

# An update on the potential for male contraception: emerging options

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**Abstract:** The human population continues to grow and is estimated to rise to 10.1 billion by the end of the century. Therefore, there is still an unmet need for safe and highly effective contraceptive options for both men and women. Current options available to men include withdrawal, condoms, and vasectomy. Methods in development fall into two categories: hormonal and nonhormonal. This review will provide an overview of the testosterone combinations and immunocontraception of hormonal targets. Nonhormonal immunocontraception of sperm proteins will also be examined, together with the use of agents to disrupt other sperm-associated targets and pathways. The categories focused on include epididymal proteins, testicular kinases, epigenetic reader proteins, opioids, lonidamine derivatives, retinoic acid, microRNAs associated with spermatogenesis, and plant extracts. Considering these developments, the number of options available to men is likely to increase in the near future.

**Keywords:** hormonal, immunocontraception, nonhormonal contraceptives

## Introduction

Despite the number of contraceptive methods available, unintended pregnancies still occur worldwide. This is in part due to a lack of appreciation of the unintended pregnancy risk, particularly among teenagers in developed countries where contraception is readily available. However, there is still a worldwide unmet need for more affordable, effective, and practical contraceptives, indicating that further technological advancements or innovations to existing products are required.<sup>1</sup> The oral contraceptive pill for women has had significant impact on societal dynamics and socioeconomic benefits, while the development of male contraceptive options equivalent to female products has proven an elusive goal.<sup>2</sup> The main reason for this is that while sperm production can be controlled by the administration of sex steroids, there is also a decrease in testosterone that requires “add-back” therapy.<sup>3</sup> Nevertheless, while the human population continues to rise – from 7 billion people in 2011 to an estimated 10.1 billion by the end of the century<sup>4</sup> – there is still an unmet need for safe and highly effective contraceptive options for both men and women. Further, expansion of available products allows both partners to share family planning responsibility. Better contraceptive availability and use also has an impact on reducing maternal deaths through preventing high-risk pregnancies and unsafe abortions.<sup>5</sup> This review focuses on emerging options in male contraception and looks at potential future directions.

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## Male contraceptive options

Current options available to men include withdrawal (coitus interruptus), condoms – categorized as behavioral and barrier methods, respectively – and vasectomy.<sup>6</sup> While the withdrawal method is considered unreliable, condom use has increased due to recognition of a need for protection against sexually transmitted infections and few adverse side effects. Current condom developments include the use of newer polyurethane materials, which are thinner, stronger, and less allergenic, and the inclusion of more effective spermicides.<sup>7</sup> In contrast, vasectomy is considered a safe and simple method, but the drawback is that it is not reliably reversible and there is still a <1% chance of unwanted pregnancy.<sup>8</sup>

In recent years, a growing number of new methods have emerged, such as reversible inhibition of sperm under guidance (RISUG), or “Vasalgel”, as an alternative to vasectomy, most of which are still under development. RISUG is in Phase III clinical trials in India and is now also being investigated in the USA. RISUG involves the injection of a polymer into the vas deferens, rather than severing or clamping it, as in vasectomy. The polymer coats the inside walls of the vas deferens and solidifies and anchors itself to the microscopic folds of the inner walls of the vas deferens. As sperm come into contact with the polymer, the combination of positive and negative charges on the polymer damage the sperm, rendering them immotile.<sup>9</sup> It is proposed that the polymer can be removed from the vas deferens, thereby restoring fertility.

Apart from mechanical methods, which have seen few emerging options, new technologies generally fall into two categories: hormonal and nonhormonal. The requirements for the ideal male contraceptive include that it:

- Be acceptable to both partners.
- Be effective (preferably without a lag period).
- Can be applied independently of the sexual act.
- Should not interfere with libido or sexual activity.
- Not have unacceptable side effects (long or short).
- Be fully reversible without impact on subsequent offspring.
- Have equivalent effectiveness to female methods.

A summary of emerging male contraceptive options is given in Table 1.

## Male hormonal contraceptives

Male hormonal contraceptive methods are based on the suppression of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) to decrease testosterone levels. In particular, intratesticular testosterone has to be drastically curtailed to effectively disrupt spermatogenesis.<sup>10</sup> However, circulating testosterone has to be maintained at a particular level to

retain androgenicity and this is usually achieved by add-back therapy.

