INJECTABLE HA-HYDROGELS FOR MALE CONTRACEPTION

NAVIGATING SOCIETAL ATTITUDES TOWARDS MALE FERTILITY CONTROL

A Thesis Prospectus
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By
Samir Muhammad

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On my honor as a University student, I have neither given nor received unauthorized aid on this assignment as defined by the Honor Guidelines for Thesis-Related Assignments.

ADVISORS

Catherine D. Baritaud, Department of Engineering and Society

Steven R. Caliari, Departments of Chemical Engineering and Biomedical Engineering

The United Nations Population Fund (UNFPA) records around 121 million unintended pregnancies across the world each year, indicating a global crisis (2022). The global sexual health agency reports "profound consequences for societies, women, and girls" resulting from the family planning crisis, with over 45% of unintended pregnancies ending in unsafe abortions sometimes causing maternal death (para. 2). Worldwide, this crisis is attributed to a variety of factors including gender inequality and a lack of contraceptive options for women and men alike. University of Virginia researchers Khourdaji et al. argue that the rapid increase in the Earth's population calls for more effective methods of contraception, and while there are numerous contraceptive choices for women, the researchers conclude that "methods of contraception for the male partner are limited to condoms and vasectomy" (Abstract section). These currently used methods of male contraception are inadequate amidst a global crisis, as condoms have a failure rate of 3%, and vasectomies are less utilized due to their low chance of reversibility. The socioeconomic implications stemming from the global family planning crisis mandates the need for an effective male contraceptive.

The proposed technical project and STS research project are tightly coupled, and will address an issue the lack of a concrete male contraceptive presents. The technical project will outline the development of a novel solution to the problem through the design of an injectable hyaluronic acid (HA) hydrogel into the ejaculatory ducts as a means of blocking ejaculation. In light of the absence of a widely available male contraceptive causing female partners to "unequivocally shoulder the primary responsibility for family planning" (Introduction section, para. 1), the STS research portion proposed in this prospectus aims to analyze global societal attitudes in relation to male fertility control in an attempt to explain the lack of a contraceptive.

Along with a deep knowledge of foundational scientific literature in the topic of male contraceptive, laboratory experimentation and medical engineering design will be needed for the project. This independent project will be conducted over two semesters with a review of previous scientific journal literature and a completed concept design done in Fall 2022, with a finished STS paper and novel product in Spring 2023. This project is supervised by Steven Caliari, aligned with the Departments of Chemical Engineering and Biomedical Engineering.

INJECTABLE HA-HYDROGELS FOR MALE CONTRACEPTION

At the forefront of the movement to develop a male contraceptive are hormonal methods – contraception that aims to suppress the production of sperm by interrupting "a naturally occurring hormonal feedback loop, the hypothalamic pituitary-gonadal (HPG) axis" (Abbe et al., 2020, Mechanisms of Male Contraception section). Hormonal male contraception has advanced further in testing than other novel methods of male fertility control, with androgen and progestin synthetizations demonstrating efficacy and potential reversibility in clinical trials. Abbe et al. argues that this slow progression of the hormonal method is plagued by a lack of pharmaceutical investment emanating from prominent side effects monitored in clinical trials, as well as shortfalls in the confidence of their reversibility. The heavy implications from current hormonal male contraceptives in development come in the form of decreased sexual libido and severe depression as side effects (Abbe et al., 2020, Testosterone-based Contraceptive Efficacy Trials section). This imposes a negative influence on funding prospects from pharmaceutical companies, suggesting that an FDA-approved contraceptive for men is distant whilst accidental pregnancies annually increase.

Guided by Professor Steven Caliari, Principal Investigator of a research lab specializing in biomaterials at the University of Virginia, this independent technical research project will explore a nonhormonal avenue of male contraception. This novel idea will encompass the development of a biocompatible injectable hydrogel, ultimately to be placed into the ejaculatory ducts of the male reproductive system to prevent the efflux of semen. As depicted in Figure 1, a hydrogel is formed *in situ* as a result of a precursor polymer combined with physical and chemical crosslinkers (Kharkar and Kloxin, n.d). The use of injectable hydrogels as a form of male contraception has been developed in prior art, most notably by the Charlottesville-based biotechnology company Contraline. Contraline's product ADAM™, along with Vasalgel™ being developed by the Parsemus Foundation, are vas-occlusive devices that block the transport of sperm in the vas deferens (Khourdaji et al., 2018).

