Non-Pharmaceutical Male Contraception

Technology Opportunity Assessment

Prepared for the Merck for Mothers Program
Non-Pharmaceutical Male Contraception

Summary

For men interested in methods they can use to prevent pregnancy in their partners, the only contraceptive options available are male condoms or vasectomies. However, new technologies are currently in development, such as RISUG (reversible inhibition of sperm under guidance) in which a clear gel is injected into the vas deferens to inhibit sperm function.

Statement of Need

Improving access to effective family planning methods offers numerous health and development benefits to women and families. Research suggests that between 1990 and 2005 an estimated 1.2 million maternal deaths were averted because of declining fertility, largely due to increases in contraceptive use.\(^1\) Family planning improves maternal health by reducing births among women who are too young or too old, births that are too closely spaced, and high parity births (4 or more births). Use of family planning also contributes to broader health and development goals; improved educational and employment opportunities for women; and easier achievement of social and economic development goals. Use of family planning methods also has an impact on other health outcomes. For example, increased use of condoms for contraception reduces transmission of HIV and other sexually transmitted diseases.\(^2\)

Globally, more than 215 million women have an unmet need for contraception.\(^3\) An estimated 31 million women in India\(^4\) and 35 million women in sub-Saharan Africa have an unmet need to space their pregnancies (spacing) or to stop having children altogether (limiting).\(^5\) Based on women’s preferences, unmet need for spacing is higher than unmet need for limiting in sub-Saharan Africa, while in India the unmet need for limiting is slightly higher than unmet need for spacing.\(^6,\)*

Many factors influence the use of family planning methods for both women and men including cultural norms, religion, poverty, lack of access to information and services, provider bias, and spousal or familial disapproval. Some contraceptive users find available contraceptive methods to be unacceptable, while others confront challenges using a method consistently because of limited availability of supplies and services. In many developing countries donors pay for a significant proportion of the cost of contraceptives, which means that funding constraints further limit contraceptive supply levels.

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\(^{*}\) MEASURE DHS Demographic and Health Surveys use the following definitions of unmet need, spacing, and limiting in all country reports. "Currently married women who are not using any method of contraception but who do not want any more children are defined as having an unmet need for limiting; those who are not using contraception but want to wait two or more years before having another child are defined as having an unmet need for spacing."
At a minimum, any contraceptive method should be safe for the user, effective at preventing pregnancy, and have minimal and acceptable side effects. Ideally, each user should also be able to select a method that suits his or her personal preferences and lifestyle. Most contraceptive methods focus on controlling women’s fertility. A woman’s fertility cycle offers more and easier points to control. Male methods tend to have a more singular focus on preventing sperm from leaving a man’s body, blocking it from entering a woman’s body, rendering sperm immotile or interfering with the sperm’s ability to fertilize an egg. Despite more than two decades of research on birth control methods for men, few options exist. Many men are interested in methods they can use to prevent pregnancy in their partners. Research over the past decades points toward methods that may soon become available that men can use for family planning.

Technology Solutions Landscape and Gap Analysis

Many men express interest in trying male contraceptive methods, especially methods that are reversible. Yet currently, the only contraceptive options for men are male condoms or vasectomies (permanent male sterilization). A vasectomy is a surgical procedure in which the vas deferens (tubes that carry sperm from the testicles to the seminal vesicles) are cut, tied, cauterized (burned or seared), or otherwise interrupted.

As illustrated in Table 1, at this time only 2.4% to 5% of married couples of reproductive age worldwide have used vasectomies as their contraceptive option. The highest prevalence is in North America (Canada and the United States), Western Europe (the United Kingdom), Oceania (New Zealand and Australia), and Asia (China, Bhutan, and the Republic of Korea). Because of the many vasectomy users in China, Asia accounts for 77% of all male sterilization users.