Testosterone-based therapies have been developed to suppress LH and FSH. Historically, these have included testosterone enanthate (200 mg administered by weekly intramuscular injection)<sup>11</sup> and testosterone undecanoate (1000 mg administered every 4 weeks by depot injection – this is now sold as Nebido® (Bayer Healthcare, Monheim, Germany) for treating hypogonadism).<sup>8</sup> However, since testosterone-only therapies do not achieve azoospermia in all ethnicities (eg, lower response in Caucasians compared with total azoospermia achieved in East Asian men), other fertility disrupting agents are also required with longer lasting effects.<sup>12</sup> Developments included testosterone plus depot medroxyprogesterone acetate (administered at 3-weekly intervals),<sup>13</sup> testosterone plus 19-norethisterone enanthate (administered 8-weekly by injection),<sup>14</sup> and testosterone plus etonogestrel (injection and implant).<sup>15</sup> However, the organizations/firms that initiated this research subsequently abandoned these male contraception programs and the work on them ceased. More recently, combinations of testosterone with gonadotropin-releasing hormone (GnRH) analogs and newer progestogens such as nesterone have been examined. However, the costs of manufacture and need for daily or weekly administration of the GnRH preparations proved prohibitive for further research to be pursued.<sup>12</sup> In contrast, daily use of testosterone/nesterone gel formulations has been shown to suppress sperm levels to  $\leq 1$  million sperm/mL in 89% of men, with few adverse effects.<sup>16</sup> Nieschlag<sup>12</sup> has comprehensively summarized the advantages and disadvantages of the various testosterone and testosterone combination formulations.

A potential androgen for the future, which may enable single-agent development, is dimethandrolone undecanoate (DMAU). This androgen binds to progesterone receptors and can be administered orally or by injection<sup>17</sup> but has yet to be tested clinically.

## Immunocontraception of hormonal targets

Contraceptive vaccines (immunocontraception) against various hormonal targets have been investigated over the last two decades. The most successful of these is currently used to control animal fertility and is based on the neutralization of GnRH (GonaCon™, United States Department of Agriculture, PA, USA).<sup>18–20</sup> Figure 1 shows how immunoneutralization of GnRH affects synthesis of LH and FSH, which in turn affects testosterone production and spermatogenesis. A recent review examined other hormonal targets for male immunocontraception, including immunization against LH

**Table 1** Emerging contraceptive targets

Contraceptive	Mechanism	Target	Commercial possibility	Reversible	Reference
<b>Barrier and vasectomy</b>					
Condom	Sperm barrier	Sperm containment	Yes	Yes	Qureshi and Attaran <sup>7</sup>
Reversible inhibition of sperm under guidance	Vasectomy	Sperm motility	Yes	Yes	Chaudhury et al <sup>9</sup>
<b>Hormonal</b>					
Testosterone	Inhibiting gonadotropin production	Spermatogenesis and testosterone	Possibly	Yes, though may depend on length of time administered	Nieschlag <sup>10</sup> Nieschlag et al <sup>78</sup>
Testosterone combinations	Inhibiting gonadotropin (LH, FSH) production	Spermatogenesis and testosterone	Possibly	Depends on length of time administered	Nieschlag <sup>10</sup>
Immunocontraceptives	Inhibiting gonadotropin-releasing hormone and gonadotropins (LH, FSH)	Spermatogenesis and testosterone	Possibly	Depends on length of time administered	Ferro and Garside <sup>21</sup>
<b>Nonhormonal</b>					
Sperm protein vaccines	Inhibiting sperm function	Sperm motility, sperm–egg binding	Yes: depends on vaccine development	Yes	Naz <sup>32</sup>
Epididymal proteins	Inhibiting sperm function	Sperm motility, sperm–egg binding	Possibly: EPPIN, SEMG I	Unknown	Silva et al <sup>41</sup> Robert and Gagnon <sup>42</sup>
Testicular kinases	Spermatogenesis and fertilization	Disrupt sperm production and fertilization	Unknown	Unknown	Xu et al <sup>47</sup>
Blood-testis boundary	Spermatogenesis	Disrupt sperm production	Unknown	Unknown	Mital et al <sup>34</sup>
Opioids	Hormone production, sperm function	Act at several levels of sperm production and function	Unknown	Unknown	Subiran et al <sup>52</sup>
Lonidamine derivatives	Spermatogenesis	Prevent release of sperm from Sertoli cells	Unknown	Unknown	Cheng et al <sup>54</sup>
Retinoic acid	Spermatogenesis	Disrupt sperm production	Unknown	Unknown	Brooks and van der Horst <sup>58</sup>
miRNAs	Spermatogenesis	Disrupt sperm production	Research stage too early	Unknown	Papaoannou and Ne <sup>60</sup>
Plant extracts	Spermatogenesis	Disrupt sperm production	Unknown: most have shown toxicity	Unknown	Ogbuewu et al <sup>66</sup>
Heat treatment	Spermatogenesis	Disrupt sperm production	Possibly	Yes: for short-term application	Setchell <sup>69</sup>

