Vagina-on-Chip Model for Elucidating Underlying Mechanisms of Vaginal Cell Interactions

(Technical Paper)

A Sociotechnical Analysis of Gender Bias in Biomedicine

(STS Paper)

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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

Thesis Prospectus

Introduction

Between 1997 and 2000, ten prescription drugs were taken off the market by the FDA due to severe adverse effects; eight of them caused greater health risks in women. According to a 2018 study, this imbalance was a result of "serious male biases in basic, preclinical, and clinical research" (Lee, 2018). Women have been excluded from clinical trials for decades, as they have been viewed as "confounding" and "more expensive" test subjects due to "fluctuating hormone levels" (Liu & Mager, 2016). Rather than acknowledging that physiological sex differences may translate into different biological responses to certain drugs, researchers have instead solely studied males, and simply extrapolated the results to females. This discrepancy has led to a major knowledge gap, where diseases presenting differently in females are often missed or misdiagnosed, preventing women from receiving adequate healthcare (Jackson, 2019). There has been advocacy to improve this situation for decades, yet these healthcare disparities are still prevalent today.

Recently, there has been unprecedented growth in the number of technology start-ups designing products to improve women's health. This emerging sector, known as Femtech, is transforming the landscape of disease diagnosis, providing solutions to conditions that affect women solely, differently, and/or disproportionately (Lu, 2019). While this industry shows promise for improving female health, Femtech founders often struggle to gain traction, as they experience difficulty acquiring funding from male-dominated venture capital firms (Das, 2019). This proposal will analyze the factors that have led to the historical male bias in biomedical research and explore the sociotechnical implications of the rise of female innovation seen today. The technical project will involve the development of a vagina-on-chip system, a novel device to mimic the three-dimensional (3D) cell interactions of native vaginal tissue. This device has the

potential to serve as a more efficient, accurate method of drug testing than the two-dimensional (2D) cell culture and animal models that are currently employed. This vagina-on-chip seeks to help shrink the gender-knowledge gap by providing a novel research platform for an understudied female organ; this method will escape the inaccuracies of current preclinical methods while avoiding the associated risks to female bodies that are presented in clinical trials. Therefore, this technical project will develop a platform to study vaginal physiology, grow the body of knowledge surrounding female health, and serve as a crucial step towards improved drug development for women.

Vagina-on-Chip Model

The vagina is a female reproductive organ that serves a multitude of functions in response to hormonal changes throughout a person's lifespan. This organ plays many vital roles in female health, serving as a canal for menstrual fluid and tissue to leave the uterine cavity, a receptacle for sperm, and a vessel for childbirth. Additionally, the vagina serves as a line of immune defense, protecting the body against harmful pathogens via its acidic pH, local flora, and chemical signaling (Gold & Shrimanker, 2020). Recent evidence also indicates that the vagina may have potential as a drug delivery route for both systemic and local therapy due to the ability to avoid first-pass metabolism, ease of administration, and high permeability for low molecular weight drugs (Hussain & Ahsan, 2005). Despite these critical roles for female health, the vaginal organ remains relatively understudied, with many key cell interactions still uncovered. Many vaginal conditions require improved targeted therapeutics; however, current methods provide insufficient and often inaccurate representations of human tissue behavior. While the use of 2D monolayer cell culture, organoid cell culture, and animal models demonstrate improving physiological relevance, the dynamic, multi-layer composition of the vagina makes native tissue

response difficult to replicate *in vitro* (Raya-Rivera et al., 2014). Therefore, as current research highlights the impact of women's health and the susceptibility to diseases, there is an increasing necessity for new ways of creating therapeutic modalities.

The costs of drug development have risen in recent years, two-thirds of which are spent in the clinical trial stage. Meanwhile, the number of drugs approved annually has declined significantly, with the ultimate rejection of 90% of the drugs that enter Phase I clinical trials (Skardal et al., 2017). As drug development costs and failure rates continue to grow, it becomes increasingly clear that the cell lines and animal models currently used for discovery, preclinical, and clinical testing fall short in predicting the pathophysiology of human disease, personalized drug sensitivities of specific patient groups, and off-target toxicity (Zhang et al., 2018). Innovative methods to culture cells for testing new compounds are therefore necessary to properly replicate tissue properties, experiment under biomimetic physiological conditions, and measure therapeutic effects.

