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## Innovations in Sexual and Reproductive Health 2

# Biomedical innovations in contraception: gaps, obstacles, and solutions for sexual and reproductive health

*Deborah J Anderson, Jonathan M Bearak, Frances W Grimstad, Thesla Palanee-Phillips, Ariane van der Straten*

**Contraception and family planning are vital aspects of sexual and reproductive health and rights. Despite major advances in modern contraception over the past 60 years many gaps remain, and the rate of unplanned pregnancies and abortions remains high. These issues have given rise to a new era in contraception research with great opportunities and many challenges. These opportunities include new innovations, particularly in the areas of male contraception, non-hormonal female contraception, and multipurpose prevention methods that provide contraception in combination with protection against leading sexually transmitted pathogens; fast tracking new inventions currently in the pipeline by intensifying support from government, non-profit, and industry entities; the provision of new methods, services, and messaging for underserved populations including men, marginalised women, and transgender individuals; and better understanding the needs of diverse populations. Major challenges in contraception research include inertia, especially in industry involvement; a new wave of conservatism and government interventions that threaten to impede contraception development, services, and education; and understanding what people want and how to provide solutions. The best way to improve family planning and promote women's health is to offer better contraception options to those who wish to avoid unplanned pregnancy. This can be done by renewed commitment from scientists, private foundations, and government institutions, and from industry partners who are needed to bring promising developments to market.**

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This is the second in a **Series** of five papers about innovations in sexual and reproductive health. All papers in the Series are available at thelancet.com/series/sexual-reproductive-health

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## Introduction

Modern contraception is an integral component of sexual and reproductive health and rights; it enables family planning and provides substantial social, health, and economic benefits globally.[1] The contraception revolution of the mid-20th century was propelled by three forces: a concern about exponential population growth; growing pressure from women seeking reproductive autonomy; and innovative scientific research coupled with bold clinical trials that demystified human reproduction and laid a road map for modern female contraception. By the end of the 20th century, nearly half of women of reproductive age worldwide (871 million women)[2] were using modern contraception, the global fertility rate had decreased from 5·0 children per woman in 1960 to 2·5 children per woman, and the contraception revolution was seen as a success. However, research on new contraception methods has slowed substantially and reliance on existing methods has produced many gaps and unintended consequences, such as 259 million women of reproductive age worldwide not using contraception despite wanting to avoid pregnancy,[2] high incidences of both unintended pregnancies and abortion, large numbers of underserved individuals (ie, men, adolescent and young women, and transgender people), concerns about hormonal contraceptive-associated side-effects, and the high cost of many methods limiting their accessibility. In addition, the contraception revolution has increased the incidence of sexually transmitted infections (STIs) due to an increase in condomless sex. In 2018, *The Lancet* published a landmark Guttmacher–*Lancet* Commission report[1] describing the benefits of reproductive health for all and outlining a number of problems that provided roadblocks for the goals of sexual and reproductive health and rights. This Series paper updates and extends upon the Guttmacher–*Lancet* Commission focusing specifically on contraception. The contraception field has embraced several promising new innovations, but there has been little impact on the number of unintended pregnancies worldwide, and the field faces dramatic moves by the US Government to criminalise abortion and defund contraception programmes worldwide. A total of 112 countries worldwide prohibit or restrict access to abortion affecting 38% (750 million) of women.[3]

## Overview

The UN, using survey data available as of April, 2024, estimated that 57% of reproductive-age women worldwide want to avoid pregnancy, highlighting a desire to postpone, space out, or stop childbearing.[4] Of these women, an estimated 77% use a modern method of contraception to prevent pregnancy and approximately 15% do not use any method of contraception.[4] The proportion of women who want to avoid pregnancy but are not using modern contraception varies substantially between UN Sustainable Development Goal regions, ranging from 53% in Oceania (excluding Australia and New Zealand) to 86% in eastern and southeastern Asia. There are substantial differences within regions as well. Among the subregions of sub-Saharan Africa, modern contraceptive use in women wanting to avoid pregnancy ranges from 40% in middle Africa to 83% in southern Africa. Among high-income global subregions, modern contraceptive use in women

wanting to avoid pregnancy ranges from 77% in southern Europe to 89% in western Europe. Although the number of women that do not use modern contraception despite wanting to avoid pregnancy is highest in low-resource regions, it is also an important issue worldwide, including in high-income settings.

Several factors can contribute to the decision not to use contraception, including disparities in access to health care, socio-cultural norms, side-effects, and insufficient information and misinformation. In addition, some people make informed, autonomous choices to not use contraception as fertility intentions can fluctuate along a spectrum and women can be differently motivated to avoid becoming pregnant. Of the 250 million pregnancies worldwide each year, 50% are unintended,[5] and there are 2·1 abortions for every unplanned birth worldwide according to the latest estimates from the Guttmacher Institute[6] (also see the first paper of this Series). In part, these findings suggest a strong desire to manage fertility that current contraceptive options do not fully address.

Owing to disparities in contraceptive use and because all present contraceptive methods can potentially fail, the annual rate of unintended pregnancies per 1000 women who want to avoid pregnancy ranges from 36 pregnancies in western Europe to 283 pregnancies in middle Africa, with substantial variation between countries within regions (figure 1).[6] Even in low-fertility settings with robust health systems and high levels of contraceptive use, the number of women who will experience unintended pregnancies within their lifetime is substantial. Notably, sexually active women in low-fertility settings spend most of their reproductive years trying to avoid becoming pregnant.

## Current contraception use

According to 2022 UN estimates, approximately 30% of women in partnerships worldwide use contraceptives with hormonal mechanisms of action (eg, pills, rings, implants, injections, and hormonal intrauterine devices).[7] These methods are highly effective at preventing pregnancy and have other reproductive benefits, such as the management of dysmenorrhoea and endometriosis and reduction in some cancers in the reproductive organs. However, hormonal contraception is also associated with serious side-effects and health risks. Progestins are associated with abnormal bleeding patterns, headaches, mood swings, weight gain, and other actual or perceived side-effects that can cause end-user dissatisfaction and discontinuation. Furthermore, oestrogens are contraindicated in women at risk for thrombosis due to smoking, hypertension, obesity, or previous thrombosis and after hormone-dependent cancer.[8] Owing to these issues, approximately half of women initiating oral hormonal contraception and 21% of women using injectable hormonal contraception discontinue within 1 year.[9] Alternatively, tubal ligation, a permanent sterilisation method, is used by 23% of women worldwide. Other available non-hormonal methods are used less frequently worldwide, such as non-hormonal intrauterine devices (17% of women), female condoms (1% of women), and vaginal spermicides (1% of women).[7] Notably, women often indicate a desire for more non-hormonal reversible methods.[10]