<table>
<thead>
<tr>
<th></th>
<th>Male Sterilization</th>
<th>Female Sterilization</th>
</tr>
</thead>
<tbody>
<tr>
<td>World</td>
<td>2.4%</td>
<td>18.9%</td>
</tr>
<tr>
<td>Canada</td>
<td>22%</td>
<td>11%</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>21%</td>
<td>8%</td>
</tr>
<tr>
<td>New Zealand</td>
<td>19.5%</td>
<td>14.6%</td>
</tr>
<tr>
<td>Republic of Korea</td>
<td>16.8%</td>
<td>5.9%</td>
</tr>
<tr>
<td>Australia</td>
<td>13.7%</td>
<td>15.9%</td>
</tr>
<tr>
<td>Bhutan</td>
<td>13.6%</td>
<td>3.1%</td>
</tr>
<tr>
<td>United States</td>
<td>12.7%</td>
<td>23.6%</td>
</tr>
<tr>
<td>China</td>
<td>4.5%</td>
<td>28.7%</td>
</tr>
<tr>
<td>India</td>
<td>1.0%</td>
<td>37.3%</td>
</tr>
<tr>
<td>Uganda</td>
<td>0.1%</td>
<td>2.4%</td>
</tr>
<tr>
<td>Zambia</td>
<td>0%</td>
<td>1.9%</td>
</tr>
</tbody>
</table>

In most countries in Africa, Eastern Europe, and Latin America, vasectomy rates rarely exceed 1%. The level of male sterilization is lower than female sterilization in all countries except the United Kingdom,
Canada, Republic of Korea, Bhutan, and New Zealand. According to a Centers for Disease Control and Prevention publication, “If both [sterilization options] were equally acceptable to couples, vasectomy would be medically preferred because it is a comparatively minor procedure, more effective in the long run, and less costly.”

A 2004 study in Tanzania highlighted six overarching factors contributing to actual and potential vasectomy clients’ and their partners’ decision to have a vasectomy:

1. Economics.
2. Spousal influence.
3. Religion.
4. Provider availability and reputation.
5. Future uncertainty.
6. Vasectomy knowledge and understanding.

Fear of impotence and the equation of vasectomy with castration have been reported in multiple studies. Past research has also addressed such barriers as wives’ concerns about the sexual functioning and physical strength of their husband after the procedure. There is evidence that the low use of vasectomy is also because many health professionals fail to make information and services available and accessible. Evaluations in Latin America and Africa have shown that where providers and the media promote vasectomy and provide quality services, the number of vasectomies increases.

Of available vasectomy techniques, the no-scalpel vasectomy (NSV) is becoming the standard around the world. Unlike a traditional vasectomy, the NSV uses forceps and a clamp to gain entry into the vas deferens. The NSV was developed in China in 1973 and has been widely studied and promoted since then. By the mid-1980s, the World Health Organization (WHO) and the Association for Voluntary and Safe Contraception had adopted and recommended the procedure. Since then, over one million procedures have been performed in North America using NSV and nearly 20 million in China. NSV advantages include fewer complications, less pain during the procedure, and earlier resumption of sexual activity after surgery. Because it requires no incision, it is believed to decrease men’s fears about vasectomy. The procedure time is also shorter than other vasectomy techniques when performed by a skilled provider.

There are variations on how the vas deferens can be occluded (to obstruct or close the passageway such that sperm from the testes do not enter the seminal stream). According to the K4Health publication Family Planning: A Global Handbook for Providers:

“Most procedures use ligation and excision. This entails cutting and removing a short piece of each tube and then tying both remaining cut ends of the vas deferens. This procedure has a low failure rate. Applying heat or electricity to the ends of each vas (cauterizing) has an even lower failure rate than ligation and excision. The chances that vasectomy will fail can be reduced further by enclosing a cut end
of the vas deferens in the thin layer of tissue that surrounds the vas (fascial interposition) after the ends have been tied or cauterized."