There has been a recent movement toward the utilization of Organ-on-chip (OoC) models to reproduce *in vitro* tissue and organ- level functionality of living organs and systems. OoC technology utilizes advances in tissue engineering and microfluidics to enable the design of customized cellular microenvironments with precise fluidic, mechanical, and structural control (Zhang et al., 2018). These models have been applied for the study of specific functions of many other organs, including the female reproductive tract, but none have been developed to model the dynamic and layered structure of the vagina (Mancini & Pensabene, 2019). Therefore, this individual technical project seeks to create the minimum functional unit for the first vagina-on-chip device that will mimic native vaginal tissue physiology and allow for predictive drug response.

This model will consist of a cell culture chamber to mimic 3D vaginal tissue physiology, porous biomaterials with mechanical congruence to native tissue, and a series of microfluidic networks to allow for nutrient exchange and drug delivery. First, the organization of the 3D cell culture chamber will be determined and a computer-aided design (CAD) will be generated using Autodesk Fusion 360 software. Next, the necessary biomaterials to sustain the vaginal cell culture within the proposed chamber design will be selected using multi-criteria decision making and dynamic force simulation. Lastly, the fluidic network and pump method to deliver cell media will be determined via pressure gradient calculation and fluid flow simulation in COMSOL Multiphysics software. This technical project will be conducted throughout a twelve-week period and will result in the production of a functional design for the very first organ-on-chip system to model the vaginal organ. This innovation has the potential to revolutionize the way the vagina is studied and serve as a crucial step toward predictive physiological behavior in response to treatment stimuli.

Gender Bias in Biomedicine

Since the early 1990s, when federal law began requiring women and racial minorities to be included in research funded by the National Institutes of Health (NIH), clinical trials have changed substantially to improve gender-inclusivity; however, the majority of preclinical studies continue to use only male cell lines and male animals (Jackson, 2019). Despite recent advances from the NIH to acknowledge this problem and even mandate the allotment of research funding to include female animals, many researchers still do not analyze study results to determine differences by gender. In a 2015 review of 150 federally funded trials, 75% of studies did not report any gender-based outcomes (Mazure & Jones, 2015). While recent signs of potential

change in both policy and scientific inquiry have begun to remedy this underrepresentation, not nearly enough progress has been made for gender equality in biomedical research.

Even though women control 80% of healthcare decisions in the U.S. and spend 29% more per capita on healthcare compared to men, the sector of digital health for women, known as Femtech, has only recently started to draw investor attention (Sandhu et al., 2020). While there has been a recent surge of interest, only 3% of the 2,728 U.S. digital health investment deals since 2011 have focused on women's health. Femtech founders face serious challenges in securing investments in the male-dominated venture capital community, where women's health issues are not always understood (Das, 2019). There is often a stigma surrounding issues such as menstruation, pregnancy, nursing, and menopause that often prevents male investors from fully comprehending the value proposition of Femtech products. Although the Femtech industry is expected to be worth over $50 billion by 2025, the total addressable market for women's healthcare is estimated at nearly $500 billion (Lomas, 2020). Therefore, even as sex-based research begins to expand and female technologies continue to emerge, progress is still halted by the lack of acceptance in a male-centric society. The relationship between these social and technical elements will be the center of analysis for this proposal.

The issue of gender bias at all levels of biomedicine has prevented women from accessing adequate healthcare for centuries. The extrapolation of data from research conducted on male subjects has led to a wide range of diseases that are missed or misdiagnosed in women. For example, women are more likely than men to die of heart attacks, as they often present different symptoms that are largely under-researched. According to the American Heart Association (AHA), an estimated 44 million women in the U.S. are affected by cardiovascular disease, but only 90% have one or more of the known risk factors (Sadick, 2019). In the

biopharmaceutical industry, the testing of many drugs solely in men has led to negative side effects, inefficacy, and improper dosing for women. A drug approved by the FDA for the treatment of HIV infection in 2016 specifically excluded cisgender women, a population that accounts for nearly 46% of all HIV infections globally (Goldstein & Walensky, 2019). These examples are only a small subset of the ways that gender bias has threatened, and continues to threaten women's health.