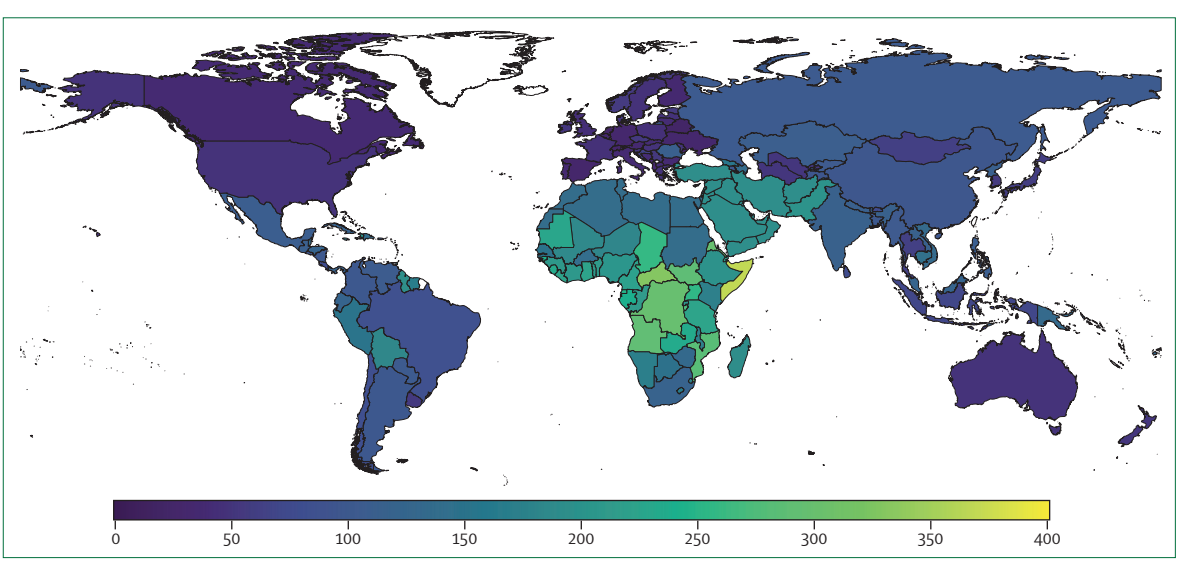



***Figure 1:*** **Annual conditional unintended pregnancy rates by country (average from 2020 to 2024)**
Estimates for annual numbers of unintended pregnancies per 1000 women who want to avoid pregnancy. Estimates are statistically modelled for all countries and used to construct global and regional averages. Grey reflects data limitations on whether country-specific results are published. A Bayesian statistical model produces estimates for all countries. However, regional averages are shown rather than country-specific estimates for countries grouped statistically in the Middle East or north Africa, where no reliable abortion data exist. Data provided by the Guttmacher Institute (Bearak JM, unpublished).

Although men share responsibility for 100% of unintended pregnancies, they comprise less than one-quarter of the population using contraception. Vasectomy—a surgical method that is highly effective but is generally considered permanent—has been adopted by only 2% of men worldwide, whereas approximately 20% of couples use male condoms as their primary contraception method. Modern latex condoms are highly effective if used correctly and regularly but are only 85% effective in typical use owing to forgetfulness, interruption of intimacy, and decreased sexual sensation.[7] Cross-sectional probability-based sample surveys conducted between 2021 and 2022 on 18 748 heterosexual men and 9122 female partners from seven countries in Asia, Africa, and North America indicate that on average 61% of men would be interested in using a novel male contraceptive.[11]

Types of contraceptive methods in use vary considerably across different age groups and geographical regions (figure 2).

## Obstacles

### Barriers to contraceptive use

Global health and international development policies and programmes have long sought to supply reliable contraceptives, in part motivated by disparities in the incidence of unintended pregnancy. With changes in sexual activity, age at family formation, active workforce

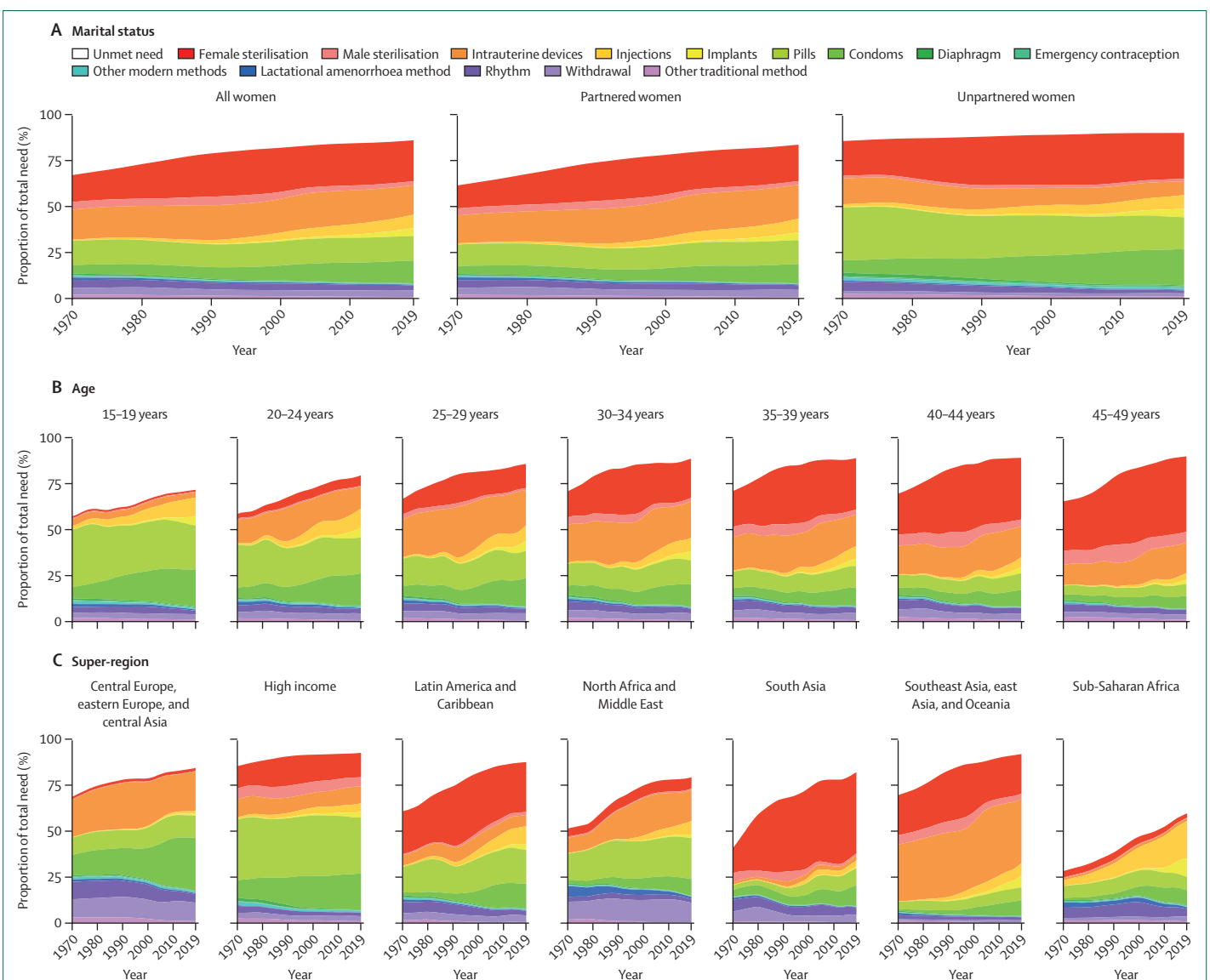



***Figure 2:*** **Use of different contraception methods by marital status, age group, and geographical location**
Reproduced from Haakenstad and colleagues.[12]

