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# TheScientist

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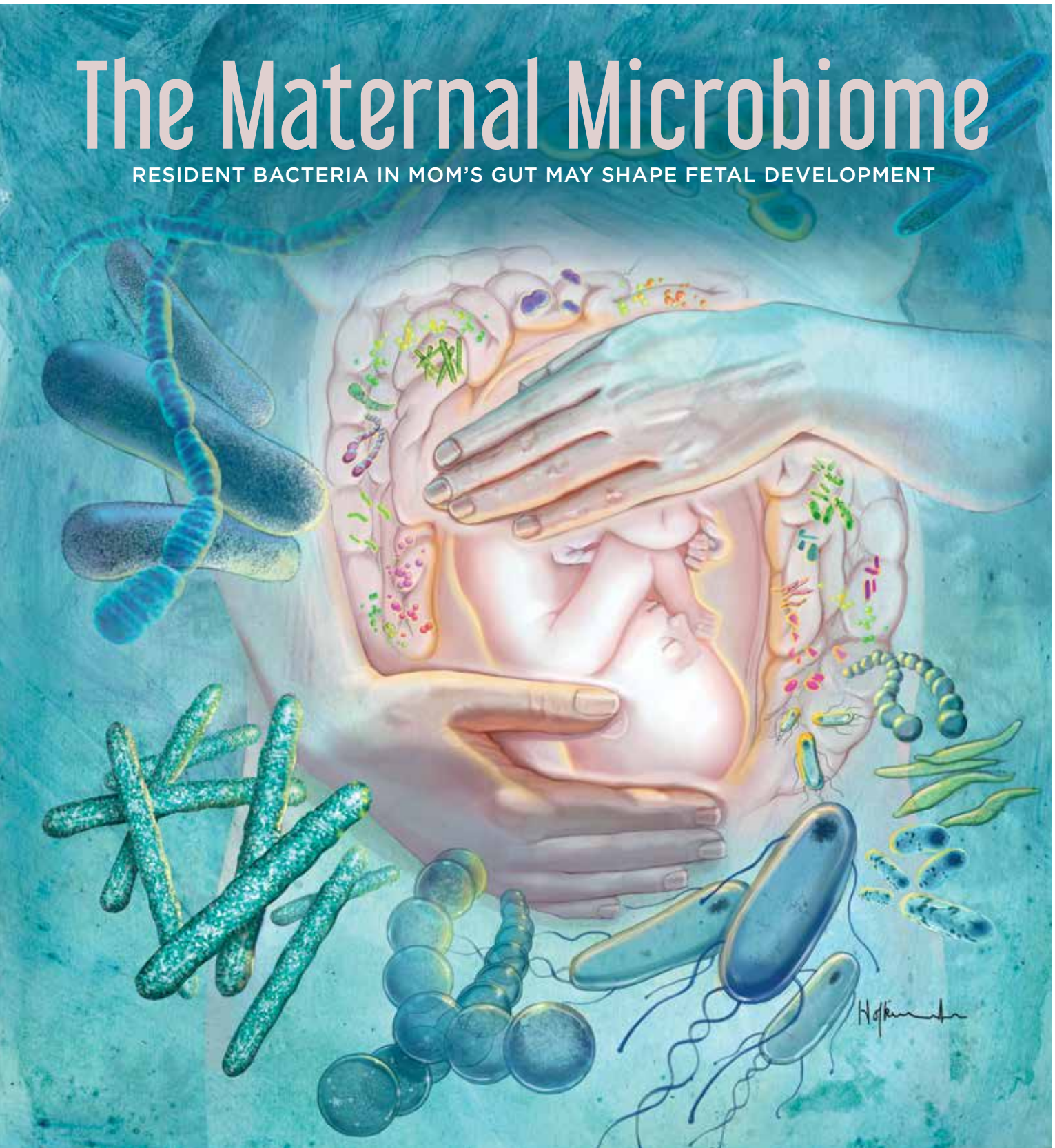

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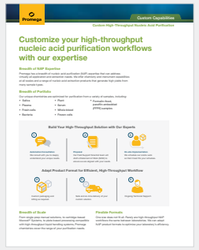


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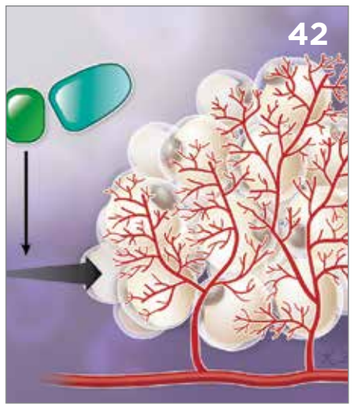






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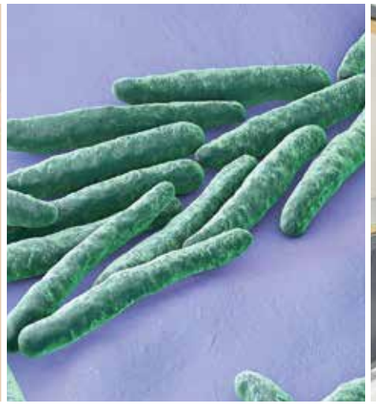




ONLINE AT THE-SCIENTIST.COM:

**The Inside Guide: The Gut Microbiome's Role in Host Evolution**
Bacteria that live in the digestive tracts of animals may influence the adaptive trajectories of their hosts.

**Tuberculosis: The Forgotten Pandemic**
This month marks the 100-year anniversary of BCG, still the only vaccine against a pathogen that has killed more people than any the world has known. But there are new vaccines for this wily foe on the horizon.

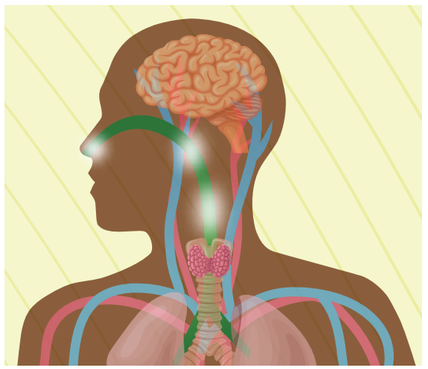
**Quest for Research Freedom Fuels African Biotech Boom**
Tired of dancing to the tunes of international funders, and doubtful that long-promised national grants will come, a handful of African biomedical scientists have turned to private investors to bankroll their dreams of autonomy in the lab.

AS ALWAYS, FIND BREAKING NEWS EVERY DAY ON OUR WEBSITE.

# Coming next month

- Researchers' painstaking examinations have begun to reveal how SARS-CoV-2 wreaks havoc in multiple organs and tissues, but many open questions remain.
- A year and a half into the pandemic, the long-term effects of COVID-19 are garnering more research attention.
- Mistakes happen. But what happens when people spot mistakes in published studies and try to get them corrected?

AND MUCH MORE



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# Contributors

Growing up on a farm in northern Alberta, **Kathy D. McCoy** always loved science, she says. Nevertheless, she found it difficult to get inspired when she went to study chemistry at a community college near home for a couple years. So in the mid-1980s she left school, became a medical tech, and traveled the world. Eventually, she decided to go back to university, enrolling at Victoria University of Wellington in New Zealand, where she'd recently settled, and followed that up with a PhD in immunology from the Malaghan Institute of Medical Research and Otago University. McCoy then changed continents for a postdoc at the Institute of Experimental Immunology in Zürich, Switzerland, where she found her research passion: the intersection of the microbiome and immunology. Her research revealed that IgE, the antibody that is induced during an allergic reaction, is heavily regulated by the microbiome. "That discovery for me was a realization that it was probably just the tip of the iceberg of what [the microbiome] was doing," she says. She started her own lab at McMaster University in Ontario, followed by six years at the University of Bern, before returning to her home province in September 2016 as a full professor in the Cumming School of Medicine at the University of Calgary, where she continues to study how resident microbes influence immune development and function.

In 2017, **Carolyn A. Thomson** joined McCoy's lab as a senior postdoc. Hailing from rural Scotland, Thomson had attended the University of Glasgow for her bachelor's degree and PhD in immunology, and had stayed on at the school for her first postdoc. That's when she was introduced to the world of intestinal immunology, which she says she considers "the most fascinating area of immunology." The gut has "the biggest component of the body's immune system," she says. "There's so much going on there . . . [and] interactions between the immune system and the gut microbiota can have such far-reaching effects." On page 32, McCoy and Thomson write about how a person's microbiome can even influence the immune development of her gestating fetus, with implications for offspring health later in life.

---

Although he'd long been interested in science, **Henry "Hank" T. Greely** gave up on it—for a time—after a disappointing grade on a midterm in advanced math during his freshman year at Stanford University. Instead, he focused on his other major interest, government, and later earned a JD from Yale Law School in 1977. He then clerked for federal appellate judge John Minor Wisdom and Supreme Court Justice Potter Stewart—which he describes as analogous to completing "very prestigious postdocs"—before working in then-President Jimmy Carter's administration. When Carter's term came to a close in January 1981, Greely, who'd grown up in southern California, headed back to Los Angeles and began practicing civil law. He soon realized that being a practicing lawyer didn't hold his interest, however, and after marrying a doctor, his passion for science was reignited. He took a faculty position at Stanford in 1985 teaching oil and gas law and has remained there ever since, even as he transitioned first to health law and later to specializing in thorny ethical quandaries within biomedicine. The topics upon which Greely has focused include genomics, cloning, embryonic stem cell research, neuroscience, and assisted reproduction. His latest book, *CRISPR People* (see page 51), tells the story of He Jiankui's foray into editing the genomes of embryos who would become twin girls, and the resulting fallout. "One of the great things about being a law professor is you don't need a lab, you don't have to get grants," he says. "If there's something that interests you . . . you just go and do it."

---

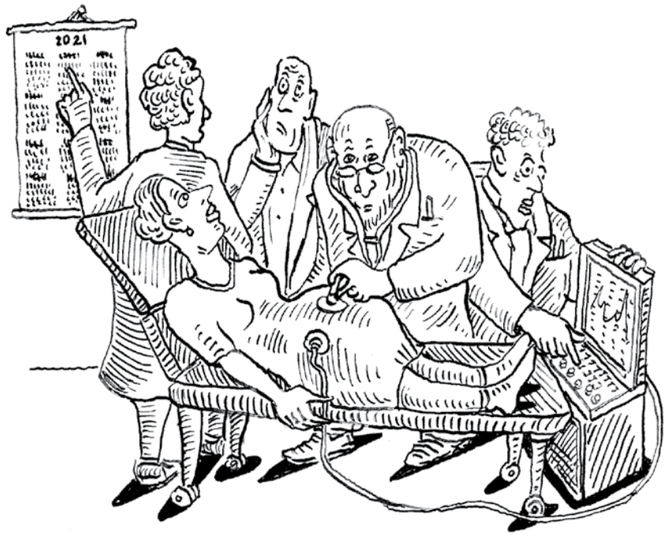
As a child in Hawaii, a teacher once asked about **Christie Wilcox** her interests, and the five-year-old matter-of-factly replied, "I like to open the mouths of dead geckos to look at their tongues," she recalls. Her penchant for hands-on scientific investigation continued into college, leading her to receive a bachelor's degree in marine science from Eckerd College in 2007. Before starting graduate school, Wilcox started blogging, quickly discovering how much she enjoyed writing about science. In 2009, she returned to Hawaii for her doctoral program in cell and molecular biology at the University of Hawai'i at Mānoa, where she studied lionfish genetics. Wilcox also started writing her first book, *Venomous*, while finishing her dissertation. Although she loved doing experiments, writing the book "sealed the deal" for her to embrace science communication as a full-time career, she says. She wrote and edited scripts for the educational YouTube channel SciShow and freelanced for outlets including *National Geographic*, *The Washington Post*, *Science News*, and *The Scientist*. In April 2021, Wilcox joined the *TS* staff as newsletter editor, taking charge of the brand's numerous email newsletters while also reporting pieces for the website and magazine. On page 43, she writes about a gene that may control the switch that initiates labor.

COURTESY OF THE UNIVERSITY OF CALGARY; AMANDA Z. ZUCOLOTO; STEVE GLADFELTER; JAKE BUEHLER

# A New View of My Own Past

Hearing others' perspectives on infertility and pregnancy has me reconsidering my own reproductive journey.

