serum testosterone remained in the normal range and no serious adverse events emerged. However, some men experienced mild side-effects, including acne, weight gain and a reversible decrease in HDL-cholesterol. Researchers are developing a single gel that contains both Nestorone and testosterone.

More recently, researchers developed orally active drugs with androgenic and progestogenic properties that raise the prospect of a single-agent MHC. In a recent study, for example, 10 men received single, escalating, oral doses of dimethandrolone, which binds to androgen and progesterone receptors. Two men received placebo. Dimethandrolone reversibly suppressed LH and testosterone production. These preliminary results are promising, but it will probably be several years before dimethandrolone reaches the market. “Dimethandrolone doesn’t get around the problem that some men continue to make sperm despite gonadotropin suppression,” Professor Amory notes.

Against this background, Professor Page says that testosterone plus progestins and dimethandrolone seem to be the most promising of the various approaches to MHC. “We have the most experience with these steroids, in both men and women, which provides lots of related safety data. The newer chemical entities, like dimethandrolone, are great as they are single compounds that act through the same mechanisms as testosterone and progestins, which has a lot of appeal for development and ease of administration. In my mind, these are the most promising current agents, particularly if we can deliver them as long-acting, reversible injections.”

**Safety concerns**

Safety remains another challenge, especially as many healthy men will take MHCs for several years. For example, previous studies reported that long-acting injectable testosterone undecanoate and the progestin norethisterone enantate achieved near-complete and reversible suppression of spermatogenesis and was acceptable to many men. However, a recent large study assessing intramuscular injections of norethisterone enantate combined with testosterone undecanoate administered every eight weeks was stopped early due to a high rate of severe adverse events including acne, injection pain, erectile dysfunction and mood changes.8

“There is a lot of current concern about the safety of androgens in men,” Professor Page says. “It is important to emphasise that current male hormonal contraceptives are designed to utilise physiological doses of testosterone.” Professor Amory adds that someone using a hormonal contraceptive will “test positive” in athletic competitions, which could pose an issue for some men. “Acne and mood issues may be side-effects,” he says. In addition, only one placebo-controlled study is available, which makes assessing adverse events difficult.

Moreover, the potential long-term adverse events associated with MHCs – including the long-term cardiovascular and prostate effects – need to be fully characterised. Current data show “no clear indications” of cardiovascular or prostate harm. But this awaits confirmation in large numbers of men, probably once MHCs reach the market. Moreover, oestradiol seems to be important in men to maintain bone mineral density and sexual function. This underscores the need for long-term studies of the synthetic androgens used in MHCs. “MHCs look to be very safe but still require long-term safety data,” Professor Page cautions.
Prescribers might also need to be cognisant of drug interactions. “MHCs, like oestrogen and testosterone, are metabolised by the cytochrome P450 system. So, there might be some minor dose adjustments necessary for some concomitant medications.” Obviously, further studies will need to identify any clinically significant interactions with other drugs.

In addition, sperm counts seem to recover relatively slowly following treatment with testosterone-based MHC: 67% of men seem to attain sperm counts of at least 20 million per ml (which is sufficient for normal fertility) by six months. Recovery rates seem to reach 90% and 100% by 12 and 24 months respectively. The recovery rate seems slower with longer duration of treatment. Nevertheless, there have been no studies of MHCs that lasted more than 30 months.

“I don’t think that the recovery time is a major issue,” Professor Page says. “Many female methods have a longer recovery time and that is not a major impediment to use. The likelihood is that people who are interested in long-acting contraceptives don’t immediately want to have a family and are willing to plan ahead. Granted, a recovery of weeks rather than months might be more desirable, but many men who are at least temporarily ‘finished’ with their family size, or young men, may not care.”

Uncharted territory
Despite their undoubted promise, MHCs aren’t reaching the market, largely, Professor Page says, because of the lack of support from pharmaceutical companies. “I think pharmaceutical companies see these products as too risky to invest in because they are unsure of the regulatory requirements to get them to the market. This makes designing and carrying out the large, expensive phase 3 trials a nonstarter.”

Professor Amory agrees. “Pharmaceutical companies have funded this work in the past – about 10 years ago – but appear to have lost interest in the hormonal approach to contraception,” he notes. “Some industry folks appear interested in our nonhormonal work, however.” For example, researchers realised that vitamin A was essential for sperm development in 1925. Blocking vitamin A’s metabolite retinoic acid – either by antagonising the receptor or inhibiting synthesis – is showing promise as an alternative way to inhibit spermatogenesis. Several reversible barrier formulations are also under investigation.

Against this background, Professor Page calls for guidance from the regulatory agencies – such as the Food and Drug Administration (FDA) in the USA and the European Medicines Agency – to give renewed impetus to the phase 3 studies. “To make that happen, there probably needs to be more public awareness and demand,” she says. “These products are really uncharted territory.”

“The lack of an approved product is the biggest barrier to development or the widespread use of male hormonal contraceptives,” adds Professor Amory. “We also need to counter the stigma around the use of hormones in men.” However, it is likely that once one MHC reaches the market, others will follow.

“Many men would like to control their own fertility and many women are unable to use hormonal contraceptive due to health concerns,” Professor Page concludes. “Unplanned pregnancy rates remain astonishingly high, so people need more options. MHC are effective and seem to be safe; the remaining barriers to a product coming to market are not scientific. Funding and regulatory clarity are required.”

So, some 50 years after the research began, MHC is at last a realistic prospect and, despite the barriers, a formulation will eventually reach the market. But quite when doctors and nurses will be able to prescribe the first MHC remains uncertain.

References

Declarations of interest
Mark Greener is a full-time medical writer and, as such, regularly provides editorial and consultancy services to numerous pharmaceutical, biotechnology and device companies and their agencies. He has no shares or financial interests.

Mark Greener is a freelance medical writer

Share your views
If you have any issues you would like to air with your colleagues or comments on articles published in Prescriber, the editor would be pleased to receive them and, if appropriate, publish them on our forum page. Please send your comments to:

The editor, Prescriber, The Atrium, Southern Gate, Chichester, West Sussex PO19 8SQ, or e-mail to prescriber@wiley.com

prescriber.co.uk