participation, and fertility desires, the growth in the number of women trying to avoid pregnancy has exceeded the overall population growth. Increases in contraceptive supply have contributed to an individual's ability to achieve their reproductive goals.[13] However, gains in modern contraceptive use have stagnated over the past 25 years.[14] Although the scarcity of access to or awareness of methods contributes to the decision not to use contraceptives, these are among the least commonly cited reasons for minimal uptake. In contrast, side-effects, health risks, infrequent sex, religious beliefs, and individual or social opposition are much more frequently cited reasons for not using contraceptives.[15] Health concerns also have a greater effect on contraceptive use in women in more affluent countries; in a study conducted from 2011 to 2017 21% of women in the USA reported that they did not use contraception because they were concerned about side-effects.[16,17] Overall, this evidence suggests that sociocultural norms and the limitations of currently available contraceptive technologies are more prominent factors for not using contraceptives than restrictions to contraceptive access, highlighting the need for new developments in effective contraceptive technology to provide people with methods they will find acceptable to use.

### Religion as a barrier to contraception

The Catholic church has historically taught against the use of artificial contraception, such as birth control pills, and many global religions espouse pro-natal philosophies. Conservative men and women in many countries seek to restrict access to contraception due to a desire to return to a more traditional society with monogamous marriage at its core. Nonetheless, many women across religious affiliations and geographical locations will use a modern contraception method at some point in their lives.[12,18]

### Effects of anti-abortion legislation on contraception and reproductive health

Abortion and contraception are inexorably linked. The provision of effective contraception can reduce the number of abortions, and in settings where contraception is not readily available, women might rely on abortion for birth control.[19] In countries with legalised abortion, medical abortion (ie, oral administration of mifepristone followed by misoprostol before week 10 of pregnancy) is now used by most women seeking abortion, and is considered very safe and effective. However, when women do not have access to legal abortions, they often resort to unsafe abortions that have an extremely high risk of maternal mortality and complications (see the first paper of this Series and the WHO Abortion Fact Sheet[20]). Global estimates from 2010 to 2014 indicate that 45% of all induced abortions were unsafe. The legal status of abortion varies widely across the globe. As of July, 2025, abortion is completely banned in 22 countries worldwide, and 43 countries allow for abortion only when the woman's health is at risk, or in cases of rape, incest, or fetal abnormalities. In the USA, the Supreme Court's 2022 reversal of *Roe v Wade* in *Dobbs v Jackson Women's Health Organization* overturned the constitutional right to abortion; as of July, 2025, 12 US states have banned abortion outright and 29 others severely restricted the right to safe abortions.

Anti-abortion sentiment in the USA has also had wide-reaching effects on financial policies and support for family planning abroad. In 1984, the Mexico City Policy was implemented, specifying that US federal funding could not be provided to non-governmental organisations, such as universities and hospitals that offer abortion counselling or services; this policy affects 64 low-income countries, primarily in Africa, Asia, and Latin America. The Mexico City Policy has been enforced when the conservative Republican party is in control of the US Government and results in substantially decreased provision of contraception particularly to lower income countries. Evidence indicates that this decrease in contraception is associated with an increased incidence of unplanned pregnancies, unsafe abortions, and maternal death.[21] The second Trump administration doubled down on restricting the use of government funding for family planning services in the USA and abroad. Funding was abruptly withdrawn from Planned Parenthood and Title X, programmes that provide crucial reproductive health care for low-income and uninsured individuals in the USA. This administration also froze funding for major global family planning and reproductive health programmes, such as the US Agency for International Development and the UN Family Planning Assistance Program, which provided modern contraceptive care to 47·6 million women and girls across 150 countries in 2024.

On other fronts, anti-abortion groups in the USA have sought to restrict the use of mifepristol by declaring it unsafe and challenging the US Food and Drug Administration (FDA) approval of the drug, and by invoking the 1873 Comstock Act, which prohibits the use of postal carriers to transport abortion-related material across state lines. They have also advocated for censorship of contraception literature containing so-called pornographic content to individuals younger than 18 years and have advanced the concept that many contraceptives induce abortion. To counter this claim the American College of Obstetricians and Gynecologists issued a statement specifying that none of the FDA-approved contraceptive methods are abortifacients because they do not interfere with pregnancy after implantation;[22] specifically, current scientific evidence indicates that barrier, surgical, and hormonal contraception methods primarily prevent pregnancy by blocking fertilisation.[23]

## Underserved populations

### Adolescent girls and young women

Adolescent pregnancies are a universal challenge and occur in high-income, middle-income, and low-income countries; however, they are more likely to occur in marginalised families and communities. Several factors contribute to adolescent pregnancies and births. One key factor is little access to and use of modern contraceptive methods. Adolescent girls and young women have unique needs and experience more barriers to accessing available reproductive health services than adults because of restrictive laws and policies, little awareness of available services, knowledge gaps, restricted transportation or financial resources, stigma, or little family or community support. Supportive social networks, respect for privacy and confidentiality, and affordability and accessibility of contraceptives, as well as the desire to prevent unintended pregnancy and STIs were the motivators of contraceptive use among young people in sub-Saharan Africa.[24] Despite these motivators, a myriad of personal, societal, and health system-based barriers (including myths and misconceptions, known side-effects of contraceptives, prohibitive social norms, and negative attitude of health professionals) were the major barriers to contraceptive use among young people in sub-Saharan Africa. A framework from the International Center for Research on Women lists three demand-side and two supply-side factors for not using contraceptives.[25] Demand-side factors include no expressed interest in avoiding, delaying, spacing out, or limiting childbearing; no expressed interest in using modern contraception; and poor confidence and ability to seek and negotiate contraception use. Supply-side factors include poor access to contraceptive services and to quality—including respectful—service provision. A foundational principle of this framework is that adolescents are a diverse group with varying needs. For example, girls and young women aged 10–19 years include those who are married or in union and those who are not, first-time parents, those living with HIV, and those living with disabilities. Data from Kenya from 2015 indicate enormous disparities in contraceptive use, in contraceptive methods used, in the primary sources of contraceptive methods, and in the reasons for not using contraceptives between those who are in union and those who are not.[26] These differences reinforce the need to understand the realities of key subgroups in adolescents and to tailor approaches to their needs and preferences. Even if adolescents want to avoid, delay, space out, or limit pregnancy and childbearing and want to obtain and use contraception, they might not have the self-assurance, organisational skills, or the autonomy to do so. They might be reluctant to admit that they are sexually active or embarrassed to seek contraception. They might also face opposition from their partners or other influential family members, who can overrule their decisions in some settings.[27]

