GENDER EQUALITY TOOLBOX

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CASE STUDY IN GENDER INTEGRATION

Contraception and Gender in Microbicide Trials

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OVERVIEW

Early vaginal microbicide trials were challenged by poor contraceptive use among participants and high rates of incident pregnancy; the reasons may be rooted in the same gender norms and barriers that affect women's use of contraception outside of the clinical trial context.

Clinical trials of experimental products that include women of reproductive age typically require that female participants use contraception during the trial. Women may nevertheless become pregnant during a trial either because of contraceptive failure, lack of adherence to contraceptive use requirements, or for a host of other reasons when contraception is not required. When women experience a pregnancy in a clinical trial, they often are asked to discontinue use of the product for safety reasons or to ensure less variability in study results. High rates of incident pregnancy in a clinical trial can potentially dilute study outcomes if product use is suspended among pregnant women, or it can make trials less efficient by requiring recruitment of a larger study population, as well as follow-up of pregnancy outcomes.[1]

Incident pregnancy rates in trials of vaginal microbicides, products intended for HIV prevention, have contributed to challenges in demonstrating product efficacy.[2] The first efficacy trial of a vaginal microbicide was initiated in 1996,[3] followed by dozens of trials enrolling thousands of women, but it wasn't until 2016 that a product reported effectiveness sufficient to potentially warrant licensure.[4,5] In one meta-analysis, 15% of 4,107 participants became pregnant, and incident pregnancy rates from 8 microbicide trials (N=25,551) yielded an overall incidence of 23.37 (95% CI: 17.78 to 28.96) pregnancies per 100 woman-years.[6] High rates of incident pregnancy were observed in the first wave of microbicide trials due to poor contraceptive adherence and use of less effective methods.[7] The reasons for poor contraceptive adherence in trials vary, yet reflect "real-life" contraceptive use and may be rooted in the same gender norms and other barriers that affect women's use of contraception outside of the clinical trial context.[8-11]

This case study explores the evolution of contraception policies and practices in the context of microbicide trials, and the influence of gender on trial participants' contraceptive use. It draws on the published literature, as well as interviews conducted with microbicide researchers.

This case study in gender and clinical trials is part of the Bill & Melinda Gates Foundation's Gender Equality Toolbox, which includes a series of case studies and other resources for supporting Program Officers in applying a gender lens to their investments. Note that not all of these case studies are foundation-funded programs and a program's inclusion in this series does not indicate an endorsement by the foundation. It is one of four case studies developed for the Bill & Melinda Gates Foundation Internal Gender Challenge: Gender Considerations in Clinical Trials.

BACKGROUND

Gender and contraception: "Gender" refers to sets of social roles and expectations for human behavior based on whether an individual is considered to be or identifies as male or female. A central and pervasive gender-based role for women is bearing children and caring for them. Contraceptive use helps women to control their fertility, resulting in positive health, social and economic benefits to mother and child.[12,13] In some settings, the idea of women controlling their own fertility contradicts gender norms dictating that decisions around childbearing should be shared or made by men or other family members. A woman might choose to become pregnant against her partner's wishes, or refuse to do so when he or his family want her to and initiate contraceptive use without the explicit knowledge or approval of her partner or others.

Women, Fertility and Clinical Trials: As recently as 1990, women were excluded from early phase clinical trials due to concerns over reproductive toxicity or teratogenicity, which is the potential harm to the embryo or fetus. Protectionist policies of the '60s and '70s emerged in response to events in clinical research, including birth defects caused by Thalidomide and DES, that led to the development of policies to protect "vulnerable populations," which includes pregnant women.[14-16] Although these policies focused on phase I and II trials, they inadvertently led to systematic exclusion of women from phase III drug trials and trials for those with life-threatening diseases.[17]