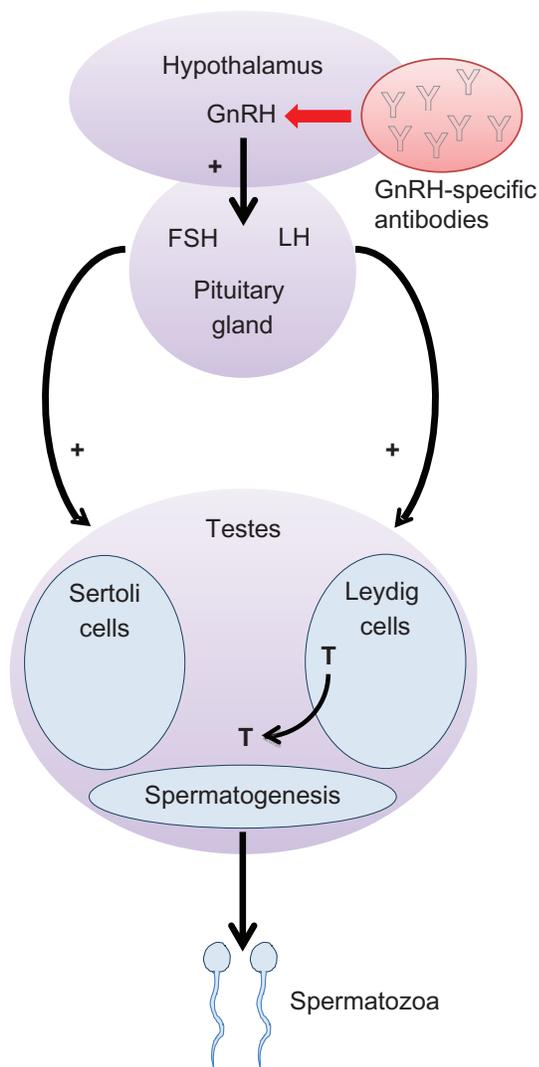
**Abbreviations:** miRNA, microribonucleic acid; LH, luteinizing hormone; FSH, follicle stimulating hormone; EPPIN, epididymal protease inhibitor; SEMG I, semenogelin I.

and FSH, but this work on these gonadotrophins is no longer being investigated clinically for contraception.<sup>21</sup>

### Risks and benefits associated with hormonal contraceptives

Achieving acceptable levels of oligospermia or, if possible, azoospermia, requires intratesticular serum testosterone levels to drop to the hypogonadal range (typically below 350 ng/dL)<sup>8</sup> – this potentially increases the risk of loss of androgenicity, affecting the male sexual organs and characteristics, bone structure, and libido, as well as resulting in negative psychotropic effects.<sup>10</sup> This can be improved by targeting intratesticular testosterone using a dual-action con-

traceptive – that is, combining the addition of testosterone with substances that suppress the secretion of LH or FSH (or both), while replacing systemic testosterone by combining the contraceptive with an androgen. It is believed that by doing so the vast majority of hormonal contraceptives can maintain a high level of efficacy with minimal side effects, although most have not focused on the side effects.<sup>22</sup> The most common of which include acne, suppression of high-density lipoprotein cholesterol, and a slight increase in hematocrit (due to suppression of hepcidin), all of which can be satisfactorily monitored.<sup>23</sup> Other side effects – such as night sweats and decrease in testis volume – are reversible and, although commonly experienced, raise little concern and



**Figure 1** Control of male fertility by immunization against gonadotropin-releasing hormone (GnRH).

**Notes:** Vaccination against GnRH produces antibodies that act by neutralizing GnRH in the hypothalamus, which in turn affects secretion of follicle-stimulating hormone (FSH), luteinizing hormone (LH), and testosterone (T) and, ultimately, spermatogenesis.

are unlikely to result in discontinuation of the treatment.<sup>24</sup> However, as with a large number of hormonal treatments, there is a risk of psychotropic effects, including irritability, anxiety, depression, and an increase in emotionally fragile states – these psychotropic effects can be severe enough to result in the subject withdrawing from the treatment program.<sup>25</sup>

Of course, the side effects vary depending on the contraceptive used and the administration route. Apart from the increase in testosterone levels causing acne, general skin irritation and tenderness is frequently found at the site of injection, patch application, or transdermal preparations.<sup>25</sup> For hypogonadal men, there is a further risk of gynecomastia

(development of larger than normal mammary glands in males).

