A sponsored Supplement to *Science*

Frontiers of Medical Research: Women's Health

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Introductions

Articles

Minding the gender gap

Although women make up about half the global population, outnumbering men in the U.S. since 1946, there's a persistent health gap of women being underdiagnosed with certain conditions compared to men. Historically, medicine and art have functioned on the assumption that male bodies represent all of humanity. Artists like Michelangelo used male models to depict women in sculpture and painting. In the 19th century, medical students primarily studied the cadavers of men. Even today, some studies have found that women make up only a third of clinical trial participants. This overrepresentation of men in medical research has contributed to standards of care that may not accurately apply to women, possibly leading to underdiagnosis and undertreatment in women.

Notably, a 2019 study of 7 million people in Denmark found that women were diagnosed with health conditions later than men. As examples, diagnoses for diabetes came four and a half years later, while diagnoses for cancer came two and a half years later in women compared to men. Certainly, genetics and environment are factors, but gender bias also plays a part in the difference. A recent story in *The New York Times* reported that doctors have been accused of ignoring the discomfort of inserting an intrauterine device; a 2019 survey showed less than 5% of doctors offered an injection of local anesthetic during the procedure, while many opted to prescribe less effective over-the-counter painkillers. This modern anecdote illustrates how pervasive gender stereotypes that women "exaggerate" pain may impact the care they receive from healthcare professionals.

This supplement is a step in the right direction. It is the sixth in a "Frontiers of Medical Research" series *Science*/AAAS and the Icahn School of Medicine at Mount Sinai have co-published. Previous topics in this series include cancer, brain science, artificial intelligence, and immunology. The nine articles in this supplement shed light on the unique health challenges women face across their lifespan—from reproductive health issues, such as endometriosis and menopause, to aging and management of chronic conditions that can present differently in women, like heart disease and diabetes. Also among these articles are discussions on how the microbiome affects women's health, why there are gender-based differences in mental disorders, and what role gender plays in the progression of autoimmune disease.

So how do we begin to narrow the gender gap? Appropriately representing women in clinical trials is a start, so that findings can be more broadly applied. With the advent of personalized medicine, there is a growing recognition that understanding sex-specific biology is crucial to developing more effective treatments for all patients. Research is increasingly focused on identifying how hormonal, genetic, and environmental factors interact differently in women and men, leading to more tailored approaches to prevention, diagnosis, and therapy.

Jackie Oberst, Ph.D.
Science/AAAS

The emerging frontier of women's health research

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For too long, many of the conditions and diseases that burden women's health have remained a mystery to science. Why does endometrial-like tissue grow outside of the uterus in 1 of every 10 women, often causing severe pain and infertility? Why do many women develop high blood pressure during pregnancy, a potentially fatal condition for mother and infant, the incidence of which is increasing in the United States of America—up 25% in the past two decades? Why are there no reliable diagnostic tests, effective therapies, or cures for these two common diseases: endometriosis and preeclampsia? President Biden pointed to a reason these questions remain unanswered when he signed an executive order earlier this year to advance and fund women's health research: Science has long prioritized the study of men over women, focusing almost exclusively on male organisms in attempting to understand the biology of mammals in health and disease. The same is true for the study of potential therapeutics. For years, clinical trials were conducted predominantly on men. Indeed, from 1977 to 1993 the U.S. Food and Drug Administration excluded most women of reproductive age from phase 1 and phase 2 clinical trials, a response to the thalidomide tragedy in which the drug, approved in Europe and Australia for morning sickness, was later found to cause severe birth defects. Even to this day, women remain underrepresented in clinical trials, particularly women of color. The fact is, there are large gaps in our knowledge of fundamental female biology. Hence, our understanding of the etiology and progression of disease across the female lifespan remains elusive, as does our ability to build effective therapeutic toolkits to combat these diseases.

Now scientists are working to lift the cloak of mystery surrounding female-specific diseases as well as many other diseases that occur in men but cause greater burden in women. This special supplement—the sixth in a series on "Frontiers of Medical Research" that the Icahn School of Medicine at Mount Sinai has developed in collaboration with *Science*—reports on the latest findings in women's health research and identifies priorities for advancing our understanding of disease in girls and women and our ability to find cures.

This is critical work because limitations in understanding sex-specific biology are impacting medicine's ability to address diseases that afflict women more than men. Women are far more susceptible to neurological disorders, including Alzheimer's disease and other dementias—even after factoring out age as a causal factor—as well as multiple sclerosis. Depression and anxiety are two-fold more common in girls and women than in boys and men. More than 75% of Americans experiencing autoimmune diseases are women.

As we expand our knowledge of the biological differences between women and men, we will develop sex-specific treatments for diseases—a fundamentally new approach to making medicine more personalized. In this supplement, scientists and physicians from Icahn Mount Sinai Women's Biomedical Research Institute and the Blavatnik Family Women's Health Research Institute discuss how they are working to better understand the molecular, cellular, and biomechanical processes responsible for female-specific health disorders, and translate the emerging scientific knowledge to develop new diagnostics and therapeutics for a wide range of diseases in women.

Advances in genomics, for example, are driving successful customized treatment of breast cancers, allowing many patients to avoid the toxic side effects of chemotherapy. Meanwhile, investigators are pursuing new approaches to treating cervical, ovarian, and endometrial cancers.

The following pages include discussion of many other exciting projects in biomedical exploration:

- Scientists are learning how microbial communities in different organs influence women's health, which is creating the potential for microbial therapeutics that can produce anti-inflammatory reactions to suppress immune responses, such as the use of fecal microbiome transplants for treating gastrointestinal disorders in women.
- OBGYNs, immunologists, and genomic scientists are working together to build an atlas of epithelial and immune cells to gain an understanding of the biological drivers of endometriosis.
- Cardiovascular researchers studying cardiometabolic risk in overweight and obese women have learned how dysfunctional crosstalk among cell types within adipose tissues, and between adipose depots and other organs, heightens atherosclerotic coronary disease and heart failure risk.
- Mental health researchers are studying the interplay between hormonal fluctuations and brain neurotransmitters to understand mood disorders.
- Dermatologists are using translational research and immunophenotyping to advance our understanding of scarring alopecia and introduce new potential therapeutic targets.

We also discuss the critical issue of health equity. Researchers find that disparities in maternal mortality and other adverse pregnancy outcomes, as just two examples, are a function not only of race, but also of structural racism.

This collection of essays demonstrates how researchers are working to compensate for the fact that women historically have been underserved by science and medicine. With increasing investment and growing collaborative research efforts, investigators are generating new insights into female biology and disease, knowledge that will open the path to innovative diagnostics and therapeutics that can improve the health of girls and women around the globe.

Obesity and cardiometabolic risk in women

Leslee J. Shaw[1-4*], Susan K. Fried[1,5], Ryan W. Walker[6], Zahi Fayad[1,7,8], Jeanine Albu[9], and Anuradha Lala[1,2,10]

Over the past five decades, overweight and obesity rates in women have surged—now impacting 65% of women and heightening their risks of a wide range of health conditions, particularly cardiometabolic disorders. By 2030, the percentage of women classified specifically as obese is projected to exceed 50%—with the incidence of severe obesity increasing sharply to 27.6% (from 11.5% in 2018) (*1*). Obesity is even more prevalent among African American and lower income women. Targeting the untoward metabolic and pathophysiologic sequelae of obesity in women requires insight into the mechanistic links that accelerate disease pathways. In this essay, we will introduce the varied obesity endotypes in women which provide much-needed insight as to the role of novel lifestyle modifications and therapeutic interventions to promote weight loss without disproportionate loss of lean body mass and averting obesity-associated cardiovascular complications, such as heart failure (HF) or myocardial infarction.

Sex differences in adiposity

Body fat is stored in highly specialized cells, adipocytes, located mostly (80%) in subcutaneous depots, with the remaining contained in visceral depots located intraabdominally, closely associated with the digestive tract. Women have higher total percent body fat compared to men, notably in lower body (thigh and gluteal) regions. Greater storage in upper body depots (abdominal subcutaneous and visceral depots) is associated with greater cardiometabolic risk in both sexes, while higher amounts of lower subcutaneous fat (gluteal and femoral regions) typical of 'pear-shaped' women, attenuates risk, The mechanisms linking regional fat deposition to metabolic health, and sex differences in risk, remain poorly understood. A recent study showed that in vivo rates of fatty acid release from the upper body compared to leg fat depots are less sensitive to insulin's ability to inhibit fat mobilization (*4*). The resulting higher fatty acid flux contributes to higher cardiometabolic risk vis-a-vis hypertriglyceridemia and insulin resistance.

Via secretion of ~100 adipokines, cytokines, and other secreted factors, some packaged in exosomes, adipose tissue plays active endocrine and metabolic roles in the regulation of metabolism (*2*). Accumulating evidence indicates that crosstalk, via extracellular vesicles, among different cell types within adipose tissues and between adipose depots and other organs, including the heart, is crucial to maintain systemic homeostasis and dysfunction of these pathways and contributes to specific cardiometabolic abnormalities, (*3*). Another exciting avenue of research includes the identification of genetic loci that may uncouple adiposity from cardiometabolic risk including FAM13A, IRS1, and PPARG that influence fat distribution and have stronger effects in women.

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Obesity and risk of HF

The relative hazard for HF (particularly with preserved ejection fraction, HFpEF) due to obesity is two-fold higher for women than men (*5*). The higher percent body fat in women along with elevated high sensitivity C-reactive protein, a generalized inflammatory marker, heighten this risk (*6*). Mechanisms of HF for the aging woman with obesity include a pathway of worsening diastolic function, concentric left ventricular remodeling, and diffuse myocardial fibrosis (*7*). Excess weight also heightens risk with greater volumes of epicardial fat as well as intramyocardial fat infiltration. These findings are key long-term predictors of HF—especially for HFpEF, which is decidedly more common in women.

Inflammation and atherosclerosis

Cardiac risk factors, such as hypertension, diabetes, and dyslipidemia, are common in obese women and contribute to risk of atherosclerosis, notably during postmenopause where fat redistributes centrally to more atherogenic depots (*8*). The pro-inflammatory state associated with obesity heightens inflammation in epicardial fat surrounding the coronary arteries and contributes to atherosclerotic plaque destabilization and risk of an acute coronary syndrome (*9*). It is plausible that the chronic, low-grade inflammation observed in obesity compounded with prevalent hypertension, dyslipidemia, and diabetes heightens cardiovascular risk multi-fold over time. This concept supports key sex differences not only for provoking angina with nonobstructive coronary artery disease but also the female-dominant endotype of plaque erosion in acute coronary syndromes.

Lifestyle-modifying behavior and therapeutic interventions

For decades, comprehensive prevention strategies have largely failed to demonstrate durable weight loss for patients who are overweight or obese (*10*). This is particularly true for women who typically lose less weight than men and who may be impacted by muscle loss and less improvement in physical functioning. Weight loss has well-established beneficial effects on obesity-related complex metabolic diseases and type 2 diabetes, yet behavioral interventions with established effectiveness remain elusive. Newly approved therapeutic agents for weight loss (e.g., glucagon-like peptide-1 receptor agonists [GLP-1 RAs]) are effective at weight loss with anti-inflammatory properties and marked reduction (~20%) in cardiovascular risk endpoints (*11*). It is hypothesized that mechanisms responsible for improved cardiovascular outcomes with GLP-1 RAs include reversing myocardial fibrosis, reducing inflammation, and halting formation and/or stabilizing culprit lesions from acute plaque instability. Despite the cardioprotective benefits of these newer therapies, the persistently low enrollment of women in clinical trials (*12*) and longstanding undertreatment of women creates challenges for implementation of trial findings for women with obesity. Further, sex-specific analyses demonstrate the need for mechanistic studies to understand unique differences in weight loss and the relationship to outcomes for women.

