Preparing for Pregnancy

A TEST OF THE UTERINE LINING IMPROVES CHANCES OF SUCCESS

It takes a healthy embryo and a healthy mother to nurture the microscopic meeting of a sperm and an egg through nine months of development before a baby can be born.

Even as four million babies are born in the United States every year, about 6 percent of married women of reproductive age in the United States cannot become pregnant after a year of trying. And about 25 percent of all women who become pregnant have a first-trimester loss.

There are many causes of infertility, including secondary effects of various disorders as well as hormonal and genetic conditions in either the man or woman. And many factors can influence how or if an embryo grows into a healthy breathing baby.

One factor that Dr. Harvey Kliman has studied for nearly three decades is the function of the endometrium, the mucous membrane that lines the inside of the uterus and serves as the nutrient-rich medium into which an embryo must implant before it can grow.

“You can have the perfect embryo, but if you don’t have perfect medium, it won’t grow,” Kliman said, noting how the endometrium feeds the embryo until the ninth week of pregnancy, when the mother’s blood takes over through the embryo’s placenta.

Kliman serves as Director of the Reproductive and Placental Research Unit in Yale School of Medicine’s Department of Obstetrics, Gynecology and Reproductive Sciences. He began

CONTINUED PAGE 6

Learning to Lead

Women’s Health Research at Yale’s Undergraduate Fellowship mentors students who seek to expand their studies with a focus on the incorporation of sex and gender in contemporary science and medicine.

This hands-on training program allows students to adopt WHRY as their “scientific home” under the mentorship of WHRY-affiliated faculty members. Whether conducting research in a laboratory, assisting in a clinical setting, or advancing public health literacy through a communications campaign, these students learn “up close” how sex and gender have an influence and an impact on health outcomes.

All our students have the talent and initiative to carry this knowledge wherever their promising careers take them and to continue leading our efforts to change the landscape of medical research and practice to fully consider women and improve public health for everyone.

Meet the 2017 Fellows on page 3
Women’s Health Research at Yale was founded in 1998 with initial funding from The Patrick and Catherine Weldon Donaghue Medical Research Foundation.

Women’s Health Research at Yale is a program within Yale School of Medicine. Yale University is a 501(c)(3) nonprofit organization.

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Professor of Psychiatry and Psychology

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Our Society of Friends ensures the future of Women’s Health Research at Yale. Gifts are welcome at all levels.

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Learning to Lead

THE NEW 2017-18 FELLOWS:

**DHIKSHITHA BALAJI**, a senior in Pauli Murray College majoring in pre-med and English Language and Literature, is working on science literacy under the mentorship of WHRY Director Carolyn M. Mazure, Ph.D., Communications Officer Rick Harrison, and Media and Design Specialist Carissa Violante, designing, researching, and writing a new blog on the advancement of women’s health research for the center’s website. In addition, Balaji is creating public health literacy videos and testing their ability to inform, influence attitudes, and change behavior.

**KAVERI CURLIN**, a junior in Berkeley College majoring in Ecology and Evolutionary Biology, is mentored by Dr. Njeri Thande, an active cardiologist who has a special interest in women’s cardiovascular health as well as HIV and heart disease. Curlin, who is preparing her medical school applications, is shadowing Dr. Thande and assisting in her ongoing project to integrate data on the influence of sex and gender on health into Yale’s medical school curriculum.

**SEYRAM DODOR**, a junior in Saybrook College majoring in History of Science, History of Medicine, and Public Health, is also working with Dr. Njeri Thande, studying the factors that influence whether cardiac patients correctly follow medical advice involving medication, self-care, and other steps to improve the effectiveness of treatment. Dodor, a first-generation Ghanaian American from North Carolina, is a member of the Global Health at Yale program interested in how health affects those within the African diaspora. While pursuing a career in medicine and global health, she aims to explore ways of improving reproductive health among women of color and linking the connection between communicable diseases and non-communicable diseases in women.

UNDERGRADUATE TRAINING FELLOWSHIP

**RETURNING 2017-18 FELLOWS:**

In addition, we are thrilled to welcome back two students for a second year in the fellowship program.