It should be noted that targeting LH and FSH decreases sperm production but does not affect sperm that have already been produced; therefore, other contraceptive methods must be used until existing sperm have reached maturity and exited the testicles – this typically takes 2–3 months.<sup>26</sup> There is also a delay in return to the male's natural sperm count after discontinuing the treatment<sup>26</sup> – in the case of testosterone plus depot medroxyprogesterone acetate, this delay can last several months.<sup>10</sup> Overall, however, the high efficacy of hormonal contraceptives outweigh the small concerns of side effects. It should also be noted that early concerns about an increase in cardiovascular disease or prostate cancer risk have so far been unfounded.<sup>25</sup>

## Male nonhormonal contraceptives

Research into nonhormonal methods of male contraception are numerous and the focus of this section is on novel technologies that are at various stages of development and/or in clinical trial, thus may be the male contraceptives of the future. Three significant areas of development include (1) the immunization (active or passive) of males with antigens/antibodies that can block sperm function; (2) the administration of site-directed compounds to block spermatogenesis or specific sperm function(s) necessary for normal fertilization; and (3) the administration of herbal extracts or compounds to suppress sperm production and/or function. These approaches, which are noninvasive and aim to be reversible, are discussed in the following sections.

### Immunocontraception: sperm proteins

Immunocontraception against various nonhormonal reproductive targets has been investigated over the last decade. These targets include the successful zona pellucida targets used for animal castration in females (SpayVac™, SpayVac™ for Wildlife Inc, Princeton, NJ, USA).<sup>27,28</sup> Sperm proteins are an attractive target as they are highly immunogenic, having both auto- and isoantigens, are often specific to sperm, and thus do not affect other biological processes. Sperm proteins that have been investigated to date have been chosen especially for their sperm specificity, surface expression, involvement in fertility, and ability to raise high antibody titers that can neutralize fertility components. Antigens that are involved in human immune infertility are particularly attractive candidates. One of the first sperm proteins shown to induce specific serum immunoglobulin (Ig) G antibodies and IgA antibodies in vaginal fluids after administration to female

**Table 2** Sperm proteins under investigation for contraceptive potential in males and females

Sperm protein	Investigator/s	Year
PH-20	Primakoff et al <sup>79</sup>	1988
SP10	Herr et al <sup>80</sup>	1990
ZRK	Alexander <sup>81</sup>	1995
PH30	Vidaeus et al <sup>82</sup>	1997
SP17	Lea et al <sup>83</sup>	1998
CD52	Diekman et al <sup>84</sup>	2000
Acrosin	Howes and Jones <sup>85</sup>	2002
SPAG9	Jagdish et al <sup>86</sup>	2006
SAGA-I	Xu et al <sup>87</sup>	2007
Izumo	Wang et al <sup>88</sup>	2009
ESP	Lv et al <sup>89</sup>	2010
CatSper	Hildebrand et al <sup>90</sup>	2010
Proacrosin	García et al <sup>89</sup>	2012
LDH-C4	Gupta <sup>91</sup>	2012

mice was SP10.<sup>29</sup> Some of the most researched sperm proteins are given in Table 2. As several reviews have provided detailed overviews of the research and status of anti-sperm contraceptive vaccines and details of many of the sperm proteins investigated,<sup>30–32</sup> these will not be addressed here.

The list of sperm proteins being investigated for immunocontraception continues to grow and gene knockout technology has provided an invaluable tool for identifying numerous sperm peptides that may have a role in sperm function. However, many of these have only been investigated in the female for their ability to prevent sperm function within the female reproductive tract (eg, sperm–egg binding, capacitation). Few have been investigated for their ability to inhibit sperm function, such as motility, when administered to the male. This is primarily due to the incomplete understanding of male reproductive tract immunobiology and also to the large numbers of sperm that are required to be neutralized in the male epididymis and testis. The female reproductive tract poses fewer challenges to the successful inhibition of sperm function by an anti-sperm immunocontraceptive, due to the lower numbers of sperm presented in each ejaculate. Recent research has helped to move forward our understanding the immunological roles of both the testis and epididymis and the blood–testis barrier.<sup>33,34</sup> This can only help facilitate the development of contraceptive vaccines for the male.

It also seems that the use of a single antigen in the development of an anti-sperm vaccine may not provide a sufficient antibody response to reliably and consistently block fertility. Researchers are now looking at developing vaccines with more than one sperm protein in a single vaccine design.<sup>35</sup>

In addition, new developments in vaccine technology, such as improved adjuvants<sup>36,37</sup> and DNA vaccines,<sup>38</sup> offer the potential to develop more effective and reliable contraceptive vaccines. Such vaccines have already shown efficacy when administered to male mice,<sup>39</sup> thus may provide a way forward for reliable male immunocontraception.