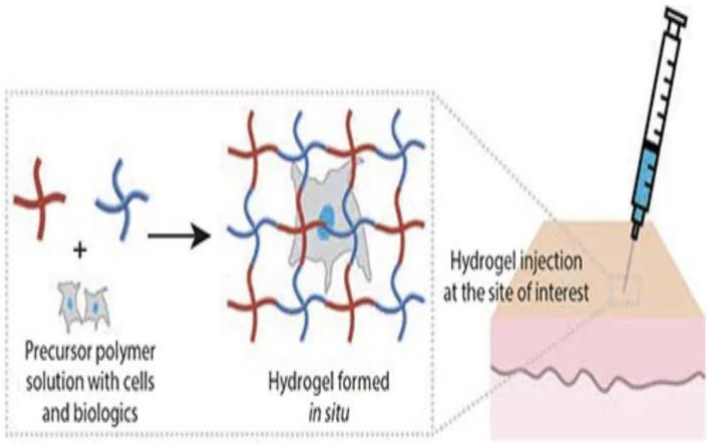

Figure 1: Injectable hydrogel synthetization. The hydrogel is first prepared with a precursor polymer solution and crosslinked, then can be injected into a site. (Kharkar et al., n.d)

According to Park et. al (2019), the integration of hyaluronic acid (HA) in injectable hydrogels show "good capacity for water absorption" (Introduction section, para. 6), suggesting proficient efficacy and reversibility in the idea. The authors claim that HA is commonly used in the synthetization of biomaterials, due to its biocompatibility, low levels of toxicity, and minimal inflammatory properties. The hydrogels to be used in this project will be crosslinked with the

copolymer styrene maleic anhydride (SMA), which is shown to be effective in acting as a long-term contraception (Lohiya et al., 2001). Bettahar et al. have also shown styrene maleic anhydride to have high biocompatible properties and low toxicity in their experiment designing hydrogels with SMA. The copolymer HA will be solved in an acetone/dimethyl formamide mixture along with the crosslinker SMA, and allowed to react for 3 days as in the Bettahar et al. experiment.

Unlike the contraceptives produced by Contraline and the Parsemus Foundation, the technical design outlined in this prospectus is designed to be implanted onto the ejaculatory ducts in the urethra. According to researchers at the University of Colorado Richard E. Jones and Kristin H. Lopez (2015), the vas deferens is a tubular structure in the male reproductive system with a lumen of only 5mm across. This may make it difficult for surgeons to accurately place the hydrogel which would be easier to apply in the area where the vas deferens leads to, the ejaculatory ducts in the greater prostate urethra area. The prostatic urethra is the most dilatable part of the ejaculation canal, and is wider in the middle at a total length of 3 cm long (Henry Gray et al., 1918). The larger size in comparison with the vas deferens is paired with an approach to access the ejaculatory ducts outlined by Faure et al. in 2018, involving the use of an endoscopic injection at the site of the verumomantum located in the posterior urethra.

The intended outcome of this project is a hydrogel exhibiting good swelling ability that could be used to induce azoospermia, a lack of semen. Ultimately, the hydrogel should be implanted into rat models to observe its ability to occlude the ejaculatory ducts, and then tested in human clinical trials. The research will be conducted in the Caliari Lab at the University of Virginia and compiled into a scholarly article to be published in a scientific journal.