The advent of the AIDS epidemic was accompanied by a shift in public sentiment regarding exclusionary policies in clinical research. Such policies are now viewed as paternalistic and a violation of basic human rights.[18] Today, federal regulators (such as the European Medicines Agency and U.S. Food and Drug Administration) and research bodies (such as the National Institutes of Health) encourage the enrollment of women (including adolescent women) in all relevant medical research. Due to the lack of data to make an evidence–based decision about drugs that can be taken during pregnancy, there is now a push for the inclusion of pregnant women in phase III trials,[19,20] including vaccine trials for drugs that could confer immunity to the child in utero.[21] In other types of trials, inclusion criteria for women of reproductive age might include use of an effective method of contraception. If no pre-clinical data exist to indicate that an experimental drug is not teratogenic, women who become pregnant during a clinical trial are taken off product for the duration of their pregnancy, sometimes longer. When product use is suspended for participants in a drug trial, the ability to fully analyze the product's safety and effectiveness may be compromised due to lower statistical power; [22] some studies are overpowered and increase enrollment goals in order to compensate for potential product discontinuation due to pregnancy.

Trial Requirements and Choice: Clinical trial protocols typically require that sexually active women of reproductive age use contraception for a period of time before, during and/or after using an investigational product as part of their participation, particularly when the safety of a product has not been fully established. Other trials may recommend but not require contraception, and increase enrollment in order to compensate for potential pregnancies and product discontinuation. In addition to safety concerns, it is important to minimize incident pregnancies to ensure that a sufficient population is using a study product throughout the course of a trial so as to adequately measure outcomes. Trial requirements vary in terms of who is required to use contraception, for how long, and the types of contraceptives that satisfy study requirements.

Determining the right approach to contraceptive use in clinical trials can be challenging. On the one hand, research has shown that women are more likely to use a contraceptive method when they have a full range of contraceptive choices.[23] On the other hand, researchers may be inclined to promote the most effective methods possible in order to protect the trial population and the validity of the trial.

CONTRACEPTION AND PREGNANCY IN MICROBICIDE TRIALS

Microbicide Trial Practices: In early microbicide trials, researchers struggled to minimize pregnancy risks and women often experienced challenges accessing contraceptives.

Clinical trial site practices vary in their approach to helping women access contraceptive services. Some microbicide or other trial sites are co-located with family planning clinics and women are referred for contraception within the same physical site. Other trial sites are based in communities where some type of service is available and women are asked to seek services off-site. In other cases, the trial site may provide contraceptives.

In advanced (phase IIb/III) microbicide trials, pregnancy is always a factor to consider given that the study population for these trials has exclusively been sexually active women of reproductive age. Since these trials recruit women at risk of HIV infection, ethical requirements stipulate that the trial provide condoms and condom counselling to all participants for HIV prevention; however, earlier trials did not require use of condoms or other contraceptive methods.[24-28] To minimize risks, these trials did not enroll pregnant women or women who planned to become pregnant during the study period, and women who enrolled were informed that the products' effects on pregnancy were unknown. When an incident pregnancy was confirmed, product use was suspended.[29-33]

The trial sites also offered or made referrals for family planning. Some research sites asked participants to bring their contraceptive cards from services outside the site to study visits to aid in their counseling efforts and ensure that women consistently used contraception. Those that were co-located with family planning services could refer women internally for contraceptives, and women were counseled about correct and consistent contraceptive use. Although condoms were provided, and women were encouraged to use them for HIV prevention, more effective methods of contraception were recommended. However, women in trials often faced some of the same challenges to accessing and using contraception that women faced in these communities overall.[34] These challenges applied not only to women referred off-site for contraception, but also to those who were referred to co-located services.

Pregnancy in early trials: Higher than expected pregnancy rates caused concern about dilution of study results, prompting trials to shift their approaches to contraceptive requirements and services.