### Men

Men can face cultural pressure to prove their fertility and are limited to three contraception methods: withdrawal, condoms, and vasectomy; all have unique problems that impact their acceptability, accessibility, and effectiveness.[28] No new male contraception methods have entered the market in over 100 years primarily due to a scarcity of financial backing. The development of male contraceptives lags the development of female contraceptives considerably; furthermore a disproportionate number of men do not use the few existing methods. Among male–female couples using contraception worldwide, 25% of men take the lead role in contraception.[7] In the case of surgical sterilisation, which carries a similarly low risk for both men and women, 2% of men worldwide have had a vasectomy, whereas 23% of women have been sterilised with tubal ligation.[7] As of 2022, the two most populous countries on earth, India and China, as well as most countries in Latin America and Africa, have a very low prevalence of men who have had a vasectomy; only a few countries (eg, South Korea, the UK, and Australia) have more men who have had a vasectomy than women who have had tubal ligation (figure 2). Contraception is widely considered a woman's obligation in current prevailing gender norms, since women usually shoulder heavier responsibilities and consequences with childbirth and rearing. Will men choose to do more to share the burden of contraception, and importantly, will women trust them?[29]

Introducing new male contraceptives will do more than just prevent unintended pregnancy. There could be benefits of fostering integrated health services, strengthening health systems for men to access seamlessly, enhancing health information and education, strengthening sexual and reproductive health metrics, and ensuring universal access to sexual and reproductive health care for all within a gender transformative and equitable environment.[28] It is imperative that men are engaged not just as supporters but beneficiaries of sexual and reproductive health services and products if gender equity in sexual and reproductive health and rights is to be fully realised.

### Transgender and gender non-binary populations

Transgender and gender non-binary individuals have a gender that differs from their sex assigned at birth. Transfeminine individuals include transgender women and non-binary individuals who were assigned male at birth and transmasculine individuals include transgender men and non-binary individuals who were assigned female at birth. Many cultures worldwide have long acknowledged more than two genders, and there is growing acceptance of the difference between gender and sex. Between 2007 and 2018, adults describing themselves as transgender ranged from 0·02 to 0·5% worldwide.[30]

Transgender and gender non-binary individuals might seek out sexual and reproductive care for a variety of reasons, including reasons similar to those of their cisgender peers (eg, fertility concerns and STIs), as well as reasons related to gender-affirming therapies.[31] Additionally, transgender and gender non-binary individuals might use gender-affirming medical therapies (eg, puberty blocking medications, oestrogen, antiandrogens, and testosterone) and undergo surgeries that influence their sexual and reproductive health.

Although there have been many advancements in gender-inclusive clinical care, there are also increasing legal, medical, and social barriers to transgender and gender non-binary individuals' rights to live safely and fully.[32] Conservative groups and administrations have increasingly focused on transgender issues, and used them to advocate for a range of restrictive measures.[33] Many transgender and gender non-binary individuals struggle to receive treatment owing to financial barriers, travel burdens, and prolonged waiting periods.[34] As noted by surveys, there is a scarcity of clinicians who have experience with gender-affirming care; most gynaecologists are not prepared to care for the transgender and gender non-binary population and less than a third report being comfortable with the provision of care for these patients.[35] As such, patients can have difficulty accessing both culturally and clinically competent care, particularly with regard to the influence of gender-affirming therapies for sexual and reproductive care.

Some transgender and gender non-binary individuals might engage in sexual activity that has the potential for pregnancy.[36] Although most gender-affirming genital surgeries are sterilising, individuals who have not yet undergone or do not desire to undergo these procedures could be at risk of contributing to a pregnancy or carrying one. Furthermore, no gender-affirming hormones are FDA approved for the purposes of contraception;[36,37] thus counselling is particularly important in contemporary care, especially as more transmasculine patients are desiring to take lower doses of testosterone (colloquially termed microdosing), which creates a hormonal environment more akin to polycystic ovary syndrome owing to the lower serum testosterone levels. Similar to patients with polycystic ovary syndrome, although taking testosterone interferes with ovulation, it can and does still occur. In patients taking testosterone it is important to discuss the use of progestins, both for contraception and for endometrial protection because of potential for unsuppressed oestrogen.[31]

Transfeminine individuals with male genitals can use the same contraceptive options as cisgender men, including barrier methods and vasectomy. Transmasculine individuals with a uterus and ovaries can use the same contraception options as cisgender females; all forms of this are considered acceptable to take alongside testosterone for those who use it. Despite nearly half of transmasculine adolescents and young adults who have a uterus reporting having sex with sperm-producing partners,[31] studies reveal that contraceptive counselling for this group has been inconsistent; some patients and clinicians incorrectly believe testosterone is a contraceptive.[31] Thus, many transmasculine individuals have discontinued contraception after achieving amenorrhoea on testosterone despite pregnancy risk.[38]

Transmasculine individuals report heterogeneous preferences for contraception and might have contraceptive goals and priorities that differ from their cisgender peers, including concealability or avoidance of invasive examinations.[36,37] Over 90% of transmasculine individuals have reported use of condoms by their partners as their preferred form of contraception, with 4–63% using combined oral contraceptives and 6–25% using a hormone-based (ie, levonorgestrel) intrauterine device, based on three US studies, including two clinical datasets and one population-based study conducted between 2013 and 2020.[38–40] They might also favour non-hormonal contraceptives owing to concerns about side-effects and interactions between testosterone and hormonal birth control.[36] Additionally, some transmasculine patients might also seek contraceptives for other indications including menstrual suppression monotherapy, as menses and menstrual-related concerns, including dysmenorrhoea or premenstrual syndrome, can worsen gender dysphoria.[40] Pelvic pain or breakthrough bleeding can also occur on testosterone, prompting desire for contraceptive use.[41–43] Lastly, up to 71% of transmasculine individuals in the USA desire to undergo, or have undergone, a hysterectomy for the purposes of gender affirmation or the desire to prevent future pregnancy.[31,34] Guidelines have been published to guide contraceptive counselling for transmasculine patients, including adolescents.[31,36,37] These guidelines aim to provide contraceptive counselling with a gender-inclusive approach.

