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Infectious Diseases

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Director's Corner

Janine Austin Clayton, M.D., FARVO
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Despite groundbreaking advances in vaccines and treatments, infectious diseases continue to depress population health. Infectious diseases pose unique risks to women because of profound sex-based differences in immunity. In addition, gendered power dynamics and structural sexism can place women at elevated risk for contracting certain infectious diseases, such as HIV and sexually transmitted infections (STIs), and limit their ability to access and maintain treatments.

In this issue of In Focus*, we review several exciting areas of research on infectious diseases that are female specific (e.g., bacterial vaginosis) or that affect women differently than men (e.g., influenza, COVID-19). The feature story highlights several critical areas of NIH-supported research: the vaginal microbiome and its role in protecting women from STIs; the use of 3D brain organoids to study neurological complications of infectious diseases; efforts to combat the resurgence of syphilis in the United States and abroad; and progress on preventing and treating HIV infections in U.S. populations disproportionately at risk for HIV.*

For our Women in Science interview, we hear from Jeanne Marrazzo, M.D., M.P.H., who joined NIH as the sixth director of the National Institute of Allergy and Infectious Diseases in 2023. We are delighted to share her perspectives on advancing the progress of women in biomedical careers and the research areas she considers critical for improving women's health.

This issue also spotlights several recent ORWH events and research articles relevant to women's health. Please share In Focus *with your colleagues. You can subscribe to* In Focus *online.*

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Sex and Gender Differences and Infectious Disease

Erica Ollmann Saphire, Ph.D., M.B.A.,

La Jolla Institute for Immunology

Sex and gender affect health, including vulnerability to infectious disease. One prominent example is the profound influence of sex on immune function and response to infections. These sex differences stem from two sources: (1) differences in sex steroid hormone levels and (2) chromosomal differences between the sexes, says Sabra L. Klein, Ph.D., a professor of molecular microbiology and immunology at Johns Hopkins University who studies sex differences in the immune system. Nearly all immune cells—including innate immune cells, antibody-producing cells, and cells involved in cellular immunity—have sex steroid hormone receptors. When sex steroids such as estrogen, progesterone, and testosterone bind to these immune cell receptors, they can act like dimmer switches, up- and downregulating gene expression and the activity of the immune cells. In general, estrogen increases immune responses, while androgens such as testosterone dampen them, says Erica Ollmann Saphire, Ph.D., M.B.A., president and CEO of the La Jolla Institute for Immunology. During pregnancy, for example, progesterone upregulates the activity of a type of T cell known as a regulatory T cell, which reduces inflammation and helps protect the pregnancy.

Sex and Gender Are Multidimensional Constructs

Sex is a multidimensional biological construct that encompasses what are sometimes referred to as "sex traits" (i.e., anatomy, physiology, genetics, and hormones).[1] By contrast, gender is a multidimensional construct that encompasses gender identity and expression of social and cultural expectations about status, characteristics, and behaviors associated with certain sex traits.[1] Sex and gender interact in complex ways to affect health and vulnerability to disease. In this article, we use the terms "male" and "female" to refer to individuals with XY and XX chromosomes, respectively. (Rarely, individuals inherit additional Y or X chromosomes, or only a single X chromosome. For example, approximately 1 in 500 males inherit an additional X chromosome.[2])

Sex differences in immunity also stem from sex chromosomes. Chromosomes are packages of genetic material found in our cells. Humans typically have 23 pairs of chromosomes, including a pair of sex chromosomes—typically either XY for males or XX for females.

In humans, the X chromosome is much larger and contains considerably more genetic material than the Y chromosome. To maintain normal levels of gene expression, female (XX) cells therefore inactivate one of their two X chromosomes.[3] Which X is inactivated in a cell is determined at random early in development.[4] A classic example of the consequences of X-inactivation is calico cats, which are always female. The genes for cats' hair color reside on the X chromosome. X-inactivation causes their cells to express different hair color genes, resulting in their characteristic patchwork colored fur.

Sabra Klein, Ph.D., Johns Hopkins University

X-chromosome inactivation was once thought to be a simple story, but research over the past two decades has revealed that X-inactivation is incomplete. Roughly a quarter of the genes on the inactivated chromosomes are still transcriptionally active, says Dr. Saphire, with the result that these genes are expressed more in female (XX) cells than in male (XY) cells. In addition, the X chromosome contains more than 1,000 genes involved in the functioning and regulation of the immune system, many of which escape inactivation, Dr. Saphire explains. As a result, females express many immune-related genes on both of their X chromosomes, leading to greater gene expression than in males, who typically have a single X chromosome. Moreover, female (XX) cells can express these genes from either X chromosome, resulting in a wider palette of immune-related genes than in male (XY) cells, adds Dr. Saphire.

These sex-based differences in gene activation and diversity, in combination with females' generally higher levels of estrogen, mean that females typically mount stronger immune responses to infections than males—a sex difference found throughout the animal kingdom, from sea urchins to mice to humans, notes Dr. Saphire. In humans, for example, after the same degree of viral exposure, males typically have higher viral loads (i.e., more copies of virus in bodily tissues) than females. In addition, females generally produce more robust antibody responses to vaccination. The downside of females' stronger immune reactions is a greater risk for long-term inflammation following infection and higher risk for developing autoimmune diseases, she adds.

Recognizing the profound nature of sex differences in immunity can help move fields such as immunotherapy away from a one-size-fits-all to a sex-based approach that determines whether males and females need different dosages or types of immune-activating therapeutics. "Assuming men and women are identical and then averaging them together results in one-size-fits nobody," says Dr. Sapphire. "We understand that women and men need different styles of blue jeans, so why are we assuming men and women will have the same reaction to an immune-activating therapeutic?"