**ROSE DAVIS**, a senior majoring in Molecular, Cellular and Developmental Biology (MCDB), will continue to work with Dr. Lisa Freed, Director of Yale New Haven Hospital’s Women’s Heart and Vascular Program, as she explores the unique health challenges women face and pursues a career as a surgeon.

**HALEIGH LARSON**, a senior majoring in Molecular Biophysics and Biochemistry (MBB), will work with Dhikshitha Balaji and the Communications staff to expand the production, distribution, and efficacy testing of the center’s health literacy videos, designed to help people make more informed health decisions.

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WHRY DIRECTOR CAROLYN M. MAZURE, PH.D., MEETS WITH THE MEMBERS OF THIS YEAR’S UNDERGRADUATE FELLOWSHIP AT THE WOMEN’S TABLE OUTSIDE STERLING MEMORIAL LIBRARY.
Dr. Karyn Frick was puzzled. Her two-year study, begun with funding from Women’s Health Research at Yale in 2005, found that long-term treatment with the sex hormones estrogen and progesterone did not improve memory as anticipated. “It was surprising, because we thought for sure we’d see a benefit of at least some of our treatments,” said Frick, now a Professor of Psychology at the University of Wisconsin-Milwaukee.

So Frick and her colleagues pivoted from longer hormone treatment regimens to a single treatment with estradiol, the most biologically active form of estrogen, to allow the researchers to better isolate the neural mechanisms behind memory formation. “Those original null findings actually set us on the path we’ve followed for the past decade,” Frick said of her work with animal models. “We’re still using the single treatment directly targeting the brain. And we’ve been quite successful in identifying specific signaling events, receptors, and cellular processes that are necessary for estradiol to help form a memory.”

This sex difference in the risk of Alzheimer’s disease has motivated Frick’s work identifying the molecular mechanisms through which sex hormones regulate memory formation, a topic she recently presented in Montreal at the annual meeting of the Organization for the Study of Sex Differences.

Frick and other researchers believe that the decrease in estrogens following menopause might explain what’s happening. Nerve cells in cognitive regions of the brain that are earliest affected by Alzheimer’s disease depend on estrogens for proper functioning. The precipitous loss of estrogens at menopause leaves these cells more vulnerable to the detrimental effects of the disease. Although estrogen treatment can reverse cognitive impairment in animal models of aging and dementia, its effectiveness in women isn’t clear and carries risks of side effects. “We need to find out how estrogens work to regulate memory in the first place,” Frick said. “Because you can’t design better treatments if you don’t know how something works. Understanding the molecular events in the brain that estradiol uses to facilitate memory formation might be the key we need to unlock the therapeutic potential of estrogens for dementia.”

Frick’s WHRY-funded study sought to investigate an unexpected finding from the Women’s Health Initiative Memory Study (WHIMS), a randomized, double-blind, placebo-controlled clinical trial of 7,510 women to determine the ability of the sex hormones estrogen and progesterone to prevent cognitive impairment when administered an average of 10 years after menopause. Despite previous studies in women and animal models demonstrating the ability of hormone therapy to reduce age-related memory loss, the WHIMS researchers found that treatment with estrogens, with or without a synthetic form of...
Frick explored whether her team could tweak the WHIMS design to show memory improvement in an animal model by administering estradiol to simulate the natural menstrual cycle and by using natural progesterone, as opposed to the synthetic form used in the WHIMS.

“We thought the sustained hormone therapy might be less effective than cyclical treatment because the female brain is most sensitive to the cyclical estrogen and progesterone fluctuations to which it is exposed for most of its life,” Frick said. “And synthetic progesterone reduces the neuroprotective effects of estrogens whereas natural progesterone exerts similar neuroprotective effects as estrogens.”

Surprisingly, neither therapy improved memory and, in several instances, impaired memory in middle-aged and aged subjects. But for motivated scientists, seeming setbacks only serve to help fill out the big picture and push progress.

Using a mouse model, Frick’s team began to administer a single dose of estradiol directed at the brain’s hippocampus, an important site in which short-term spatial, contextual, and object memories consolidate into long-term memories. They found that if they administered estradiol directly into the hippocampus within three hours of exploring an object, they enhanced the ability of their female subjects to later remember the identity and location of that object.