BY JEF AKST




ANDRZEJ KRAUZE

According to standard OB/GYN practices, pregnancy starts even before conception. Day 1 of pregnancy, according to the 40-week calendar that calculates a person's due date, is the first day of her last period, when the uterine lining is shedding and any egg that may have been ovulated is expelled. Fertilization of the egg that will result in pregnancy occurs two or more weeks later, and implantation—the physiological trigger for the hormonal changes that will elicit a positive pregnancy test—another week after that.

Beyond these clinical technicalities, for many people pregnancy also starts before conception in a figurative sense. Reproductive planning can become a big part of their lives, both in the short and long term. As editor Amanda Heidt reports on page 46, academics often delay having children as they establish their career paths. And once an individual or couple decides to move forward with starting or growing a family, that goal can become all-consuming. The process can be stressful and exhausting in a normal situation, and that emotional turmoil becomes immeasurably harder for people, like me, who have struggled with infertility.

Adding to such challenges is the pervasive mindset, both inside and outside of the medical profession, that infertility is a mere inconvenience, not a true disease that warrants the respect and attention of the healthcare enterprise. Indeed, in the US and abroad, infertility treatment is often not covered by insurance companies or national healthcare systems. As OB/GYN Kate O'Neill of the University of Pennsylvania notes on page 16, part of the problem is that the harm inflicted upon people suffering from infertility is not readily observable by others, nor is it typically talked about openly. "Unlike other diseases, infertility scars its victims invisibly, making it easy for society to ignore." she writes.

Despite the lack of funding and other supports, infertility medicine pushes forward, driven by widespread patient need. One type of infertility for which there were, until recently, no solutions is what's known as absolute uterine factor infertility—when something is wrong with the uterus, or the uterus is missing entirely, such that pregnancy is not possible. But as of this year, two medical centers in the US, Baylor University Medical Center and the University of Alabama at Birmingham, are now offering uterus transplants to allow XX-carrying people lacking a functional uterus to gestate their own children after all. (While some have speculated that transgender women may one day be able to receive a donated womb, so far the procedure is limited to XX individuals.)

Jennifer Dingle of Dallas, Texas, was one recipient who participated in Baylor's uterus transplantation trial, which included a total of 20 transplants before the medical center performed its first transplant outside the context of a trial this April. In reporting a feature on the new procedure (see page 24), I listened to Dingle's story—how she'd learned at age 14 that she had ovaries but no uterus, how she'd married and moved to Bahrain and then Italy for her husband's military assignments, and how she'd come home to Dallas to receive a uterus from a then-anonymous donor. She was the fifth recipient in the trial, and three of the first four transplants had failed. But for her, it worked, and just over a year later, she gave birth to her first daughter, Jiavannah.

Although my own reproductive journey was quite different, listening to Dingle I could relate to the emotional highs and lows she experienced. And I began to understand O'Neill's point about infertility deserving the weighty title of "disease," which the American Medical Association finally granted the phenomenon in 2017. Infertility stands between many people and their life goals and, ultimately, their well-being. For the three years that I was either pregnant or trying to get pregnant, I was physically healthy by medical standards, but I was fighting a depression that didn't stem from an imbalance of neurotransmitters in my brain. It resulted from my inability to maintain a pregnancy, which in my case, was a very physical problem—I had a septum in my uterus that limited blood flow to any embryo that implanted there.

Fortunately, the septum could be surgically removed, and the procedure was (partially) covered by insurance, but it took me four miscarriages over two years to get the help I needed. The OB/GYNs I saw during that time seemed to be focused more on the people having babies than on those who were unable to. And for women requiring other sorts of remedies for infertility, from IVF to uterus transplantation, costs are often paid from their own pockets.

The researchers behind innovative solutions to the tribulations of infertility are setting out to change this, but according to Liza Johannesson, a gynecologist at the Baylor Scott & White Research Institute (BSWRI), which organized the uterus transplant trial that Dingle took part in, real change will have to come from the patients. She says that it was patients who drove the creation of new guidelines for breast cancer screening and for support for reconstructive surgeries following mastectomies. "It comes down to making people understand that infertility is a major trauma in people's lives," she says. "Women have been driving the machine." ■

Managing Editor
jef.akst@the-scientist.com

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## A note from the EIC regarding the language used in this issue:

I happily turned over the editorial pen to *The Scientist*'s managing editor, Jef Akst, for this special issue on pregnancy. But the *TS* editorial team had such a rigorous conversation surrounding the language we used in these stories that we thought it was necessary to include a brief mention of this facet of creating this body of work. Specifically, we wanted to be mindful of using inclusive language in discussing the science of pregnancy. From my own perspective, considering pregnancy as a phenomenon that extends beyond "women" did not occur automatically. But as we got down into the nitty-gritty of the subject matter at hand, I was made aware (via the thoughtful input of my colleagues) that we risked excluding nonbinary and transgender individuals from the discussion if we did not carefully consider our words.

For example, when Akst wrote about uterus transplantation trials, we focused on the specific language she used to describe participants. Did they all, in fact, identify as "women"? Did the researchers who conducted these studies ask questions that went further than just a Male or Female checkbox? As the editorial team further chewed over how to employ language that was inclusive, accurate, and readable, it became clear that getting the answers to these questions, as they pertained to the research we cover in the issue, was paramount.

So we went back and asked.

The responses we received were mixed. For example, researchers involved in uterus transplant trials made it clear to prospective trial participants that only individuals with XX chromosomes were eligible, justifying this criterion based on the animal research findings that undergirded the human trial, but only in some cases did they ask about gender identity. Similarly, other studies of pregnancy simply recorded that subjects were female. Where possible, we included these types of specifics in discussing particular studies (see the mention of "XX individuals" above). In other spots that considered the broader applications or impacts of research or healthcare involving pregnancy, we referred to "people" rather than "women." And in some cases, when researchers described participants in their studies as "women," we adopted that language, even if the individuals were not asked about gender identity.

As journalists, we know that words matter, and that our job is to reflect, in as comprehensive a way as possible, the experiences of our readers. We also always strive to be as clear and accurate as possible in everything we write. I can't promise that we used exactly the right word in every instance in this issue. And I can't ensure that no one will take offense at the writing it contains. Heck, I can't even say with confidence that I have considered or fully appreciate every possible scenario that may affect a reader's feelings of inclusion. But I can say that we approached this project thoughtfully and in good faith. We hope that you find the pieces contained in this special issue relevant, inclusive, and thought-provoking, and as always, we welcome your feedback. ■

—Bob Grant

Editor-in-Chief
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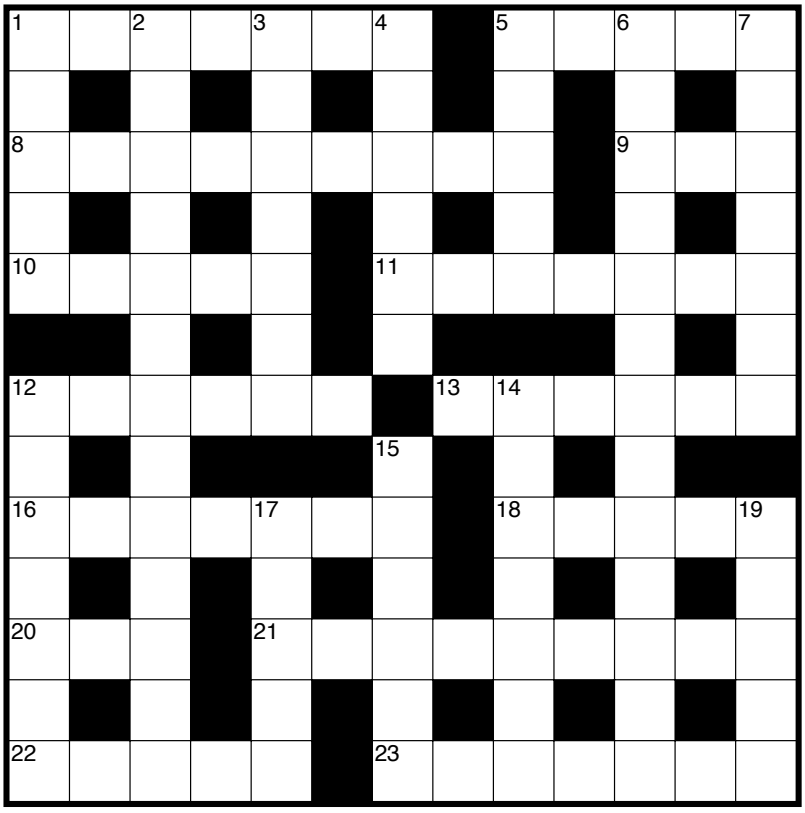

Note: The answer grid will include every letter of the alphabet.

BY EMILY COX AND HENRY RATHVON

## ACROSS

1. Legume grown for hay and forage
5. Game bird in a covey
8. Ecosystem of Tanzania
9. Ursine neonate
10. Like 2017 but not 2018
11. Fruit also known as alligator pear
12. Articular structures
13. Where to spot an epiglottis
16. Great Plains ecosystem
18. Quarry of many NASA searches
20. Prefix on glyceride
21. Approximate weight of a grain of sand
22. Divisions in dendrochronology
23. Drug used to treat atrial fibrillation

## DOWN

1. Author of "Venus and the Cat"
2. Fusion of two gametes
3. Like the day of the summer solstice
4. Cryptozoological creature like Bigfoot (hyph.)
5. National capital closest to the equator
6. Feathered fossil in Solnhofen Limestone
7. Something to do experiments in (2 wds.)
12. Fifth out of eight
14. Cosmologist who appeared on *The Big Bang Theory*
15. Meteor in a November shower
17. Petrologist's concern
19. Part of a cow's gastrointestinal tract

*Answer key on page 5*



Generally speaking, coronavirus is not more dangerous for pregnant mothers, but its effect on the foetus, both short term and long term, is still not well understood.

—**Wahyudi Gani**, a gynecologist and obstetrician in Indonesia, where more than 500 pregnant women have tested positive for COVID-19 since the pandemic began (*Al Jazeera*, July 7)

Because there haven't been studies like this that have been done before, we have the ability to find new genes that are essential for [fetal] development and viability and reveal new biology about what types of mutations affect fertility.

—**Ira Hall**, a professor of genetics and director of the Yale Center for Genomic Health, in a Yale School of Medicine story announcing an $8 million federal grant awarded to Hall and colleagues to study recurrent pregnancy loss (July 2)

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**TAMARA HEERMANN**
Senior doctoral researcher
Max Planck Institute of Biochemistry

**FREDERIK STEIERT**
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**BRYAN JAMES BLACK,** PHD
Assistant Professor, Biomedical Engineering
Francis College of Engineering
University of Massachusetts

**LUCAS THAL,** PHD
Scientist II
PhenoVista Biosciences

# Treating the Disease of Infertility

For too long, a physiological inability to conceive or carry a child through to birth has been seen as a minor medical issue.

BY KATE O'NEILL

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As a reproductive medicine specialist in the US, I often find talking with patients about the cost and coverage of fertility care a discouraging discussion. Despite infertility being an incredibly common and devastating disease, the extremely effective treatments that have been developed to enable infertile individuals and couples to have children are often not affordable and are therefore out of reach. This made me wonder: Why is the cost of care for some diseases covered by insurance while others are not? Instead of criticizing payers for consigning infertility to the "not covered" bin, I choose to be curious. Why this disconnect?

Infertility is clearly a disruption to the normal functioning of the body that results in harm or morbidity. But despite this clear fact, it took the American Medical Association more than eight years to join the World Health Organization in defining infertility as a disease. This may seem an obvious or inconsequential point, but this declaration has an enormous bearing on how society views infertility and sends a clear message that infertility is not a mere inconvenience; it is a medical condition. Officially designating infertility a disease was a necessary but unfortunately not a sufficient step to securing public and private payer coverage of fertility care. Even the medical community often views infertility differently from other diseases. Why?

Infertility may be treated differently because it is perceived as rare; however, data strongly contradict this. One in eight couples in the US has trouble getting pregnant, and estimates suggest that more than 100 million individuals suffer from infertility worldwide. These figures are hard to conceptualize, and perhaps understanding the prevalence of infertility relative to other conditions would have more impact: more women of reproductive age are affected by infertility than by high blood pressure, by diabetes, or by cancer. Although infertility is common, its associated stigma and an absence of physical manifestations can leave sufferers feeling alone and hide them from the unaffected, who therefore remain unaware of the sheer volume of people affected.