Key strategies aimed at weight loss also require patient engagement in lifestyle changes including diet (especially protein consumption), exercise, and strength training. Weight loss induced by novel therapeutics or caloric restriction dieting is often accompanied by significant loss of lean body mass, which is variable, but often exceeds 20% of total weight lost. Rapid loss of muscle mass, especially in women at risk for sarcopenia, can contribute to reduced physical mobility and health risks (*13*). The importance of strength training is often overlooked in women as they initiate aerobic exercise-based weight loss. Optimal physical activity strategies for weight loss while maintaining muscle mass, which combine aerobic exercise and strength training, alone or in combination with drug therapies, are fundamental to reducing the burden of obesity and enhancing longevity

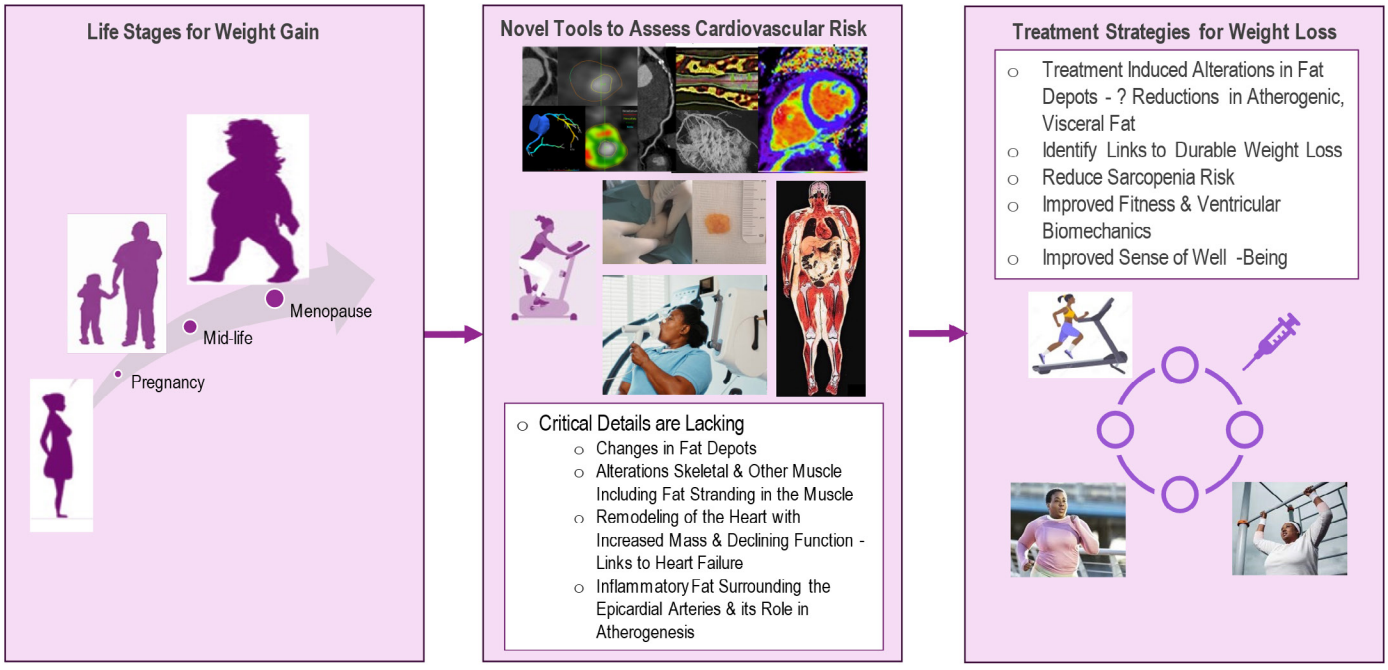

Figure 1. Strategies to Risk Stratify and Targeted Treatment Approaches for Women with Obesity

and physical functioning in women. Compliance with prescribed training programs in women may be hindered by inner city or rural environments lacking dedicated or safe facilities.

Innovative technologies to personalize obesity strategies of care for women

Novel approaches may help to advance risk assessment of obese women. Both computed tomographic (CT) and magnetic resonance imaging (MRI) provide artificial intelligence (AI) approaches to image fat and muscle in the chest or as a total body assessment. CT is associated with ionizing radiation and should be used when the clinical benefit is established. However, the ability of CT to provide insight into the inflammatory nature of fat and the presence of fat within the muscle could prove helpful to assess the obese women for atherosclerotic and sarcopenic risk.

It is well-established that substrate utilization (i.e., fat or carbohydrates are metabolized by muscle for energy) exhibits sex-based differences (*14*), which can have negative health implications in obese women, especially those from underserved populations (*15*). Compounding sex differences in substrate metabolism, a high variability in maximum lipid oxidation during exercise (*16*) could have implications for the efficacy of weight loss interventions. Personal substrate utilization could be measured and leveraged to guide design of individualized weight loss in obese women.

Summary

There is an evolving understanding of women's cardiovascular health and disease, with those who are obese being exceedingly at high risk. In this essay, we highlight key issues of cardiovascular risk in obese women as well as hurdles for effective intervention that must be balanced using diverse approaches to lifestyle-changing behaviors, especially physical fitness and strength training (**Figure 1**). The newer therapeutic agents herald an exciting era in the care of women with obesity that when effectively implemented hold promise to reduce inflammation and the adverse cardiovascular sequelae of heart failure and atherosclerosis.

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Coronary microvascular dysfunction in women

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Coronary microvascular dysfunction (CMD) refers to a heterogeneous group of disorders resulting from structural or functional abnormalities of the heart's microvasculature that disproportionately affects women, often at younger ages (*1*). Historically, CMD has been overshadowed by a focus on epicardial obstructive coronary artery disease (CAD). However, CMD is one of the most prevalent forms of ischemic heart disease, being present in two-thirds of all patients with angina/ischemia and non-obstructive coronary arteries (ANOCA/INOCA respectively), 60%–70% of whom are women (*2*). CMD is associated with high clinical and economic morbidity, as patients have high rates of repeat testing; invasive procedures and hospitalizations; increased depression, anxiety, and worse quality of life from delayed diagnosis and treatment; and high risk of adverse cardiovascular outcomes (Figure 1) (*3*). Lack of widespread availability of advanced testing modalities coupled with limited physician and patient awareness is a key reason for under-diagnosis, under-treatment, and consequently poor outcomes related to CMD. Still, gaps remain in our understanding of the pathophysiology underlying the sex differences in prevalence of CMD, optimal diagnostic strategies, and therapeutic options for women with CMD.

Pathobiology and prognosis

CMD can be limited to the coronary microcirculation with or without co-existing epicardial atherosclerotic disease (primary CMD) or occur secondary to other systemic disorders, such as cardiometabolic diseases, autoimmune disorders, or various cardiomyopathies (secondary CMD). CMD arises from multifaceted interactions involving endothelial dysfunction, inflammation, oxidative stress, and neurohumoral dysregulation within the coronary microcirculation, causing structural or functional abnormalities (*4*). Structural abnormalities in the microvasculature, collectively referred to as microvascular remodeling, include intimal and smooth muscle cell thickening and proliferation, perivascular fibrosis, capillary obstruction, or decreased capillary density known as rarefaction. Functional abnormalities are characterized by impaired vasodilatory response or increased vasoconstriction of the microvasculature secondary to endothelial dysfunction or vascular smooth muscle hyperreactivity. Dysregulation of endothelium-derived vasoactive substances, involving impairment in nitric oxide (NO)-mediated vasodilation and endothelin-1 and rhokinase-mediated vasoconstriction, predisposes to CMD. Furthermore, heightened oxidative stress and inflammatory cascades perpetuate endothelial injury, exacerbating CMD. While mechanisms underlying the sex-specific variation in CMD are not well understood, endothelial dysfunction resulting from immune dysregulation, anti-angiogenetic milieu, and systemic inflammation seen in women with a history of adverse pregnancy outcomes (APOs) such as pre-eclampsia, pre-term birth, and intrauterine growth restriction are thought to be contributory (*5*). Estrogen causes NO-mediated vascular smooth muscle dilation and inhibition of vascular smooth muscle proliferation. As such, estrogen loss in menopause may lead to endothelial dysfunction, inflammation, and resultant damage of coronary vascular smooth muscle cells. This along with increased extracellular matrix deposition and myocardial fibrosis from oxidative stress contributes to CMD in postmenopausal women (*6*). This risk is reduced by menopausal hormone therapy in some but not all women. There is a strong bi-directional relationship between CMD and heart failure with preserved ejection fraction (HFpEF). Impaired microvascular function is present in 85% of patients with HFpEF, while also exacerbating myocardial stiffness and diastolic dysfunction, contributing to HFpEF development and progression (*7*). Co-existent non-obstructive atherosclerosis in the epicardial coronary arteries is present in 80% of patients with CMD (*8*). CMD is also the predominant cause for persistent symptoms and morbidity among patients with obstructive CAD post revascularization. Both in men and women, CMD portends a high risk for adverse cardiovascular events, especially HFpEF (*9*), independent of the presence and extent of epicardial atherosclerotic disease (*10*).

Clinical manifestations and diagnostic evaluation

Symptoms of CMD mirror that of obstructive CAD, including angina at rest or with physical or emotional stress, exertional intolerance, and dyspnea, making it hard to distinguish without testing. Natural history studies show waxing and waning of symptoms and ischemia over time, with worsening of angina in 14% and disappearance of angina and ischemia observed in half of the INOCA subjects enrolled in the CIAO-ISCHEMIA study at 1 year without any structured treatment (*11*). Coronary flow reserve (CFR), a ratio of stress to rest myocardial blood flow, measures the integrated hemodynamic effects of disease across the entire coronary circulation on myocardial tissue perfusion. Non-invasive assessment of myocardial blood flow at rest, stress, and CFR with quantitative vasodilator stress positron emission tomography (PET) or stress cardiac magnetic resonance imaging (MRI) is considered the non-invasive gold standard to diagnose CMD in absence of any flow-limiting epicardial CAD. Flow assessment is also possible with Doppler echocardiography with adenosine stress but is not routinely performed clinically. Inability to identify endothelial dependent and vasospastic etiology of CMD remains a disadvantage of the non-invasive testing, however, efforts are ongoing to assess coronary endothelial function non-invasively using cold-pressor testing, dobutamine, exercise, or mental stress. Comprehensive invasive coronary functional testing (CFT) employs low and high dose intracoronary acetylcholine testing to identify endothelial dysfunction, endothelial dependent microvascular spasm as well as epicardial spasm; adenosine testing to measure CFR and isolated microvascular resistance based on thermodilution (index of microcirculatory resistance IMR); or Doppler methodology (hyperemic microvascular resistance hMR) to diagnose endothelial independent CMD (*12*). CFT was 4-fold more likely to help with diagnosis of coronary vasomotor dysfunction among patients with ANOCA in the corCTCA trial, leading to improved treatment satisfaction (*13*).