### Epididymal proteins

The epididymis is the site where sperm maturation occurs and is therefore a reasonable target for a male antifertility product. Spermatozoa become motile and are able to recognize and fertilize an egg once they have progressed through the epididymis. As such, it is desirable to identify targets that interfere with this process and therefore be likely to inhibit sperm function. However, to date, attempts to interfere with either sperm maturation or epididymal function have not been successful.<sup>40</sup> Some potential epididymal targets have been identified using transgenic animals but none has provided effective inhibition of sperm function.

The most promising target is proving to be the epididymal protease inhibitor (EPPIN), a cysteine-rich protein that has antimicrobial properties and is thought to play a critical role in sperm motility. Eppin messenger RNA (mRNA) and the protein itself are found in abundance in both testis and epididymis of rats. Reverse-transcriptase polymerase chain reaction studies have demonstrated that the mRNA is also found in Sertoli and spermatogenic cells. Surgical castration downregulates EPPIN (mRNA and protein) expression levels in the caput and cauda epididymis, an effect that is reversed by testosterone replacement.<sup>41</sup>

During ejaculation, semenogelin (SEMG1) from seminal vesicles binds to EPPIN, initiating a series of events that includes the modulation of prostate-specific antigen (PSA) enzyme activity, provision of antimicrobial protection, causing inhibition of sperm motility.<sup>42</sup> As PSA hydrolyses SEMG1, spermatozoa gain progressive motility. The immunization of male monkeys with recombinant EPPIN resulted in total, but reversible, contraception, demonstrating that it has a key role in male fertility.<sup>43</sup> Currently, compounds that inhibit EPPIN function are being developed to provide additional information on its activities and whether it will become a suitable target for a prospective male contraceptive.<sup>44</sup>

In relation to the EPPIN studies, research has shown that the treatment of live spermatozoa with SEMG1 decreases the straight-line velocity and linearity of human spermatozoa.<sup>45</sup> This occurs in a dose- and time-dependent manner and subsequent treatment with PSA reverses the inhibition of progressive motility. Cysteine 239 of SEMG1 appears to be

critical for binding to EPPIN and inhibiting sperm motility.<sup>46</sup> SEMG1 may also have potential as a candidate target for male contraception.

### Testicular kinases

Recently, there has been interest in testis-specific serine/threonine kinases (TSSKs) as contraceptive targets and, as a result, focus on the development of small-molecule kinase inhibitors, which may inhibit fertility. These kinases and the substrates TSSK1–4, small serine/threonine kinase (SSTK), and testis-specific serine kinase substrate (TSKS) are part of a family that is abundant in the testis and may provide tissue-specific targets for contraceptive development.<sup>47</sup> In rodents, *in situ* hybridization has confirmed that TSSK2, SSTK, and TSKS are post-meiotic in their expression patterns. This makes them possible targets for reversible contraceptive intervention by preserving spermatogonia and spermatocytes. The current research may indicate that high-throughput screening of inhibitors for TSKS phosphorylation could provide targets for male contraception. However, this family of kinases is not strictly testis specific and may, therefore, not be suitable for human contraception.

Another group of kinases that has a role in spermatogenesis is the tyrosine kinases, specifically the Src family and its subfamilies – for example, the Fes-related protein (Fer) subfamily. FerT (the truncated form) regulates actin assembly and disassembly, mediated by phosphorylation of cortactin. It is present in the “acroplaxome,” a cytoskeletal plate containing an F-actin network that links the acrosome to the spermatid nuclear envelope. This finding indicates that Fer kinase may represent one of the tyrosine protein kinases that contributes to spermatid headshaping.<sup>48</sup>

The specific roles of kinases in spermatogenesis and fertilization are a relatively new area of research and more information is required before it will be possible to evaluate if kinases will play a role in male contraceptive development.