In addition to misconceptions of infertility's prevalence, could the condition be viewed differently because it is seen as preventable? Some assume most tubal factor infertility is caused by sexually transmitted infections, and individuals older than 35 years of age are often left wondering if they brought their difficulty conceiving on themselves by "waiting too long." In truth, behavioral or social factors contribute to a minority of infertility cases, so it is false to state that modifying these factors alone could eradicate the disease. But even if lifestyle issues did cause the bulk of infertility cases, why should that matter? The cost of treatment for many diseases with behavioral components, such as heart disease, lung cancer, and diabetes, are covered by public and private insurance.

Is infertility distinct because it is not life-threatening? Broken bones, blindness, and arthritis are typically not life-threatening, but treating these conditions improves quality of life and is covered by most insurance policies.

Would these attitudes persist if the trauma associated with infertility and the reduction in quality of life suffered by those who cannot build a family had a physical manifestation? For those who have not experienced infertility, the pain is difficult to imagine. Unlike other diseases, infertility scars its victims invisibly, making it easy for society to ignore. In contrast, failure to provide treatment for diabetes can result in amputation—an outcome that would be unimaginable in this day and age. Everyone can see the loss of a limb and the disability it would entail. If insulin can prevent amputation, then it is clearly in the patient's and society's best interests to ensure that the medication is made affordable and accessible to diabetics. Because many people cannot see the havoc the disease wreaks, infertile couples often hear trite sentiments from friends and family such as: "Kids are a lot of work—you can have one of mine." Or, "You should buy a puppy or travel the world!" No one would ever tell a diabetic, "Losing a foot isn't that bad. You have two, after all!"

Finally, the late ethicist Amnon Goldworth described a very common argument against expanding coverage for fertility care: "Such efforts are extremely expensive and, in terms of number of individuals affected, could be used more effectively in other medical arenas." But surely the more than 8 million babies born worldwide by IVF are enough to prove that fertility care affects a large number of individuals and is effective. Why should other medical arenas be prioritized? If so, which ones? Who is assessing what people value and ensuring that the care provided aligns with their priorities? In the US, well-intentioned organizations such as the Association of American Medical Colleges and the American Medical Association that avowedly work with policymakers to improve the nation's well-being and public health are focused on myriad other issues, and ultimately, their review and approval of healthcare policy is not binding on insurance companies' coverage decisions.

This is a mind-boggling disconnect. Family is highly valued by both individuals and society in the US, yet the care that is required for a significant proportion of the population to build a family is not accessible. Black and Hispanic individuals have less access to assisted reproductive technology, as well as to other gold-standard disease treatments, than their white counterparts are, exacerbating longstanding inequities in healthcare.

Despite all of this, I am choosing to see fertility care in America through a lens of radical optimism. I believe the stigma surrounding infertility is lessening, and individuals are increasingly willing to talk about their experiences of suffering from this devastating, all-consuming, life-altering disease. I have faith that we are becoming smarter healthcare consumers, and we will demand that the services covered by public and private insurance plans align with our healthcare priorities. I am confident that we recognize the inequality that has plagued healthcare delivery in the US and that there is a genuine desire to reform the system to provide nondiscriminatory care. I am convinced that surviving this pandemic has inspired decisionmakers to rebuild this fragmented and inefficient framework from the ground up. Until then, I will continue to be one of the loudest voices in the room fighting for support for infertility care, and I hope that everyone will join me. ■

*Kate O'Neill is an attending surgeon specializing in reproductive endocrinology and infertility at the University of Pennsylvania. She also serves as an assistant professor of obstetrics and gynecology and is the co–principal investigator of the Uterus Transplant for Uterine Factor Infertility (UNTIL) Trial. Reach out to her on Twitter @KateONeill_MD.*

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URBAN AIR: Researchers are investigating the effects of pollution in cities such as Barcelona (pictured) on the health of pregnant people and their children.

## Pollution on Board

For two days in June 2020 and another two days that October, environmental epidemiologist Ioar Rivas wore a special backpack whenever she left her home. As she rode her motorbike to the lab, or picked out fruits and vegetables at the grocery store, an air pump on one shoulder strap hummed quietly, while a tube on the other passively sampled the environment. "People look at you like you are carrying something weird [that is] making some noises," she recalls of the experience. "They don't understand what is going on."

Rivas was (and still is) taking part in a research study aiming to measure how much air pollution pregnant people are exposed to, and to identify associations between those pollutant levels and the neurodevelopmental outcomes of their children. She recalls having her baby's brain examined during an ultrasound in her third trimester, and later nursing her one-month-old son to sleep before placing him in an MRI machine for further scanning. Rivas is not just a study participant; she also happens to be a scientist involved in the project, working as a postdoc in the lab of the study's director, Jordi Sunyer, a developmental epidemiologist at the Barcelona Institute for Global Health (ISGlobal).

"We are . . . looking into the brain development of the fetus," says Rivas. "We would like to study how the exposure during the pregnancy is really affecting the brain."

The project, called the Barcelona Life Study Cohort (BiSC), is a follow-up to a study of school-age children that identified correlations between kids' neural activity and the levels of air pollution they were exposed to in classrooms and on the playground—children with higher exposure showed brain activity patterns typical of younger kids, Sunyer explains (*PLOS Med*, 12:e1001792, 2015). But the researchers didn't find any structural differences in the children's brains. The kids in that study were age seven to nine years, so their brains were more than 90 percent developed, notes Sunyer. "Our question is: What would happen . . . if air pollution exposure occurs early in life, during the prenatal life, when the [development] of the brain is much faster?"

For more than a decade, research has been uncovering potential negative effects of exposure to air pollution on neurodevelopment. In 2009, for example, a group of researchers at Columbia University linked higher in utero exposure to one type of air pollution, polycyclic aromatic hydrocarbons (PAHs), with reduced IQ at age 5 (*Pediatrics*, 124:e195–e202). Since then, Sunyer notes, longitudinal studies from numerous countries have similarly found an association between exposure levels and reduced intelligence or mental functions. Preliminary data from various research groups have also revealed an association between prenatal air pollution exposure levels and risk of behavioral syndromes such as autism spectrum disorder, although there the results are less consistent, Sunyer says.

To better assess the potential influence of prenatal exposure on neurodevelopment, Sunyer's team launched BiSC in mid-2018. Although COVID-19 has complicated some of the project's data collection, the team has nearly completed its planned enrollment of 1,200 pregnant people, who for two days during their first or third trimester (or two days during each, as Rivas did), will wear the air pollution–detecting backpacks whenever they leave their homes. Around 500 early participants in the study carried backpacks fitted with a tube for sampling $NO_2$, a monitor for black carbon, and an air pump attached to a filter that captured particulate matter 2.5 micrometers in diameter or smaller ($PM_{2.5}$). They also wore smartwatches to monitor their activity and vitals. The backpack required some setup, though, so once pandemic-related lockdowns prevented researchers from entering participants' homes, participants simply wore the $NO_2$ tube and the smartwatch.

"It's these kinds of studies that help you tease apart what's contributing to the exposure," says Rima Habre, an environmental health scientist at the Keck School of Medicine of the University of Southern California. Habre is the director of exposure assessment and a project lead at the MADRES Center for Environmental Health Disparities, where she and her colleagues have similarly been collecting personal exposure data of pregnant people—using a purse-like design, rather than a backpack—and tracking health outcomes of both mothers and children. With regard to the BiSC program, she adds: "It's really nice that they're starting early and that they're doing this very personal exposure assessment and . . . this very cutting-edge neurocognitive assessment. . . . That's very innovative and probably unique as far as I know."

Emory University environmental and reproductive epidemiologist Audrey Gaskins agrees that the BiSC cohort study will generate valuable data for understanding the link between prenatal air pollution exposure and neurodevelopmental outcomes in babies and kids, but notes that assessments also need to be made at an even earlier stage: pre-conception. Her research has shown that higher levels of air pollution are associated with lower fertility among people undergoing assisted reproductive technologies, suggesting potential toxic effects on the ovaries, and it remains an open question whether there could be any effects of pre-conception exposure on the offspring themselves.

"We think a lot of these air pollutants have a specific negative effect on the ovary, and particularly we think it might be affecting the epigenetic signature of the egg," she says. "So that again might have downstream consequences for neurodevelopment. . . . Does air pollution have an impact on the epigenetic profile of the egg, and can that translate to outcomes even in childhood?"

The answers to this and many other questions about the influence of air pollution of brain development are outstanding. Rivas, Sunyer, and their colleagues have yet to publish results from BiSC, and specifically from the AirNB part of the project focused on fetal and early-life neuro-development. So far, Sunyer says, the team can see that personal levels of exposure are highly variable, and that "a high proportion of pregnant women in Barcelona have high levels of exposure to

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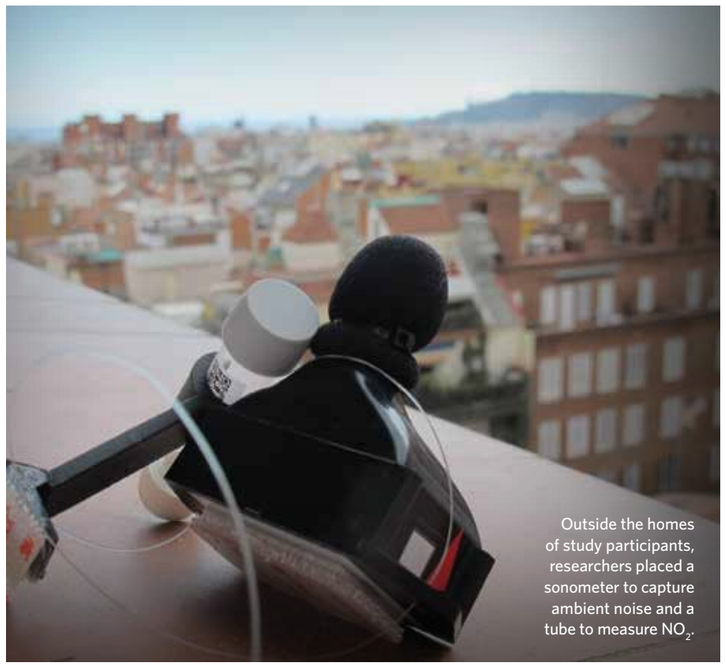
PORTABLE DEVICE: Inside a backpack, an air pump with filter (left) measures personal exposure to fine particulate matter that is 2.5 micrometers or smaller, while a second device (right) monitors personal exposure to black carbon.



Outside the homes of study participants, researchers placed a sonometer to capture ambient noise and a tube to measure $NO_2$.

BiSC participant Yasmina Díaz wears the air pollution–measuring backpack on the streets of Barcelona.

PAU RUBIO / ISGLOBAL

air pollutants," but he doesn't anticipate that the group will finish collecting and analyzing the neural data until later this year.

Going forward, it will be important to examine when during pregnancy the fetus is most vulnerable, as well as to identify possible mechanisms by which air pollution might influence fetal health, says Ferran Ballester, a public health researcher at the University of Valencia who is not involved in BiSC. "It is also very important to look at the nature of the exposure—which . . . pollutants or characteristics are playing a role in the potential detrimental health effects," he adds. "All of the above will help not only to increase knowledge on the relationship, but more importantly, to develop actions and measures to prevent potential harm."

In the meantime, evidence is building that air pollution exposure may have adverse effects for birth outcomes generally—so much so that it's time to act to monitor and limit those exposures, argues Bruce Bekkar, a retired clinician who is now a full-time climate change activist. Last year, Bekkar coauthored a systematic review on the link between air pollution exposure and birth outcomes; although the studies varied widely in their methodology and outcome measures, the research strongly pointed to increased rates of preterm birth, lower birth weight, and stillbirth among people with high exposures, he says (*JAMA Netw Open*, 3:e208243). "We felt that [there was] strong evidence of association, and also ample reason to think that this was cause-and-effect and not just a statistical association. . . . We have enough data to start taking action."

With respect to her own pregnancy, Rivas says that she didn't worry too much about her exposure to pollution because Barcelona was in lockdown as a result of COVID-19, and the levels of air pollution in the area were very low as a result. She now lives in an area with very little road traffic, she adds, which also eases her mind regarding any exposures her infant son may have. Still, she notes, "I try to avoid streets with high levels of road traffic."

—Jef Akst



# Pregnancy on High

COLLEEN GYDE JULIAN

HIGH ALTITUDE: La Paz, Bolivia, is the highest capital city in the world, providing researchers with a living laboratory to study human pregnancy at elevation.