Treatment

There is a paucity of high-quality evidence and large randomized trials to inform CMD management. Current therapeutic strategies for CMD, mainly informed by empirical evidence and small preliminary studies, encompass lifestyle modifications, pharmacotherapy, and emerging interventional approaches aimed at optimizing cardiovascular risk factors and alleviating angina symptoms (*14*). Lifestyle interventions, including regular physical activity, cardiac rehabilitation, weight loss, dietary modifications, and smoking cessation, enhance endothelial function and improve CMD-related symptoms and exercise capacity in small studies. Pharmacological approaches should focus on cardiovascular risk factor

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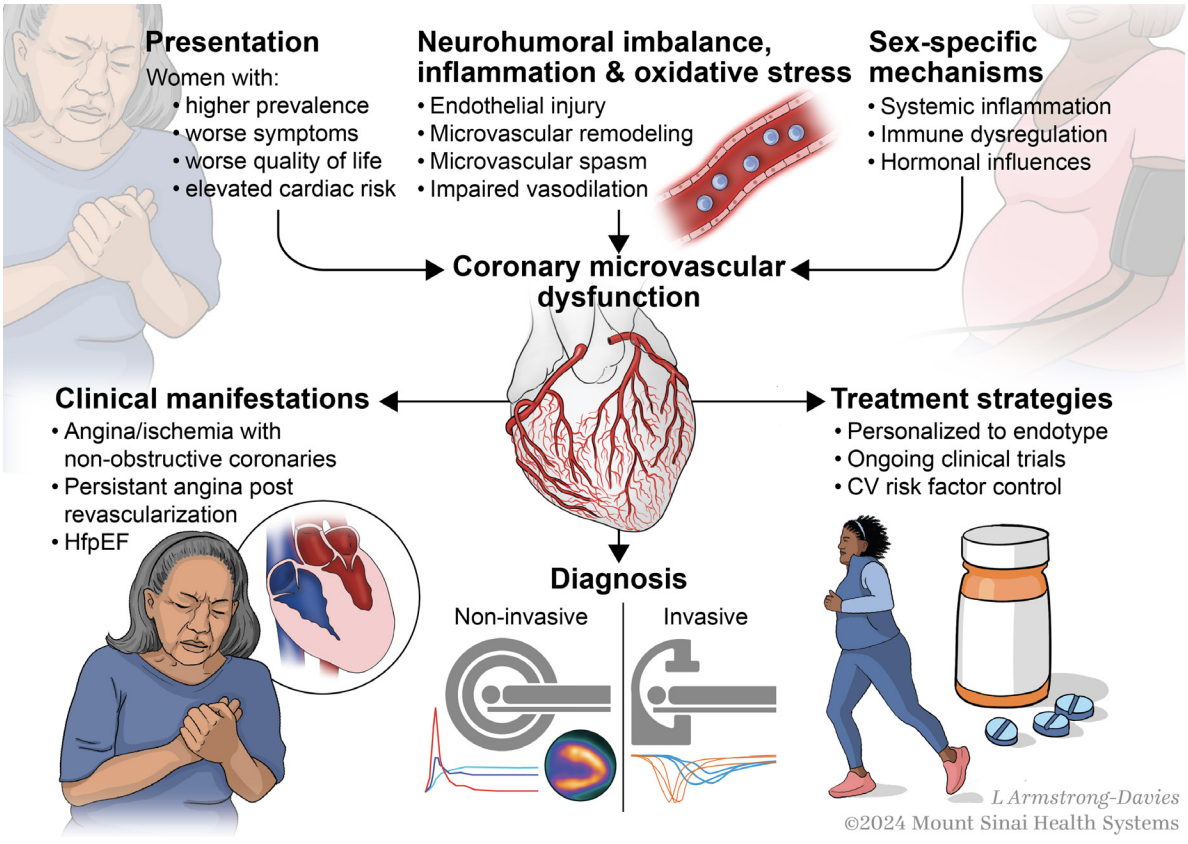

Figure 1:Coronary Microvascular Dysfunction in women: Presentation, pathophysiology, clinical diagnosis, and management strategies.

management and be tailored to specific CMD endotypes. The CorMICA trial showed improvement in anginal symptoms, function, and quality of life at 6 months and 12 months with stratified medical therapy linked to CMD endotype on invasive CFT compared to usual management among 151 patients with ANOCA (*15*). Currently, high-intensity statins, ACE inhibitors, or angiotensin receptor blockers (ACEI/ARBs), and ß-adrenergic antagonists without intrinsic sympathomimetic properties (e.g., nebivolol) as tested in the corMICA trial are recommended as first-line therapy for all patients with CMD. Non-dihydropyridine calcium channel blockers are recommended as second-line treatments particularly among patients with a vasospastic endotype. Preliminary studies have shown benefit with ranolazine, long-acting nitrates, nicorandil, L-arginine, and phosphodiesterase type-5 inhibitors, which can be used as third-line agents. An oral endothelin-1 antagonist, zibotentan, intracoronary autologous $CD34^{+}$ cell treatment, and coronary sinus reducer device therapy are currently being tested in clinical trials as potential treatment options. Importantly, to date, there have been no clear therapeutic options to reduce hard clinical endpoints (i.e., death, MI, stroke) other than symptom relief. The ongoing WARRIOR trial is testing an approach of intensive medical therapy that includes statin and ACEI/ARBs in reducing adverse cardiovascular events among 4,422 symptomatic women with ANOCA *(16)*.

Future directions

CMD represents a prevalent yet underrecognized contributor to cardiovascular morbidity and mortality in women. Ongoing research seeks to better understand the intricate pathophysiological mechanisms underlying CMD in women and identify novel diagnostic and therapeutic strategies to optimize patient care and outcomes. Advancements in non-invasive imaging modalities, genomic and proteomic biomarker discovery, and precision medicine hold transformative potential for early CMD detection, risk stratification, and personalized therapeutic interventions tailored to individual patient characteristics. Furthermore, addressing gender disparities in cardiovascular research and healthcare delivery remains paramount for ensuring equitable access to optimal diagnostic and management options for CMD and improving cardiovascular outcomes for women worldwide.

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Healthcare equity through the lens of preeclampsia

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Background

Stark racial and ethnic disparities define the state of maternal health in the United States (U.S.). Nationally, rates of maternal mortality are nearly three times higher for non-Hispanic Black (subsequently 'Black') birthing individuals compared to their non-Hispanic White (subsequently 'White') counterparts (*1*). Hypertensive disorders of pregnancy (HDP) represent a spectrum of conditions unique to pregnancy with elevated blood pressure as a common feature. Preeclampsia is a severe form of HDP and a leading cause of maternal morbidity and mortality. While the precise mechanisms leading to preeclampsia remain unclear, endothelial dysfunction is a common pathophysiological feature that results in multisystem injury in the mother, including renal dysfunction, bleeding disorders, and seizures, all of which can be fatal (*2*). Black birthing individuals are disproportionately affected by preeclampsia and are 60% more likely to be diagnosed than White birthing individuals (*3*,*4*). In addition to the adverse implications for short-term maternal and neonatal health, individuals affected by HDP are more likely to experience future cardiovascular disease, further entrenching health disparities across their life course (*2*). Alarmingly, despite some improvements in management, the incidence of new onset HDP doubled between 2007 and 2019 (*5*,*6*). Given the implications these statistics pose for future trends in maternal health, our efforts as providers and researchers are critical to remove misperceptions and barriers to equitable care.

Structural racism as a root driver of racial ethnic disparities in preeclampsia

Evidence demonstrates that disparities in preeclampsia and other adverse maternal health outcomes are rooted in structural racism rather than race alone (*4*). For example, higher rates of preeclampsia are documented among Black birthing individuals born in the U.S. relative to Black birthing individuals who immigrated to the U.S. The same study found that neither nativity nor duration of residence in the U.S. affected the odds of preeclampsia among White birthing individuals (*3*). Although the definitive molecular pathophysiology of preeclampsia remains unknown, many mechanisms that stem from structural racism have been proposed (*7*). These include chronic psychosocial stress due to intrapersonal and institutional discrimination, high rates of trauma, increased exposure to place-based environmental contaminants, lower access to health-promoting resources, and barriers to engagement as well as timely access to quality care across the preconception to postnatal continuum (*7-9*).

Immunomodulatory characteristics of chronic stress and adverse pregnancy outcomes

High or repetitive stress has been shown to disrupt metabolic and neuroendocrine homeostasis, leading to higher allostatic load, a cumulative marker of biological 'wear and tear' among racial and ethnic groups. Chronic activation of the hypothalamic-pituitary axis due to stress can impact the long-term functioning of the immune system and lead to epigenetic-mediated changes in gene expression (*10*). These mechanisms have been linked to adverse pregnancy outcomes, such as preterm birth and low birth weight through an immunomodulatory pathway marked by inflammatory changes (*10*,*11*). The accumulation of chronic stressors can manifest across biological systems (e.g., cardiovascular, renal, metabolic) and result in a higher prevalence of comorbidities even prior to pregnancy. Such comorbidities in turn also increase the risk for perinatal complications (including preeclampsia) and impede postpartum recovery (*5*,*6*). Historical discriminatory practices contribute to these chronic stressors and provide one major reason for the observed racial disparities in pregnancy outcomes. One example of this systemic racism is 'redlining'—city maps generated by the Home Owner's Loan Corporation that denoted inner-city, predominately Black and immigrant neighborhoods as 'high loan risk,' which diminished home values and resulted in communities of color having closer proximity to sources of hazardous toxins and pollution that increase the risk of adverse birth outcomes (*12*).

Engagement and timely access to care

The U.S. healthcare system is complex and often fractured with documented racial/ethnic inequities across disease states and healthcare services. Recent U.S. birth record data show that Black birthing individuals were nearly twice as likely to receive delayed or no prenatal care as White individuals. For example, clinical concerns surrounding pain and pregnancy complications, particularly among Black patients, have been dismissed and/or disregarded (*13*). This degree of marginalization may lead to later presentations to care, distrust within the health care system, delayed diagnoses, and the persistence of health care inequities by race/ethnicity even after adjustment for socioeconomic status. Addressing these disparities must be wide-ranging and involve patient, provider, and system-level interventions. A major system level intervention is now under consideration. The U.S. Centers for Medicare and Medicaid Services (CMS) recently proposed obstetrical services conditions of participation (CoPs). The CoPs would require CMS participating hospitals—as a condition for continuing to receive payment from CMS—to comply with nationally recognized safety measures. These would represent the first federal guidelines specific to maternal–child services (*14*).

Interventions: Our health system's strategies

Within the Mount Sinai Health System (MSHS), we have adopted a Roadmap to Address Racism. Led by a Task Force comprised of a diverse cross-section of disciplines and experiences within our community, the goal is to provide a resource for evaluation, investigation, and engagement for all who provide care to our patients. We highlight several examples of how this framework has been adopted, with a specific focus on patients with HDP.

Provider health equity and learning education

The importance of a research-based curriculum for faculty and staff led us to create a Health Equity and Learning initiative in partnership with a digital health organization. Courses focused on perinatal health equity, cultural competence and humility, implicit bias, and social determinants of health. These approaches are intentionally designed to center the voices, inform the care team, and empower patients as drivers of their care.

Providing person-centered care in the prenatal period and beyond

Given Black birthing individuals are more likely to be affected by HDP, person-centered and coordinated care, with access to obstetric and cardiology specialists from early pregnancy to the postpartum period, is paramount. To this end, we have implemented group prenatal care; perinatal

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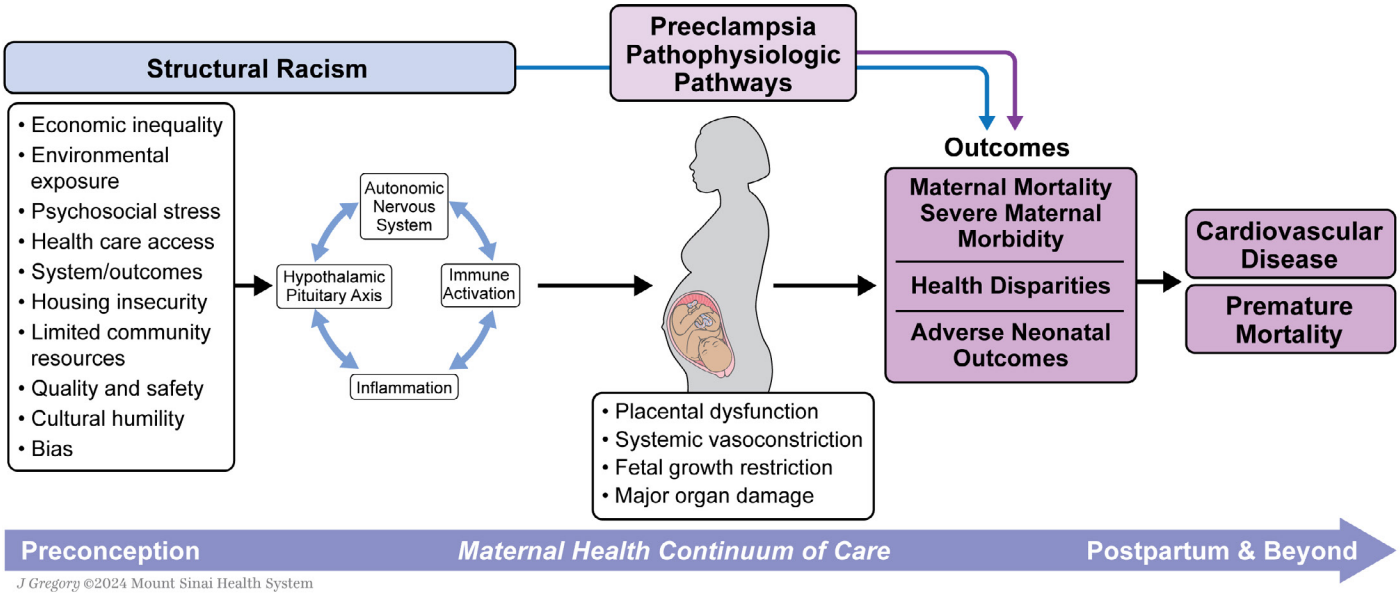

Figure 1: Integrated conceptual framework for preeclampsia.

mental health resource programs; linkages to doula services; a digital platform for post-discharge text/calls; an integrated patient education platform; and a data-driven infrastructure to evaluate key perinatal metrics through a health equity approach.