Women participating in early microbicide trials[35] experienced higher rates of pregnancy than researchers expected.[36] These pregnancies created concern about the potential "dilution" of study results since pregnant women are asked to stop use of the product.[37,38] Clinical trial designs had taken into account expected numbers of incident pregnancies, and when faced with higher than expected pregnancy rates, some researchers argued that sample sizes and/or study endpoints in future trials should be adjusted to accommodate this, while others argued that contraceptive use should be improved.[39]

The high pregnancy rates observed in early trials stimulated subsequent trials to require use of contraceptives considered to be highly effective, such as sterilization, hormonal methods and intrauterine devices.[40-42] Recognizing constraints that women face in accessing and using contraception, trial sites strengthened counseling services, and many began offering contraception on-site to better meet women's needs. As microbicides researchers were refining their approaches to addressing pregnancy in trials, long-acting contraceptive methods, including implants and intrauterine devices, became increasingly available in some settings, enabling sites to provide products that were previously unavailable or difficult to access in the area.[43] Trial researchers saw the benefits both to the trial and the woman of directly providing contraceptives whenever possible.

For example, one trial implemented an "intensive comprehensive contraceptive curriculum" in order to increase contraceptive uptake and reduce pregnancy rates, resulting in a low overall pregnancy rate of 3.95 per 100 women years. These results compared favorably to the 17.7 per 100 woman-years pregnancy rate observed in the earlier preparedness study without the curriculum.[44]

These shifts or evolutions in contraceptive requirements and services were critical as it became clear that many trial participants were not adherent to microbicide use-requirements, and clinical researchers were keen to remove any potential barriers to trial participation and adherence to study requirements.[45] Providing contraceptives on site also enabled researchers to reinforce and more accurately monitor contraceptive adherence.[46]

GENDER IMPLICATIONS OF CONTRACEPTIVE USE BY CLINICAL TRIAL PARTICIPANTS

Autonomy in decision-making: **Gender norms often constrain a woman's autonomy to make decisions about when and whether to use contraception and can also constrain her decision about whether to join a trial.**

Women's ability to make an autonomous decision about contraceptive use is often constrained by gender and other social norms. This constraint is even more problematic for women who wish to enroll in clinical trials that require contraceptive use. Microbicide trials have excluded women who say they wish to become pregnant during the study period, and use of contraceptives is typically required for trial participation. Women who were not previously using contraceptives are thus faced with two important decisions (to join the trial and to use a contraceptive), and they may be conflicted about how or if to discuss these decisions with their partner or other family members. Women may want to join a trial that requires or encourages contraceptive use, but may feel unable to do so due to social expectations around fertility that may pressure women to reproduce, and their own or their partner's fears about the effects of contraceptives. Trials have reported that many women fear negative repercussions such as gender-based violence, being shunned, or being abandoned if they join a trial without informing their partner.[47-49] These partner objections may be based, in part, on contraceptive use requirements. While study staff may counsel women about their right to make autonomous decisions as part of the consent process, their ability to do so is tempered by the realities of gender norms, and trials often provide resources to women to help explain trial requirements to partners if they wish or feel compelled to do so.[50]

I think it's another area of false assumptions about autonomy that all decisions about where and when to become pregnant is on women. A lot of women don't have that choice. There is pressure to get pregnant from family [or they may become pregnant] from forced sex, etc. I think we are working towards contraception being a choice that all women can make – but let's not make bogus assumptions that all women in trials have free choice. It's not true.

Biomedical researcher/clinician, thought leader in women's health

Access to quality services – undue inducement to participate?: **While offering services with a higher standard of care than is generally available has raised questions about undue inducement, researchers concluded that offering quality contraceptive services on-site was the better choice.**

In many developing countries and other low-resource settings women lack access to reliable sources for contraceptives, choice of contraceptive method, or broader high-quality health care services. Barriers to access are many, including gender-related factors such as women's time, poverty, restrictions by partners and other family members, lack of mobility and financial resources, and inadequate knowledge of contraception options in addition to poor product availability and quality services. Questions have been raised about whether provision of high quality contraceptive and other health services within a trial constitutes undue inducement to participate, particularly if that standard of care is not readily accessible to women in the surrounding community who aren't participating in a trial. While some researchers may argue that women may enroll in a study in order to access the services provided,[51] most feel that the attractiveness of health services provided to research participants is a good thing, and instead of offering a lower standard of care in the trial, they should strive to improve the standard of care in the communities where they work.[52] Although the ethical implications of providing a higher standard of care in a clinical trial has often been debated, the fact that women need access to quality contraceptive services is not.[53,54]

I think the general rule is that providing access to contraceptives is a good thing and the undue inducement argument didn't wash. Some people raised it, but it was overruled by the idea that we should provide the best treatment that we can to women in the trial.