To navigate the political, cultural, and language barriers that come with researching pregnancy in another country, Colleen Glyde Julian says she channels the properties of chewing gum. Julian, an integrative physiologist at the University of Colorado's Anschutz Medical Campus, says that remaining flexible under grinding pressure is "the defining characteristic that somebody must have to do this kind of work"—wisdom she cultivated as a PhD student working under another Anschutz researcher, biomedical anthropologist Lorna Grindlay Moore. "You just have to take it all in stride."

Working in Bolivia has meant, for example, balancing coolers of blood during hair-raising taxi rides through congested streets en route to the local hospital, crammed shoulder to shoulder with colleagues. And because luggage is often delayed in transit, the researchers sometimes have to get creative with equipment. One time while carrying out similar work in Tibet, Moore connected a boombox to her ultrasound machine to hear the blood passing through a pregnant woman's uterine artery.

Julian and Moore study pregnancies at altitude, where lower air pressure means that each breath draws in less oxygen than at sea level. Because the success of a pregnancy is predicated in part on how much oxygen gets to the fetus, disruption of oxygen flow is associated with various pregnancy complications—

ANDRZEJ KRAUZE

including fetal growth restriction, preeclampsia, and gestational hypertension. Even though such conditions kill thousands of people and their fetuses each year, much about their underlying physiology remains unknown.

Despite the inherent practical difficulties, the two women agree that studying pregnancy at elevation, where all fetuses develop under chronic hypoxia, can inform what goes wrong in pregnancies worldwide, while also revealing how local Indigenous populations have adapted to low oxygen over millennia. "The only way to ethically manipulate maternal oxygenation is really altitude," Moore tells *The Scientist*. "A lot of studies use experimental animal models . . . but the best model for human pregnancy is humans." The pair's findings, based primarily on studies of Andean women in Bolivia, have uncovered potential treatments for conditions linked to hypoxia.

The thread of that work began in the late 2000s, when Moore and Julian traveled to South America, working alongside colleagues at the Bolivian Institute of High Altitude Biology to compare pregnancies between Andean women and those of European descent living in the region. At low elevations, the two populations were similar, but above 12,000 feet, Andean infants were born larger and heavier than European babies. Uterine artery blood flow, and therefore oxygen delivery, was also twofold higher in Andean women (*Am J Physiol Regul Integr Comp Physiol*, 296:R1564–75, 2009).

Comparing gene expression patterns between the two populations revealed a clue about why: two genes in Andeans contained mutations that were positively associated with birth weight at high altitude, and one of the mutations—in a gene called *PRKAA1*—was also linked to increased uterine artery blood flow (*Physiol Genomics*, 46:687–97, 2014). "The interesting thing is that it's associated . . . only at high altitude, not at low," Julian tells *The Scientist*. "That suggests a gene-by-environment interaction that provides some specific benefit at high altitude."

*PRKAA1*, the researchers learned, is part of the AMP-activated protein kinase (AMPK) signaling pathway, a regulator of metabolism, cell growth, and vascular function that switches on under hypoxic stress. AMPK activation also regulates vasodilation, and variations in *PRKAA1* may bolster uterine artery blood flow at altitude, thereby reducing the effects of hypoxia. Back in aptly named Summit County, Colorado, where the average elevation is above 10,000 feet, the team is now probing the pathway using animal models and pieces of human myometrial arteries collected during C-sections at local hospitals. Julian sometimes sleeps in her car as people undergo their surgeries so that she can drive a cooler of samples—belted into the passenger seat—back to the lab.

Julian and Moore's colleagues have designed special chambers, essentially barrels fitted with vacuum pumps, that can simulate altitudes of up to 20,000 feet, or two-thirds the height of Everest. When pregnant mice were exposed to hypoxia inside, the animals gave birth to smaller young than control mice, but pups born to mothers treated with an AMPK-activating drug during pregnancy were closer in size to the controls, if not entirely protected from hypoxia's shrinking effects (*J Physiol*, 598:4093–105, 2020). Exposing isolated arteries taken from the pregnant mice to an AMPK-activating drug in vitro showed that the drug keeps vessels more dilated, evidence that the pathway does help preserve oxygen flow to a fetus at elevation. The team found similar effects in arteries taken from pregnant women at altitude. Notably, the vessels from women who gave birth to growth-restricted babies dilated less than those taken from women with normal pregnancies, a finding the team is still investigating.

The goal of all this work is to identify therapies for complications such as preeclampsia. Several AMPK-activating drugs exist, and some, such as the diabetes medication metformin, are approved for human use. Researchers in South Africa recently completed a Phase 1/2 trial testing whether metformin could help extend the pregnancies of people with preeclampsia. Currently, delivering the baby is the only treatment. While the results aren't yet published, Catherine Cluver, a maternal-fetal medicine specialist at Stellenbosch University who led the research, says in an email that the trial "went very well," and Julian is now planning a similar trial in Bolivia.

Julian, Moore, and their colleagues are also investigating links between hypoxia in utero and disease in adults. Under hypoxic conditions, oxygen gets diverted away from a fetus's peripheral circulation to protect the brain. As a consequence, scientists have found, those babies sometimes develop cardiovascular diseases in adulthood. "Virtually every adult-onset disease has a relationship to development in utero," notes Moore.

Dino Giussani, a developmental cardiovascular physiologist at the University of Cambridge who was born in Bolivia, studies this phenomenon, called fetal reprogramming, using large altitude chambers. Giussani found that in sheep, which have similar gestational milestones to humans, exposing pregnant ewes to hypoxia resulted in growth-restricted lambs that developed high blood pressure more frequently in adulthood (*PLOS Biol*, 17:e2006552, 2019).

Rather than targeting AMPK, Giussani treated ewes with an antioxidant called MitoQ that reduces oxidative stress by scavenging free radicals (*Sci Adv*, 6:eabb1929, 2020). "We're finding that you can rescue some of the fetal growth restriction and some of the later cardiovascular disease by giving antioxidants following the start of hypoxia," he tells *The Scientist*, adding that he is now delaying the therapy until a time equivalent to when clinicians might detect a hypoxic pregnancy in humans. "The next step would be to apply this to obstetric practice."

The promise of real-world solutions for the millions of mothers living at altitude, who are still most at risk of developing hypoxia-related complications whatever their ancestry, has been central to the relationships between the researchers in Bolivia and Colorado.

"Our collaborative research projects have already yielded important scientific findings related to improving the identification of at-risk pregnancies," Lilian Toledo-Jaldin, an obstetrician at the Hospital Materno-Infantil in Bolivia, tells *The Scientist* in an email (translated from Spanish with Google Translate). Moore and Julian recently trained Bolivian physicians on how to standardize their metrics for diagnosing preeclampsia, and Toledo-Jaldin is helping to analyze medical records to see whether diagnoses have changed since. "It's really important for the work that people are doing internationally to benefit the community that they are working with," Julian says. "I'm really proud of our Bolivian team, and it's nice to see the long-lasting effects of what we're all doing."

—Amanda Heidt

LORNA MOORE

**SOUND INTERRUPTED:** A Tibetan physician named Droma—most Tibetans do not use family names—used a boombox to listen to an ultrasound after the machine's recorder broke.

# PREGNANCY REBORN

A handful of sites in the US and abroad are transplanting wombs into women who lack the organ but want to carry their own babies.

BY JEF AKST

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Learning at age 14 that she had a developmental abnormality that left her with no uterus, Jennifer Dingle didn't immediately understand or share the devastation that she could see in her mom's eyes. But years later, after she got married and her friends began getting pregnant, she fell into a depression thinking about how she would be able to have a family of her own. The options, gestational surrogacy and adoption, didn't appeal to her. She wanted to carry her own child.

She first heard about a more palatable solution to her predicament in her mid-20s, when her gynecologist mentioned that uterus transplantation was beginning to enter clinical trials. The doctor told her not to count on the experimental procedure, which was only just beginning to be tested in humans, but Dingle began looking into it. She found an ongoing clinical trial in Sweden and another in the UK that was just getting off the ground, "and then I had my hopes and dreams set on it."

Unfortunately, the Swedish trial was fully recruited, and the UK program hadn't yet begun enrolling participants—she'd hit a dead end. Then one day in early 2016, in her two-bedroom apartment on a US military base in Naples, Italy, where her husband was on assignment for the Navy, she got a call from her mom back home in Texas. "She says, 'You're never going to believe what I seen on the news here,'" Dingle recalls. "'Baylor Dallas is starting a uterine transplant trial for women like you.'"

Dingle quickly tracked down the uterine transplant nurse at Baylor University Medical Center and asked to be considered for the trial. By the end of the year, she was headed to the hospital for the study's fifth transplant surgery—and she did it knowing that three of the first four had failed. Even facing those odds, "there was nothing in me that wanted to cancel my uterus transplant," she recalls.

On December 8, 2016, the Baylor team made an incision in Dingle's abdominal wall, identified the top of her vagina, and placed the donated uterus, which less than an hour earlier had been removed from an anonymous living donor, into the cavity where Dingle's own uterus should have been. The surgeons then sewed the organ's veins and arteries to blood vessels that extended down Dingle's legs and watched as it began to circulate her oxygenated blood. Finally, they connected the cervix and small piece of the vagina that had come with the donor organ to the top of Dingle's own vagina.

With the help of immunosuppressant drugs, Dingle's body accepted the uterus, and six months later, her doctors placed an embryo made from her egg and her husband's sperm into her new womb. It worked. For nearly 37 weeks she experienced an anxiety-ridden but uneventful pregnancy, and on February 19, 2018, she underwent a Cesarean section to welcome her daughter Jiavannah—the second baby born to a woman with a transplanted uterus at Baylor, and among the first dozen such babies in the world.

SHANNON FAULK FOR BAYLOR SCOTT & WHITE

**A MIRACLE IS BORN:** Jennifer Dingle and her husband Jason welcome their daughter Jiavannah on February 19, 2018.

The idea of uterus transplantation to treat infertility caused by the lack of a functional uterus is less than 25 years old. Clinical trials testing the procedure in humans all started within the past decade, primarily for the condition that Dingle has: Mayer-Rokitansky-Küster-Hauser syndrome (MRKH), in which XX-carrying individuals are born with ovaries but no uterus. Despite its short history, uterus transplant is now becoming clinically available. This past April, Baylor surgeons performed the country's, and possibly the world's, first uterus transplant outside the context of a clinical trial, and the University of Alabama at Birmingham (UAB) is beginning to screen patients for its brand-new uterus transplant program. "It has been very fast," says transplant surgeon Paige Porrett, who is spearheading the UAB program. "This is a tempo that we don't usually see in medical innovation."

Some doctors urge caution in recommending uterus transplantation to patients when gestational surrogacy is legal in many countries and most US states, providing people lacking a uterus the means to have children who are biologically their own. Meanwhile, ethicists are actively discussing factors such as the use of living donors, who are putting themselves at risk, and the value people place on carrying the pregnancy themselves. Patients must also consider the price tag—just under $300,000 for the donor's and recipient's surgeries and care—and the fact that uterus transplantation is not currently covered by health insurance companies.

The transplant surgeons and obstetrician-gynecologists involved in developing and trialing the procedure express passionate beliefs that uterus transplant is safe, effective, and addresses a need felt by hundreds of thousands of people. In addition to MRKH, which affects roughly 1 in 4,500 XX individuals worldwide, more than 600,000 people undergo hysterectomies each year in the US alone, and many of them are still of reproductive age. Uterus transplant could provide a way for those people to carry their own children even after having their own wombs removed. Some in the uterus transplant field even envision a future in which transgender women will be able to carry their own children.

> Brännström had never thought about transplanting a uterus before, and at first blush it seemed a bit crazy, he admits.

"It's going to be a transformative transplant," says surgeon Cristiano Quintini, who runs the Cleveland Clinic's uterus transplant trial, the first of three clinical studies to be launched in the US. "It's a life-creating, life-enabling type of transplant."

## Mice to humans in a decade

One Friday afternoon in 1998, during a stint as a gynecological oncology surgery fellow at Royal Adelaide Hospital in Australia, Mats Brännström spoke with a cervical cancer patient who was about to have her uterus removed. Wanting to one day carry her own child, the patient asked Brännström if she could get a replacement womb.

He'd never thought about transplanting a uterus before, and at first blush it seemed a bit crazy, he admits. But after discussing the idea with a colleague over beers at a pub after his shift that day, Brännström began to consider it more seriously. With his background in treating infertility, he was intimately aware of the needs that uterus transplantation could meet, and having just learned the complexities of hysterectomies and other uterine surgeries, "I could see that this was possible." And so, returning to his home country of Sweden the following year, Brännström started an animal research program at the University of Gothenburg to investigate the feasibility of the procedure, and the ability of a transplanted womb to gestate a fetus to term.