NAVIGATING SOCIETAL ATTITUDES TOWARDS MALE FERTILITY CONTROL

Support for a male contraceptive from government agencies comes with a weak infrastructure for drug development and a lack of interest from pharmaceutical companies due to side effects and liability concerns (Wang, 2022). The lagging development of a solid male contraceptive is compounded with wildly varying perspectives on its need and potential use. Published in 2005, German health researchers Heinemann et al. conducted a multinational survey of men and women to gauge their perspectives on male fertility control (MFC) claiming that although male hormonal birth control had been considered for years, "only now have MFC products reached a stage of development sufficient to enter Phase II trials" (Introduction, para. 3). Seventeen years have passed since the survey was published, making the absence of a male contraceptive on the market still a question to be answered. The authors found "a more 'paternalistic' view which may be particularly present in Latin American society" (Discussion section, para. 4) with 8-12% of stating that they alone would make the decision to use male contraceptives. In addition to this, Heinemann et al. cite that the majority of Muslims and Buddhists would not try a new method of male fertility control (MFC) compared to Christians, indicating a diverse geographical and cultural shift in attitudes toward MFC. These results suggest a patriarchal standard of women being primary child caretakers and upholding the sole responsibility of family planning, an idea shared by Journalist Raizel Joleigh of the Male Contraceptive Initiative (2020) that modern society has socialized some women into believing they should "have to bear the fruit of their actions" (A Matter of Trust section, para. 1).

Kim et al. attempt to frame the deep chasm in attitudes pertaining to MFC using a social network through a study conducted in Benin, Nigeria. The authors find innate gender roles and power imbalances sustaining socioeconomic boundaries that contribute to the family planning

crisis, such as men not wanting to seem less masculine as a result of having less children and women afraid of being labeled as promiscuous by the community. In addition to this, writer for The Guardian Moira Donegan (2019) argues that many men are against male contraception options like condoms and vasectomies, either because of the diminishing of pleasure for them or that "the procedure will inhibit their bodies' ability to create and absorb testosterone, rendering them effeminate" (para. 10). Coupled with the results of the study conducted by Kim et al., an ingrained stigma around sexual reproduction, reinforced by gender roles, is visible in global societies.

Who is involved in the development of a male contraceptive? While the technical project introduced in this paper attempts to provide a solution to absence of a male contraceptive, an analytical framework should be implemented to understand its implications in a nuanced society. This analysis will be done through the use of the Social Construction of Technology (SCOT), first developed by Wiebe Bijker and Trevor Pinch in 1984 (Bijker, Hughes, and Pinch, 1987; Bijker and Pinch, 1984; Kline & Pinch, 1999). As depicted in Figure 2, the engineer at the center of the novel technology is influenced by social groups that provide a prospective into the development of the

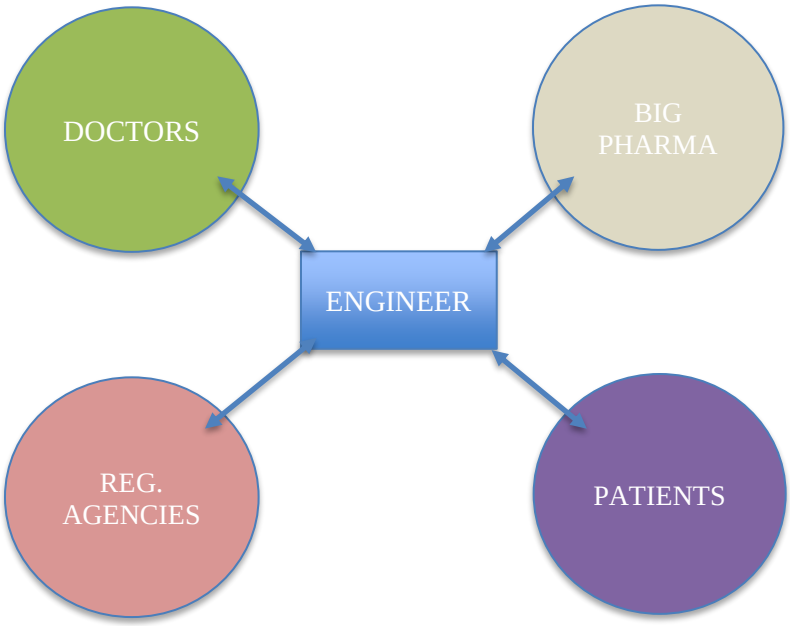

Figure 2: Male Contraceptive SCOT Model. The engineer in this model is tasked with considering the concerns and interests of social groups involved in the design process. (Muhammad, 2022)

technology. In turn, the product designed by the engineer has an impact on the social groups that affect it, ultimately mirroring their interests. For a male contraceptive to be effective in its implementation, the concerns of all actors involved in the development process must be taken into consideration. Engineers not only have to design a product that effectively halts contraception to remedy the unintended pregnancy crisis, but they will have to do so in a way that increases the low funding from pharmaceutical companies to fund the project (Vahdat et al., 2020). Funding prospects can positively or negatively impact the efficacy of development, leading to further implications for analysis from doctors, patients, and regulatory bodies like the FDA.