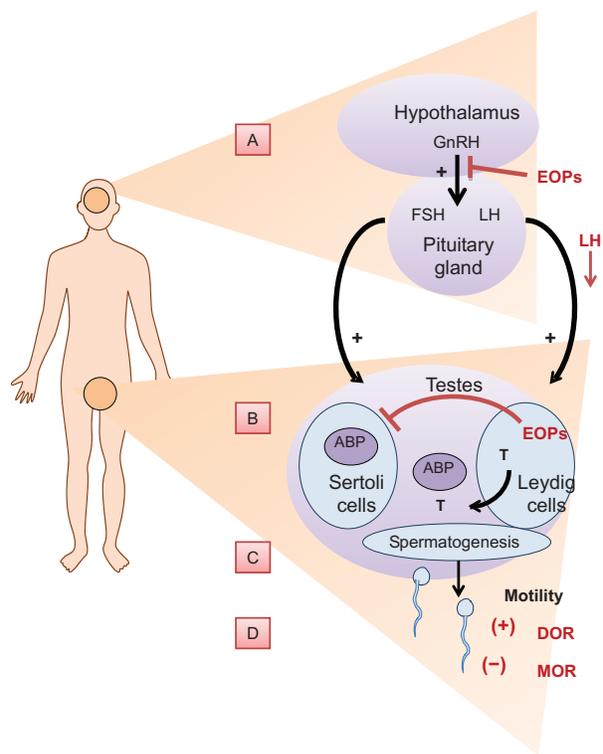
### Blood–testis boundary: epigenetic reader proteins (ERPs)

A new and interesting approach to male contraception has come from advances in the understanding of spermatogenesis at the molecular level. ERPs are involved in the chromatin remodelling of spermatogenesis, particularly bromodomain testis-specific protein (BRDT), a member of the bromodomain and extraterminal family of ERPs. “BRDT” is a tissue-restricted chromatin-associated protein located in pachytene and diplotene spermatocytes and spermatids.<sup>49</sup> It has recently been associated with both azoospermia and

oligospermia in men.<sup>50</sup> Interestingly, it has also been shown that suppression of BRDT function by a small-molecule, bromodomain inhibitor exerts a dose- and time-dependent inhibition on spermatogenesis in mice.<sup>51</sup> Both human and mouse BRDT are highly conserved and seem to have nearly identical bromodomain pockets, indicating that the findings might be able to be translated to human males; this would potentially provide a novel and exciting approach for a small-molecule-based male contraceptive.

### Opioids

Opioids, which comprise part of the neuroendocrine system, are involved in the control of the male reproductive system on several levels. They are involved in the release of gonadotropins from the pituitary (Figure 2A); the function of Sertoli cells in the testis (Figure 2B); and the function and motility of spermatozoa (Figure 2C and D).<sup>52</sup> The opioid system is controlled by endogenous opioid peptides (EOPs), which exert their action through opioid receptors for which the EOPs exhibit different affinities. Within the testis, the EOPs



**Figure 2** Control of male fertility using the opioid system. **(A)** Control of gonadotropin-releasing hormone (GnRH) secretion, which in turn suppresses luteinizing hormone (LH) release; **(B)** control of opioid synthesis by LH in Leydig cells, which inhibits Sertoli cell function and testosterone levels that inhibit production of androgen-binding protein (ABP), which is stimulated by follicle-stimulating hormone (FSH) in Sertoli cells; **(C)** genetic control of opioid precursors that control spermatogenesis; and **(D)** further control of spermatozoa motility via receptors (mu-opioid receptor [MOR] and delta-opioid receptor [DOR]).  
**Abbreviations:** EOPs, endogenous opioid peptides; T, testosterone.

are present in different cell types and appear to intervene in the control of spermatogenesis. Opioid precursors are expressed differentially in testicular somatic and germ cells, suggesting that EOPs regulate testicular function locally by de novo synthesis. For example, LH stimulates production of EOPs in Leydig cells, and these suppress the role of Sertoli cells in a paracrine manner. However, the role of EOPs in germ-line sperm cells is still unknown. In addition, opioid receptors have been located on human sperm, which may indicate that EOPs directly affect sperm function, particularly sperm motility.<sup>53</sup> With further research, EOPs may open up an area of novel contraceptive research and contribute to the development of novel nonhormonal male contraceptives.

#### Lonidamine derivatives: adjudin and gamendazole

Adjudin disrupts adhesion of spermatids to Sertoli cells and, in animals (male rats), weekly doses can induce total infertility 5 weeks after treatment.<sup>54</sup> Similarly, another derivative, H2-gamendazole, has been shown to induce 100% infertility after just one dose in male rats, and it is possible that this compound will progress to clinical trial.<sup>55</sup> However, it will need to show that it does not have long-term effects on the testis and that its contraceptive effect is reversible.