He started in rodents, publishing on the first successful births from transplanted uteruses in mice in 2003.[1] Around this time, other physicians and researchers independently began to consider the concept. The year before, a research group in Saudi Arabia had published a case study of the first uterus transplant in a human being, completed in April 2000.[2] Unfortunately, doctors had to remove that uterus within a few months due to major blood clots in the uterine vessels. "Of course, I was a little worried because it had failed," Brännström says, but he adds that he felt confident that the procedure was possible; it just needed some basic research to support it. Over the next several years, he and his colleagues began transplanting uteruses in larger and larger animals—first rats, then pigs, sheep, and baboons.

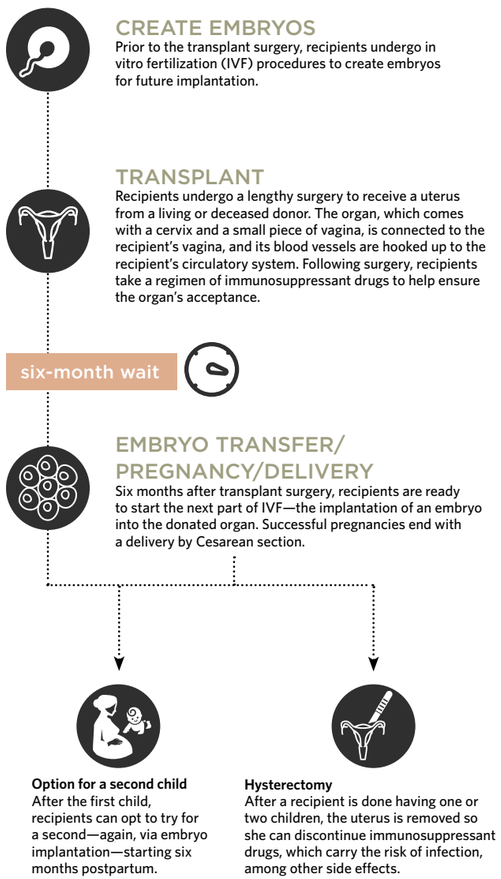
In May 2013, the team was ready to move the technology into human patients and launched the world's first uterus transplant clinical trial, based at Gothenburg's Sahlgrenska University Hospital. Nine women, eight of whom were born without a uterus and one who'd had a hysterectomy, had their eggs extracted for in vitro fertilization (IVF) and underwent the transplantation procedure. In most cases the living donors were family members, but in one case, a close friend. Two of the transplanted uteruses had to be removed after an artery in one became blocked and the other developed an antibiotic-resistant bacterial infection, but the other seven were accepted by their hosts, and in September 2014, the first baby was born.[3] Several other births followed, with six participants from the trial having at least one child each; three of those individuals had two each before having the organs removed to allow them to discontinue immunosuppressant drugs, which increase risk of infection, among other side effects.

Although some of these infants had to be delivered up to eight weeks before their due date due to the risks of preeclampsia, all of the babies were healthy. Overall, Brännström and his colleagues reported no red flags for a procedure that was allowing XX individuals once missing a uterus to carry their own children. Other institutions around the world were beginning to take notice.

## Trials to the clinic within another decade

When Kate O'Neill, then a fellow at the University of Pennsylvania (UPenn), heard Brännström give a talk at the American Society for Reproductive Medicine (ASRM) about uterus trans-

### THE UTERUS TRANSPLANTATION PROCESS

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### A NEW DATA STREAM TO TACKLE MANY QUESTIONS

First and foremost, proponents say, uterus transplantation helps address an unmet medical need, and from the get go researchers have developed the approach with the ultimate goal of serving patients. But scientists involved in uterus transplant also see it as an invaluable opportunity for studying uterine biology and immune rejection. "This is a very unique model," says Giuliano Testa, a transplant surgeon at the Baylor Scott & White Research Institute (BSWRI) in Dallas. "The implication of this transplant is huge for the transplant world and the OB-GYN world."

Reproductive endocrinologist Kate O'Neill of the University of Pennsylvania is most excited about the new ways that she and others can investigate the endometrium that lines the uterus. "This is such a fascinating tissue," she says, noting that it undergoes monthly regeneration some 400 to 500 times over the course of a woman's life. "In some individuals it grows too much; in other individuals it doesn't grow enough. You can have overgrowth leading to abnormal bleeding in cancer; you can have insufficient growth leading to infertility and scar tissue." Unfortunately, researchers don't have a great model to turn to for studying endometrial turnover, she adds, because mice don't have monthly cycles like humans do and there are significant challenges when working with nonhuman primates. Uterus transplantation, and the numerous samples that are taken from organ recipients, can provide researchers with the human data they've been missing.

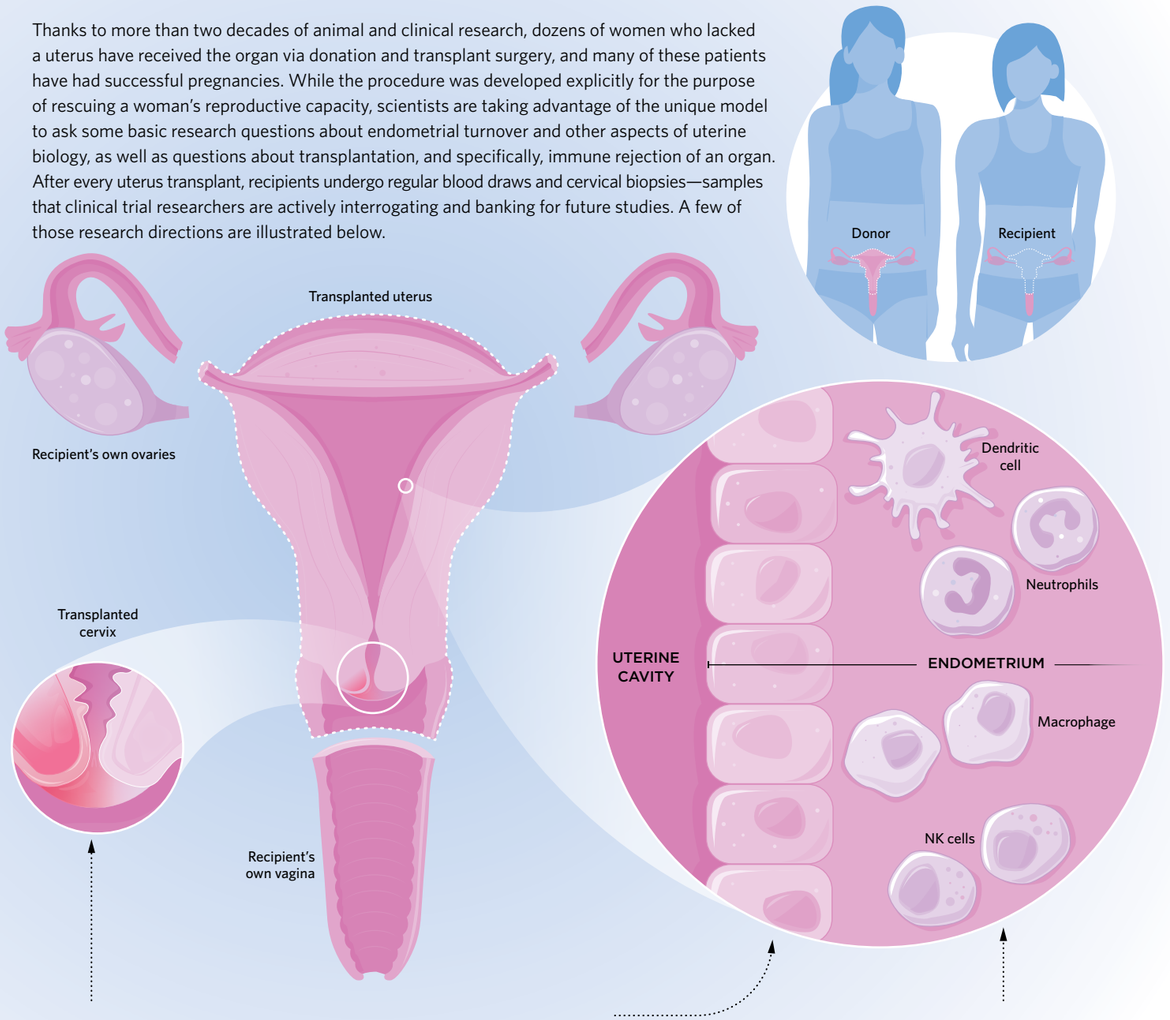
Turning to regular blood draws from recipients and biopsies of transplanted uteruses, among other sample types, O'Neill and others have the raw materials to answer a laundry list of research questions. One of O'Neill's pursuits is to identify the source of various uterine cells, including epithelial cells, endothelial cells, stromal cells, and the immune cells that are critical for the establishment of pregnancy. Back in the early 2000s, Hugh Taylor of Yale University looked at epithelial and stromal cells in the uteruses of bone marrow transplant recipients and found that up to half were of donor origin, indicating the cells had migrated in from the periphery—the first evidence that cells from outside the uterus can contribute to endometrial regeneration (*JAMA*, 292:81–85, 2004). "Nobody thought that they were migrating in," says Taylor, who recently showed in mice that this migration is essential to supporting pregnancy (*PLOS Biol*, 17:e3000421, 2019).

With biopsies from transplanted uteruses, O'Neill is essentially doing the reverse experiment. In this case, migration of cells into the uterus would be evidenced by cells not of donor origin, but from the recipient—and so far, that's exactly what she and her colleagues have found, she says. "We are using single-cell RNA-seq to differentiate donor and recipient in all of the cell types. [Preliminary data] supports what Dr. Taylor saw." She adds that it will be interesting to examine whether cell populations shift during pregnancy, as the uterus works to accommodate the foreign fetus. "We've made a lot of progress in figuring out this concept of maternal-fetal tolerance . . . but how is that altered if some of the cells that are important for the establishment of pregnancy are of a completely different origin than the fetus?"

Uterus transplants also offer a unique opportunity for studying transplantation, and specifically, organ rejection. Because the organs will be removed, patients can stop taking immunosuppressant drugs leading up to the hysterectomy, giving researchers the opportunity to take a series of samples to look for biomarkers of mounting rejection. "For the first time we can really sequentially follow how and which cells are involved in the rejection from the get-go and what happens until the organ is completely destroyed by the inflammatory process," says Testa, whose team is in the process of writing up these results. "It's not easy to find, in clinical science in human beings, a model of transplantation that is so free of noise that can be a groundwork for understanding many different processes."

# EXPLORING UTERINE AND TRANSPLANT BIOLOGY

Thanks to more than two decades of animal and clinical research, dozens of women who lacked a uterus have received the organ via donation and transplant surgery, and many of these patients have had successful pregnancies. While the procedure was developed explicitly for the purpose of rescuing a woman's reproductive capacity, scientists are taking advantage of the unique model to ask some basic research questions about endometrial turnover and other aspects of uterine biology, as well as questions about transplantation, and specifically, immune rejection of an organ. After every uterus transplant, recipients undergo regular blood draws and cervical biopsies—samples that clinical trial researchers are actively interrogating and banking for future studies. A few of those research directions are illustrated below.




**IMMUNE REJECTION OF ORGAN**
Immunosuppressant drugs designed to help recipients accept the transplanted uterus can be discontinued prior to having the organ removed. From cervical biopsies and other samples, researchers can watch for signs of rejection and look for biomarkers that could provide a less invasive way to test for rejection following transplant surgeries involving uteruses or other organs.

**SOURCE OF UTERINE CELLS**
Researchers have long wondered about the origin of the various cells that make up the internal lining, or endometrium, of the uterus, which is shed and regenerated monthly as part of a normal menstrual cycle. With uterus transplantion, researchers can look at the genetics of the cells in the uterus and determine if they came from the organ itself, with genetic signatures of the donor, or from outside the organ, with genetic signatures of the recipient.

**SOURCE OF IMMUNE CELLS IN UTERUS**
Immune cells called natural killer (NK) cells are important for the establishment of pregnancy and, specifically, the development of the vasculature in the placenta. As with cells that replenish the endometrium, researchers can determine whether these and other immune cells come from within the uterus or from elsewhere in the body by testing to see if they have donor or recipient genes.