The human centered design (HCD) process is a tool used to understand the clientele for which a technology is being developed for, and as described by Vahdat et al., it can be used by engineers as a "process of identifying the challenges facing their product development efforts" (Materials and Methods section, para. 2). In Figure 3, HCD is seen as a five-step process that can

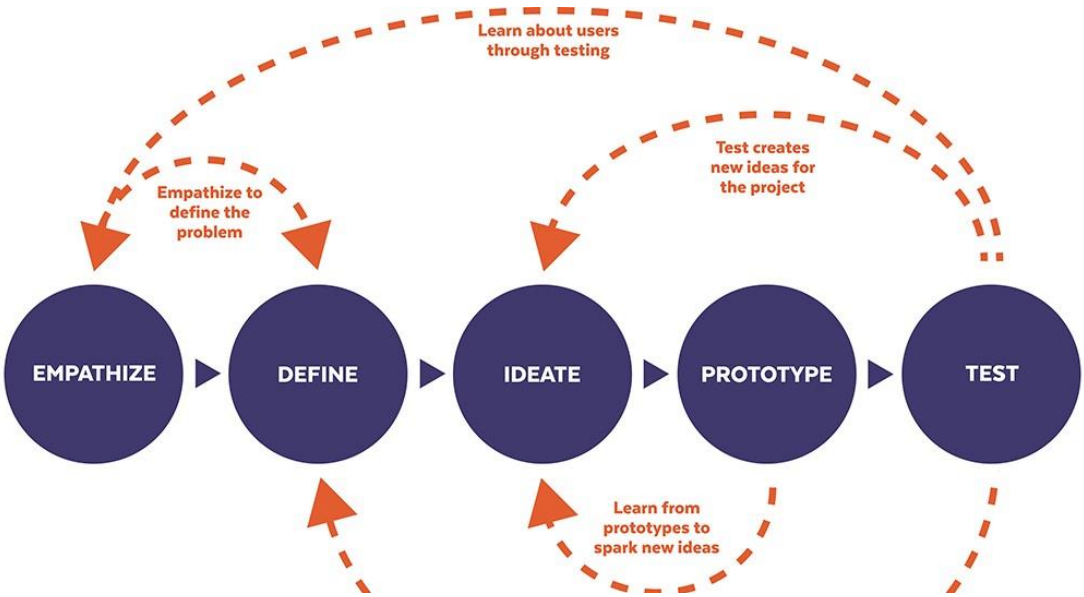

Figure 3: Human centered design (HCD) process. This process first involves a holistic understanding of a particular problem, empathizing with it and correctly defining the issue. Each step in the process provides feedback to a future or previous step, establishing interconnectedness the entire way. (Vahdat et al., 2020)

facilitate discussion around technology implementation eventually leading to a collaborative brainstorming of solutions.

THE FUTURE OF MALE FERTILITY CONTROL

Engineers of male contraceptives need to be proactive and aware of the social groups they are designing for in order for a project's impact to match its intent. In the development of a male contraceptive, it is imperative that the opinions of all actors influenced by the design are considered for a successful implementation. This STS project will be a scholarly article outlining perceptions barring the progression of male fertility control with an analysis of social groups involved in the process. Along with the novel technical idea, this research aims to provide an avenue to ending the family planning crisis and establish male contraception as a more attainable option than it is currently.

REFERENCES

Abbe, C. R., Page, S. T., & Thirumalai, A. (2020). Male Contraception. *The Yale journal of biology and medicine*, *93*(4), 603–613.

Bettahar, F., Bekkar, F., Pérez-Álvarez, L., Ferahi, M. I., Meghabar, R., Vilas-Vilela, J. L., & Ruiz-Rubio, L. (2021). Tough hydrogels based on maleic anhydride, bulk properties study and microfiber formation by electrospinning incorrect capitalization. *Polymers*, *13*(6), 972. https://doi.org/10.3390/polym13060972

Bijker, W. E., Hughes, T. P., & Pinch, T. J. (1984) The social construction of technological systems. *Zeitschrift für Wissenschaftsforschung*, 2, 39-52

Donegan, M. (2019, June 6). *It's time for men to step up and share responsibility for birth control.* The Guardian. https://www.theguardian.com/commentisfree/2019/jun/05/male-birth-control-step-up-responsibility

Gray, H. (1918). *Anatomy of the Human Body*. Gray's Anatomy.