#### Retinoic acid (RA)

It is well established that the sperm production process, “spermatogenesis,” relies on the presence of vitamin A.<sup>56</sup> RA, the active metabolite of vitamin A, is required for spermatogonial differentiation and the production of sufficient numbers of sperm for fertilization.<sup>57</sup> RA binds RA receptors that control gene expression.<sup>55</sup> Certain compounds, such as bisdichloroacetyldiamines (eg, WIN 18446) have been shown to reversibly inhibit spermatogenesis by inhibiting testicular RA synthesis.<sup>58</sup> However, to be a viable contraceptive, they also must not interfere with retinoic function or synthesis in non-testicular tissue. Currently, research is continuing on the development of novel inhibitors of retinoic synthesis that only affect spermatogenesis, but none are currently available.

Further, an RA receptor antagonist, BMS-189453, is also showing promise based on results in male rodents.<sup>59</sup>

#### MicroRNAs (miRNAs) and spermatogenesis

A new and exciting area of male reproductive research is the role of miRNAs in male fertility. The process of spermatogenesis is strictly regulated to enable and maintain the continuous production of spermatozoa. A novel mechanism of the post-transcriptional control of spermatogenesis, mediated by miRNAs, has recently been shown to be an

important regulator of this process.<sup>60</sup> miRNAs are endogenous, small, non-coding fragments produced through a multistep enzymatic process, which involves the action of Dicer (Dcr), an RNase III endonuclease.<sup>61</sup> Dcr plays a key role in the biogenesis of miRNAs. To study RNA interference mechanisms in mammals, the first Dcr knockout mouse was generated by Bernstein et al.<sup>62</sup> In their work, loss of Dcr led to early embryonic lethality and was characterized by almost total absence of embryonic stem cells, showing that Dcr is essential for murine embryonic development.<sup>62</sup>

Following on from these studies, the role of miRNAs in spermatogenesis<sup>63,64</sup> and in Sertoli cell function<sup>65</sup> was investigated. It was found that spermatogenesis was disrupted if miRNAs were absent and the selective ablation of Dcr in Sertoli cells resulted in infertility, due to complete absence of spermatozoa. These experiments have opened up an intriguing aspect of testicular function and paracrine control. Although much more research needs to be undertaken on the role of miRNAs in spermatogenesis, such future work will increase our understanding of male fertility and possibly lead to new areas of male contraceptive research.

#### Plant extracts

Plants have been used for millennia for medicinal purposes, including in prevention of pregnancy and as abortifacient agents. Indeed, the first female oral contraceptive was derived from the roots of the Mexican wild yam.<sup>21</sup> A recent review has examined the effects of different plant extracts on steroidogenesis and spermatogenesis.<sup>66</sup> The most widely researched plants to demonstrate nonhormonal antifertility effects are neem (*Azadirachta indica*) and gossypol, an extract of cottonseed oil. The latter has been studied in more than 8000 men and found to be very effective in producing azoospermia. However, it is very toxic and causes hypokalemia and irreversible infertility as a result of damage to the seminiferous epithelium.<sup>67,68</sup> While many plant compounds have been researched, the quality control, safety, and mechanisms of action of plants have been less well studied. If this hurdle can be overcome, plants could offer a cost-effective source for male contraceptives, which could have relevance in low-income countries.

#### Heat treatment

One method that does not fit into the chemical nonhormonal category is heat treatment. The use of local testicular heat treatment can cause reversible oligospermia or azoospermia via germ cell apoptosis.<sup>69</sup> This method has recently been investigated as a possible male contraceptive. Liu<sup>70</sup> showed

that single exposure of rat or monkey testes to a temperature of 43°C resulted in specific and reversible damage to the seminiferous epithelium. Local warming (30 minutes/day for 2 days) of monkey testes at 43°C showed that the sperm counts in the semen decreased by up to 80% at 28 days; further, this effect was reversible. In addition, when heat treatment was given in combination with a testosterone implant, the sperm count dropped to zero within 2 months. Withdrawal of the testosterone caused the count to recover to normal levels after 2–3 months. As such, this research has provided a theoretical, though perhaps impractical, basis for designing a combined male contraceptive.

## Acceptability

For the past 50 years, researchers and family planning organizations have focused on female methods of contraception in the belief that women bear most of the health and economic impact of childbearing and child raising. However, since the mid-1990s, there has been a change in attitude and it is now recognized that contraceptives should be developed for both men and women.