Ultimately, recognizing and studying sex differences is a wellspring for scientific discovery, notes Dr. Saphire. Discovering sex differences for infectious diseases allows researchers to probe what is different about male and female cells that leads to differential susceptibility, which biological pathways are involved in disease, and what might be druggable targets.

Respiratory Infections

Males and females differ considerably in their responses to respiratory infections, such as influenza, COVID-19, and tuberculosis. Reproductive-age women typically have stronger antibody responses to influenza vaccination than reproductive-age men, but also report more side effects from vaccination.[5] Males typically experience more severe symptoms and higher mortality rates from COVID-19 than females, while females are more likely to report experiencing prolonged symptoms following acute COVID-19 infections.[6]

To study the causes of sex differences in response to respiratory infections, Dr. Klein has employed an elegant mouse model system, known as the four core genotype mice. The four core genotype mice have the Sry gene—which is responsible for testes versus ovaries development—deleted from the Y chromosome. The gene is then optionally inserted into chromosome 3 to separate gonadal sex (i.e., having ovaries or testes) from sex chromosome complement (i.e., having XX or XY sex chromosomes).

Using these mice, she has shown that reproductive-age mice with ovaries have stronger antibody responses to inactivated influenza vaccines than reproductive-age mice with testes, regardless of sex chromosome complement. And when challenged with live influenza virus, immunized mice with ovaries fared better than immunized mice with testes regardless of sex chromosome complement.[7] Aged female mice with low estrogen levels generally had poor antibody responses to inactivated influenza vaccines. However, Dr. Klein has shown that estrogen replacement therapy boosted their antibody responses. Together, these studies demonstrate that differences in estrogen levels accounted for the observed sex-based differences in antibody responses to vaccination and subsequent protection from disease.

Dr. Klein's findings underscore the importance of studying sex as a biological variable and of carefully evaluating how sex-based biology contributes to observable sex differences. Dr. Klein is also probing how sex-based biology affects responses to other respiratory infections such as tuberculosis, noting that the complex host-microbe interactions dictate the outcomes associated with underlying sex differences in immunity.

Infectious Disease, Sex, and Gender

Gender interacts in complex ways with sex-based differences in immunity and susceptibility to infectious diseases. Throughout the world, gender-based roles, norms, and power structures affect women's risk for exposure to infectious diseases and their ability to be tested and treated for these diseases. For example, gender-biased roles and responsibilities, such as caregiving, nursing, and certain farming practices can place women at increased risk for exposure to certain infectious

Investigating the Neurological Consequences of Infectious Diseases

Karin Peterson, Ph.D., NIAID

Numerous diseases can have neurological consequences. For example, poliovirus can attack the central nervous system, leading to paralysis and, in especially severe cases, death. The La Crosse virus, a mosquito-borne virus, is a leading cause of pediatric encephalitis and can result in long-term learning and memory deficits.[8] For some viral infections, neurological consequences can present long after the acute infection. Although rare, measles can cause a condition known as subacute sclerosing panencephalitis 7–10 years after infection.[9] Subacute sclerosing panencephalitis has no cure; it invariably leads to brain inflammation and death. Recent research suggests that the autoimmune disease multiple sclerosis (MS), in which the immune system attacks and destroys the myelin sheaths surrounding nerve cells, is a result of infection with the Epstein Barr virus.[10] Like many autoimmune disorders, MS predominantly affects females; three quarters of people with MS are women.[11]

To study these diseases, researchers often use a variety of models and techniques, such as animal models, human cell culture, imaging, and human autopsies. But now, newly developed bioengineering techniques enabling researchers to study the effect of these diseases on multiple human brain tissues in 3D.[12] Using these techniques, researchers can build 3D model brain organoids that can be maintained in laboratory cultures for up to a year.[12] Grown from human pluripotent stem cells, brain organoids can be cultured to include brain areas such as the cerebral cortex, choroid plexus, and ventral telencephalon.

The ability to grow 3D human brain tissue in a laboratory opens new vistas for research on human brain development and on preventing and treating a diverse range of neurological conditions, including those stemming from infections. For example, Karin E. Peterson, Ph.D., a senior investigator at the National Institute of Allergy and Infectious Diseases (NIAID), has used these organoids to screen a library of Food and Drug Administration (FDA)-approved small molecules for the ability to protect neurons from the harmful effects of La Crosse virus.[13] She is now collaborating with Bibiana Bielekova, M.D., another senior investigator at NIAID, to study how immune cells derived from patients with MS interact with these organoids.

diseases and for receiving antibiotics, which can breed antimicrobial resistance and place them at increased risk for adverse drug reactions.[14] In addition, gender inequality and reduced societal and economic status can limit women's ability to refuse unsafe sex, placing them at elevated risk for contracting sexually transmitted infections (STIs). Stigma and power imbalances in romantic partnerships can hinder women's ability to access and adhere to treatment for infectious diseases such as HIV.

HIV

Worldwide, women and girls comprise just over half of the people living with HIV.[15] In 2021, 18% of new HIV diagnoses in the U.S. were among women, with most women acquiring HIV from a male sex partner living with HIV.[16] Significant disparities exist in HIV acquisition by race, geography, socioeconomic status, and sexual and gender minority status.[17]

So much attention is focused on racial disparities among men living with HIV that disparities among women are sometimes overlooked, says Nada Fadul, M.D., who serves as assistant dean and professor of medicine in the University of Nebraska Medical Center (UNMC) Department of Internal Medicine's Division of Infectious Diseases and medical director of the UNMC Specialty Care Center. Yet, disparities among women are often stark. In Nebraska, for example, Black women are diagnosed with HIV at eight times the rate of White women. Although effective antiviral regimens are available, multiple social and structural factors can reduce women's ability to adhere to therapy and maintain viral suppression, including substance use, lack of health insurance or health care access, and intimate partner violence.[18] In addition, health care access can be particularly challenging for women living in rural areas. Dr. Fadul is now testing a new program to facilitate access to long-acting antiviral injections, taken every 2 months, at rural clinics. Women living in rural areas often cannot drive for hours every 2 months to receive their injections, so this program is providing injectables to local clinics and then using telehealth to monitor for viral suppression and side effects.