This effect proved more rapid than the previous understanding of how sex hormones classically affect cellular functioning, which requires hours or days for the hormone to diffuse into the cell, bind to receptors, move into the cell nucleus, bind to a specific part of the cell’s DNA,
Exploring a way to test the ability of the endometrium to support a pregnancy shortly before arriving at Yale from the University of Pennsylvania in 1991, hoping to find a clue within the endometrium’s constantly changing nature.

“Various organs within our bodies, such as the liver and kidneys, are constant,” he said. “They are basically the same, day in and day out. But the endometrium is unique. It’s the only organ that changes over 28 days.”

Over the course of a normal menstrual cycle, the endometrium alters its structure every day under the influence of fluctuating hormones in preparation for the possibility it will be needed to support a fertilized egg. The lining slowly builds up and then sheds, passing through the vagina as menstrual fluid before the process starts again.

“The endometrium then needs to get to a second phase, when it is no longer growing, before the embryo arrives,” Kliman said. “If this process stops prematurely, it won’t support implantation.”

**The Search for a Telltale Clue**

In 1998, newly founded Women’s Health Research at Yale awarded Kliman one of the center’s first Pilot Project Program grants to study whether the presence or absence of a particular mucin — a protein with many long sugar groups — at a certain stage of the menstrual cycle could serve as an indicator of healthy endometrial function and better chances for a successful pregnancy.

The mucin, named MAG, creates long filaments that the endometrium sends out to slow down a newly created embryo approaching from a Fallopian tube.

“It’s like sending lines from a dock to a boat floating downstream with help from workers on the shore,” Kliman said. “The embryo is the boat, and the mother is the shore.”

About 90 percent of embryos don’t attach, mostly due to genetic problems with the embryo, Kliman said. But for some women, the endometrium doesn’t work properly to allow implantation.

Kliman noted that MAG is only present in the first phase of the menstrual cycle, when the endometrium is growing. Using the WHRY grant, Kliman studied biopsies obtained from women with and without fertility problems and found that 85 percent of fertile women displayed normal patterns of MAG. But only 20 percent of women with infertility issues showed normal MAG patterns. Almost 30 percent of women with fertility problems had none of this mucin at all.

“This was a significant step,” Kliman said. “That first study gave us the framework to look for something... It showed the potential pathway.”
AN EVEN BETTER TEST

Armed with this new knowledge and now adept at obtaining biopsy samples from women with different degrees of fertility, Kliman and his colleagues shifted their attention. And their thinking.

Instead of looking at one or more markers produced by the endometrium to facilitate implantation, Kliman began to examine something fundamental to all cell growth.

Whenever a cell divides to create new cells, it must bypass biological checkpoints that regulate whether the process continues or stops. Cancer cells, for example, open all the checkpoints so they can continue to divide and spread uncontrolled.

Cyclin is a type of protein that forms one of these checkpoints to control the cell cycle and determine how cells spread. In the menstrual cycle, a cyclin known as Cyclin E allows the creation of DNA that guides the first phase buildup of the uterine lining. In the second half of the cycle, a gene known as p27 creates a protein that inhibits cell division and stops endometrial growth.

“This provides a much simpler, much more reliable, more uniform way to determine endometrial function,” Kliman said. “And it is present in every patient.”

Kliman and his colleagues published their findings in 2003 and soon trademarked and patented their Endometrial Function Test® (EFT®). His lab has found that women with an abnormal EFT are 10 times less likely to become pregnant than a woman with normal results. But after successful treatment, the women with abnormal EFTs show the same success rates as the general population.

The most common cause of an abnormal EFT is endometriosis, a condition in which the endometrial tissue grows outside the uterus and has no way of leaving the body after it thickens and breaks down during menstruation. After medical or surgical treatment, women with endometriosis are more likely to carry a pregnancy to term, Kliman said.

Other problems leading to an abnormal EFT include obesity or extreme thinness, which is often a sign of excessive exercise and high levels of stress that can make the body inhospitable for an embryo. Anatomic problems might include something called hydrosalpinx, in which fluid builds up in the Fallopian tubes and backs up into the uterus.