## UTERUS TRANSPLANTS BY THE NUMBERS

Sweden and the US have led the world in performing uterus transplants in women lacking the organ and in delivering babies from those donated wombs.

| | PROGRAM LAUNCH | DONORS | NUMBER OF TRANSPLANTS | NUMBER OF BIRTHS |
|---|---|---|---|---|
| **Sahlgrenska University Hospital at the University of Gothenburg** | May 2013 | Living and deceased | 21 | 15 from 12 women |
| **Cleveland Clinic** | October 2015 | Deceased | 8 | 4 |
| **Baylor University Medical Center** | January 2016 | Living and deceased | 21* | 14 from 12 women |
| **University of Pennsylvania** | October 2017 | Living and deceased | 3 | 1 |
| **University of Alabama Birmingham** | October 2020 | Deceased | 0 | 0 |

*One transplant done outside the context of a clinical trial

plants in October 2014, she thought the approach "was a little fringe," she says. Outside of the Gothenburg trial, very few sites in the world, and none in the US, had attempted uterus transplantation in humans, and investing time and resources into the procedure was controversial, she says. But O'Neill was drawn to the idea. "You have transplants used to save and extend lives, and here was an application of transplant to generate new life." Just a few years later, she would launch a uterus transplantation trial at UPenn, on the heels of two other programs in the US.

> It's going to be a transformative transplant. It's a life-creating, life-enabling type of transplant.
>
> —Cristiano Quintini, Cleveland Clinic

The Cleveland Clinic was the first to launch, in October 2015. After conducting his own animal work and traveling to Sweden to observe Brännström's team complete a uterus transplantation, Cleveland Clinic transplant surgeon Andreas Tzakis, who collaborated with the Swedish group, helped launch a trial of 10 people seeking the procedure. The trial would be the first in the US to use uteruses from deceased donors, which eliminates the risks involved with harvesting uteruses from living donors (see also "Bioengineering a Uterus" on page 30) and allows for a shorter organ retrieval surgery that could also give surgeons the opportunity to harvest more, larger blood vessels that might reduce the risk of blockage after transplantation. "We do see this as the future in the field," says Quintini. But the Cleveland Clinic program got off to a rocky start, with the first transplanted uterus having to be removed within a couple weeks after the recipient developed a severe yeast infection that was transferred from the donor. Additional transplantations were then delayed as the team reworked the protocol to reduce the time the donated organ was in cold storage and take other measures to minimize the risk of complications.

Baylor Scott & White Research Institute (BSWRI) in Dallas launched its 10-patient trial at Baylor University Medical Center in January 2016, headed by transplant surgeon Giuliano Testa and gynecologist Liza Johannesson, a former member of Brännström's transplant team in Sweden. The Baylor group chose to use both deceased and living donors, though in contrast to the Swedish trial, living donors and recipients didn't typically know each other. As it planned its trial, BSWRI launched a registry that was quickly filled with hundreds of volunteer donors. But like the ongoing study at the Cleveland Clinic, the Baylor trial also had a rough start: as Dingle learned just a few months before she underwent her own surgery in December 2016, three of first four transplanted uteruses had to be removed before the women were able to attempt pregnancy.

O'Neill, by this time an assistant professor of obstetrics and gynecology at UPenn, had been following these events closely. When Baylor announced its early failures, she was already working with other faculty and administrators at the university, including Porrett, then lead surgeon at UPenn, to start its own program. The trial officially launched in the fall of 2017, just a few months before Baylor's first successful birth.[4] More births followed, including several more from Baylor using living donors and a report from Brazil of the first baby born from a uterus transplanted from deceased donor, something the Cleveland Clinic then achieved twice over. And in between those two births, UPenn celebrated the delivery of its first baby from a transplanted uterus (from a deceased donor). Ongoing trials in Europe have been sharing similar news.

Now, several physicians and researchers tell *The Scientist*, it is time to widely offer the procedure to women with uterine factor infertility. Earlier this year, Baylor moved toward doing just that, completing its first uterus transplant outside the context of a clinical trial. And a similar program, launched last October at UAB, is close on its heels. Officially launched in October 2020, the university has committed to covering the costs of 25 uterus transplanta-

tions from deceased donors over the next five years, with its first transplants expected in the next few months, Porrett says.

"There comes a transition point where this is no longer research," she argues. "We, as medical professionals and scientists, need to make this jump: label it clinical care and to have the expectation that it will be paid for by the patient or hopefully by insurance companies."

## On the cusp of a transition

Performing uterus transplants in the clinic is not without its dissenters. And unlike new drugs and medical devices, surgical interventions don't require approval from the US Food and Drug Administration (FDA), so there are no hard-and-fast rules about when it is acceptable to go from doing clinical trials with the oversight of institutional review boards to offering a surgical intervention widely to patients in need. "Surgical research is known as the wild West of medicine for a reason, and that's because there is so little ethical guidance," says Lancaster University bioethicist Nicola Williams.

As a result, some physicians are hesitant to recommend uterus transplant to patients at this stage, with the technique being so new and with so much research ongoing. "My concern is about the safety of this approach," says Eric Forman, a reproductive endocrinologist at the Columbia University Fertility Center. "I'm not saying [uterus transplantation] shouldn't be explored or shouldn't be done. . . . This is an exciting area, and it's pretty amazing that some women who could not have delivered otherwise were able to. But again, I think there should be transparency about the unknowns, the potential risks, and the alternatives." The ASRM, for now, seems to agree. In June 2018, the society put out a position statement recommending that uterus transplant remain an area of research, not clinical practice.

> There comes a transition point where this is no longer research.
>
> —Paige Porrett, University of Alabama at Birmingham

Undeterred, the researchers and clinicians involved in uterus transplant are moving forward with this transition. Porrett notes that there have been 32 uterus transplants performed to date at three independent centers in the US—enough, she argues, to give doctors have a good sense of the procedure's safety, efficacy, and reproducibility. "That to me is grounds to move out of the research realm."

In support of this, surgeons from UPenn, Baylor, and the Cleveland Clinic traveled to Washington, DC, to speak with members of Congress about the importance of the procedure, as some of the researchers made the case for creating Current Procedural Terminology (CPT) codes for the surgeries involved in uterus transplantation. These codes would allow the procedure to one day be filed with insurance companies for coverage. "It's the code that's attached to a price you can claim," says Johannesson, who was involved in these processes. "It's a big step."

But at what point patients can reasonably expect the procedure to be covered by insurers remains an open question. In countries such as the UK with public healthcare, there is already political hostility over the idea of government funding for infertility treatments in general, including IVF, notes Williams's Lancaster colleague, bioethicist Stephen Wilkinson. "As long as it's safe and effective, and as long as it's sufficiently cost-effective . . . then absolutely it's a candidate for being funded and should be funded," he says. But "if it were funded," he adds, "it would be extremely controversial."

Uterus transplants also raise additional ethical concerns, such as challenges in evaluating the intangible value of pregnancy itself, notes Williams, who has published on the ethics of live versus deceased donation in uterus transplantation.[5] "There's a really important balance to strike between exploring . . . social norms and values that we think might valorize biological parenthood [and devalue its alternatives] yet also recognizing the harm that women with [absolute uterine factor infertility] experience" as a result of not being able to carry a child. Laura O'Donovan, who is finalizing her PhD at Lancaster on the legal and ethical analysis of uterine transplant, adds that racial and social inequalities must also be considered as the medical community considers offering the procedure to the general population. "We are at the stage now where we're thinking about clinical translation of uterine transplantation. . . . It's probably about time that researchers came together to develop a concrete framework."

However widely the procedure is offered, experts who spoke with *The Scientist* agree that research must continue. (See "A New Data Stream to Tackle Many Questions" on page 27 and illustration on page 28.) This will involve tracking not just the success of the procedure itself, but medical and psychological outcomes for the children born from transplanted wombs and for the people undergoing these procedures. Last year, Brännström's group published on two- and three-year follow ups with uterus transplant recipients in Sweden.[6] "This is a new chapter in the literature that has already been written about the psychological trauma of infertility."

Such evaluations are a key part of any new medical innovation, but Testa notes that this particular surgery is especially charged. "I was completely blown away about the emotional response [to] this transplantation—much more so than any other transplant I've done in my life," he says. He notes that when it comes time to remove the organ, recipients in the Baylor trial were often upset, and some even initially refused to schedule the hysterectomy. "We have to go through several conversations to make sure they understand the value of doing what we're doing," Testa says. "This was one of the things that was unexpected for me."

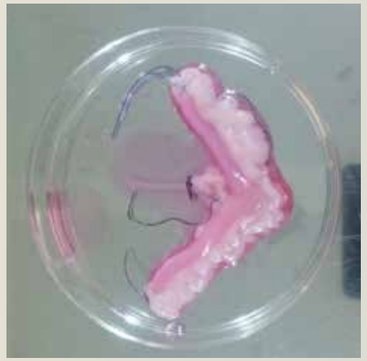
Dingle can personally attest to the emotions of the process. Following the high of giving birth to her daughter Jiavannah, Dingle suffered a series of miscarriages when she and her husband tried for a second child. They were down to their last embryo frozen as part of the initial IVF process when a pregnancy finally took. In February 2020, just two days after Jiavannah's second birthday, Dingle gave birth to a second daughter, Jade. Then, for the final drop in the emotional rollercoaster, Dingle had her uterus removed.

"As time goes on, I'm starting to mourn the loss of the uterus," she says. "Because even though I had a uterus transplant and it allowed me to carry my two miracle girls, it didn't fix me." She adds that, if given the opportunity, she'd continue to grow her family in this way. "I definitely would love to have another chance to have another baby, and I would do it over and over again." ■

### BIOENGINEERING A UTERUS

Women who receive a transplanted uterus must take immunosuppressive drugs to lower the risk that the foreign organ will be attacked by their immune systems. And in the case of transplants from living individuals, the procedure holds significant risks to donors, who are undergoing major abdominal surgery that makes them vulnerable to various complications, including bleeding, infection, and damage to the urinary tract. Paige Porrett, a transplant surgeon at the University of Alabama at Birmingham (UAB) who is running a new uterus transplant program there, notes that such issues are not all that uncommon. The Baylor group and European centers have observed complication rates of approximately 12 percent (*Am J Transplant*, 17:2901–10, 2017)—five- to tenfold higher than rates of complications seen in living kidney or liver donors, Porrett notes.

"Every program who has performed a living donor uterus transplant has had major complications occur in the living donor," she says. "And while there's been no living donor deaths, thank god, there has been significant morbidity for the patients," including requiring additional surgery to correct the problems that were caused by the donation.



MATS HELLSTRÖM

**BUILDNG A WOMB:** A rat uterus that has been decellularized and then recellularized with mesechymal stem cells

To sidestep these issues, researchers are now working to bioengineer a uterus in the lab. Mats Brännström and colleagues at the University of Gothenburg in Sweden first started working on the challenge in animal models about 10 years ago. The researchers use detergents and other reagents to decellularize uteruses taken from dead animals, then seed those organs with endometrial and mesenchymal stem cells to generate tissue that can be transplanted into a living animal. So far, they've had success engineering and transplanting patches of uterine tissue in rodents, and the group has begun to try out the same approach in sheep. But the "efficiency of recellularization is not as great as we hoped," Brännström says. "We are not able to make a whole copy of a uterus."

Regenerative medicine researcher Mats Hellström, the preclinical lab manager in Mats Brännström's group, says the team is now testing out different culture systems, modern perfusion bioreactors for supporting the organs prior to transplantation, and various protocols for seeding the scaffold, including introducing various cell types in different orders. "There are obviously a lot of different cell types in the uterus: endothelial cells for the vasculature, muscle cells for the muscular layer, glandular cells for the endometrium, and we also need a lot of stroma cells for the endometrium as well. Then there is another type of cell that lines the inner side of the lumen: epithelial cells," Hellström says. "It's challenging [to determine] in what sequence should we add all these cells."

While the Swedish group has not yet tried to establish pregnancy in animals that have received uterine grafts, another team has. In June 2020, a group led by Anthony Atala, director of the Wake Forest Institute for Regenerative Medicine, took the field a step closer to reality with live birth from cell-seeded uterine constructs in rabbits (*Nat Biotechnol*, 38:1280–87, 2020). "He's got the best results so far in terms of using bioengineered uterus graft," Hellström says.