Addressing the need for postpartum care continuity: Remote patient monitoring

In addition to the need for holistic prenatal care, missed opportunities in the critical first year postpartum compound racial and ethnic disparities among patients who were affected by severe maternal morbidity, including HDP (*6*). Advancements in technology through remote patient monitoring can expand access to care. We piloted an innovative pharmacist-led remote blood pressure care model for our ambulatory practice, primarily serving patients supported by Medicaid. Recent randomized control trial evidence has demonstrated that access to remote blood pressure monitoring led to improved detection of blood pressure abnormalities in the 10 days following discharge, with implications to significantly improve health equity (*15*).

Future research goals

Interventions targeting structural racism are key to alleviating current disparities in maternal health and must be at the core of health equity research (**Figure 1**). Lived experiences have been linked to health outcomes, therefore a shift in focus and investment in tools to address the disparate care have been envisioned. Preeclampsia offers a unique window for future maternal health research to investigate the implications of race as a social construct and provides opportunities for interventions within a framework that encompasses structural racism and its impact on access and quality of care.

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Burden of mental health disorders in women

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Introduction

Mental health disorders are a significant burden worldwide, with women encountering unique challenges that contribute importantly to disease burden. This essay explores the impact, contributing factors, and specific mental health disorders affecting women (see Figure 1). By examining these key areas, we aim to provide an understanding of the unique challenges that mental health conditions present to women and innovative steps being taken at the Icahn School of Medicine at Mount Sinai (ISMMS) to address them.

Overview of mental health disorders in women

Mental health disorders are prevalent among women, with anxiety and depression being the most common. According to the Office on Women's Health, more than 1 in 5 women in the United States of America experience a mental health condition annually (*1*). These disorders have a profound impact on society, families, and the women themselves—leading to increased societal costs and diminished quality of life. Reproduction-related dynamics, such as hormonal fluctuations during menstruation, pregnancy, and menopause, are important biological factors that impact women's mental health. Psychological factors, including higher rates of exposure to trauma and stress, also contribute. Socio-economic factors, such as poverty, racism, gender-based violence, and unequal access to education and healthcare, further exacerbate mental health conditions among women. These intertwined factors necessitate a comprehensive approach to addressing mental health disorders in women.

Specific disorders

Eating disorders, including anorexia nervosa (AN), bulimia nervosa (BN), and binge eating disorder (BED), affect roughly 1 in 10 individuals, with the greatest sex disparity of all psychiatric diagnoses: a male to female ratio of roughly 1:10 in AN to 1:4 in BED (*2*,*3*). Despite this striking disparity, very little is known about what biological factors interact with larger sociocultural pressures to accelerate such a greater risk among girls and women. At the ISMMS, we are testing sex-specific risks in hormone-dependent general brain arousal on the development and maintenance of these disorders, with the goal of identifying sex-specific interventions for females. This work builds on the theory that general brain arousal arises from developmental effects of gonadal hormones on genetically mediated cohesion of neural networks in the brain responsible for motor control, sensory sensitivity, and emotional reactivity (*4*). We applied this theory to eating disorders and have begun formally testing this model to understand sex differences in developmental risk for eating disorders and how pubertal timing and magnitude of gonadal hormone changes in youth affect risk in the Adolescent Brain Cognitive Development (ABCD) study (*5*). We are particularly interested in the role played by aromatase, an enzyme critical to the conversion of androgens to estrogens, in arousal-specific effects on feeding as preliminary collaborations identified a strong link between aromatase levels in the brain and weight in healthy adults.

Anxiety and depressive disorders are the most prevalent mental health conditions affecting women. Across the lifespan, women experience onset, or worsening, of anxiety and depression in association with hormonal and psychosocial transitions, such as menarche, pregnancy, and menopause. While rates of anxiety disorders are higher among boys than girls prior to puberty, this pattern shifts dramatically, with adolescent girls having higher risk for anxiety disorders, and this differential then persists throughout the lifespan (*6*). Likewise, following puberty females are approximately twice as likely to experience depression compared to men (*7*). During and following pregnancy, when levels of estrogen and progesterone rise dramatically and then rapidly fall, women are at markedly elevated risk for depression and anxiety, with potential for profound long-term consequences of both the woman and newborn. While anxiety and depression risk periods in women align with ovarian hormone fluctuations, affected women do not consistently show differences in hormone levels or temporal dynamics. Sex steroids strongly influence neural development and function, with their regulation of neurobiology and stress sensitivity likely explaining observed risk differences. Changing levels of allopregnanolone, a neuroactive steroid hormone and progesterone metabolite, may help mediate anxiety and depression risk in women through its $GABA_A$ receptor agonist properties (*8*). Basic research showing allopregnanolone's ability to mitigate deleterious effects of stress during the peripartum period led to the development and approval of brexanolone and more recently zuranolone—both formulations of allopregnanolone, as the first approved U.S. medications for the treatment of postpartum depression. [Please see accompanying essay by Bergink et al. in this supplement for additional discussion of peripartum psychiatric disorders.]

Substance use disorders (SUDs) significantly affect all populations, but women face particular challenges. Women experience quicker onset, known as *telescoping*, and often delay treatment compared to men (*9*). These differences arise from physiological factors, gender roles, and life changes such as pregnancy, and parenting responsibilities, all of which limit treatment opportunities. Access to SUD treatment is further hindered by fragmented care and the unavailability of key options for pregnant women or those with children (*10*). The fear of custody loss if a SUD is disclosed further exacerbates these barriers (*10*). Additionally, racial and ethnic disparities and stigma complicate treatment access for many women of color (*11*). The ISMMS is addressing these issues by offering wrap-around services for women, including integrated obstetrics, gynecologic, and addiction treatment in the outpatient setting, with inpatient addiction care available throughout a woman's lifespan, including pregnancy. Mount Sinai also leads groundbreaking addiction research, translating findings from the bench to the bedside to improve care for women with SUDs. For example, clinical trials and preclinical animal models (e.g., neuroimaging and molecular studies) are leveraged to expand knowledge regarding biological differences between males and females underlying addiction. Such research now guides new avenues in developing individualized treatment strategies focused on women. This includes leveraging strategies to monitor biological signatures in the placenta, aiming to understand the effects of in utero exposure on offspring outcomes (*12*), thereby enhancing SUD treatment and clinical care for women and their children. Addressing the multifaceted challenges faced by women with SUDs requires a holistic approach, as exemplified by Mount Sinai's integrated and research-

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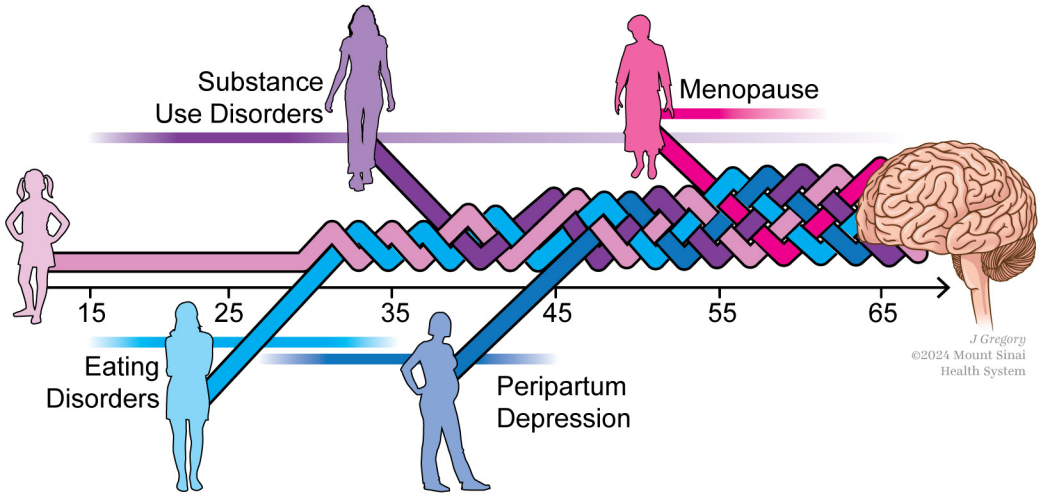

Figure 1: Mental health disorders among women throughout the lifespan by type and age group of prevalence.

driven model. This approach enhances access to care and supports women in overcoming their unique barriers.

The menopausal transition at later stages in life continues to exemplify the critical interplay between hormonal transitions and mental health—warranting further inquiry. In the United States of America, about 1.3 million women enter menopause every year, with many experiencing symptoms including mood swings, anxiety, and depressive symptoms (*13*). The higher prevalence of mood disorders during these transitions suggests a complex interplay between hormones, neurotransmitters, and individual susceptibility including the effect of estrogen decline on serotonin, and that of progesterone on the GABAergic system. At Mount Sinai, we are addressing these issues through care integration between obstetrics and gynecology together with psychiatry and mental health services using a combination of behavioral, hormonal, and pharmacologic approaches. These efforts exemplify the importance of research in this exciting area, including efforts to identify sex-specific hormonal biomarkers in mental health. By combining cutting-edge science and medicine, we are pioneering innovative solutions and transforming mental healthcare and beyond for girls and women throughout their lives.

Conclusion

Addressing women's mental health requires understanding distinct challenges, such as hormonal fluctuations and neurobiological differences unique to females. Mount Sinai integrates comprehensive care and pioneering research to develop effective treatments for mental health and substance use disorders in women. By combining cutting-edge science and medicine, we are striving to pioneer innovative solutions and transform mental healthcare for girls and women throughout their lifespan.

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Maternal and peripartum psychiatric disorders

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Introduction

Pregnancy, childbirth, and the first year postpartum are formative for the child and transformative for the mother. For the child, optimal conditions during early development are foundational for lifelong physical and mental health. For the mother, pregnancy and childbirth are associated with major physiological changes as well as a neuroanatomical reorganization of the brain. The early postpartum period is the time of greatest risk for psychiatric illness in a woman's lifetime, with 10-fold increased rates of first-onset psychiatric hospitalization. Thus, the critical time for the infant's development coincides with an extremely vulnerable period for the mother's mental health. Clinicians manage both facets when treating the mother–child dyad. However, the evidence base for the benefits and risks of preventative and treatment strategies in the perinatal period is currently insufficient.

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Maternal mental health during pregnancy

During pregnancy, the maternal brain must adapt to the upcoming task of parenthood, leading to both behavioral and cognitive changes. Animal studies have shown that at a neuroanatomical and cellular level, pregnancy is a period of profound brain changes and increased neuroplasticity.