Heinemann, K., Saad, F., Wiesemes, M., White, S., & Heinemann, L. (2005). Attitudes toward male fertility control: results of a multinational survey on four continents. *Human reproduction (Oxford, England)*, *20*(2), 549–556. https://doi.org/10.1093/humrep/deh574

Joleigh, R. (2020, August 5*). Factors Contributing to Social Attitudes Towards Male Contraception*. Male Contraception Initiative. https://www.malecontraceptive.org/blog/factors-contributing-to-social-attitudes-towards-male-contraception

Jones, R.E., Lopez, K.H. (2013). *Human Reproductive Biology*. Academic Press.

Kharkar, P.M., Kloxin, A.M. (n.d). *Injectable Hydrogels for Cell Delivery and Tissue Regeneration*. Millipore Sigma. https://www.sigmaaldrich.com/US/en/technical-documents/technical-article/materials-science-and-engineering/tissue-engineering/injectable-hydrogels

Kharkar, P.M., Kloxin, A.M. (n.d). Figure 1: Injectable hydrogel synthesization.

Khourdaji, I., Zillioux, J., Eisenfrats, K., Foley, D., & Smith, R. (2018). The future of male contraception: a fertile ground. *Translational andrology and urology*, *7*(Suppl 2), S220–S235. https://doi.org/10.21037/tau.2018.03.23

Kim, T. Y., Igras, S., Barker, K. M., Diakité, M., & Lundgren, R. I. (2022). The power of women's and men's Social Networks to catalyse normative and behavioural change: evaluation of an intervention addressing Unmet need for Family Planning in Benin. *BMC public health*, *22*(1), 672. https://doi.org/10.1186/s12889-022-12681-4

Lira, F. T., Neto, Bach, P. V., Miranda, E. P., Calisto, S., Silva, G., Antunes, D. L., & Li, P. S. (2020). Management of ejaculatory duct obstruction by seminal vesiculoscopy: Case report and literature review. *JBRA assisted reproduction*, *24*(3), 382–386. Advance online publication. https://doi.org/10.5935/1518-0557.20190075

Lohiya, N. K., Manivannan, B., & Mishra, P. K. (2000). Repeated vas occlusion and non-invasive reversal with styrene maleic anhydride for male contraception in langur monkeys. *International journal of andrology*, *23*(1), 36–42. https://doi.org/10.1046/j.1365-2605.2000.00203.x

Muhammad, S. (2022). *Male Contraceptive SCOT Model.* [Figure 2]. *Prospectus* (Unpublished undergraduate thesis). School of Engineering and Applied Science, University of Virginia. Charlottesville, VA.

Nearly half of all pregnancies are unintended – a global crisis, says new UNFPA report. (2022, March 30). *United Nations Population Fund*. https://www.unfpa.org/press/nearly-half-all-pregnancies-are-unintended-global-crisis-says-new-unfpa-report

Park, S. H., Park, J. Y., Ji, Y. B., Ju, H. J., Min, B. H., & Kim, M. S. (2020). An injectable click-crosslinked hyaluronic acid hydrogel modified with a BMP-2 mimetic peptide as a bone tissue engineering scaffold. *Acta biomaterialia*, *117*, 108–120. https://doi.org/10.1016/j.actbio.2020.09.013

Vahdat, H.L, Shane, K., Nickels, L.M. (2020). The role of team science in the future of male contraception. *Biology of Reproduction*, *103*, 167-175. https://doi.org/10.1093/biolre/ioaa086

Vahdat, H.L, Shane, K., Nickels, L.M. (2020). Figure 3: Human Centered Design (HCD) process.

Wang, C.C.L. (2022, October 13). *Male birth control is in development, but barriers still stand in the way*. Scientific American. https://www.scientificamerican.com/article/male-birth-control-is-in-development-but-barriers-still-stand-in-the-way/