But Kliman cautions women not to consider the EFT a magic pill to cure their infertility, which can be caused by problems involving the sperm as well as problems with functions in organs such as the brain, pituitary gland, and ovaries. He said that the process and his recommendations are complex and should be addressed by experts who are board certified in reproductive endocrinology and infertility.

Still, Kliman sees his test as a way to address the emotionally devastating clinical problem of infertility for women who wish to have children and to effectively guide women to the best fertility treatment plan for them, possibly avoiding the expensive effort of in vitro fertilization (IVF).

“No, the most common way to test for endometrial function is to see how a pregnancy develops,” Kliman said.

“But an embryo is so important, we should first make sure the endometrium is receptive. Because we want to implant that embryo in an environment that gives it the best opportunity to grow.”
Men and women are different. And there is more to those differences that affect our health than we might immediately grasp.

“Medical education has traditionally focused on reproductive health when considering women,” said Dr. Njeri Thande, a cardiologist and Assistant Professor at Yale School of Medicine. “But we know that women’s health is that and more.”

And we know that differences, both biological and social, between men and women hold consequences for their health.

For example, women suffer more often from osteoporosis and non-contact sports injuries. Recommendations for taking aspirin to prevent a first heart attack or stroke differ for men and women. If a woman drinks the same exact amount of alcohol as a man, more often than not the woman will get more intoxicated and it will happen more quickly, even if they weigh the same. Women suffer more often from Alzheimer’s Disease and other dementias. Among all Americans suffering from autoimmune disease, 75 percent are women. Women are less likely than men to receive adequate pain medication for chronic pain.

Those are just some of the differences discovered by researchers since they have begun including women in clinical studies over the last two decades.

“A comprehensive understanding of women’s health is important, including patient sex and gender as significant factors in medicine,” Thande said. “Gender is a complex sociocultural identity. I was never more aware of the complex interplay between gender and health than when I had to discuss the cardiac implications of hormonal therapy with one of my transgender patients who had coronary artery disease. To practice good medicine, physicians and our students need to be sensitive to the complex identities of their patients.”

But it’s unclear how many students are getting this message. In a 2016 study, researchers at the Mayo Clinic surveyed 271 residents across the health organization’s campuses and found that 55 percent of the respondents reported only occasionally having an instructor discuss how a patient’s sex or gender affected diagnosis or treatment. Sixteen percent of the residents reported never having an instructor address sex or gender as influencing a patient’s care.

“This is a widespread problem in academic health centers,” said Women’s Health Research at Yale Director Carolyn M. Mazure, Ph.D. “Yale needs to help lead an ongoing national effort to address this pressing issue.”

Mazure has praised The Sex and Gender Women’s Health Collaborative (SGWHC), composed of the American Medical Women’s Association, the American College of Women’s Health Physicians, and the Society for Women’s Health Research, for its efforts to close the gaps in medical education concerning sex and gender.

To advance this shared goal, Mazure worked last year with Yasmin Zakinaieiz, a graduate student pursuing a Ph.D. in neuroscience, on an issue of the student-run Yale Journal of Biology and Medicine dedicated to sex and gender topics. Inspired by the experience, Zakinaieiz is collaborating with Dr. Michael Schwartz, Director of Medical Studies in Neurobiology.
and Associate Dean for Curriculum, to add the study of sex differences in the brain to the curriculum of the first-year neuroanatomy course she helps teach. But to take a more holistic step, Mazure and Thande are working with the medical school’s administration on integrating a focus on sex and gender into the curriculum. Their goal is for faculty to teach the latest findings concerning sex and gender across different disciplines, countering false assumptions and leading to more efficient medical care with better outcomes for patients.

“We want the best for our patients,” Thande said. “To get the best outcomes, we need to practice individualized medicine, which must include a consideration of sex and gender, along with other important biological and sociocultural determinants of health. For example, we know that women are less likely than men to get adequate treatment for pain. We know that black patients are less likely than white patients to get adequate treatment for pain. Hence, one can suspect that a black woman’s presumed lack of believability is compounded by the intersection of her identities.”