Nada Fadul, M.D., University of Nebraska Medical Center

One area Dr. Fadul would like to see explored further is promoting a sense of self-efficacy among women living with HIV. Researchers have found that higher self-efficacy

Tonia Poteat, Ph.D., Duke University School of Nursing

corresponds to better treatment adherence and viral suppression among women.[19,20] She shared that clinicians and other health care workers should do more while "working with women living with HIV to improve their self-efficacy and to empower them to see themselves as still beautiful, still worthy, still effective, still contributing to the society in a positive way while living with HIV."

Another group disproportionately impacted by HIV are transgender women, particularly Black and Latina transgender women, says Tonia Poteat, Ph.D., professor at the Duke University School of Nursing who studies HIV treatment and prevention among sexual and gender minorities. An estimated 1 in 10 transgender women in the U.S. are living with HIV—a rate much higher than the 0.3% of the general population living with HIV.[21] For Black transgender women, the prevalence is greater than 40%, and for Latina transgender women it is 25%, says Dr. Poteat.

Multiple social and structural factors contribute to transgender women's high rates of HIV, chief among them being stigma and discrimination, says Dr. Poteat. Discriminatory policies affect transgender women's ability to access public bathrooms and health care. Stigma and discrimination limit their education, work, and housing opportunities. This confluence of factors heightens their vulnerability to depression, substance use, and sexual coercion, she adds.

Through extensive interviews with transgender women, Dr. Poteat noted that providing gender-affirming care provides an opportunity to connect and promote interventions to protect HIV-negative transgender women from infection. "Gender-affirming care is an area where clinicians, health systems, and public health workers can take action and use our spheres of influence to create affirming environments for people," she says. She is currently conducting an 18-month-long randomized controlled trial with transgender women across five cites (four in the United States and one in Brazil). The trial will assess the benefits of providing pre-exposure prophylaxis (PrEP) alongside gender-affirming care. Drawing on research showing the importance of self-efficacy in treatment adherence, this intervention uses a strengths-based approach to promoting adherence. As part of the trial, participants work with health care navigators who help them identify their personal strengths, such as persistence and social support, to overcome challenges to adhering to PrEP.

Long-acting preventive therapies such as lenacapavir are another promising approach to preventing HIV infection. Lenacapavir is a new twice-yearly injectable antiviral therapy that inhibits the formation of HIV's protein capsid—the outer coating that protects viral enzymes and RNA. Results from a landmark trial comparing lenacapavir with once-daily oral PrEP were so striking they received a standing ovation at the AIDS 2024 conference in Munich, Germany, this summer: Of the more than 2,000 girls and women living in sub-Saharan African who received lenacapavir, not one contracted HIV. Results from a similar trial in men are expected later in 2024 or early 2025.

NIH is funding two clinical trials comparing lenacapavir with once-daily oral PrEP focused on two populations underrepresented in clinical research on HIV treatment.[22] The first trial will recruit cisgender women who identify as Black and/or Latina, and the second will recruit individuals who inject drugs.

Many people hope that these long-acting therapeutics will rekindle now-stalled progress on ending the HIV epidemic. Ultimately, whether the promise of these treatments is realized depends on many factors, some of them difficult to predict, including what adherence looks like in practice, outside the context of carefully managed clinical trials; whether health systems in different areas of the world can administer the therapy; how rapidly HIV develops resistance to these new therapies; and, importantly, cost. The yet-to-be-determined price of lenacapavir for low- and middle-income countries will have a tremendous impact on whether people who could benefit the most from these treatments can access them.

In addition to these clinical trials, ORWH and the Office of AIDS Research (OAR), in collaboration with other NIH institutes, centers, and offices, are working to advance research on HIV and women's health. Although researchers have made considerable progress in addressing the HIV epidemic, women of color, young women, transgender women, and gender-diverse individuals continue to be disproportionately impacted by HIV. Intersectional, equity-informed, and data-driven research is therefore essential for advancing prevention, treatments, and clinical care for all women. To highlight NIH's interest in funding HIV-related grants that center the health needs of cisgender women and girls and gender-diverse people, ORWH and OAR have developed a joint signature program that includes a Notice of Special Interest (NOT-OD-24-119) and a Notice of Information (NOT-OD-24-117).

Bacterial Vaginosis

Bacterial vaginosis is the most common vaginal infection in reproductive-age women, affecting roughly a quarter of women worldwide.[23] Common symptoms include itching, irritation, burning during urination, and changes in vaginal odor and discharge, but often women with bacterial vaginosis experience no symptoms.

Even when asymptomatic, bacterial vaginosis increases women's risk of contracting STIs such as gonorrhea and HIV—the latter by approximately 60 percent.[24] During pregnancy,

Surpriya Mehta, M.H.S., Ph.D., RUSH University and University of Illinois

bacterial vaginosis also increases the risk of premature labor.