The STS framework that will be used to support this analysis is co-production. This framework, discussed in *States of Knowledge* by Sheila Jasanoff, demonstrates how scientific ideas, beliefs, and associated technological artifacts evolve together with the representations, identities, discourses, and institutions that give practical effect and meaning to ideas and objects (Jasanoff, 2004). Co-production allows for the explanation of how science and technology can cross time, space, and culture, as well as how they are made legitimate and meaningful in society. This framework will be utilized in this proposal to reveal key insights into the relationship between women's health and society throughout the 20th century and recent decades. Studying this sociotechnical connection throughout time allows for a large scope and a comprehensive analysis of this topic. To avoid an overly broad application of co-production, the power dynamics that exist between variables must be acknowledged and each instance must be properly understood in its historical context (Tembo et al., 2019). Therefore, in this proposal, co-production will be applied specifically to the knowledge gap in regards to gender and biomedical research in the United States.

Research Question and Methods

The proposed research question is: what are the sociotechnical implications of gender-inclusive healthcare research? This paper will explore the effects of the historical exclusion of

women from all stages of drug development and reveal the challenges that are still faced today. This issue will be analyzed using historical case analysis, documentary research methods, and wicked problem framing. A historical case study involves gathering archival or published accounts and systematically organizing them to reconstruct chronological events (Widdersheim, 2018). This approach will be used to support answering questions about past events and dynamics that shaped the narrative of the female health knowledge gap over time. This section will use articles analyzing gender bias in biomedical research as sources of analysis to support new ways of interpreting and understanding the historical context of the issue.

Documentary research methods are used to organize and analyze documentary evidence in a manner that can support an interpretation or reinterpretation of the topic at hand. The sources that will be used in this section include research studies on the conditions affecting women differently or disproportionately that do not receive sufficient female representation in preclinical and clinical studies, as well as evidence for the negative healthcare outcomes that women experience as a result (Beery & Zucker, 2011; Gandhi et al., 2004; Montastruc et al., 2002; Ngo et al., 2014). These articles will be used to analyze the systematic biases in the biomedical research system and illustrate why they are problematic.

Wicked problem framing is a method of understanding complex and dynamic problems. This method is used to gather and assemble evidence in a way that reveals indirect and hidden connections between symptoms and root causes of an issue. Wicked problem framing will be used to support the organization and re-interpretation of this problem that remains unsolved despite the potential for technical solutions. This section will draw upon comprehensive texts such as *Outrageous Practices: How Gender Bias Threatens Women's Health* by Leslie Laurence and Beth Weinhouse, *Doing Harm: The Truth About How Bad Medicine and Lazy Science Leave*

Women Dismissed, Misdiagnosed, and Sick by Maya Dusenbery, and *Pain and Prejudice: A call to arms for women and their bodies* by Gabrielle Jackson (Dusenbery, 2018; Jackson, 2019; Laurence & Weinhouse, 1997). Additionally, this section will utilize recent articles discussing trends and problems within the femtech industry, such as "*Femtech is expansive—it's time to start treating it as such*" by Sandhu et al. and "*Is Technology Pink*?" by Reenita Das (Das, 2019; Sandhu et al., 2020). These sources will be used to reveal important connections between the social and technical components at the center of this issue.

Conclusion

Despite its critical roles for female health, the vagina remains relatively understudied, with many key cell interactions still uncovered. Developing a system to effectively study physiologically relevant vaginal tissue will provide a platform for elucidating these critical mechanisms and lead to an increased understanding of female physiology. The vagina-on-chip device developed in this technical project will provide a novel method of replicating native tissue response to stimuli, an essential breakthrough for improving drug development for female healthcare. The lack of data surrounding the female body has resulted in an incredible injustice to women in the healthcare system. Despite the scientific progress that has been made, technological improvements for female health are often not widely accepted due to societal stigma and lack of awareness of women's issues. A solution to this problem would allow for an increased body of research studying female physiology, which, when coupled with societal acceptance of female technology, would lead to significantly improved medical care for women. It is expected that this endeavor will reveal key insights into the relationship between historically male-based science and the current problems faced by the growing femtech industry. This will

allow for the examination of the factors impeding progress towards gender equality in healthcare today.

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