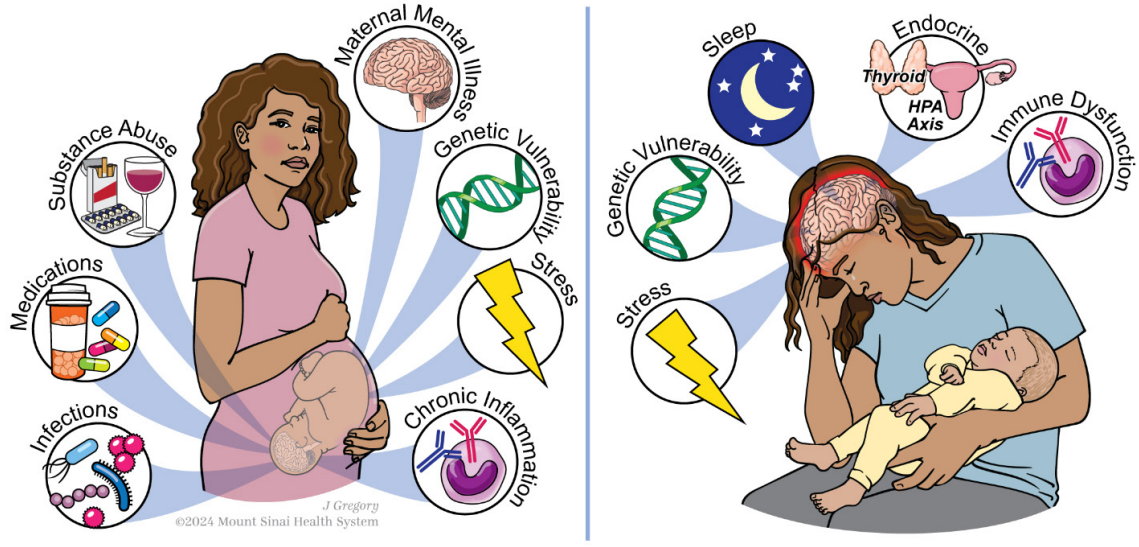

Figure 1: Mother–child dyad of mental health. Left: Various exposures can have an adverse impact on fetal brain development which makes offspring more vulnerable for mental illness later in life. Right: The postpartum period is a high-risk period for severe maternal mental illness, which could be triggered via different pathways.

Over the last few years, the first human neuroimaging studies have been performed, which have confirmed major prenatal changes in the maternal brain including substantial reductions in gray matter volume and altered functional connectivity (*1*). It remains to be determined whether these physiological brain changes are associated with increased risk for psychopathology. However, epidemiologic studies suggest that pregnancy in general is not an unusually high-risk period for mental illness.

Nonetheless, pregnancy and delivery are emotionally and physically challenging for most women, and those with a history of psychiatric disorders are particularly vulnerable during this period. Stable mental health during pregnancy is paramount not only for the future mother, but also for the developing fetus (Figure *1*). However, many women stop or lower psychotropic medication during this period out of concern for adverse fetal effects. While this may be a good strategy for women with less severe mental health disorders (*2*), medication tapering puts patients with a history of severe mental illness at high risk of relapse (*3*). Psychiatric instability brings increased risk of unhealthy behaviors, such as poor diet; limited exercise; and use of alcohol, cannabis, and tobacco, all of which can have adverse effects on the fetus. Recent research suggests that cannabis use during pregnancy has effects on fetal epigenetic reprogramming, which may have long-term adverse impact on the child's mental health, and even across generations (*4*). Multiple research groups including ours are working on short- and long-term neurodevelopmental sequelae of prenatal exposure to substance abuse as well as various psychotropic medications. Whereas safety data are well established for antidepressants (*5*), there is an urgent need for better data on mood stabilizers, stimulants, and antipsychotic drugs, given that use of these medications during pregnancy has been steadily rising (*6*).

In addition to the effects of prenatal exposure to medications and recreational drugs, the direct effects of maternal stress and mental illness on fetal and infant development cannot be underestimated. While the past two decades of research have established that maternal mental illness in pregnancy predicts a broad variety of offspring health outcomes, from preterm birth to impaired childhood cognition and behavior, the biological mechanisms by which these effects are exerted and sustained remain a topic of active investigation. The mechanisms involved are certain to be complex and multifactorial. Investigations by our group and others of the effects of maternal depression on the infant epigenome revealed changes in pathways related to functions as diverse as developmental patterning, gonadotropic effects, inflammation, cell–cell communication, and growth factor signaling (*7*).

Childbirth as trigger for (severe) mental illness

Postpartum mental illness is one of the most common complications of childbirth, and suicide in this period is one of the main contributors to maternal death. While rates of anxiety and depression are high before pregnancy, during pregnancy and after childbirth (one in five women is affected), episodes of severe mental illness, such as psychosis and mania, occur specifically after delivery (the absolute risk is 0.1% but the relative risk is more than *10*). One of the reasons for that may be that the postpartum period is characterized by a rapid fall in estradiol and progesterone (Figure *1*). In line with this idea, the neurosteroid metabolite allopregnanolone was recently approved for the treatment of postpartum depression (*8*). Interestingly, patients with postpartum mood disorder might have increased sensitivity to abrupt ovarian steroid changes, rather than altered circulating hormone levels. New studies support this hypothesis by showing a differentially expressed transcriptome of cell lines in hormone conditions mimicking pregnancy and parturition in patients with postpartum depression compared to controls (*9*).

In addition to endocrine sensitivity, immune alterations postpartum might contribute to the flare in severe mental illness after delivery. This specific 'postpartum flare' pattern is well documented for a range of autoimmune disorders (e.g., autoimmune thyroid disease, multiple sclerosis, rheumatoid arthritis), while pregnancy seems to be protective for these disorders. In line with this idea, our research has found high co-occurrence of autoimmunities (including encephalitis) with postpartum psychosis as well as multiple signs of immune dysregulation in patients with postpartum depression and psychosis compared to controls (*10*).

Gene identification in psychiatric disorders is nascent. Genome-wide association studies (GWASs) have not yet identified significant markers for postpartum depression but have revealed genetic correlations with bipolar disorder and posttraumatic stress disorder, distinguishing it from major depressive disorder (*11*). Further insights have come from focusing on a more severe phenotype, postpartum psychosis. Polygenic risk score

analyses for women with postpartum psychosis show a shared genetic architecture with bipolar disorder. Additionally, family-based studies have found a higher familial risk among female full siblings than those seen in bipolar disorder or schizophrenia, indicating a unique risk architecture and a strong familial, possibly genetic, predisposition specific to postpartum psychosis (*12*). The exploration of rare genetic variants in these disorders remains largely unexplored. Investigating variants related to neurological functions, hormonal regulation, or immune responses is crucial, as they could potentially influence key physiological processes during the postpartum period and significantly impact maternal mental health.

Future directions

Neuroscience has only just begun to explore the effects of pregnancy and the postpartum period on the human brain, behavior, and cognition, and the role of genetic, immune, and endocrine factors. Fortunately, mother–child cohort studies, clinical trials, and neuroimaging studies in pregnant and postpartum women are emerging. Yet, some of the traditional barriers that have hampered human research in pregnant and postpartum women remain and there is a pressing need for novel translational research methods. An important advance by researchers at Mount Sinai involves the use of central inflammatory and neuroendocrine biomarkers instead of peripheral biomarkers in peripartum women (*13*). Other novel lines of research focus on neuroplasticity in the perinatal period by transplanting human stem cell–generated neurons and microglia into perinatal mouse models. In addition to neurobiological studies, psychosocial research is equally important given that new parenthood presents an array of major psychosocial stressors. Sleep loss, role transition, interpersonal conflict, and increases in domestic demands all contribute to increased psychiatric risk, both for women with severe psychiatric illness as well as milder episodes of depression and anxiety (*14*). The ability to distinguish which of these biological and psychosocial stressors may have precipitated a psychiatric episode in a given individual, and identification of pathophysiological endophenotypes within the perinatal psychiatric population (*15*), will improve our ability to provide targeted prevention and treatment.

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The enormous burden of endometriosis

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The clinical quandary of diagnosing endometriosis

Endometriosis is a common, chronic disease that globally affects 10% of women of reproductive age. Despite this burden, diagnosis is typically delayed by years, misdiagnoses are frequent, and prolonged therapy is required and not always effective. Endometriosis is classically defined by the presence of endometrial-like tissue outside of the uterus. The clinical presentation is varied, and the location of extra-uterine lesions is heterogeneous. An obstacle in prompt diagnosis is that endometriosis does not have pathognomonic signs or symptoms; in fact, common symptoms associated with endometriosis overlap with other gynecological and gastrointestinal conditions (*1*). The clinical presentation of individuals with endometriosis is diverse, with pelvic pain being a common and troubling symptom. Other symptoms include dysmenorrhea, dyspareunia, dyschezia, and dysuria. Individuals with endometriosis are much more likely to have infertility than individuals without endometriosis (*2*). Physical examination findings, such as tender uterosacral ligaments, nodules palpated on rectovaginal examination, limited uterine mobility, or adnexal mass, may be suggestive of endometriosis but none of these are thought to be diagnostic. Similarly, while imaging may be suggestive of the presence of endometriosis, negative findings on imaging do not rule out the presence of endometriosis (Figure *1*). While there are some biomarkers that are used clinically, like CA-125, they are not specific and have poor predictive performance (*3*). Currently, there is no reliable biomarker to identify individuals with endometriosis (*4*). There is an urgent need to understand biological drivers of endometriosis that can be clinically meaningful and to develop non-invasive methods that identify those burdened by this disease.

The impact of endometriosis and therapeutic options

Many studies across different populations have demonstrated the strong impact of endometriosis on individuals, particularly on quality-of-life metrics. Among the varied symptoms, pain is a common presentation. However, underscoring our limited knowledge of mechanisms of pain in endometriosis, the disease stage does not always correlate with patient-reported pain (*5*). The first line of treatment for individuals with endometriosis is control of hormonal fluctuations through the common use of oral contraceptive pills (*6*). While over 70% of individuals with a diagnosis of endometriosis are prescribed oral contraceptive pills, this is an off-label use—reflecting the paucity of high-quality clinical trials for this disease. In over one-third of patients, oral contraceptive pills fail to ameliorate symptoms,

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suggesting that symptoms and progression of endometriosis are not solely due to hormonal shifts (*7*). While the global burden from endometriosis is substantial, including pain and loss of work and wages (*2*,*8*), only two new drugs, elagolix and relagolix, have been approved for endometriosis in the last two decades in the United States of America (*9*). While these specific drugs are new to the market, the target—*hormonal suppression*—is not novel and represents the mainstay of current treatment for endometriosis (*9*). There is an urgent need to advance understanding of endometriosis so that more precise and personalized therapeutics can be discovered and implemented.