Vasectomy is effective, but some men have expressed interest in using a male contraceptive method that is more easily reversible. An alternative to vasectomy has been in development for over 30 years in India through the work of scientist Sujoy Guha.† The RISUG procedure involves injecting a clear polymer gel into the vas deferens, which then coats the inside walls and inhibits sperm function. The RISUG-injected male will still ejaculate millions of sperm; however, the vast majority of sperm will be unable to fertilize an egg. The mechanism of action is unclear; it may be the polyelectrolytic nature of the polymer gel that induces a surface charge imbalance on the sperm membrane system leading to the leakage of enzymes essential for fertilization.15 The contraceptive action appears to be reversible by flushing the vas deferens with another injection. This reversal procedure has been successful on non-human primates but is yet to be proven on humans.16

Much of the data available regarding RISUG is from the clinical trials in India involving approximately 250 male volunteers over the past 20 years. One unplanned pregnancy has been reported among the partners of the 250 men who have been injected using the RISUG procedure.‡,17

RISUG has been in Phase 3 clinical trials in India since 2002. Trials have been delayed multiple times for a variety of reasons.§ Currently extended Phase 3 clinical trials, which resumed in April 2007 after a delay, are under way at six centers with four more centers on board soon. If the trial has positive results, RISUG can begin India’s regulatory approval process. Limited monitored marketing of RISUG in parallel to the Phase 3 clinical trial is also under discussion. Dr. Guha has proposed both a study of reversal after six months and a study of reversal in some of the men who have had it for many years, but these studies are still in the approvals process.15

The Parsemus Foundation (based in the United States), led by male contraception advocate Elaine Lissner, licensed the RISUG technology for use outside of India and is pursuing approval of the procedure as a medical device through the US Food and Drug Administration.18 It has been rebranded under the name Vasalgel™, and a new company has been formed, the Vasalgel Development Corporation.** The Vasalgel Development Corporation has produced a batch of the polymer gel (SMA/DMSO compound) in a certified pharmaceutical plant in the United States. They have completed toxicology testing and begun a rabbit study of Vasalgel performance against critical benchmarks for effectiveness and safety. The goal was to start clinical trials in 2012, with Vasalgel on the market as an

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† Sujoy Guha is chair professor at the School of Medical Science, Indian Institute of Technology Kharagpur and at the National Institute of Medical Science and Technology, Kharagpur.
§ The Indian Council for Medical Research has reviewed the toxicology data three times and approved it each time. However, in February 2002, WHO scientists stated that the 25-year-old toxicology studies did not meet more recent international standards. RISUG was submitted for a new round of tests at a US laboratory; it was approved in July 2005. In March 2006, the trial was slated to resume at four centers around India but a manufacturing delay halted progress. The pharmaceutical company making RISUG was able to deliver a batch produced to WHO’s Good Manufacturing Practice standards in March 2007. [http://malecontraceptives.org/methods/risug.php]
** The Vasalgel Development Corporation is a newly established, for-profit company with a focus on sustainability-seeking investors.
alternative to vasectomy as early as 2015. Later studies would be conducted to support reversibility rather than delaying the initial rollout.

The gaps and challenges to bringing RISUG and Vasalgel to market, either through the ongoing efforts in India or through the Vasalgel Development Corporation’s US-based efforts, include the following:

- **Clinical trials.** In India, more volunteers are needed for extended clinical Phase 3 trials of RISUG; in the United States, researchers are waiting for results of the initial rabbit study to begin clinical trials for Vasalgel.
- **Manufacturing.** Unclear ability of current producers in either location to scale polymer and syringe production.
- **Distribution.** No identified partners indicated.
- **Funding/financing.** Uncertainties concerning capital available to support the product through the next critical stages to market introduction.

**Investment Opportunity**

Two distinct investment opportunities could be considered: (1) supporting RISUG development for the Indian market and (2) supporting the Vasalgel Development Corporation for other global markets.

With regard to RISUG, an investment would enable the launch and expansion of this procedure within India:

- Fund gaps in financing for ongoing clinical trials and new studies related to reversibility (longitudinal); undertake work for the regulatory approval.
- Support for scaling up manufacturing, setting up distribution, developing marketing, and establishing training programs.

With regard to the Vasalgel Development Corporation:

- Invest in Vasalgel to complete development and primary regulatory approval and reduce the critical cost of administration (injection system), with an initial focus on the United States and European markets (then other global markets).
- Provide financial support to the global approvals (major market reference approval and developing-world approvals), supply/distribution capability, and entry at a price sustainably affordable for the developing world. This support would also enable the setup of regional high-volume treatment/training centers as well as demand generation to raise awareness of the new procedure in the population.
References