## Solutions

Gaps exist, but several exciting innovations are under way in the areas of male contraception, non-hormonal female contraception, multipurpose prevention technologies (MPTs), and improving method acceptability.

### Innovative contraceptive technologies

#### *Hormonal male contraception*

The ability of exogenous androgen to reduce the sperm count and induce reversible male infertility has been known for 85 years,[44] and research in hormonal male contraception based on this finding has been ongoing since the early 1970s. Under normal conditions, gonadotropin-releasing hormone (GnRH) released from the hypothalamus is transported via the vascular system to the anterior pituitary gland, which responds to GnRH stimulation with pulsatile release of luteinising hormone (LH) and follicle-stimulating hormone (FSH) into the systemic circulation. FSH acts on the Sertoli

cells of the testicular seminiferous epithelium to support spermatogenesis. LH acts on Leydig cells in the interstitium of the testis to stimulate testosterone production, and the resulting high local concentration of testosterone in the testis promotes spermatogenesis in the seminiferous epithelium. Testosterone from the testis also enters the systemic circulation and exerts negative feedback on the hypothalamus to decrease GnRH release from the hypothalamus and gonadotropin release from the anterior pituitary, reducing testosterone synthesis. The negative feedback induced by endogenous testosterone can also be achieved by administration of exogenous androgens, as well as natural progesterone and synthetic progestins. Although numerous strategies to reduce gonadotropin release have been tried alone (eg, testosterone and GnRH antagonists) or in combination with androgen (eg, GnRH antagonist and oestrogen), the current male hormonal product pipeline is dominated by products with both androgen and progestin activity. Using these methods, sustained androgenic and progestenic activity reduces LH release, leading to decreased intratesticular testosterone, reduced spermatogenesis, and suppressed ejaculatory sperm concentrations. Ejaculatory sperm concentrations of less than 1 million sperm per ml—a concentration associated with effective contraception—are often effectively achieved by hormonal suppression.[45] When the hormonal contraception regimen is stopped, LH and FSH secretion returns to normal, normal levels of intratesticular testosterone return, and levels of spermatogenesis increase leading to normal ejaculatory sperm concentrations (figure 3).

Currently, a promising combination gel, called NES/T, has advanced into clinical trials. NES/T is a single transdermal gel product combining the progestin nestorone with testosterone that is applied daily to the shoulder and upper arm in men. NES/T formulations lowered sperm concentrations to less than 1 million sperm per ml in 88–89% of participants, compared with 23% of subjects in the testosterone only group. No serious adverse events were reported.[46] Other hormonal male contraceptive products, such as dimethandrolone undecanoate and 11B-MNTDC (synthetic testosterone derivatives that can be taken orally), are also undergoing clinical trials.[47]

### *Non-hormonal male methods*

The past 25 years have been an active period for the development of small-molecule male contraceptive methods that act on the hypothalamic–pituitary–gonadal axis. This approach identifies molecules that modulate a specific molecular target (eg, kinase) required for the formation and maturation of functional sperm. For the development of a contraceptive that has minimal side-effects, selecting targets exclusively or predominantly expressed in the reproductive system minimises potential systemic toxicity.

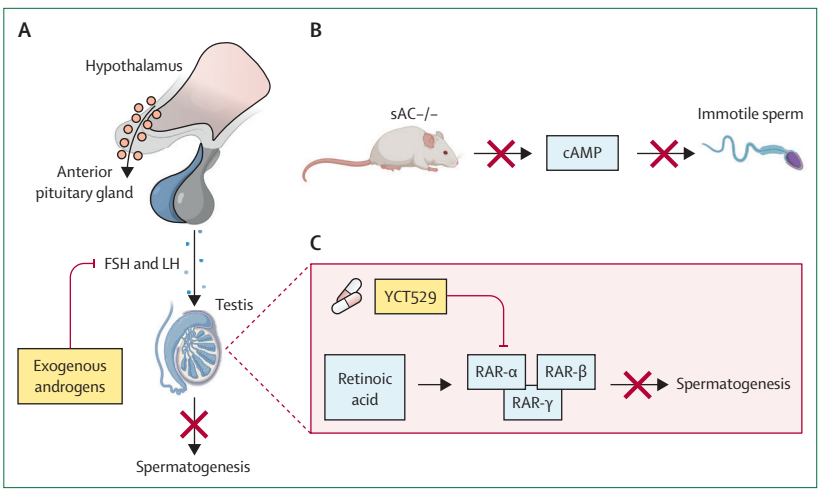



***Figure 3:*** **Mechanisms of new male contraceptives**
(A) Exogenous androgens inhibit spermatogenesis by blocking FSH and LH production by the anterior pituitary gland. (B) sAC promotes sperm motility and capacitation by generating cAMP. sAC genetic deletions and administration of sAC inhibitors impede sperm motility. (C) YCT529, a retinoic acid receptor antagonist, reduces spermatogenesis. Figure created with BioRender.com. cAMP=cyclic adenosine monophosphate. FSH=follicle-stimulating hormone. LH=luteinising hormone. sAC=soluble adenyl cyclase.

Male contraceptives designed to perturb the function of retinoic acid, which plays a crucial role in multiple areas of spermatogenesis, have been studied for more than 50 years. It has been shown that the deletion of retinoic acid receptor alpha (RAR-α) causes early postnatal lethality in mice, whereas RAR-α knockout mice that survive appear healthy but are infertile with drastically reduced spermatogenesis; this discovery targeted RAR-α for further investigation as a non-hormonal male contraceptive. YourChoice Therapeutics (San Francisco, CA, USA) is currently developing a selective RAR-α antagonist, designated YCT529, for male contraception, and has reported that single doses up to 180 mg were safe and well tolerated in phase 1a human clinical trials.[48] A phase 1b clinical trial is being planned to evaluate safety and pharmacokinetics of multiple doses.[48]

Studies have shown that soluble adenyl cyclase (sAC; *ADCY10*)—a molecule that plays a role in sperm motility and capacitation by generating cyclic adenosine monophosphate—is also a promising target for contraception. Targeted deletions of *ADCY10* in male mice result in infertility,[49] and a 2023 study showed that a single dose of a safe, fast-acting sAC inhibitor rendered male mice temporarily infertile.[50] Mating behaviour was not affected and fertility was restored within 24 h, showing reversible, on-demand male contraceptive activity. Additional research to improve drug-like properties, such as oral bioavailability and compound residence time, could extend the duration of effectiveness and lead to a clinical trial for this potential on-demand male contraceptive. Evidence that sAC might be relevant to human contraception derives from evidence that a sAC inhibitor, TDI-10229, inhibited human sperm motility, capacitation, and fertilisation

capacity in vitro[51] and that two healthy infertile men had identical frameshift mutations disrupting sAC's active site.[52]

*Non-hormonal female methods*

Ovaprene (Dare Bioscience, San Diego, CA, USA) is an investigational, hormone-free, monthly contraceptive intravaginal ring. Sperm transportation through the cervix is prevented by a knitted polymer barrier that spans the ring, and the release of ferrous gluconate—a spermiostatic agent that immobilises sperm—from the knitted polymer barrier.[53] Preliminary clinical trials indicate that the device is safe and effective at lowering numbers of progressively motile sperm in a postcoital test. The product is intended to be used continuously for up to one menstrual cycle. Patient enrolment in the Ovaprene pivotal phase 3 clinical study began in 2023. The study aims to have approximately 250 participants complete approximately 13 menstrual cycles (ie, 12 months) of product use.