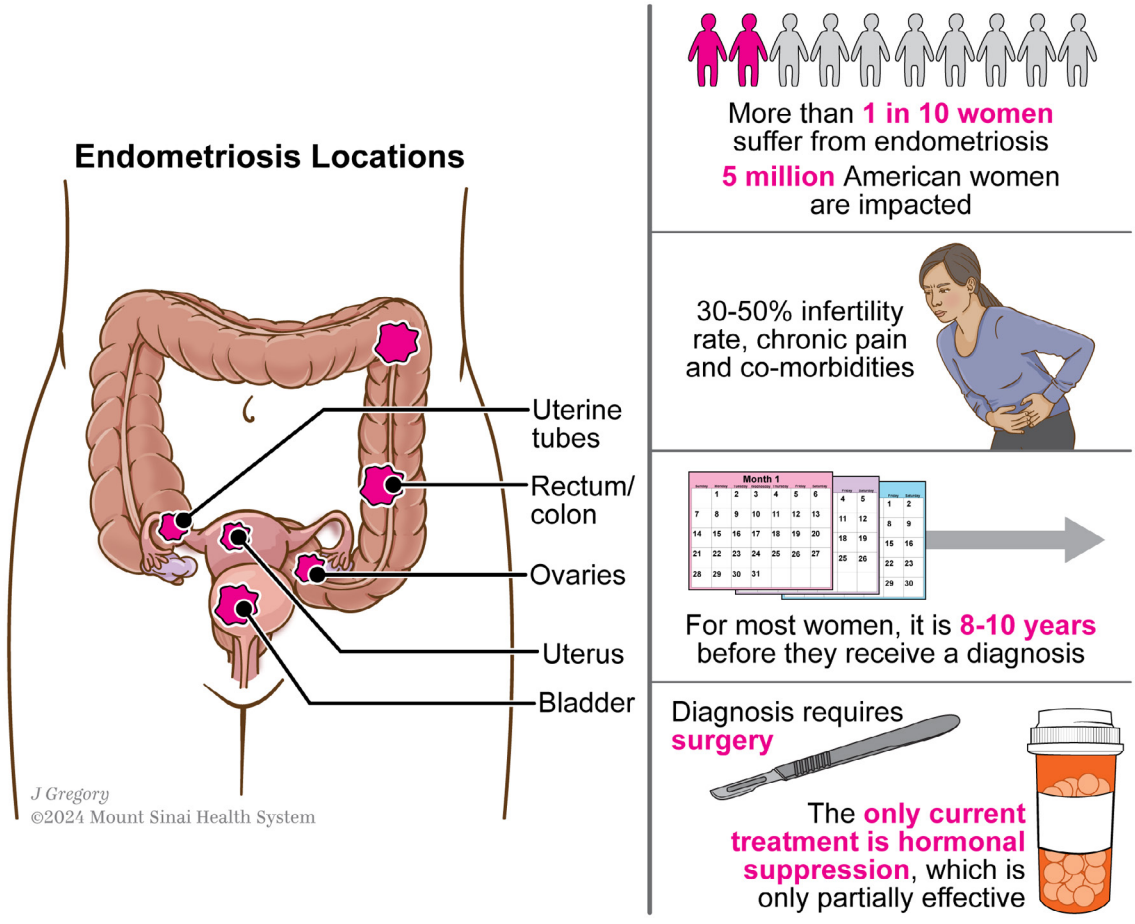

Figure 1: Endometriosis is a systemic disease.

Surgical management of endometriosis

While laparoscopy remains the gold standard for the diagnosis of endometriosis, there are limitations to its use and a reluctance by patients to undergo surgery for a diagnosis. Surgical management of endometriosis requires additional training and high-volume exposure to identify and treat early disease, with the physician experience and expertise needed, to identify the various presentations of disease as well as the complex surgical presentations found in advanced-stage disease. While cystic lesions can be found with imaging, non-cystic lesions on the ovary, and peritoneal surfaces overlying the bladder, ureters, and bowel, are not adequately identified prior to laparoscopy (*10*). These peritoneal implants, which can be deeply infiltrating or superficial, can be found in various areas in the pelvis and upper abdomen. Cystic ovarian and extra-ovarian lesions are signs of more advanced disease, but if laparoscopy is performed with early presentation, one can avoid more radical surgery and chronic progression of disease states that lead to infertility or chronic pain for some patients.

Origins of disease

While the developmental origins of endometriosis are still unclear, Sampson's retrograde menstruation theory remains the most widely accepted. This theory is supported by data showing that women commonly have retrograde menstrual flow and that, in the presence of reproductive tract obstructive defects which can increase retrograde flow, there is a significantly increased risk of endometriosis (*11*). Endometriosis is also identified at sites distant from the pelvis, suggesting that retrograde menstruation may not be the only mechanism by which endometriosis develops (*12*). Despite the large burden for women, much remains unknown as to the initiators of the disease. While many women have retrograde menstruation as observed during laparoscopic surgeries, most women will not develop endometriosis. As such, it remains unknown as to why in some women the endometrial tissue implants and evolves into hemorrhage, inflammation, and scar tissue. The recent, albeit limited, use of high-throughput, discovery-based approaches has provided some needed insight into the immune drivers of this disease. Specifically, sequencing eutopic endometrium in individuals with and without endometriosis has provided insight into possible mechanisms for impaired fertility in endometriosis (*13*). Additionally, single-cell sequencing data from endometriosis lesions in ovary and peritoneum, compared to normal tissues, created a critical cellular atlas of endometrial-like epithelial cells that provides key information about epithelial biology in this disease (*14*). Limitations of this work in informing (and changing) clinical care result from their small sample sizes and investigations of tissues from individuals on hormonal suppression therapy, thus, not attending to the known molecular impact of modulating estrogen and progesterone receptor activity in these tissues.

Targeting endometriosis

While the precise origins of endometriosis remain unclear, several studies have demonstrated perturbations of cellular immune function within the endometriosis lesions. Indeed, various studies have reported that inflammation is an essential feature of endometriosis. Emphasizing this

growing body of evidence, a recent expert review called for recognition of endometriosis as a systemic inflammatory disease (*12*). Understanding the potential inflammatory milieu in this disease and its connection to the gut microbiome remains an important yet insufficiently studied factor. Gut microbial diversity has been found to be higher in controls than in endometriosis patients (*15*). However, results are inconsistent across studies, likely due to the heterogeneity of the populations, the use of low-resolution microbial characterization techniques, and modest sample sizes (*15*). While studies are in their infancy, there is immense promise for understanding the role of immune and microbial drivers of endometriosis and the potential to leverage these findings to develop new biomarkers and novel therapies.

Outlook for endometriosis

Endometriosis research urgently needs novel methods to identify pathogenesis without the need for invasive surgery and to improve care of patients. Rigorous studies that elucidate specific immune mechanism will be critical, and the use of high-throughput techniques in well-characterized cohorts will provide novel opportunities to decrease the burden of this disease. Shortening the time to diagnosis and developing precision-based therapeutics will be fundamental to improve the lives of endometriosis patients.

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The microbiome in women's health

Jose C. Clemente[1*], Naomi Freilich[1], and Michal Elovitz[2 3]

A technological lens for a microscopic universe

As van Leeuwenhoek leveraged his mastery of optical lenses to develop the microscopes with which he discovered the microbial life that surrounds us, technological advancements in sequencing and other molecular assays now allow us to explore our own microbial diversity at an unprecedented resolution (**Figure 1**). Early studies of the microbiome in women's health were based on 16S rRNA gene sequencing, a cost-effective but low-resolution approach. Shotgun metagenomics overcomes this limitation and can identify microbial strains as well as microbial functions and pathways that provide mechanistic insights into disease pathogenesis. Metatranscriptomics further expands our understanding by sequencing the transcriptional profile of whole microbial communities, serving as a more accurate predictor of microbial metabolites that modulate host–microbe interactions in disease states (*1*). The relation between the microbiome and the immune system can be explored using techniques that combine flow cytometry and sequencing, which can identify microbes bound by different immunoglobulins or the physiological state of different microbes in the community (*2*) We have pioneered the use of these technologies and are now leveraging them to understand how microbial communities in several organs interact with the host to modulate women's health encompassing the life course from birth through menopause and to identify novel therapeutic targets.

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The gap in women's health microbiome research

While important work has been done in the microbiome of women's health, we argue that the scope and quantity are still limited, and opportunities remain to expand the field and translate research findings to improve the lives of patients. Arguably, most women's health studies to date have been in the vaginal microbiome, particularly in relation to bacterial vaginosis and preterm birth. The healthy vaginal microbiome is dominated by *Lactobacillus* species. Their absence and an enrichment of vaginal anaerobes is associated with multiple adverse outcomes across a woman's life course, including sexually transmitted infections, infertility, preterm birth, cervical dysplasia, postmenopausal atrophic vaginitis, and urinary tract infections (*3*,*4*). While the production of lactic acid from *Lactobacillus* is believed to acidify the vaginal ecosystem and prevent pathogens, the precise molecular mechanisms by which vaginal microbes contribute to health and disease are likely much more complex as we have recently demonstrated by revealing functional bacterial extracellular vesicles, which add to the complexity of the vaginal microbiome (*5*). Further research assessing the metatranscriptome will likely provide needed insights beyond microbial composition to understand how shifts in the vaginal microbiome are mechanistically involved in reproductive health.

The role of the vaginal microbiome in endometriosis has been investigated in several studies, although with moderate sample sizes and using low-resolution techniques such as 16S rRNA gene sequencing. Studies of the gut microbiome of patients with endometriosis, also using 16R rRNA sequencing, have reported changes in microbial abundance and correlation of specific bacteria with symptoms and with pro-inflammatory cytokines, such as IL-8. However, results to date have been inconsistent across studies, partially due to heterogeneity of the populations. Polycystic ovary syndrome (PCOS) has also gained attention given the role of the

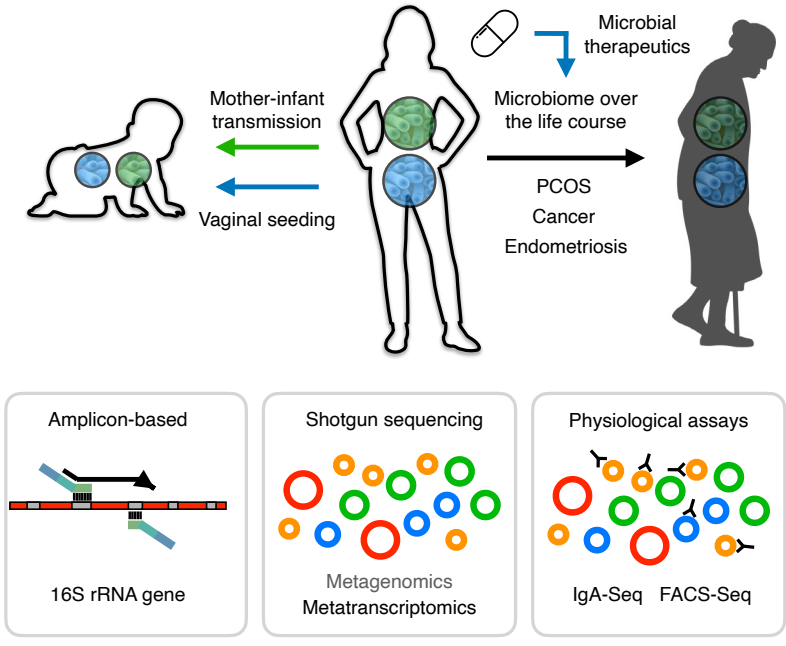

Figure 1:The microbiome and women's health across the life course. Technological developments have facilitated a deeper understanding of how the microbiome modulates women's health. Mother–infant transmission provides initial microbial colonization of the newborn, and "vaginal seeding" can partially restore microbial homeostasis in C-section delivered infants. Dysregulation of vaginal or gut microbial communities increases the risk of various diseases, with microbial therapeutics being developed to prevent or treat these conditions.

gut microbiome in insulin secretion and androgen metabolism. Bile acid disruption driven by changes in gut microbiome has been shown to be one mechanism by which the microbiome can modulate insulin resistance and reduce IL-22 levels, increasing the risk of PCOS. The role of the microbiome in gynecological cancer has also been investigated, although conclusive studies are lacking beyond the known role of vaginal pathogens in increasing cancer risk.

Today's prevention, tomorrow's health: Microbial transmission from mothers to infants

Microbial colonization starts upon birthing, when the infant is first exposed to maternal microbes either from the birth canal, in vaginal deliveries, or from the skin and environment in cesarean (C-) sections. We have shown that cohabitation with parents and siblings further strengthens this "microbial inheritance (*6*)", and microbial strains shared between family members can persist for decades (*7*). Understanding maternal health and lifestyle practices and how they shape their microbiome is thus fundamental to predict potential disease risks in the infant that are mediated by the transmission (or lack) of microbes.