This common infection results from a shift in the balance of the bacteria that live in the vagina (i.e., the vaginal microbiome). Unlike the gut microbiome, where greater bacterial diversity is generally considered beneficial, having a less diverse vaginal microbiome is considered beneficial. An optimal vaginal microbiome is one dominated by Lactobacillus bacteria, particularly a type of Lactobacillus known as L. crispatus, explains Surpriya Mehta, M.H.S., Ph.D., professor of infectious disease medicine at RUSH University and adjunct professor of epidemiology at the University of Illinois, Chicago. "L. crispatus helps maintain the acidic environment of the vagina, prevents overgrowth of 'bad' bacteria by consuming resources such as glycogen, and has anti-tumor and anti-viral effects," she adds.

Overgrowth of other bacterial species, particularly those that thrive in low oxygen environments, can shift the bacterial balance in the vaginal microbiome. These shifts can lead to bacterial vaginosis, increase inflammation, disrupt mucus production, and weaken the protective barriers between cells that are formed by cell-to-cell connections known as epithelial tight cell junctions. These changes not only increase women's risk for STIs but also are associated with a doubling of risk for cervical cancer.[25]

Worldwide, use of unsafe and unhygienic menstrual products is a risk factor for bacterial vaginosis. Women and girls who cannot afford or lack reliable access to commercial menstrual products often resort to using and reusing tissue paper, rags, cloth, or even paper, says Dr. Mehta. Use of these unhygienic products increases their risk for bacterial vaginosis by transferring harmful bacteria into the vagina and by occluding the vaginal canal, contributing to a low-oxygen environment in which harmful bacteria can thrive. Women and girls who lack access to commercial menstrual products are also vulnerable to coercive sex, which can increase their risk of STIs. A household study of 3,418 women and girls in rural western Kenya found that 1 in 4 were using unhygienic products such as cloth and rags, and 1 in 10 girls aged 15 years reported engaging in sex for sanitary pads or for the money to buy them.[26]

Reusable menstrual cups may help improve access to safe menstrual products worldwide and may help prevent bacterial vaginosis. Silicone-based menstrual cups can be sterilized and reused for up to 10 years and thus provide a low-cost alternative to other commercial menstrual products such as tampons and pads.[27] During menstruation, the blood in the vaginal canal makes the vaginal environment less acidic[28] and provides additional iron that can spur the overgrowth of harmful bacteria, explains Dr. Mehta. These changes can increase women's risk for bacterial vaginosis and STIs. However, menstrual cups help reduce these changes by sequestering blood away from the vaginal wall. Her research on 436 schoolgirls in Western Kenya has shown that girls randomized to using menstrual cups had a 24% lower odds of developing bacterial vaginosis,[27] a 37% increased chance of having a vaginal microbiome dominated by L. crispatus,[27] and a 33% lower risk of contracting Herpes Simplex Virus 2.[29]

Syphilis

Although curable with penicillin since 1943,[30] syphilis cases continue to surge in the U.S., rising from 113,739 in 2018 to 203,500 in 2022.[31] Syphilis is caused by the bacteria Treponema pallidum. It primarily spreads through sexual contact but can also be passed from a mother to her baby during pregnancy or delivery (congenital syphilis). Although still rare, cases of congenital syphilis in the U.S. have increased by a staggering 477% since 2012.[32]

Jodie Dionne, M.D., University of Alabama and UAB Center for Women's Reproductive Health

Pregnant women who acquire syphilis during pregnancy have the greatest chances of passing the infection to the fetus, says Jodie Dionne, M.D., associate professor of medicine and associate professor of obstetrics and gynecology at the University of Alabama, Birmingham (UAB), director of the Infection in Women and Pregnancy Research Program, and associate director of Global Health at the UAB Center for Women's Reproductive Health. Women who were infected years prior to pregnancy, she adds, can also transmit the infection to their fetus, because *T. pallidum* intermittently replicates for years following untreated infection. Fetal infection can lead to miscarriage, stillbirth, premature birth, and congenital syphilis in the infant. Infants born with congenital syphilis may have low iron levels (anemia), deformed bones, neurological complications such as blindness or deafness, an enlarged liver or spleen, and other health problems.[33]

Unlike HIV, which often passes from mother to baby during delivery, syphilis more commonly infects the fetus during pregnancy—underscoring the importance of screening and treatment during pregnancy. Studies show that treatment during pregnancy can prevent adverse outcomes about 90% of the time, says Dr. Dionne. Screening throughout pregnancy is particularly critical, she adds, because screening only early in pregnancy can miss infections acquired later in pregnancy.

Further complicating screening and treatment, syphilis is often difficult to diagnose. The first sign of syphilis is a painless skin

ulceration known as a chancre. In women, chancres often occur inside the vaginal canal, where they are not readily detected. Some clinical tests for syphilis assess the presence of blood-based antibodies to T. pallidum and remain positive for life following infection. Detecting and treating repeat infections is therefore extremely challenging.

To begin to address these issues and to better understand the immune response to syphilis during pregnancy, Dr. Dionne is conducting an NIH-funded observational study of pregnant women with and without confirmed syphilis infections in Cameroon and Zambia, where Dr. Dionne has found extremely high rates (2%–6%) of syphilis during pregnancy.[34,35] All women diagnosed with syphilis during the trial will receive antibiotic treatment. Dr. Dionne will collect pre- and post-treatment blood samples, cord blood, and placentas from pregnant women and swabs from the oral cavity, genital tract, and chancres, and will assess infant outcomes throughout their first year of life.

The study advances several important goals. Data from this study will help characterize the specific aspects of the infection involved in disease progression and transmission to the fetus. The data will also improve understanding of the maternal immune response and how it affects transmission of the infection to the fetus and infant outcomes. Dr. Dionne will test the oral and chancre swabs using quantitative polymerase chain reaction to determine whether they can improve syphilis diagnosis in pregnant women. Longer term, these data may help inform the development of a syphilis vaccine.