In collaboration with the educational leaders at YSM, Thande has undertaken an assessment of how students are taught about sex and gender influences on health during their first and second year courses. She selected six first- and second-year students to help create and administer a survey asking questions about the sex and gender content of their classes. Questions include: When a research study is discussed, is there any mention of the sex or gender of the subjects and whether or not the results were analyzed by sex or gender? Is there any discussion of gaps in knowledge due to an absence of basic or clinical research surrounding sex and gender aspects of health? Is sex/gender discussed as a binary category? How much time was spent on the subject matter? And which specific topics could have been presented through a sex and gender lens but weren’t?

Over the summer, Dr. Thande analyzed the data and began working with her students on a report to present to the school’s curriculum committee with proposals for potential changes. She also reviewed the clerkship curriculum to get a sense of what opportunities exist to integrate sex and gender research beyond the students’ first two years.

Thande noted how the effort aligns with the school’s mission to “educate and inspire” the next generation of medical practitioners and leaders, “advance medical knowledge to sustain and improve health,” and “provide outstanding care and service for patients.” And she stressed the need to work the topic into all pertinent aspects of the curriculum as opposed to offering a stand-alone course or lecture.

“We want our efforts to be sustainable,” she said. “We want students to understand that sex and gender aspects of health are not to be considered independently. I hope they learn to adopt a sex and gender lens that impacts every aspect of their medical research or practice. And that won’t happen if it’s taught separately.”

She recognized potential cost savings for the medical industry, noting that drugs have been recalled and dosing changed because of inadequate assessments of efficacy and safety concerning sex. And refocusing on sex and gender shouldn’t cost more time and money.

“It’s just a different way of presenting the same content,” she said. Thande, the Co-Director of the Homeostasis (cardiovascular, renal and pulmonary physiology and pathophysiology) integrated course for first year medical students, understands the challenges of changing or adding content to curriculum. But she expressed hope that the administration will embrace the challenge to better prepare students for the reality they will face when treating patients.

“We need to get this information to the students early,” Thande said. “Then they will spend the entirety of their careers conscious of how the influence of sex and gender affects health.”
and lead to the process in which inherited traits encoded in DNA are transcribed to carry out their designed functions.

“The kinds of biochemical mechanisms we’ve been examining in the past decade are rapid, or non-classical, effects,” Frick said. “We know that these rapid biochemical events are responsible for the memory-enhancing effects of estradiol because if we block them from happening, we prevent the formation of memories.”

ACTING LOCAL

Frick, who was recruited to the University of Wisconsin-Milwaukee in 2010, turned her attention to a process called local protein synthesis, in which estradiol in females increases the spiny projections of the information receiving, branched ends of nerve cells called dendrites. The more dendritic spines, the more contacts the nerve cells can make with other nerve cells, increasing plasticity — the brain’s ability to change its physical structure and potentially increase cognitive function.

“But in order to make new cellular structures like spines, you need proteins,” Frick said. “You can generate proteins by increasing activity in the cell’s nucleus, but estradiol increases spines pretty quickly — as early as 30 minutes after treatment. That’s too fast to be a nuclear effect, so it’s likely due to local protein synthesis within dendrites. All the machinery to make the proteins that build new spines is present locally in the dendrites, and so spines can be made without going through the nucleus.”

NEXT STEPS

To understand how estradiol promotes the formation of spines, Frick focuses on a form of chemical chain reaction called cell signaling. Cell-signaling pathways consist of proteins called enzymes that activate the next enzyme in the chain after their own activation. Within dendrites, two cell-signaling pathways in particular are essential for estradiol to enhance memory and increase dendritic spines.

Frick and her team have shown that when the activation of these pathways, called ERK and mTOR for short, is blocked, estradiol can no longer enhance memory or increase spines in the hippocampus of females. The mTOR pathway triggers local protein synthesis, and so the group’s findings demonstrate that estradiol may enhance memory by rapidly activating cell signaling, which then increases protein synthesis, spine density, and synaptic plasticity.

Frick’s successes with the ERK and mTOR pathways have led her team to examine other cell-signaling pathways related to ERK and mTOR to determine other possible molecules that estradiol might use to influence memory formation.