We have also demonstrated that families with farming lifestyles, increased rates of home birthing and breastfeeding, and reduced use of antibiotics can result in significant differences in the microbiome of infants and potentially lower the incidence of allergic outcomes (*8*). Further, the microbiome of infants born from mothers with inflammatory bowel disease have lower microbial diversity compared to healthy controls, and their transplantation to a mouse model results in more colitogenic responses, suggesting a potential causal role (*9*). The benefits of maternal breastmilk for the infant microbiome are also well-known, an effect that is not limited to bacteria but also extends to the virome (*10*). These findings thus point to the maternal microbiome being critical for the health of both the mother and the infant.

The road to microbial therapeutics

The plasticity of the microbiome facilitates interventions to modify its composition for therapeutic purposes. We have previously shown how the use of fecal microbiome transplants holds promise in some conditions, particularly *Clostridioides difficile* infections (*11*) and ulcerative colitis (*12*). Importantly, recent findings point to endometriosis being a chronic condition driven by a systemic inflammatory response. This suggests that microbial interventions that curb pro-inflammatory responses could be an innovative approach to existing therapies, such as hormonal suppression. The use of collections of bacteria, or individual species, to produce anti-inflammatory short-chain fatty acids can lead to suppression of immune responses, an area of research that remains to be explored in women's health. In infectious conditions, such as bacterial vaginosis, the use of vaginal microbiota transplants has been previously explored with encouraging results. The combined use of intravaginal antibiotics with multiple vaginal microbiota transplants was effective in eliciting long-term clinical response in four out of five women, although larger studies will be required to confirm these findings.

In parallel with efforts to develop microbial therapeutics for women's health, interventions that restore the microbial transfer from mothers to infants are already underway. We have previously demonstrated that transferring maternal vaginal microbes to C-section delivered infants ("vaginal seeding"), who lack important microbial immunomodulators, partially restores their microbiome to resemble that of vaginally delivered infants (*13*). We have recently shown that such restoration of early life microbiome in C-section infants can modulate neurodevelopment and are currently investigating whether it can also shape immune development and lower the risk of food allergies (clinicaltrials.gov: NCT03567707).

Given the large differences in microbial composition across people, designing personalized therapies that consider the patient's own microbiome, and can maximize engraftment of the transferred microbes, will be critical to ensure efficacy. Importantly, a broader understanding of social determinants of health, including access to nutritious foods, toxic environmental exposures, or stress (*14*,*15*), is also likely to be of high relevance, given its role in shaping women's microbiomes and the need to personalize microbial therapeutics. Joint efforts between women's health scientists and microbiome researchers will therefore be fundamental to develop microbial therapies that prevent and treat women's diseases.

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The immunologic basis of skin aging and inflammatory disorders in women

Helen He[1*], Daniel Liu[1], William Zhao[1], and Emma Guttman-Yassky[1*]

Introduction

Due to gender-related differences in intrinsic factors (e.g., skin pathophysiology, sex hormone influences) and extrinsic factors (e.g., sociocultural behavior, environmental exposures), women face unique challenges in skin aging and inflammatory dermatoses. Several dermatologic conditions are more prevalent and/or have unique clinical manifestations in women; these include contact dermatitis and both non-scarring and scarring hair loss disorders. Skin profiling across healthy female subjects and disease states at different ages is beginning to unravel the immune dysregulation in skin aging and inflammatory skin/hair conditions (Figure 1).

Skin aging

Skin aging is a complex, multifactorial process influenced by gender differences in skin hydration, elasticity, thickness, pigmentation, and sebum production (*1*). Female skin is susceptible to the effects of estrogen, which is protective against oxidative damage and senescence (*1*). 17β-estradiol levels, which correlate with collagen and elastin content and dermal thickness, increase from ages 25–30, and subsequently decline starting in the 30s (*2*). After menopause, collagen content decreases at ~2% per year. Estrogen also promotes gut microbiome diversification with positive effects on dermal health, while the skin microbiome showed increased alpha diversity of the cheek and forehead after menopause (*2*,*3*) Topical estrogens and estrogen analogues are actively being explored as anti-aging treatments.

Cutaneous transcriptomic studies in female adults provide insights into the molecular changes that occur with skin aging. Cohort studies of >100 Caucasian women ranging from age 18 years to 70s/80s reported progressive shifts with chronological age in pathways related to adhesion, extracellular matrix organization, immune dysregulation, oxidative stress, and senescence (*4*,*5*). A subset of patients whose skin appeared more youthful than their chronological age showed enrichment of genes associated with DNA repair/replication, oxidative stress response, cell growth/survival, mitochondrial structure/metabolism, epidermal barrier function, and dermal matrix production pathways like hyaluronan synthesis (*4*,*5*). In postmenopausal women, photo-exposed facial skin had more inflammation, thinner epidermis, decreased dermal collagen type IV, and differential expression of lipid synthesis/metabolism genes compared to photo-protected skin (*6*).

More recently, aging has been associated with low-grade inflammation and immunosenescence from cumulative immune remodeling spanning decades, termed "inflamm-aging." With aging, decreased Langerhans cells and increased skin infiltration of lymphocytes, mononuclear cells, and eosinophils were suggested (*7*). One skin profiling study compared healthy subjects across an age spectrum with atopic dermatitis (AD), a common inflammatory skin disease characterized by Th2 dysregulation, with varying involvement of other T-helper axes (Th1/Th17/Th22) (*8*). Healthy adults age>60 showed higher activation of Th1/Th2/Th17/Th22 and dendritic cells (DCs) than younger adults, resembling the immune signature of AD, suggesting that AD should be further investigated as a potential disease model for healthy skin aging. In a female cohort, FOXP3 increased with chronological age and decreased with skin youthfulness, inferring that regulatory T-cell (Treg) dysfunction may contribute to immunosenescence and accelerated aging in women (*5*). Comprehensive immune profiling specifically of female cohorts is needed to better characterize inflamm-aging and identify potential disease drivers of aging in women.

Contact dermatitis

Contact dermatitis (CD) is a common eczematous skin condition. Irritant contact dermatitis (ICD), accounting for 80% of CD, involves direct skin damage and innate immune activation. Allergic contact dermatitis (ACD), the other 20%, is mediated by type IV delayed hypersensitivity with hapten-specific T-cell responses. Global epidemiological studies showed a higher overall prevalence of CD in females, with increased ACD to specific allergens due to lifestyle and occupational exposures, including nickel, fragrances, thimerosal, cobalt, and paraphenylenediamine (*9*). ACD to nickel, which is more common in females due to the higher incidence of pierced ears, has been associated with hand eczema and smoking in females (*9*). Female skin may be inherently more susceptible to CD given the decreased thickness and collagen content and increased transepidermal water loss compared to male skin, findings which become more pronounced with aging (*1*).

The unique hapten-specific clinical features and comorbidities of ACD suggest that underlying molecular mechanisms may vary based on the inciting allergen. Indeed, immune profiling of human skin challenged with common allergens revealed distinct immune activation patterns. Nickel induced innate immunity and Th1/Th17 skewing, while fragrances induced stronger Th2/Th22 polarization with weaker Th1/Th17, as seen in AD (*10*). Thus, Th2 immunomodulation, which is efficacious in AD, may have a role in fragrance-induced ACD. AD patients with nickel-induced ACD have attenuated Th1 responses and may thus mount weaker responses to vaccination and certain infections. As nickel and fragrance allergens are disproportionately seen in women, characterizing the immunologic heterogeneity of ACD in women, based on the inciting sensitizer, also accounting for environmental exposures and comorbidities like AD, can facilitate individualized management approaches.

Non-scarring and scarring alopecia

Scalp hair, which is integral to self-esteem and identity, is considered a sign of beauty and femininity in women. Women with both scarring and non-scarring alopecia are reported to have impaired quality of life, increased marital and career-related problems, and psychological disturbances like depression (*11*).

Alopecia areata (AA) is a common, non-scarring, autoimmune hair loss disorder associated with depression and anxiety. Large North American and European cohorts showed that women have higher AA prevalence and a higher likelihood of co-morbid autoimmune disease, nail involvement, and adolescent onset (*12*). In AA, there is loss of immune privilege at the hair follicle, mediated by cytotoxic CD8+ T-cells, Th1, and JAK/STAT signaling (*13*). Scalp biopsy and blood studies demonstrating Th1/Th2 elevations at baseline and post-treatment reductions suggest an additional pathogenic role for Th2 (*13*). Until recently, AA treatment options were limited to topical/intralesional corticosteroids, contact immunotherapy, and broad systemic immunosuppressants. The increased mechanistic

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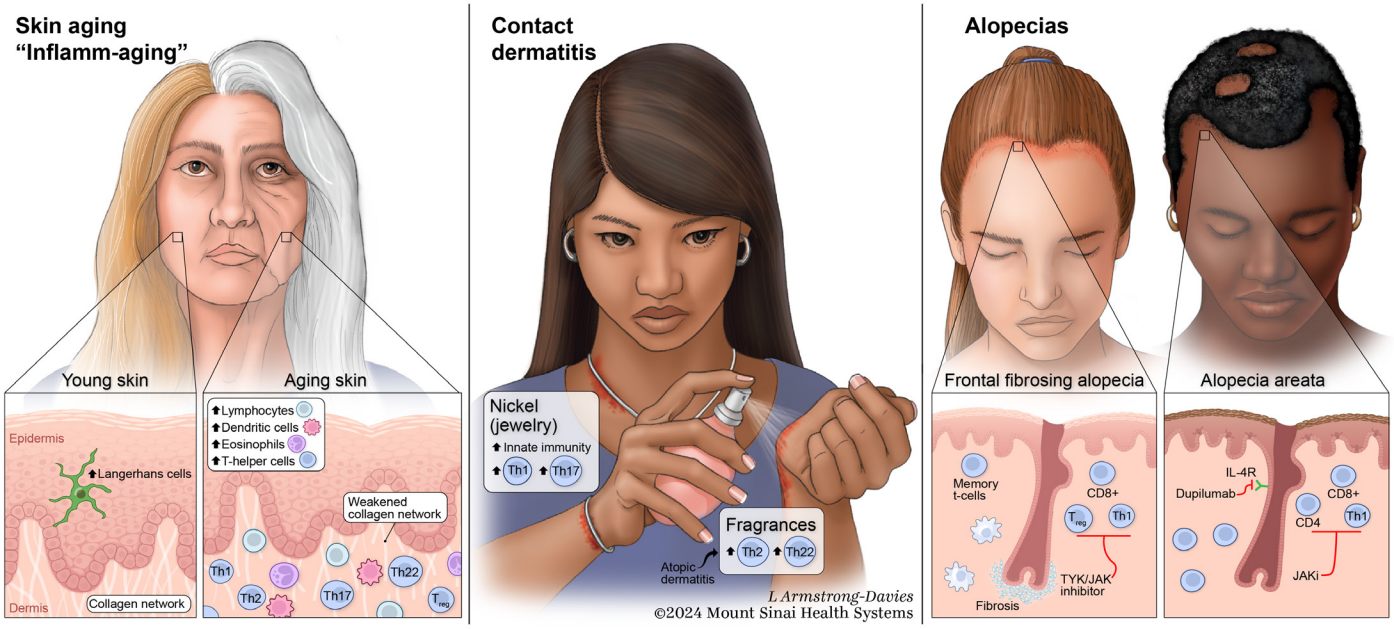

Figure 1: Clinical and/or histologic findings and immune abnormalities in skin aging and inflammatory skin/hair disorders that disproportionately impact women.

knowledge of AA has bridged this therapeutic gap, where JAK inhibitors and other biologics are now available or undergoing clinical trials. IL-4Rα inhibition with dupilumab showed hair regrowth and improvement of skin inflammation, especially in patients with elevated serum IgE levels or history of atopy (*13*). Sex-dependent responses should also be evaluated in future AA studies.