Biomedical researcher/clinician, thought leader in women's health

Contraceptive choice and coercion: Questions were raised about whether trial contraceptive requirements may coerce women to use contraception in general, or a particular method.

While desire for contraception may induce some women to participate, women who want to participate may unwillingly initiate contraception, or use a particular type of contraception, to gain the benefits of participation such as counseling, testing, healthcare or cash reimbursements. Some researchers and health advocates raised concerns when microbicide trials began to require contraceptive use because they felt that contraceptive requirements had the effect of coercing women to use contraception in a context where women had poor access to contraceptive services, poor understanding of these biomedical products and limited autonomy and agency for independent decision-making. Researchers interviewed for this case study noted that, contrary to principles of informed choice, trial staff might favor methods that are the most convenient for the trial to provide and easier to ensure use-adherence (e.g., long-acting methods such as injectables, IUDs or implants), regardless of women's preferences. Some researchers interviewed felt that the contraceptive requirement should be part of the trial since providing contraceptives simplifies access for women while benefitting the trial. Yet other researchers decided that contraception should be provided but voluntary, and women who became pregnant would remain in the trial in order to observe product effects during early pregnancy.

It's not telling women they don't have options with regard to reproduction in their lives, but if you want to join this trial, then these are the requirements...

Biomedical researcher/clinician, thought leader in women's health

APPROACH TO CONTRACEPTION

Researchers must take into account the gender barriers and norms that may exert negative pressure on women's decisions to join a clinical trial and to use contraception.

To address the needs and concerns of women participating in trials, including the constraints they face related to contraceptive and product use, while successfully recruiting and retaining adherent participants, researchers must take into account the gender barriers and norms that may exert negative pressure on women's decisions to join a clinical trial and to use contraception. Microbicides trials offer lessons in successful approaches to doing so that also help achieve contraceptive adherence and thus more efficient trials:

- **Make access real.** Provide contraceptive services onsite within the trial.
- **Choice matters.** When you give women real contraceptive choices, they are more likely to find a product they like and use it.[55]
- **Education is important.** Women need to better understand their reproductive system to allay fears about fertility and side effects of contraceptive products.
- **Respect women's realities.** Accept that women may feel the need to seek their partner's permission or support for trial participation and contraceptive use, and provide counseling, materials, and opportunities for her to do so if she wishes to, while ensuring that negative gender norms are not reinforced, and she is not encouraged to do something that could put her at risk of social or physical harm. Where possible, respect that some women may be more comfortable with contraceptive methods that can be used discretely
- **Consider the needs of specific populations** such as needs of very young women and women who want to become pregnant soon after trial participation.

CONCLUSION

The high rates of incident pregnancy experienced in early microbicides trials were not found in later trials. Researchers attribute this reduction to the changes in trial site practice related to contraception that they undertook to ensure good trial outcomes. However, dilemmas regarding when and how to mandate contraception in clinical trial settings remain. The systematic exclusion of pregnant women – to protect the fetus – means that products are rarely tested on pregnant woman. For some diseases, such as malaria or HIV, this exclusion leaves women, who are already at increased risk due to pregnancy, at risk. Similarly, women who want to have children may be less likely to participate in clinical trials requiring contraception, leaving out an important population of young women – a group increasingly at risk for HIV in some contexts.

The most promising responses in microbicide trials to the challenges around contraception attempted to address the negative pressures that gender norms exert on women's decisions to join a trial and use contraception. They addressed women's specific challenges as they related to access, choice and autonomy. Yet relatively limited research has been done to understand how gender affects a woman's decision to join a trial, to use contraception, and to continue participation, product adherence and contraceptive use, and how improved interventions around contraception for women in clinical trials impact those behaviors and practices. A better understanding of these issues would help make trials more gender-intentional, and could inform practices in microbicide and other trials that include women of reproductive age as they learn and build on the gains microbicide researchers have made to-date.

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