Specific molecular targets from the male reproductive tract (eg, testis, epididymis, and prostate) are being developed as user-controlled vaginal contraceptive products. Inhibitory molecules targeting proteins required for sperm function can be administered to the vagina to lie in wait and prevent the movement of sperm into the upper regions of the female reproductive tract where fertilisation occurs. One example is the OneRing being developed by the Oak Crest Institute of Science (Monrovia, CA, USA) to protect women from both STIs (including HIV) and unplanned pregnancy for 1 month at a time. The vaginal ring contains two drug delivery cassettes: a novel anti-HIV agent and a unique inhibitor against sAC, the aforementioned target for on-demand male contraception. The contraceptive effect of this product is to prevent motility by acting on the sperm after they are deposited in the vagina. Investigators hope to initiate phase 1 clinical trials in the USA and sub-Saharan Africa in late 2025.

The field of immunocontraception began in the early 1900s with the discovery that sperm can elicit immune responses in animals and humans, often leading to infertility, and that many infertile men and women have antisperm antibodies.[54] Several international agencies, including WHO,[55] had contraceptive vaccine programmes directed at inhibiting sperm, oocyte, placenta, and endocrine processes. In the 1980s and 1990s, WHO conducted clinical trials to test the safety and efficacy of a contraceptive vaccine targeting human chorionic gonadotropin, a hormone secreted by the blastocyst to ensure uterine receptivity. The human chorionic gonadotropin vaccine trials showed safety, but antibody levels were highly variable, indicating that some women would not be protected from pregnancy.[56] These results, as well as pushback regarding potential side-effects and irreversible infertility, curtailed contraceptive vaccine development.

Today, the immunocontraception approach is undergoing a renaissance owing to breakthroughs in bioengineering and the ability to produce clinical-grade human monoclonal antibodies. The application of defined manufactured monoclonal antibodies using passive immunisation bypasses the concerns raised with contraceptive vaccines based on active immunisation, and thus—in theory—passive immunisation is safe, reversible, and the dose and site of administration can be precisely controlled.[57] One example is an antisperm monoclonal antibody, designated the human contraceptive antibody. This antibody, produced in tobacco plants, recognises an immunodominant sperm surface carbohydrate epitope on the glycopeptide CD52g, and rapidly agglutinates and immobilises sperm.[58] A vaginal film containing human contraceptive antibody has been tested in women in a phase 1 clinical trial and was shown to be safe and highly effective in a postcoital test.[59] Additional phase 1 and 2a clinical trials are under way.

*Contraceptive MPT*

Nonoxynol-N, a vaginal spermicide introduced in the 1950s for contraception, exhibited potent efficacy against HIV and other STIs in vitro,[60] and was tested in a series of clinical trials for efficacy against HIV-1 transmission. Unfortunately vaginal administration of nonoxynol-N was not only ineffective at preventing HIV-1 transmission,[61] it enhanced HIV-1 transmission in populations at high-risk owing to its genital inflammatory effects.[62] Other early non-specific MPT candidates including Saavy (C31G), Pro2000, Carraguard PC-515 (Carageenan), Ushergel (cellulose sulfate), and Buffergel also failed to show efficacy following vaginal administration in HIV clinical trials.[63] A few potent drugs that are not antiretrovirals but have anti-HIV activity remain in the MPT development pipeline including Griffithsin, polyphenylene carboxymethylene, and zinc acetate.[64]

A new class of contraceptive MPTs (cMPTs) combine potent antiretrovirals with previously approved contraceptive hormones. Levonorgestrel was added to the dapivirine intravaginal ring developed to prevent HIV sexual transmission; this contraceptive antiretroviral ring showed safety and effective drug release profiles for 3 months in phase 1 clinical trials.[65] Other potent antiretrovirals from various drug classes (eg, nucleoside reverse transcriptase inhibitors, nucleoside reverse transcriptase translocation inhibitors, and integrase strand transfer inhibitors) have been formulated into long-acting implants that release effective drug concentrations for 6 months to 1 year;[66] plans are under way to add a contraceptive hormone (eg, levonorgestrel) to these implants to develop long-acting cMPTs. Oral and injectable anti-HIV and contraception combinations are also being explored. The Dual Prevention Pill (DPP), an oral pill formulation that combines tenofovir disoproxil fumarate-emtricitabine with ethinylestradiol

and levonorgestrel, is currently undergoing clinical trials, and could be combined with a contraceptive pill for cMPT. Long-acting cabotegravir injections have been approved for HIV prevention and could be combined with effective injectable hormonal contraceptives, such as DepoProvera or norethisterone enanthate, provided that the timing of injections is aligned.

Several programmes are also pursuing the use of combinations of anti-STI and anti-sperm monoclonal antibodies as MPTs. For example, a vaginal film containing a combination of anti-HIV-1 and anti-herpes simplex virus monoclonal antibodies was shown to be safe and effective (ex vivo) in a phase 1 clinical trial.[67] Plans are under way to combine these antibodies with contraceptive antibodies to produce an on-demand MPT vaginal film or an intravaginal ring.[64]

## Improving the acceptability of contraceptives and MPTs

### *Background*

Users make contraceptive choices including the choice to not use a product; this decision is informed not just by objective product characteristics as defined by the target product profile (eg, efficacy, safety, route of administration, and duration of protection), but also by users' perceived attributes of the product (eg, appearance, fit with current sex life, and ease of storage) based on personal experience and preferences, reproductive history, interpersonal reasons, and health system and structural contexts (figure 4). Familiarity with and the acceptability of specific contraceptive methods influence clients' decisions.[68] When options are offered that combine a favoured contraceptive delivery form with another indication (eg, cMPTs) to enhance sexual and reproductive health care, user preferences increase, at least in hypothetical surveys conducted over the years and in diverse geographical settings.[69] In 2020, WHO reported that over 350 million treatable STIs and 1·5 million new HIV cases occur each year globally and approximately 500 million adults have genital herpes (caused by herpes simplex virus-2).[70] Although many sexually active people state they would choose a cMPT, the only cMPT products currently available—male and female condoms—do not adequately address their needs.