“We want to understand how estradiol affects memory on a molecular level,” Frick said. “If we can figure that out, then we can identify potential targets for future drug development.”

Ultimately, Frick hopes that researchers can develop a treatment that acts directly on the nerve cell’s estrogen receptors without having to use estrogen therapy, reducing the risk of possible side effects.

“The possible harmful side effects of hormone therapy are caused by estrogens binding to estrogen receptors throughout the body, not just in the brain,” Frick said. “If we can bypass estrogen receptors and target the underlying biochemical mechanisms that lie downstream from estrogen receptors within nerve cells, then perhaps we can develop drugs that mimic the beneficial effects of estrogens on memory without the detrimental side effects.”

At the time she received her WHRY grant, Frick was an assistant professor who had not yet had a major grant from the National Institutes of Health like one she is using now to advance this work.

“Having an organization like WHRY supporting junior investigators to get their research off the ground is really fantastic,” she said. “It was very instrumental in helping me succeed.”

And she expressed her appreciation for WHRY’s ability to not just grow vital science, but professional science careers.

“Our WHRY funding not only benefitted me, but also each of my students who worked on the project,” Frick said. “These graduate and undergraduate students are the primary investigators of tomorrow, so WHRY’s support will be perpetuated well into the future.”
Good News

The phrase “No news is good news” calls for a bit of cautious optimism. Judging by the steady stream of headlines over recent weeks and months, perhaps a more apt saying for the current moment might be: “If not for bad news, there would be no news at all.”

But when it comes to health benefits advanced through biomedical science, there is plenty of good news to share.

The job of researchers and medical professionals is to improve the prevention and treatments of the diseases and conditions that negatively affects thousands if not millions of people every day. This requires careful investigation of the microscopic components of life as well as large clinical studies to show how people react to treatments or conduct themselves outside of a laboratory.

And sure, there are struggles and setbacks. But when accumulating knowledge about health there are no dead ends, only clearer road signs about which investigatory paths to take.

Now in our 20th year, Women’s Health Research at Yale is working to make up for the decades before 1994, when the United States first implemented a law to require the inclusion of women in studies seeking grants from the National Institutes of Health — the world’s largest single funder of biomedical research.

Yes, it took a long time to pass that law and enact its guidelines. But scientists are on board now, and that’s good news.

By focusing on the health of women and the differences that may exist between women and men, the medical community and the general public are able to make better, more informed health decisions.

Just a few examples:

One early WHRY-funded study revealed that BRCA1 and BRCA2 genetic markers predict a vulnerability to breast cancer recurrence in either the treated breast or the untreated breast. These results continue to help health care providers and their patients around the world make more informed decisions about treatments to prevent breast cancer from returning. That’s good news.

Another WHRY-funded researcher discovered that women recovering from heart bypass surgery suffer more pain, infection, lower physical functioning, and twice the likelihood of hospital readmission. Her results — the first to show gender differences in heart bypass surgery recovery — alerted the cardiology world and prompted caregivers to ensure that women recovering from heart bypass complete cardiac rehabilitation, which dramatically reduces mortality after a heart attack. That’s good news.

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Of all the people in the country with autoimmune diseases, including lupus and rheumatoid arthritis, 75 percent are women. Almost 2/3 of the 5.3 million Americans 65 and older with Alzheimer’s disease are women. Depression causes more disability for women worldwide than any other condition, and it is also more common in women. There is so much more to learn to treat these and other serious maladies.

What it all comes down to is: We don’t know what we don’t study. And when it comes to research about our health that fully considers women, “no news” is potentially bad news for us all.
Women’s Health Research at Yale

> FACTORING IN GENDER

Women’s Health Research at Yale is changing the landscape of medical research and practice by ensuring the study of women and examining health differences between women and men to improve the lives of everyone.

Visit our website:
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And join us on social media:
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> OUR 20TH YEAR

Looking Back: Connecticut Women’s Hall of Fame, October 2009

Members of the Advisory Council for Women’s Health Research at Yale and supporters of the center celebrate the induction of WHRY Director Carolyn M. Mazure, Ph.D., into the Connecticut Women’s Hall of Fame.

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