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Women in Science Spotlight: An Interview with NIAID Director, Dr. Jeanne Marrazzo

Jeanne Marrazzo, M.D., M.P.H., National Institute of Allergy and Infectious Diseases

In 2023, Jeanne Marrazzo, M.D., M.P.H., joined NIH as the sixth director of NIAID. Dr. Marrazzo is internationally recognized for her research and education efforts in the field of sexually transmitted infections (STIs), particularly those that disproportionately affect women's health. Before joining NIAID, Dr. Marrazzo served as the director of the infectious disease division at the University of Alabama at Birmingham. She is passionate about mentoring and received the American Sexually Transmitted Diseases Association's Distinguished Career Award for her research and mentoring in the field.

How did working with women affected by HIV stimulate your interest in women's health research?

During my residency, I worked with women affected by HIV before effective antiviral therapy was available. These women, often poor and with limited health care access, were particularly vulnerable, contracting HIV from partners with multiple relationships. This experience highlighted the broader networks of risk beyond individual behavior and fueled my passion for advocacy and interdisciplinary care.

My interest in STIs grew, especially because they disproportionately affect women's reproductive health. As a young faculty member, I led a Centers for Disease Control and Prevention (CDC)-funded training center, where I noticed a gap in understanding of vaginal health. This led me to focus on the vaginal microbiome, which was not taken seriously in research despite its importance.

What are some recent highlights from NIAID-supported research related to women's health?

I would like to highlight two game-changing research developments.

First, a new malaria vaccine was featured in The Lancet Infectious Diseases *in August 2024.*[1] *Malaria is particularly dangerous for pregnant women and children. What is remarkable about this study is that it included women who anticipated getting pregnant, unlike most trials that exclude them. The vaccine was highly effective, reducing malaria rates by 50%–60%, and it may have contributed to more successful pregnancies. Given that existing vaccines are only about 30% effective, this is a significant breakthrough.*

Second, the PURPOSE 1 study presented at the International AIDS Society Meeting introduced lenacapavir, a long-acting HIV drug injected every 6 months for prevention. Among 2,400 women in Uganda and Kenya who received the injection, there were zero HIV infections, compared to a 1%–2% infection rate in other groups. This approach could be revolutionary in reducing HIV risk for women.

In what areas would you most like to see additional research related to women's health and infectious disease?

We are facing an alarming increase in congenital syphilis in the U.S. We had basically eliminated it, with no detected cases for many years. Last year, however, there were more than 3,600 cases and more than 250 infant deaths, up from zero. The circumstances leading to these outcomes are complex, often involving women who face significant challenges in accessing good prenatal care. This highlights how we've likely neglected our investment in non-HIV STIs.

I would really like to see a syphilis vaccine tested in humans within the next 5 to 6 years, and the same for a herpes vaccine. Genital herpes is a lifelong infection; while we have drugs to manage it, we cannot cure it, and it increases the risk of acquiring HIV, particularly in areas where both infections are common. Women are especially vulnerable to STIs, not just in terms of pregnancy outcomes but also due to the structure of their reproductive tract. Prioritizing the development of vaccines to prevent syphilis, gonorrhea, and chlamydia would be a game changer for women's health.

What accomplishments are you most proud of?

I am most proud of the people I have mentored and supported to take over my roles. I have never felt bad about leaving a job or transferring leadership because I have prioritized building up my team, and I am incredibly proud of those individuals. I am also proud of the people I have recruited, especially during my time in Alabama, where I helped them realize their potential and how they could grow.

I am also proud of being interdisciplinary, working across both HIV and STI fields. It might seem less unusual now, but when HIV was the focus, few were talking about STIs and their role. My work on the vaginal microbiome, which has relevance for both HIV and STIs, reflects my belief in a person-centered approach. I'm proud of not being partisan about these interests because people have various infections and conditions. Embracing this holistic perspective is something I'm truly proud of.

What are some of the challenges you have faced as a female scientist and leader? And what advice would you give to fledging female scientists?

I have to say I have been very fortunate. I have had amazing female role models, especially during my time at the University of Washington in Seattle, where there were many prominent women leaders. I never felt like women were not taken seriously in that environment. It was a shock to encounter different settings where that was not the case. Being in a supportive environment where you can see yourself in leadership roles gives you a lot of power. Unfortunately, not every woman has had that opportunity, which remains a big challenge.

Like everyone, I have experienced the phenomenon of being talked over or not treated as an expert, but those instances have become fewer. I think this is partly because our male colleagues have evolved in their roles as caretakers and professionals, learning to coexist with a diverse group of people. It's definitely getting better.

Having seen women take control and own their leadership roles was incredibly empowering for me, and I have tried very hard to convey that sense of empowerment to those around me.

What do you see as some of the most important ways to support the advancement of women and underrepresented minorities in science and biomedicine?

I spend a lot of time talking to underrepresented groups about imposter syndrome. It ties back to visualizing yourself as a leader, even when there is no one who looks like you in those roles. Being a role model to these individuals is crucial. Equally important is creating an environment where diversity and inclusivity are expected in leadership. It is not just about who is there, but how the environment feels—people want to be welcomed, recognized, and acknowledged. It's about more than just numbers.

Additionally, when conducting studies, we must ensure that the participants reflect the communities that will benefit most from the interventions. This is not always obvious, so careful consideration is necessary to include those who need it most. Overall, there must be room for everyone, and everyone's lived experience needs to be valued and recognized. Creating an environment where these factors are respected goes a long way.