In this case, the researchers used a synthetic scaffold composed of more than three dozen biomaterials that will get resorbed by the body, and seeded it with the recipient rabbits' own cells. The researchers didn't replace the entire organ, but more than 80 percent of it, explains Atala, noting that the benefits will be huge if he and others can achieve a clinically viable approach. "Because the organ is your own, once it's implanted it just stays there, and you don't need antirejection medicine," says Atala, who is an inventor on two patents covering uterus bioengineering technology.

Now there are four or five groups working on bioengineering uteruses, including one in Spain and one in Japan, but it'll still be some time before the technology has been scaled up and is ready to be tried in humans, says Brännström. "To create the whole uterus will at least take 20 years."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# The Maternal Microbiome

Bacteria in the gut influence the production of antibodies and secrete metabolites. In a pregnant person, these compounds may influence the immune development of the fetus.

BY CAROLYN A. THOMSON AND KATHY D. MCCOY

Like the hands that pull the strings at a marionette puppet show, our resident microbes influence the day-to-day running of virtually all of our biological systems. For instance, host-microbe interactions during the first three years of life are particularly important for the development of the immune system, and perturbances to the gut microbiota, or dysbiosis, during this critical time in early life can have long-lasting detrimental effects on health. Until very recently, this microbe-mediated immune education was thought to be initiated when a newborn baby leaves the relatively sterile environment of the uterus and is seeded with its mother's microbes, but work from our group and others in the last few years has shown that the maternal microbiome can exert its influence even earlier—on the gestating fetus.

In the mid-2010s, when we started our work on the role of the maternal microbiome during pregnancy, there was no direct evidence that mom's resident bacteria affected the developing baby. However, it seemed naive to think that the influence of the maternal microbiota would start only at birth. We knew that maternal antibodies crossed the placenta to protect the fetus from infection, and we suspected these antibodies could also direct the maturation of the immune system. We also knew that commensal bacteria, in addition to pathogenic microbes, trigger the development of antibodies. Moreover, we thought that perhaps microbial products or metabolites could also be transferred to initiate exposure to a microbial world even before the baby is colonized with his or her own microbiome at birth. Now, just five years later, we know this to be the case: both bacteria-produced molecules and maternally derived antibodies appear to drive immune development in utero.

Many unanswered questions remain, and we are far from understanding the long-term significance of this phenomenon. However, it seems increasingly possible that our mothers' microbiomes may, to some extent, shape our health and well-being before we are born.

## Developmental origins of health and disease

During delivery, babies are exposed to the maternal microbiota. Children born by the vaginal route are colonized by vaginal and fecal microbes, while those born by Caesarean section are instead predominantly seeded by the maternal skin microbiota and sometimes hospital-acquired microbes. The importance of this vertical microbial transfer is apparent in the higher rates of immune, metabolic, and neurodevelopmental disorders among babies born by C-section.

After birth, it takes several years for a child's microbiota to fully develop and diversify. This is a dynamic process, heavily influenced by external factors including hygiene, antibiotic usage, and diet, including human oligosaccharides from the mother's milk. In the same time frame, the offspring's immune system is undergoing intense development and maturation and is highly susceptible to microbial imprinting. Exposing young children to antibiotics during this critical window has been associated with

an increased susceptibility to several diseases, likely due to the indirect effects that these drugs have on immune development.

In 2013 and 2014, as researchers began to question the role of the maternal microbiota during pregnancy, several groups launched epidemiological and animal studies to examine whether in utero antibiotic exposure poses a similar risk to a child's health. Fetuses don't have their own microbiota, so any microbe-mediated immune education that may happen in the womb falls to the resident microbes of the gestating parent, and antibiotic exposure during pregnancy would disrupt this.

Sure enough, exposing pregnant mice to antibiotics can modify the function of the offspring's immune systems and alter their disease outcomes. This was first demonstrated in 2015, when Youjia Hu and colleagues from Yale University showed that prenatal antibiotic exposure influenced the development of type 1 diabetes in the offspring.[1] Since then, a number of other studies have similarly demonstrated effects on offspring of manipulating the microbiota of pregnant mice, either with antibiotics or dietary intervention. Researchers have observed such results in a variety of models, with implications not only for diabetes, but for susceptibility to asthma, obesity, and colitis, as well as the progression of autism-like behaviors.

In most circumstances, manipulating the maternal microbiota changes which microbial communities are passed from mother to offspring at birth, and subsequently alters immune development in the neonatal host. It has therefore proven challenging to attribute the immune phenotypes described in most of these studies to the maternal microbiota directly, as opposed to those mediated by the newly seeded microbiota of the neonate. Fortunately, we are beginning to tease these differences apart, and tantalizing hints are emerging that the maternal microbiota educates the immune and nervous systems of gestating offspring remotely.

## Maternal microbiota shapes infant antibody repertoire

For decades, we have known that antibodies are passed from parent to fetus during pregnancy. They play a huge role in protecting babies from infection both before and after birth. Antibodies continue to be passed postnatally through breast milk, which is one of the many reasons breastfeeding is more beneficial to a baby's immune system than formula is, and why immunizing a person against pathogens during pregnancy or lactation can protect her baby from infections. However, we are only now beginning to appreciate the role the maternal microbiota plays in shaping the antibody repertoire. We are also gaining new insights into other roles for antibodies beyond binding to pathogens and protecting from infections.

By adulthood, the intestine is home to the body's largest collection of immune cells. As it is continuously exposed to enormous amounts of foreign antigens, derived from both the microbiota and our diet, the intestinal immune system must learn to tolerate innocuous food components and symbiotic microbes while retaining the ability to mount a successful defense against harmful pathogens. Moreover, all microbes can quickly become harmful if they enter the bloodstream, even those that are considered symbiotic when living in the gut. Antibodies such as immunoglobulin A (IgA), secreted by B cells at the mucosal surface lining the intestines, are transported across the gut epithelium into the lumen, where they bind to microbes and prevent them from passing through the intestinal epithelial barrier.

The immune system of a newborn infant is inexperienced. The fetus is not thought to be colonized with its own bona fide microbial communities. Traditionally, researchers thought that maternal antibodies transferred across the placenta were specific to infectious microbes that might infect the baby while its own immune system was still developing. We now know that maternally derived antibodies can also bind commensal bacteria—and that this helps to keep these nonpathogenic bacteria from crossing the epithelial barrier as a newborn's gut is rapidly colonized by a vast array of unfamiliar microbes.

Antibodies transferred in breast milk can interact directly with the microbial inhabitants of the infant gastrointestinal (GI) tract, where they keep populations of commensal species in check and ensure that the microbes stay in the gut lumen where they belong, thereby preventing the inappropriate activation of the local adaptive immune response.[2] This transfer of antibodies might partly explain why newborn babies fed breast milk are less susceptible to developing necrotizing enterocolitis (NEC), a severe and often fatal inflammation of the colon that can occur when babies are born prematurely.

The reason that preterm babies are highly susceptible to NEC is unclear, but it is widely postulated to be a consequence of their immature immune systems overreacting to the abrupt colonization of their GI tracts—something that full-term babies typically handle without issue. In 2019, Kathyayini Gopalakrishna and colleagues at the University of Pittsburgh Medical Center Children's Hospital demonstrated the importance of bacteria-specific IgA antibodies in preventing an overexpansion of *Enterobacteriaceae*—a classic hallmark of NEC—in the guts of preterm babies.[3] These and other results imply that immune education in the final weeks before birth is important for babies' immune systems to tolerate friendly bacteria. Maternally derived antibodies appear to put the brakes on inflammatory pathways to protect the gut from unnecessary damage when first exposed to the microbial world.

As well as functioning in the GI tract, commensal-targeting antibodies from breast milk can be actively transported across the epithelial barrier of a baby's intestine and into its circulation, ultimately disseminating throughout the body.[4] At least a portion of these anticommensal antibodies can cross-react with pathogens. Wen Zheng and colleagues at Harvard Medical School hypothesize that this transepithelial transfer of cross-reacting anticommensal antibodies, from breast milk to the infant bloodstream, could explain the observed protection of neonatal mice from systemic pathogen infection.[5] While it is unclear whether the transfer of antibodies across the placenta in utero contributed to protection in this model, it seems likely that they acted in concert with antibodies transported via breast milk to protect the neonate.

## Microbial metabolites also influence infant immunity

The maternal microbiota is not a one-trick pony; it does more to shape the offspring's immune system than induce the production of antibodies that are shared with the newborn. By breaking down the food we eat, and molecules secreted by other resident microbes, intestinal microbes produce a wealth of metabolites with wide-ranging immune-modulatory functions. At least some of these are passed from parent to child during gestation and breastfeeding.

> Manipulating the microbiota of pregnant mice can modify the function of the offspring's immune systems and alter their disease outcomes.

Best characterized are the short chain fatty acids (SCFAs), derived from the fermentation of dietary fiber by intestinal microbes. The amounts and types of SCFAs that are produced in the parent's gut and transferred to her baby depend on the maternal microbiome, which is in turn shaped by her diet. When pregnant people eat a diet rich in fiber, SCFA-producing microbes thrive, and increased amounts of SCFAs are transferred to the developing fetus. These compounds may influence the maturation of the fetal immune system—specifically, the development of regulatory T cells (Tregs), which help quiet runaway inflammation.

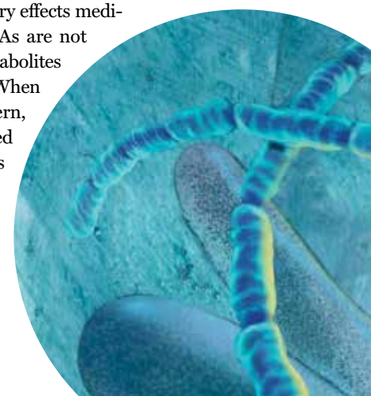
Tregs are crucial for protecting our bodies from autoimmune diseases, as well as from allergies and asthma. They also teach our immune systems to tolerate food and friendly bacteria. Although they self-renew with time, Tregs are long-lived and their progeny will likely be present throughout the life of the host. So, if the maternal microbiota influences the development or maturation of these cells, this could have far-reaching implications for the health of the offspring.

In 2017, Akihito Nakajima and colleagues at Juntendo University in Tokyo reported that three-day-old mouse pups had more Tregs in their thymuses and spleens if their mothers had been fed a high-fiber diet, compared with pups of mothers on a low-fiber diet. The pregnant dams that ate more fiber had increased amounts of the SCFAs acetate, propionate, and butyrate in their feces, as well as increased butyrate in their blood, and their pups had increased SCFAs, especially acetate, in their blood at day 11 of life. The authors suggest that SCFAs produced by the maternal microbiota may act remotely to influence T cell education in the developing thymus, accounting for this increase in Tregs.[6] However, mothers fed a high-fiber diet had differences in their own microbiota, meaning that their babies would likely be seeded with different microbes that might also contribute to circulating SCFAs. More work is needed to establish if it was really the maternal SCFAs transferred during gestation, as opposed to the altered composition of the offspring's microbiomes, that caused the varying numbers of Tregs in the mouse pups.

In addition to those that are produced in the thymus around the time of birth, another group of Tregs can develop from naive T cells in the periphery, and these are equally important for preventing autoimmunity. Alison Thorburn and colleagues at Monash University have shown that the process happens more efficiently when the SCFA acetate is transferred from mother to fetus across the placenta. By increasing transcriptional accessibility of the gene encoding FoxP3, the master regulator of Tregs, maternally derived acetate permanently altered naive T cells in the fetal thymus. This process skewed T cell differentiation toward a regulatory phenotype, as opposed to an inflammatory one, following antigen exposure later in life, thereby protecting mice from developing asthma.[4] Importantly, the authors performed a variety of cohousing and cross-fostering experiments to rule out contributions from milk metabolites and the offspring's own microbiota in driving this protective phenotype. That is not to say that the transfer of SCFAs in milk doesn't contribute to protection. But in this study, maternal acetate in the mice's milk was not sufficient to confer asthma protection, whereas transfer of maternal acetate across the placenta was.

The study by Thorburn and colleagues, published in 2015, was arguably the first to concretely and convincingly demonstrate the long-term effects of the maternal microbiota on disease susceptibility in the offspring. A recent study by Ikuo Kimura of the Tokyo University of Agriculture and Technology and colleagues showed that the placental transfer of propionate, another SCFA that is regulated by the microbiota, could reduce susceptibility of the offspring to obesity and metabolic syndrome in response to a high-fat diet later in life.[7] These phenotypes, which were driven by interactions between maternal SCFAs and their receptors in the developing fetus, could implicate the maternal microbiota in the risk of type 2 diabetes in the offspring.