As conceptualised by the socioecological framework[13] (figure 4), barriers and facilitators of contraceptive and cMPT use act at multiple levels, including individual (eg, demographics and lifestyle), interpersonal (eg, relationship dynamics and attitudes of significant others), health systems (eg, cost or access and provider bias), social and environmental (eg, social stigma, social media, and housing), and structural factors (eg, gender norms and supply chain). There is a prevailing preference for cMPTs over single-indication products across populations and geographies. Potential end users perceive cMPTs as reducing user burden, increasing discreetness by concealing the more stigmatised outcomes (HIV or STIs), and being cheaper (eg, fewer clinical visits).[71,72] A robust MPT product pipeline exists, dominated by cMPTs; however it is mostly at the preclinical stage.[72,73] Furthermore, cMPTs that target all genders and marginalised people should be developed to address diverse needs across geographies and the sexual and reproductive lifespan. However, as cMPTs are technologically and regulatorily more complex to develop and bring to market than single-indication products, research and delivery is lagging (see the fifth paper of this Series[74] and Young Holt and colleagues' review[69]). Despite these challenges, various dosages (eg, DPP, on-demand fast dissolving inserts, or long-acting rings, films, and injections), are in active development;[64] of these DPP is close to regulatory approval.

### *Acceptability and preferences of dosage and delivery routes*

Familiarity, convenience, and locus of control are key drivers of dosage preference, along with the intended duration of use and the specific health indications targeted by the product.[71,75] Among the drug-delivery routes explored for women's health products, the vaginal route has secured the most attention for contraceptives, HIV prevention, and cMPTs.[61] Vaginal drug delivery presents multiple advantages, including little to no gastrointestinal interactions, minimal systemic drug distribution or side-effects, and suitability for on-demand self-administration.[57] However, depending on geography, some women prefer oral dosage over vaginal products owing to discomfort touching genitals, leakage, product retention, or insertion difficulties. Also, despite perceived discretion, users tend to worry about interference with sex when using vaginal products.[71] Yet, vaginal rings were found to be highly acceptable among users, despite lower acceptability overall in Africa than other geographical locations.[76] Notably, in an HIV pre-exposure prophylaxis (PrEP) crossover trial, in which adolescent girls and young women in Africa could try then choose between a monthly ring or daily oral PrEP, two-thirds chose the ring once familiar with the modality, despite being initially ambivalent about the ring before use and awareness of its lower HIV prevention efficacy compared with oral PrEP.[77] Preferences were driven by comfort, discretion, and duration of protection, with important cultural variations. Non-daily contraceptives and cMPTs are preferred by women and couples worldwide, leading to preference for non-oral routes if they decrease the frequency of dosage.[75,78,79] Although the use of daily oral contraceptives is widespread (~150 million users globally), users reportedly prefer weekly, monthly, or multi-month doses, especially in settings such as sub-Saharan Africa. Non-compliance, attributed in part to inconvenience or stigma of daily pill regimens over long periods, has been an ongoing problem in contraception and HIV and STI PrEP and post-exposure prophylaxis use.[79–81] Additionally, injections are familiar for other preventative medications (eg, vaccines)

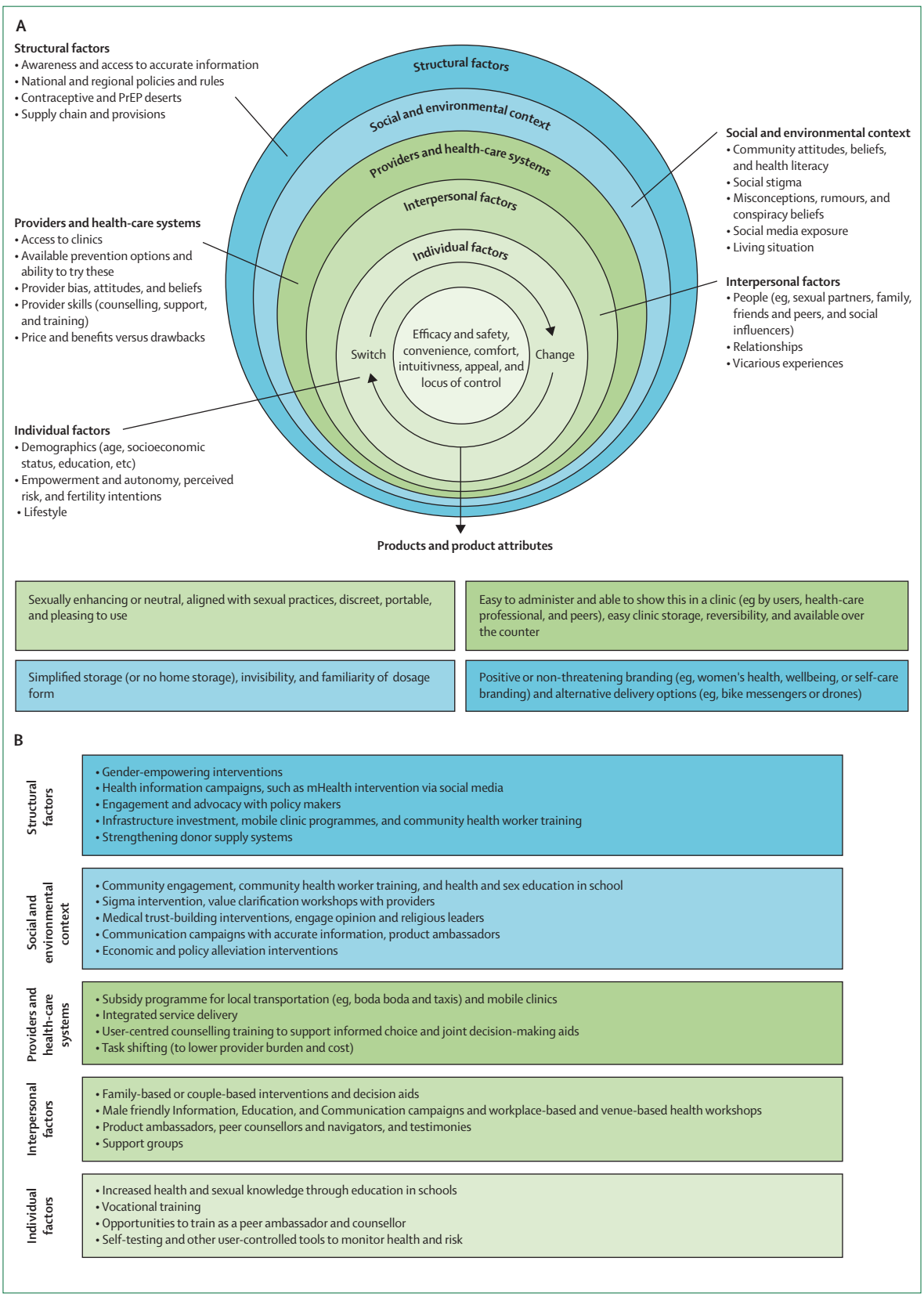



***Figure 4:*** **Socioecological framework showing influencing factors affecting acceptability and use of contraceptives and multipurpose prevention technologies**
(A) Type of factors organised according to the socioecological framework. (B) Examples of interventions to promote the adoption and use of contraceptives and multipurpose prevention technologies. PrEP=pre-exposure prophylaxis.

and for hormonal contraception (DepoProvera and norethisterone enanthate). For those engaging in infrequent sex or who dislike chronic drug exposure, including hormones, on-demand methods are appealing, especially if they do not interfere with a quick return to fertility, have fewer side-effects, and minimal menstrual perturbations, which are all major reasons for contraceptive discontinuation.