Reference

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INSTITUTIONAL SPOTLIGHT

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Pioneering Progress: MD Anderson's Transformative Approach to Gender Diversity and Leadership

In 2021, NIH recognized the University of Texas MD Anderson Cancer Center with a Prize for Enhancing Faculty Gender Diversity in Biomedical and Behavioral Science for its Office of Women Faculty Programs (WFP). Since its inception, WFP has implemented strategic initiatives aimed at increasing the representation and advancement of women in academic and leadership roles.

Among the key initiatives championed by WFP is a groundbreaking leadership search policy introduced in 2007 that mandates diverse candidate shortlists for leadership positions. This policy shifted the responsibility of diversity to search committees, leading to a remarkable increase in women leaders. By 2020, the proportion of women in leadership roles had significantly increased, with unconscious bias training for committees further reinforcing these gains.

MD Anderson has also made significant strides in enhancing the representation of women of color in leadership roles. Since 2007, the number of women of color in leadership positions has grown substantially. This advancement is largely attributed to a rise in women department chairs, reflecting the institution's commitment to diversifying its leadership and creating opportunities for underrepresented groups.

MD Anderson's success has not only transformed its own environment but also influenced broader systems. The University of Texas System adopted the institution's leadership policy, and MD Anderson's innovative approaches to gender equity have become a model in academic medicine. ORWH congratulates MD Anderson for continuing to lead by example and for fostering an inclusive and equitable academic community through intentional policies, career development, and recognition.

First State-Mandated Endometriosis Biorepository Launches in Connecticut

Endometriosis is a gynecological condition in which the lining of the uterus implants in areas outside the uterus, including the ovaries and fallopian tubes. Affecting up to 1 in 10 women of childbearing age, endometriosis can cause severe pain and infertility. The causes of endometriosis are poorly understood, and treatment options are limited to pain management and surgery.[1] Despite the high prevalence of endometriosis, the condition is understudied.

In April 2024, Connecticut started to fund a new state-based program, called EndoRISE, to create a biorepository housing tissue collected from surgeries for endometriosis performed at several hospitals around the state. The biorepository grows out of a collaboration between molecular biologist Elise Courtois at the Jackson Laboratory and gynecologic surgeon Danielle Luciano at UConn Health. Patients whose samples are collected will be contacted to complete questionnaires on symptoms and quality of life over time, to build unique longitudinal data that track outcomes from endometriosis surgery. Longer term, researchers and women's health advocates hope that other states will develop similar repositories to advance our understanding of endometriosis.

Department of Labor Updates 2015 Report on the Cost of Doing Nothing: Policies for Working Families

In 2015, the U.S. Department of Labor issued a report titled *The Cost of Doing Nothing* that assessed the economic effect of the lack of policies to support working families in the U.S. In 2015, the U.S. was a global outlier relative to other member countries in the Organisation for Economic Co-operation and Development (OECD). The 2015 report found that the costs stemming from the lack of sick leave, paid family leave, and spending on early childhood education and care were wide ranging: Insufficient support heightened families' stress and worsened their health, diminished women's lifetime earnings, and for businesses, increased employee turnover and hiring challenges. The report estimated that the resulting reduction of women aged 25–54 in the labor force led to a loss of $500 billion in additional economic activity per year.

This 2023 report finds several encouraging areas of progress in support for working families. Labor force participation among working-age women has attained new highs. Workers in 15 states and D.C. now have the right to paid sick leave, and the percentage of private-sector workers with paid sick leave has increased to 78%. Thirteen states and D.C. have enacted paid family and medical leave programs, and 27% of private-sector employees now have employer-provided family leave. However, despite these encouraging changes, the U.S. continues to lag behind other OECD member countries in support for working families. The U.S. lacks national policies that guarantee paid sick leave and paid family and medical leave. Further, U.S. spending on early childcare and education has fallen relative to peer countries, and women's labor force participation is lower than in other comparable high-income countries.

Reference

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Dr. Lucia Hindorff, Ph.D., joined ORWH as senior advisor for scientific and organizational strategy in July 2024. Dr. Hindorff received her doctorate in epidemiology from the University of Washington. Dr. Hindorff led several interdisciplinary research consortia in epidemiology and genomic medicine from 2007 to 2022 at the National Human Genome Research Institute. More recently, from 2022 to 2024, she was the extramural lead for training and launched a research initiative in genomics and health equity.

Dr. Marquitta White, Ph.D., joined ORWH as a health scientist administrator in the Careers Section in June 2024. She completed her master of science degree in applied statistics and doctorate in human genetics at Vanderbilt University. Prior to joining NIH in 2021, Dr. White developed her biomedical research, mentorship, and career development skills through several positions in academia, with her final position as assistant professor at the University of California, San Francisco. Before joining ORWH, Dr. White most recently served as a program officer at the National Heart, Lung, and Blood Institute where she managed an extensive portfolio of institutional and individual training grants, represented her division on several intra-agency committees, and provided expert guidance on issues of diversity, equity, and inclusion in the biomedical workforce.

Dr. Carmen Ufret-Vincenty, Ph.D., joined OADR-ORWH as a health science policy analyst in July 2024. She received her doctorate in biochemistry and molecular biology at the University of Maryland Medical School in Baltimore, where her research focused on intracellular calcium signaling and its association with cell growth. Dr. Ufret-Vincenty then embarked on research projects encompassing a range of disciplines, taking her from the Institute of Neurobiology in San Juan, Puerto Rico, to the Department of Physiology and Biophysics at the University of Washington in Seattle. There, as a senior fellow, she combined genetic, proteomic, electrophysiological, and microscopy techniques to study TRPV1 (capsaicin receptor), thought to be a "sensor" for heat and inflammatory pain. An interest in clinical and translational research inspired Dr. Ufret-Vincenty to transition first into clinical trial implementation at the Cystic Fibrosis Foundation (CFF) Therapeutics Development Network Coordinating Center in Seattle Children's Hospital, followed by a role as director of lung transplant research at the CFF headquarters in Bethesda, Md., developing and overseeing research programs, building novel biorepositories linked to patient registries, and directing grant peer review.