In contrast to non-scarring alopecia like AA, scarring alopecia is often irreversible with destruction and fibrosis of hair follicles. Many forms of scarring alopecia are female-predominant, including frontal fibrosing alopecia (FFA), primarily affecting postmenopausal women, central centrifugal cicatricial alopecia (CCCA), and lichen planopilaris (LPP). Given the poor prognosis and lack of effective treatment options, women with scarring alopecia often have worse psychosocial outcomes compared to those with non-scarring alopecias, with stronger feelings of anxiety and depression, loneliness, social isolation, and low self-esteem (*14*). Scalp biopsies from female FFA patients with ≤7 years disease duration were highly inflammatory, with significant increases in cytotoxic CD8+ T-cells, DCs, and tissue resident memory T-cells as well as robust upregulation of Th1, Treg, and JAK/STAT signaling pathways (*15*). Stem cell markers were diminished but still present in FFA lesions and largely preserved in non-lesional biopsies, suggesting that treatment at this inflammatory stage may halt disease progression and even regrow hair. Preliminary results from ongoing clinical trials of brepocitinib, a dual TYK2/JAK1 inhibitor, showed clinical improvement and reductions in Th1 biomarkers in female patients with FFA, CCCA, and LPP. Translational research and immunophenotyping is advancing our mechanistic understanding of scarring alopecia and introducing new potential therapeutic targets, providing hope for disease modification in a distressing condition that was previously considered untreatable, emphasizing the importance for early intervention before hair follicles become irreversibly destroyed.

Summary

Cutaneous molecular profiling has advanced our knowledge of immune abnormalities underlying physiological and pathological dermatologic processes that are of importance to women, including skin aging and inflammatory skin/hair conditions. This increased mechanistic understanding enables the development of specific, personalized treatments that promote women's skin/hair health.

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Identifying and overcoming vulnerabilities in breast and gynecologic cancers

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Introduction

One in six women will develop a breast or gynecologic cancer over the course of her lifetime, and some of these patients will have both. While anatomically distinct, these cancers are often linked by common risk factors, including genetic, hormonal, and metabolic. With understanding of the commonalities across these diseases as well as individual biological differences within each cancer type, treatment of these cancers has evolved substantially. Some treatments originating in the gynecologic space have translated to breast cancer and vice versa. At Mount Sinai, access to the most innovative technologies, latest trials and cutting-edge science allows us to bring the very best care to our large and diverse patient population to achieve the best outcomes (Figure 1).

Breast cancer: Identifying strategies for de-escalation to decrease morbidity

Breast cancer is the most commonly diagnosed cancer among women in the United States of America, with an estimated 300,000 cases diagnosed each year (*1*). Cure rates for breast cancer have never been higher, with current overall survival rates exceeding 90%. This significant reduction in mortality rate can be attributed to two areas of progress: better methods for earlier detection and better, more effective treatment options.

With such therapeutic advances, much research over the past decade has been focused on "DE-ESCALATION": determining which patients can be spared aggressive therapies (surgery, radiation, chemotherapy) while not compromising survival. As it relates to surgery, for example, the standard of care for invasive breast cancer has always involved either a lumpectomy or mastectomy to remove disease in the breast, in addition to performing sentinel node biopsy to stage axillary lymph nodes. A recent study, the SOUND trial, demonstrated that selected patients with low-risk disease may be able to safely forego axillary staging, with no significant difference in recurrence rates (*2*). As it relates to radiation, a post-surgical treatment that used to be nearly mandatory in all cases following lumpectomy, we now know that many patients can safely omit post-surgical radiation, with acceptably low risk of recurrence (*3*).

Towards optimal personalization of systemic treatment of breast cancer

Advances in therapies and genomic tools have also enabled more individualized, tailored medical treatment of breast cancers, sparing many patients the toxic side effects of chemotherapy while offering more options for others with advanced disease. Genomic tests have helped guide treatment of early-stage hormone receptor positive (HR+) breast cancer. Tests like OncotypeDx, for which the validation studies were led by a Mount Sinai breast medical oncologist, have prognostic as well as predictive power to assess benefit of chemotherapy treatment (*4*).

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Patients with more advanced stage disease have also benefited from tumor genomic profiling for a growing list of actionable mutations that can be treated with matched, targeted therapeutics that are non-chemotherapy options such as PARP inhibitors for *BRCA*-altered, breast cancers (*5*). Mount Sinai investigators participated in NCI-MATCH trials that helped lead to approval of other therapeutics such as capivasertib for *AKT*-mutated cancers (*6*) and other trials targeting cancers with alterations in the PTEN/PI3K pathway are ongoing.

There has also been an exciting increase in available treatments that have contributed to improved survival and remission rates for aggressive breast cancer subtypes. For example, combined chemotherapy and immunotherapy was recently approved as standard of care for patients with stage 2/3 triple negative breast cancers (TNBC) based on complete response rate of 65% in the Keynote-522 trial (*7*). Novel antibody-drug conjugates (ADCs), such as trastuzumab deruxtecan, have dramatically improved outcomes for patients with advanced HER2+ and HER2-low breast cancers (*8*). Mount Sinai investigators are participating in studies evaluating antibody-drug conjugates, immunotherapy, and other combinations for high-risk patients with residual TNBC in early disease settings and in patients with advanced/metastatic disease.

Endometrial cancer: Genetics drives prognosis and therapeutic response

Endometrial cancer is the leading cause of gynecologic cancer deaths and encompasses a spectrum of genetically distinct disease subtypes. Recent randomized clinical trials demonstrated marked therapeutic efficacy of chemotherapy in combination with PD-1 blockade in mismatch repair-deficient (dMMR) endometrial cancer, with close to 75% of patients remaining disease progression-free at 2 years (*9*). A recent study led in part by investigators at Mount Sinai demonstrated that tumor microenvironment features can further refine which dMMR patient populations are more likely to benefit from immunotherapy (*10*).

The remaining endometrial cancers, particularly serous carcinomas and carcinosarcomas, exhibit poor prognosis and very limited response to therapy. Emerging evidence indicates that these most aggressive histologic and molecular subtypes appear to be more prevalent in Black patients, a population that represents close to 40% of all endometrial cancers seen at Mount Sinai. Clinical and basic investigators in gynecologic oncology at Mount Sinai have partnered to address these therapeutic challenges by conducting clinical trials with a number of novel investigational agents, including ADCs and targeted drugs (*11*), and by taking advantage of patient biospecimens and pre-clinical models to identify new therapies and mechanisms of therapeutic resistance.

Therapeutic advances in cervical cancer: Preventing disease recurrence

Cervical cancer, another disease of predominantly underserved communities, affects 12,900 patients and accounts for approximately 4,100 deaths in the United States of America each year (*1*). Cervical cancer studies ongoing at Mount Sinai aim to address several critical unanswered questions across disease stages. In early-stage cervical cancer, Mount Sinai investigators are participating in a global clinical trial aiming to answer whether a minimally invasive robotically assisted hysterectomy could achieve similar outcomes as the standard open surgical approach. In locally advanced disease which is now treated with chemoradiation in combination with the PD-1 inhibitor, pembrolizumab, newly reported data from an NRG Oncology trial conducted by Mount Sinai investigators demonstrate potential utility of neoadjuvant immunotherapy in this setting (*13*).

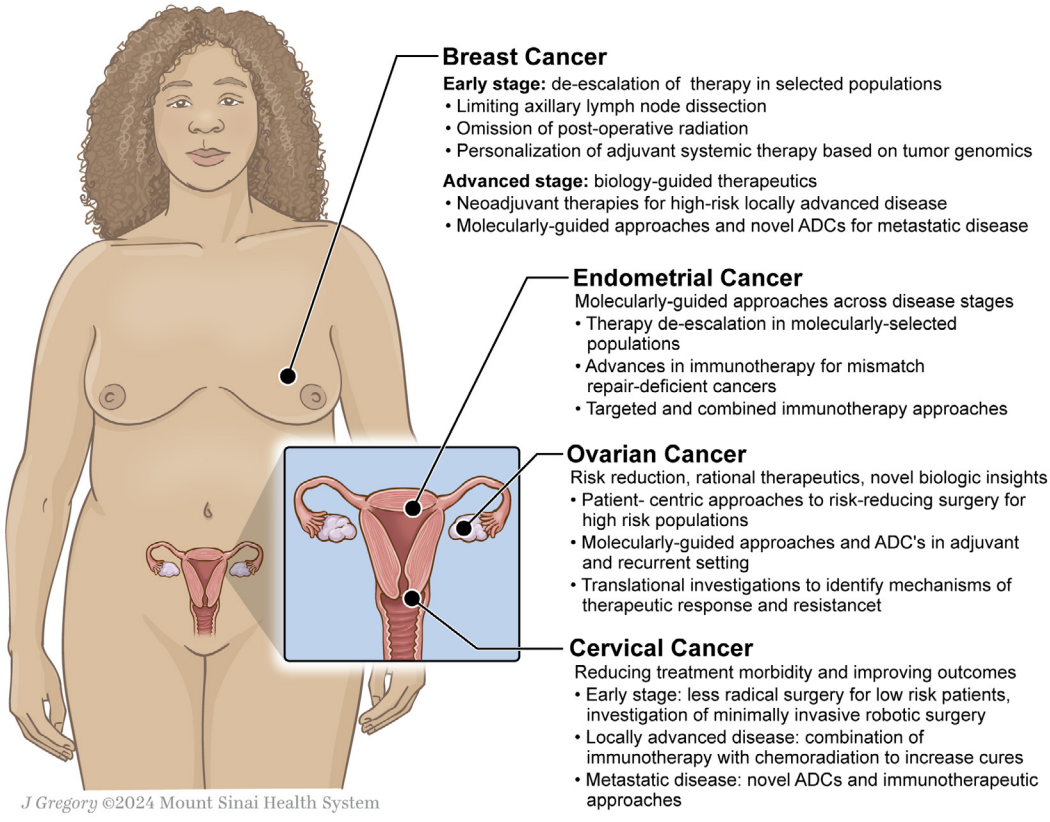

Figure 1: Therapeutic advances and ongoing investigations in women's cancers at Mount Sinai.

Ovarian cancer: A mastermind of genetic and immune heterogeneity

Ovarian cancer causes an estimated 15,000 deaths in the United States annually (*1*). Surgical prevention trials utilizing bilateral salpingo-oophorectomy in patients at increased risk of cancer due to germline mutations in *BRCA1/2* have demonstrated substantial reduction in the risk of ovarian cancer development. Recent discovery of the fallopian tube epithelium as the cell of origin in ovarian cancer led to the development of clinical trials exploring prophylactic salpingectomy as a strategy to prevent ovarian cancer in high-risk women while avoiding the adverse effects associated with early menopause; two of these trials are open and enrolling at Mount Sinai.

Advanced ovarian cancer continues to present therapeutic challenges and exhibits resistance to many novel therapeutic agents including immunotherapy (*14*). Research led in part by Mount Sinai investigators demonstrated that genomic instability that underlies the pathogenesis of ovarian cancer leads to multiple mechanisms of immune escape, which contributes to the substantial heterogeneity of this syndrome (*15*). These findings create opportunities to develop therapeutic agents against broadly expressed targets. Recently, the first ADC (mirvetuximab soravtansine) was approved to treat ovarian cancer, showing prolonged overall survival for patients with hard-to-treat platinum-resistant disease (*16*). Mount Sinai was involved in studying this agent and is now pursuing research in future ADCs, bispecific T cell engagers, and other targeted agents.

Summary

In summary, while significant strides have been made in surgical innovation and systemic therapies in breast and gynecologic cancers, clear unmet needs and deficiencies in understanding of disease biology remain. Emerging data also suggest that cancer disparities may be driven by patient genetics and very limited data are available to understand how racial or ethnic background impacts therapeutic response. Development of improved preclinical models of cancer as well as comprehensive evaluation of human biospecimens from diverse patient backgrounds are thus imperative. To this end, a collaborative research culture at Mount Sinai that integrates clinicians and basic and translational investigators will be key to drive therapeutic progress.

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