The needs of users can change over time and prevention options must align with these changes. Specifically, women might want to pivot from hormonal to non-hormonal contraceptives (or vice versa). Thus, access to multiple options with the ability to switch between methods is a lived reality that should be part of user-centred informed choice, counselling, and support.[82] One important driver of adoption of any innovation is its level of so-called triability,[83] which is mainly informed by personal experiences but can be facilitated if prevention options can be seen, tested, and tried (even on a partial basis at a clinic) or through vicarious experiences relayed by peers or providers (figure 4).[68,84]

### *Factors that influence the acceptability and use of prevention methods*

End-users' preferred characteristics regarding product formulation and composition are part of the product attributes that affect not only efficacy and safety, but also acceptability and use.[85] Although efficacy is a key attribute of any contraceptive method,[68] it is not the primary driver of choice. For example, in 2020 long-acting reversible contraceptives (LARCs; eg, intrauterine devices and implants) were used by only 15–20% of women who use contraceptives globally.[73] This number was even fewer in sub-Saharan Africa, despite showing very high efficacy; thus, efforts are being made to improve LARC access in this region to increase coverage.[73] Provider administration, invasiveness of placement, and reversibility concerns with intrauterine devices and subdermal implants might explain sub-optimal adoption, especially when providers are not appropriately trained for removal and counselling regarding side-effects,[86,87] along with practical considerations, such as transportation, clinical accessibility, and cost of delivery. Stigma and urban myths can also act as barriers to effective method use, especially for adolescent girls and young women in settings where premarital sex is frowned upon, as LARCs are plagued by misinformation.[64] Possible improvements from the perspective of end-users with LARCs or long-acting PrEP and cMPTs include subcutaneous injections (that can be self-injected), increased duration (≥6 months), and biodegradability, which would circumvent the need for method removal.

Lastly, physical and sensory attributes such as size, shape, colour, texture, softness, and smell are important when designing products to increase appeal and comfort and can influence perceptions of use and efficacy by users.[75] Additionally, branding (eg, as a wellness product) is influenced by these physical attributes, along with packaging and delivery outlets (pharmacy, supermarket if over the counter, or clinics).[72] Interpersonal factors and social factors also drive women's product preferences and choice. For example, for the DPP, relationship goals, partners' concerns of the women's increased sexual freedom, and providers' sex-related bias have all been shown to inform interest for and hypothetical acceptability by potential users.[88,89]

### *Options and informed choice to better support sexual and reproductive health outcomes*

It is well established that expanding options will increase contraceptive coverage at the population level.[90] Adding new contraceptives and cMPTs to the mix of prevention methods should continue to increase population-level coverage for those indications. In South Africa, for example, the Constitution protects the rights of all people to make their own decisions regarding reproduction, and gives them security in, and control over, their bodies. This means it is every person's own decision whether or not to have children. The South African Constitution recognises that both women and men have the right to know about contraception, and to have access to safe, effective, affordable, and acceptable methods of contraception of their choice. Each country's constitution will need to uphold their laws; however, this is likely to vary. Acceptability and willingness to use the available options for the most marginalised comes down to individual choice; the opinions of influential friends or family; and the navigation of personal, societal, and structural barriers to sustained uptake of effective options. A wider array of contraceptives must be paired with efforts to sustain provider skill-development in counselling.

Improved community sensitisation[71] along with the health literacy of users and health-care providers to solidify informed choice processes—including the pros and cons of different methods—are essential, especially for new methods reaching the market. Several possible interventions are highlighted in figure 4B to support the adoption and use of new methods. Accurate information and education are also crucial whenever innovations are introduced. Choices regarding women's health products are influenced by the environment created by opinions from intimate partners, family, and friends, and from the health-care providers who ultimately counsel women regarding preventive strategies. The engagement of health-care providers is key, as they are trusted experts, product gatekeepers, and administrators of methods that are not self-initiated. Shared decision making between clients and providers supports women's autonomy and decision making while allowing providers to advise their clients on available options and ensuring respect of constitutional rights.[91] Lastly, departments of health need to become enabling environments to ensure choice is prioritised and method switching is supported, especially

### *Panel*: Action items

Contraception and family planning are crucial components of sexual and reproductive health and rights. Despite major advances in contraceptive technologies over more than half a century, substantial unmet needs remain. Providing improved contraception choices will improve the health, economic status, and wellbeing of women and their families and is an important step towards social justice. To achieve this goal, we recommend the following:

- Current contraception gaps should be addressed by intensifying modern basic and clinical research including social and behavioural science. Scientific breakthroughs, fuelled by innovative research, are leading the development of next-generation contraceptives with new molecular targets, especially for non-hormonal contraception already in clinical trials. Intensification of financial support from government, philanthropic, and industrial entities is needed and could produce novel contraceptives that address some of the current gaps within 10 years.
- Needs of underserved populations should be addressed to achieve equity and population-level impact. Special effort should be devoted to male contraception, which seriously lags female contraception. Novel products and intensified messaging are needed for the male population.
- Technological advancements are necessary but not sufficient and thus understanding user preferences will be key to guaranteeing adoption and success.
- Providers are key actors and must be trained and supported by health systems to inform, educate, and counsel users to achieve their sexual and reproductive goals through informed choice.
- Integrating knowledge and technologies from related fields (eg, HIV and sexually transmitted infection prevention and family planning) to develop multipurpose technologies and holistic programmes that simplify the needs of users and upskill the health-care providers might be technologically, regulatorily, and financially complex, but can provide attractive options and should be pursued (see the fifth paper of this Series for an in-depth discussion on integration).
- Despite current conservative sentiments, the best way to improve family planning and promote women's health is to offer better contraception education and more options to those who wish to avoid unplanned pregnancy. Government and funder policies that impede contraception research, education, and availability should be countered with the information provided in this paper.

in resource-constrained settings, where provider-preferred method selection (eg, those with the lowest health-service delivery burden) drives delivery of methods.[82] Action items to improve contraception choices are listed in the panel.

**Contributors**
DJA conceptualised the paper and wrote the first draft. JMB, FWG, TP-P, and AvdS participated in group discussions, wrote sections of early drafts, and reviewed and edited subsequent drafts of the manuscript.

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