Study Finds High Rates of Ongoing and Severe Hypertension Among Postpartum Women After Discharge

(Original research by A Hauspurg et al. 2024. JAMA Cardiology. DOI: 10.1001/jamacardio.2024.1389)

High blood pressure (defined as blood pressure at or above 140/90 mm HG), or hypertension, is one of the most common complications of pregnancy. Gestational hypertension affects up to 1 in 12 pregnant women and can harm women's organs and lead to preterm birth, stillbirth, and other adverse birth outcomes. In combination with elevated protein in urine, gestational hypertension signals preeclampsia, a serious pregnancy complication that can cause organ damage, seizures, strokes, and death. Preeclampsia and other hypertensive disorders of pregnancy are the primary cause of rehospitalization after delivery and a leading cause of maternal illness and maternal deaths in the U.S. Although most hypertension-related maternal deaths occur after delivery, clear guidelines on optimal postpartum management of blood pressure are lacking. The American College of Obstetricians and Gynecologists currently recommends a single blood pressure check between 3 and 7 days postpartum for individuals with a hypertensive disorder of pregnancy.

To investigate postpartum hypertension after hospital discharge, Dr. Alisse Hauspurg, a maternal fetal medicine physician at the University of Pittsburgh School of Medicine and former BIRCWH scholar, remotely monitored 2,705 women for 6 weeks after discharge. All the women had experienced new-onset hypertension during pregnancy (i.e., gestational hypertension or preeclampsia). More than 4 out of 5 women continued to experience hypertension after discharge, and approximately 1 in 7 women developed severe hypertension (defined as 160/110 mm HG). These findings underscore the importance of ongoing blood pressure monitoring for women who experience new onset hypertension during pregnancy. The findings also highlight the need to standardize post-discharge monitoring across hospital systems and clinical practices. The "highly variable treatment plans [across hospital systems and clinics] highlight the need for guidelines to standardize optimal blood pressure thresholds, treatment algorithms, and monitoring strategies to achieve blood pressure control," note Dr. Hauspurg and her coauthors.

This research was supported by grants from ORWH (K12HD04344), the NIH National Heart, Lung, and Blood Institute (K23HL168356), and the American Heart Association.

Fallopian Tube Microbiota and Associations with Ovarian Cancer

(Original research by B Yu, C Liu, et al. 2024. eLife. DOI: https://doi.org/10.7554/eLife.89830.3)

A leading cause of cancer deaths among women, ovarian cancer has a relatively low survival rate. The American Cancer Society estimates that in 2024 alone, 19,680 women will receive a new diagnosis of ovarian cancer in the U.S. and approximately 12,740 women will die from ovarian cancer. New research suggests that alterations in the collection of bacteria and other microbes in the fallopian tubes (fallopian microbiota) may play a role in ovarian cancer. Dr. Bo Yu at Stanford University and Congzhou Liu, M.S., and colleagues at the Fred Hutchinson Cancer Center and the University of Washington collected and studied the microbiome composition of the fallopian tube in ovarian cancer and non-cancer patients, identifying 84 bacterial species that may represent the fallopian tube microbiota. They noticed a shift in the microbiota of the ovarian cancer patients when compared to the non-cancer patients. Patients with ovarian cancer microbiota had significantly higher prevalences of bacterial species not normally found in the reproductive tract. Of the top 20 species that were most prevalent in the fallopian tubes of ovarian cancer patients, 60% were bacteria that predominantly reside in the gastrointestinal tract, while 30% normally reside in the mouth. This study demonstrates that the fallopian tube microbiota are perturbed in ovarian cancer patients and suggests that research into the role of the microbiota in the pathogenesis of ovarian cancer is warranted.

This research was supported by funding from NIH (K08CA222835 and R01AI139189), the Stanford Maternal and Child Health Research Institute, the Stanford Cancer Institute, and Seattle Translational Tumor Research.

Menstrual Blood Composition as a Non-Invasive Diagnostic Tool

(Original research by A Zaheer, A Komel, et al. 2024. Annals of Medicine and Surgery. DOI: 10.1097/MS9.0000000000002261)

A recently published review of research suggests that menstrual blood could provide valuable information about a woman's health. Menstrual blood contains endometrial cells, immune cells, proteins, and microbial signatures. Several studies have assessed how menstrual blood can be used to diagnose hormonal imbalances, reproductive health, cervical cancer, endometriosis, chlamydia, and diabetes and other endocrine disorders. Examining menstrual blood composition and menstrual cycles may improve our understanding of many diseases, including those that predominately affect non-reproductive organs. For example, glycated hemoglobin (HbA1C) levels in menstrual blood correlate strongly with those in serum, a fact that paved the way for FDA's recent approval of the use of menstrual blood in diabetes diagnosis. To expand and facilitate the use of menstrual blood to assess health risks, researchers and clinicians will need to develop standardized collection

protocols as well as grapple with ethical considerations and societal stigma around menstruation.

Newly Identified Brain Hormone Builds Bone in Lactating Women

(Original research by ME Babey et al., 2024. Nature. DOI: 10.1038/s41586-024-07634-3)

Lactation requires large amounts of calcium for milk production. To meet the demand for calcium, lactating mammals pull calcium from their own bones. Women typically lose 10% of their bone mass during lactation, but largely recover this lost bone after ceasing lactation. Researchers have long believed that, to mitigate some of the drain on bone during lactation, women must have counterregulatory hormones that facilitate bone rebuilding during lactation, in part because blockage of the hormone responsible for stripping calcium from the bone leads to increased rather than stable bone mass in lactating animals. Although estrogen normally facilitates the building of bone mass, estrogen levels are low during lactation.