The acceptability of male contraception can be measured by the prevalence and continuation of use of a particular method. Men are mostly involved in decisions of pregnancy prevention methods when part of a married or in-union couple and male contraceptive methods account for about 26% of the global contraceptive prevalence.<sup>71</sup> Historically, the male methods of withdrawal and periodic abstinence have been the only contraceptive methods used and accepted by men<sup>72</sup> and although these methods are still currently in use by almost 35 million couples around the world, it appears that prevalence is dependent on cultural, religious, economic, and relationship status. These methods comprise only 6.6% of the contraceptives used in the world today.<sup>73</sup>

Condoms and vasectomy are so-called modern methods of contraception that are accessible to men. While use of condoms has increased, vasectomy has decreased in some countries due to the advent of female sterilization.<sup>74</sup> Differences can be seen between regions of the world, with 17.8% of male condom use occurring in more developed regions compared with 6.9% in less developed regions.<sup>73</sup> There are also variations in prevalence of male condom use within regions. For example, considering more developed regions, male condom use in Hong Kong and Japan, accounts for 50% and 40%, respectively, of all the contraceptive measures used in these countries, while it accounts for only 1.1% in Germany.

Similarly, the percentage of use in less developed regions varies from 15.5% in Botswana to 0.2% in Samoa.<sup>73</sup>

Worldwide, vasectomy accounts for about 2.4% of all used male contraception methods. It is most preferred in more developed countries and educated communities; for example, more than 20% of men in Canada and the UK choose it for preventing pregnancy. However, again, prevalence varies across regions; in Germany, for example, this method accounts for only 0.5% of all contraceptive methods used. Prevalence is much lower in less developed countries, with almost no men in African countries, for example, opting for surgical sterility.

All reported acceptability data have been based on trial surveys carried out among young men and their partners. A male pill or injection has been reported to be considered very acceptable by both men and women, as it may increase choice of reversible sterility methods.<sup>6</sup> Further, more than three-quarters of men who participated in hormonal contraception clinical trials from six different cultural settings reported their intention to definitely or probably use such methods in the future when available.<sup>75</sup> In another study, men and women were interviewed in Edinburgh, Shanghai, Hong Kong, and Cape Town and between 44% and 88% of men stated that they would use a daily contraceptive pill. In contrast, most women (70% [from Hong Kong] to >90% [Cape Town and Edinburgh]) thought it was a good idea and only 2% said that they would not trust their partners to take the male pill.<sup>75</sup> A wider survey in nine countries over four continents consisting of 9000 men aged 18 to 50 years indicated that >55% would accept use of a male contraceptive method and that the most preferred method was a daily oral pill, the second most preferred method was monthly injection, then yearly implant.<sup>76</sup> Studies have also shown that although men have an increasing knowledge of the male contraceptive choices available to them, they may not use these methods.<sup>77</sup> Education, cultural and religious beliefs remain hurdles to acceptability.

## Future prospects

From the overview of methods in development provided, the most promising new method appears to be RISUG as an alternative to vasectomy. However, this method may not be widely accepted (given the current prevalence of vasectomy for contraceptive purposes) and require specialist application. In the short-term, the likeliest method to be made readily available and be widely accepted would be a hormonal contraceptive pill. However, without commitment to a daily regime, this method would prove ineffective if compliance were compromised. Long-term, research into

suitable targets for immunocontraception may well provide a source for new-generation male contraceptive products such as those administered via mucosal vaccination. Vaccination removes the need for a daily regime, while the mucosal route potentially allows for self-administration.

## Conclusion

In the near future, the choice of male contraceptive methods may increase. However, the availability of more male contraceptive methods is insufficient by itself. There is also an urgent requirement for governments and non-government organizations to break the gender imbalance concerning contraceptive usage that exists globally, and which continues to be an obstacle to effective population control. The introduction of hormonal contraception for women was seen as revolutionary in that it empowered women and provided them with the opportunity to control their fertility. However, the success of female hormonal contraception, particularly in the developed world, has in many ways been detrimental and has perpetuated the view that contraceptive responsibility and its associated health and financial burdens remain with women. Although this has been considered to provide women empowerment and equality, which may no doubt be true, it has until recently stifled innovation in male contraception, with the focus of continued contraceptive development and adoption placed on females. Perhaps it is time for males to accept that male reproductive autonomy could also be empowering for them as it has been for women and is a valid price to pay for sexual liberalization. More widely, it also provides males with the opportunity to jointly accept and contribute to population control.

With regard to the commercial production of novel male contraceptives, the current consolidation of pharmaceutical companies has reduced competition and this has been compounded by the loss of profitability of many contraceptives due to short-lasting patents. Health care reforms – such as those in the USA – may also further discourage new product development. However, the creation of new contraceptives may still be possible through the efforts of small start-up companies, philanthropic foundations, and governmental research enterprises.

Progress is being made in terms of new hormonal and nonhormonal drug targets, as evidenced by the increase in published studies, even in the last year. While the global economy is in recession, there is an even greater need for increasing the availability of cost-effective and safe contraceptive options.

## Disclosure

The authors report no conflicts of interest in this work.

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