In new NIH-supported research published in *Nature*, Dr. Muriel E Babey and colleagues report their discovery of a novel hormone, brain-derived cellular communication network factor 3 (CCN3), which is secreted from KISS1 neurons of the arcuate nucleus (ARCKISS1) in the brain and is a powerful promoter of bone growth. They report that CCN3 stimulates bone stem cells to build bone mass and accelerates fracture repair in mice, while reduction of CCN3 in ARCKISS1 leads to increased bone loss and failure to sustain offspring in lactating mice. These findings open the door to a novel class of therapeutics to prevent and treat osteoporosis in humans.

This research was supported by numerous grants from the National Institute of Diabetes and Digestive and Kidney Diseases, the National Institute on Aging, the National Institute of General Medical Sciences, and the National Institute of Arthritis and Musculoskeletal and Skin Diseases.

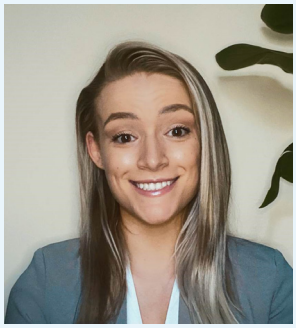
A Special Issue of Social Science & Medicine Examines Gender, Power, and Health

(Social Science & Medicine. DOI: 10.1016/j.socscimed.2024.116959)

A special supplemental issue of Social Science & Medicine explored how gender functions as a structural and social determinant of health. The issue builds on the goals of and the calls for additional research on gender shared during the scientific workshop "Gender and Health: Impacts of Structural Sexism, Gender Norms, Relational Power Dynamics, and Gender Inequities" convened by ORWH in 2022. The workshop brought together NIH staff, the external scientific community, and the public to refine the articulation of gender as a social and structural determinant of health and to develop strategies to advance methods, measurement, multilevel interventions, and intersectional approaches to research on gender and health. The issue outlines numerous opportunities in gender-related research that can improve population health, gender equality, and gender equity. Articles within the issue discuss topics such as gendered power dynamics, intersections of gender with racial and ethnic and sexual and gender minority status, and the impact on women's health of shifts in the policy environment within the U.S. and abroad.

This article was published as part of a supplement sponsored by ORWH.

Jillian Joyce



Alicia Cole

Two Junior Investigators Received ORWH Travel Awards for the Menopause Society 2024 Annual Meeting

The Menopause Society 2024 annual meeting was held in Chicago on September 10. To facilitate participation of junior investigators in the annual meeting, in July, ORWH granted travel awards of up to $3,000 to two junior investigators, Jillian Joyce and Alice Cole, to defray their costs of attending. Jillian Joyce is a doctoral student of neuroscience at the University of Southern California (USC) who is studying vascular senescence and Alzheimer's disease. Before studying at USC, Ms. Joyce studied preclinical Alzheimer's disease with a focus on women's brain health. During the annual meeting, she presented on "Age at Menopause and Cognitive Complaints Associated with Digital Cognitive Outcomes at the Well-Woman Visit." Alice Cole is a third-year medical student at the University of Pennsylvania who is studying psychosocial influences on cardiovascular disease risk in perimenopausal women. Her presentation at the annual meeting was titled "Associations Between Self-Silencing and Inflammation in Midlife Women."

UPCOMING EVENTS

Specialized Centers of Research Excellence (SCORE) on Sex Differences 2024 Annual Meeting Keynote Address
September 30, 2024 | 9–10 a.m. EDT

Building Interdisciplinary Research Careers in Women's Health (BIRCWH) 2024 Annual Meeting
October 1, 2024 | 10 a.m.–5 p.m. EDT

61st Meeting of the Advisory Committee on Research on Women's Health (ACRWH)
October 8, 2024, 9:00 a.m. – 4:30 p.m. EDT

Small Business Opportunities for Innovative Women's Health Research
October 30, 2024 | 11 a.m.–1 p.m. EDT

Research on Gender Measurement
November 4, 2024 | 11 a.m.–4 p.m. EST

FUNDING OPPORTUNITIES

Mood and Psychosis Symptoms During the Menopause Transition (R01 Clinical Trial Optional PAR-23-097; R21 Clinical Trial Optional PAR-23-102) Applications due by January 8, 2025

Research Opportunities Centering the Health of Women Across the HIV Research Continuum (NOT-OD-24-119) Applications due by January 8, 2026

Notice of Special Interest: Women's Health Research (NOT-OD-24-079) Applications due by November 5, 2027

Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) omnibus grant funding opportunities. Renewal applications due January 5, 2025.

- PHS 2024-2 Omnibus Solicitation of the NIH and CDC for Small Business Innovation Research Grant Applications (Parent SBIR [R43/R44] Clinical Trial Required) (PA-24-246)
- PHS 2024-2 Omnibus Solicitation of the NIH for Small Business Technology Transfer Grant Applications (Parent STTR [R41/R42] Clinical Trial Not Allowed) (PA-24-247)
- PHS 2024-2 Omnibus Solicitation of the NIH for Small Business Technology Transfer Grant Applications (Parent STTR [R41/R42] Clinical Trial Required) (PA-24-248)
- PHS 2024-2 Omnibus Solicitation of the NIH, CDC and FDA for Small Business Innovation Research Grant Applications (Parent SBIR [R43/R44] Clinical Trial Not Allowed) (PA-24-245)

For up-to-date information, visit www.nih.gov/women.

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