We predict these two pioneering articles will be the first of many, particularly when one considers the extent of inflammatory diseases that can be controlled and suppressed by Tregs and the wide range of immunomodulatory effects mediated by SCFAs. Moreover, SCFAs are not the only group of microbial metabolites that offspring receive in utero. When working at the University of Bern, our research group demonstrated that a broad range of metabolites are transferred during pregnancy and lactation.[8] We colonized germ-free mice with a friendly species of *E. coli* that was genetically engineered to be unable to



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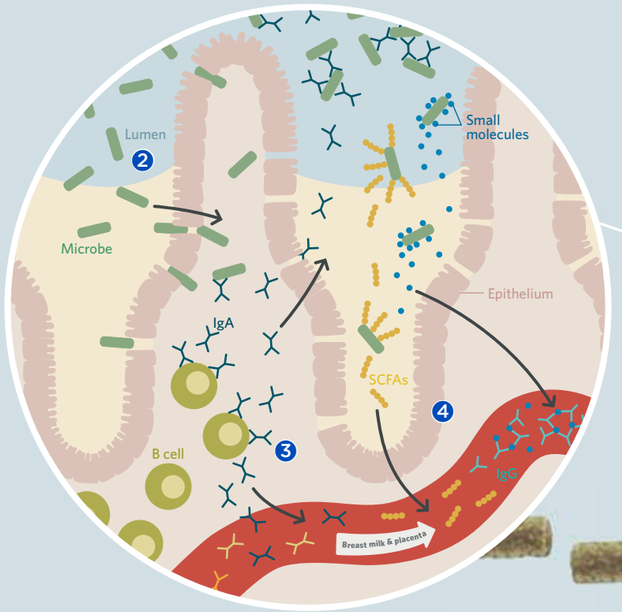
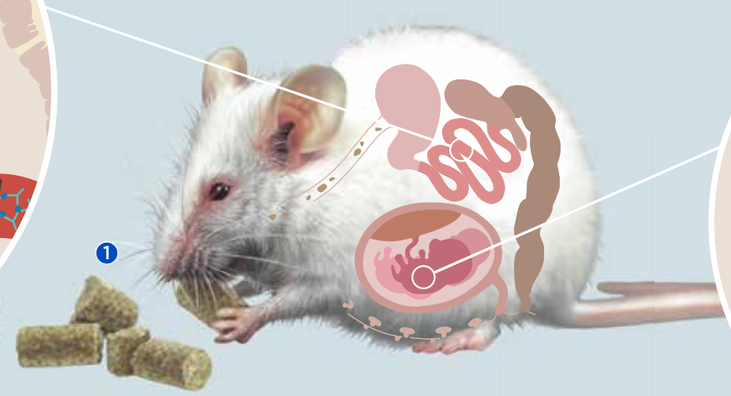
# THE MANY EFFECTS OF MICROBES ON OFFSPRING

During pregnancy, the body is subject to numerous changes. The composition of the gut microbiome shifts, metabolism changes, and the gut epithelium becomes more permeable. These alterations facilitate interactions between the immune system and gut microbiota, leading to the production of microbe-specific antibodies that are transferred across the placenta to the developing fetus, and later via the milk to the nursing offspring.

The maternal microbiota, and the external factors that shape it, influence which immunomodulatory metabolites are produced and transferred to offspring, where they support immune education and otherwise influence development, helping to protect offspring from allergic asthma, metabolic syndrome, and likely other inflammatory diseases later in life. After birth, maternally derived antibodies help newborns tolerate the bacterial colonization of their own GI tracts, while simultaneously protecting them from enteric and systemic infections.



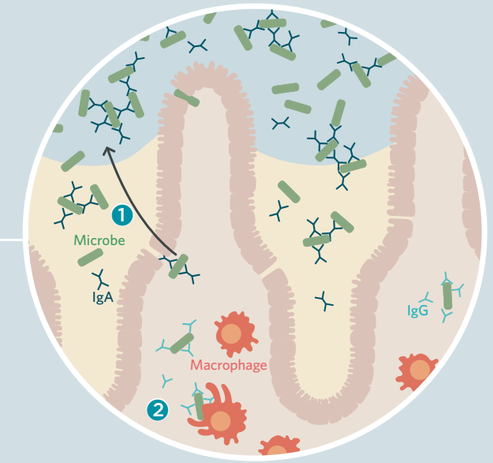

## PREGNANT MOUSE

1 External factors affect the composition of the maternal microbiota (for example, diet, antibiotics, and other drugs).

2 The permeability of intestinal epithelium increases during pregnancy, facilitating interactions between the microbiota and a mother's immune system.

3 The maternal microbiota shapes the repertoire of commensal-targeting antibodies, which cross the placenta and are transferred in breast milk to her offspring.

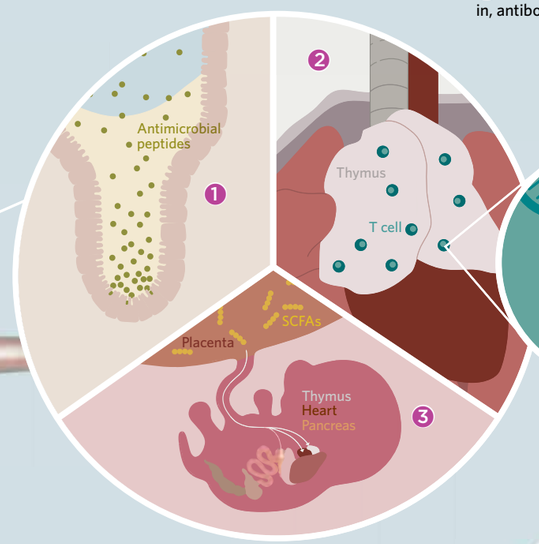
4 Gut microbes produce various metabolites, including short-chain fatty acids (SCFAs) and immunomodulatory compounds, some of which are bound by antibodies and transferred to the fetus.




## NEONATES

1 Commensal-targeting antibodies promote tolerance during bacterial colonization, largely by keeping gut bacteria inside the intestinal lumen or ushering them back in when they do escape.

2 If microbes that escape the intestinal lumen are not immediately ushered back in, antibodies from mom tag them for efficient elimination to limit inflammation.



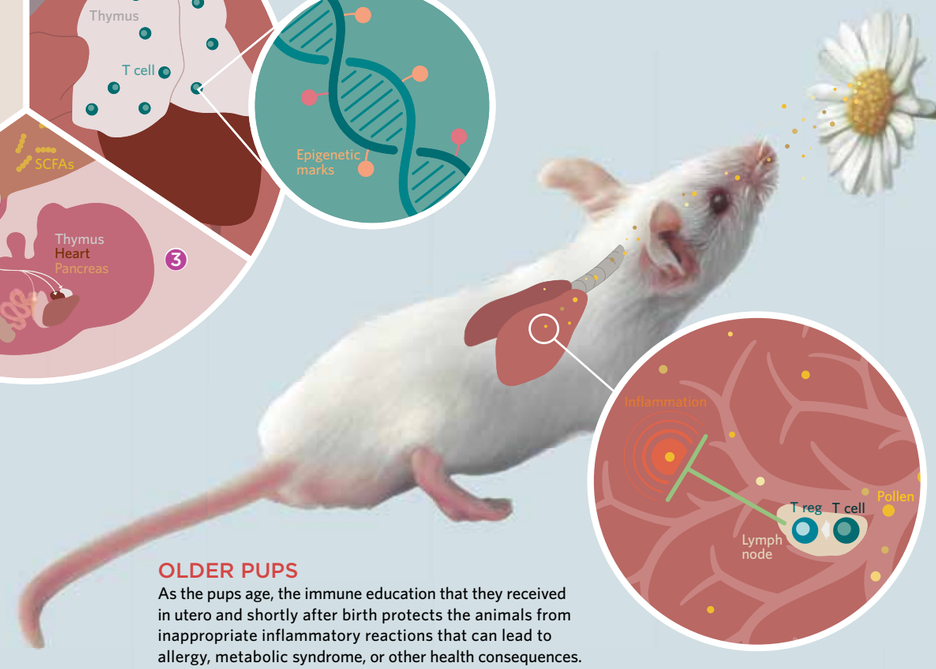

## FETUS

1 The antibody-mediated transfer of metabolites increases antimicrobial peptide production, which strengthens the epithelial barrier to prepare the gut for microbial colonization.

2 SCFAs transferred from mom travel to the fetal thymus, where they trigger epigenetic changes that nudge T cells toward becoming regulatory as opposed to inflammatory later in life.

3 SCFAs also have various effects on the heart, pancreas, thymus, and other organs.






## OLDER PUPS

As the pups age, the immune education that they received in utero and shortly after birth protects the animals from inappropriate inflammatory reactions that can lead to allergy, metabolic syndrome, or other health consequences.

replicate without supplementation with essential amino acids. This enabled us to restrict colonization to a precise period during pregnancy, allowing time for the mothers to return to germ-free status before giving birth to germ-free pups. The metabolites passed from mom to pup changed the immune cell profile in the neonatal intestine and increased the transcription of genes involved in antimicrobial defense. These processes reinforced the integrity of the epithelial barrier, so that when the germ-free offspring were colonized later in life, friendly gut bacteria were prevented from escaping the confines of the intestine to invade the host.

Surprisingly, we found that antibodies were necessary for optimal metabolite transfer, both across the placenta and via breast milk.[8] Specifically, antibodies apparently bound to metabolites in the circulation after pregnant mice were fed *E. coli*. This sheds new light on more than 100 years of antibody research—in addition to protecting against infection, these molecules appear to serve as chaperones of immune-modulating metabolites. If the mothers lacked antibodies, the effect of the maternal microbiota was largely absent; metabolites required maternal antibodies for their transfer.

We are far from fully understanding the extent to which microbial molecules are passed from mother to child, or to what degree they imprint upon the developing immune system. Our group found hundreds of metabolites in the organs of fetal mice and the milk of their mothers, and our model only involved a single species of microbe. In a natural microbiome with diverse assemblages of microbes, the range of metabolites transferred would likely be even more extensive.

## A new view of the maternal microbiome

Most of the research into the effects of the maternal microbiota on offspring has focused on immune education. However, there are some studies emerging that imply that these microbes may have further-reaching consequences. Epidemiological studies have tentatively linked maternal diet and antibiotic exposure to the development of neurodevelopmental disorders in children.

Researchers have recently begun to investigate these observations using animal models. Two separate studies, one published in 2018 by Morgane Thion and colleagues from the Université PSL in Paris[9] and the other in 2020 by Helen Vuong and colleagues from the University of California, Los Angeles,[10] showed that the colonization status of a pregnant mouse can influence gene expression in the brain of her prenatal offspring. The study from Thion's group linked these changes to differences in microglial phenotype and abundance during critical developmental stages, while Vuong's team documented the stunted development of the nerves connecting the thalamus to the cerebral cortex in the offspring of germ-free or antibiotic-treated mice. Collectively, these studies provide preliminary evidence that a mother's microbiota may modulate neurodevelopment in her offspring, possibly even protecting them from neurological disorders later in life.

In the last century, the incidence of neurological, inflammatory, and metabolic disorders has risen dramatically. What healthier way to flatten these curves than to nip them in the bud—or, more accurately, in the womb? The research to date adds weight to the developmental origins of health and disease (DOHaD) hypothesis, which suggests that prenatal and perinatal exposure to environmental factors can influence disease susceptibility later in life, and puts the maternal microbiome on the map as one important environmental factor to consider.

> Until very recently, this microbe-mediated immune education was thought to be initiated at birth when a newborn baby leaves the relatively sterile environment of the uterus.

The implications of these studies are extensive. For one, they could provide evidence for guidance about maintaining a healthy microbiota throughout gestation—for example, by eating a fiber-rich diet or avoiding unnecessary antibiotic use. Moreover, they could inspire microbial manipulation strategies tailored to prospective parents with genetic susceptibilities to certain diseases. Such prophylactic therapies could be designed to curtail the establishment of such diseases before they begin by ensuring the healthiest possible immune development during gestation. The more information we glean on how the maternal microbiota shapes neonatal development and future disease susceptibility, the more likely we are to be able to prevent certain disorders altogether. ■

*Kathy D. McCoy is a professor in the Snyder Institute of Chronic Diseases and the Cumming School of Medicine at the University of Calgary. Carolyn A. Thomson is a postdoctoral fellow in McCoy's lab, which studies microbiome-immune interactions in health and disease.*

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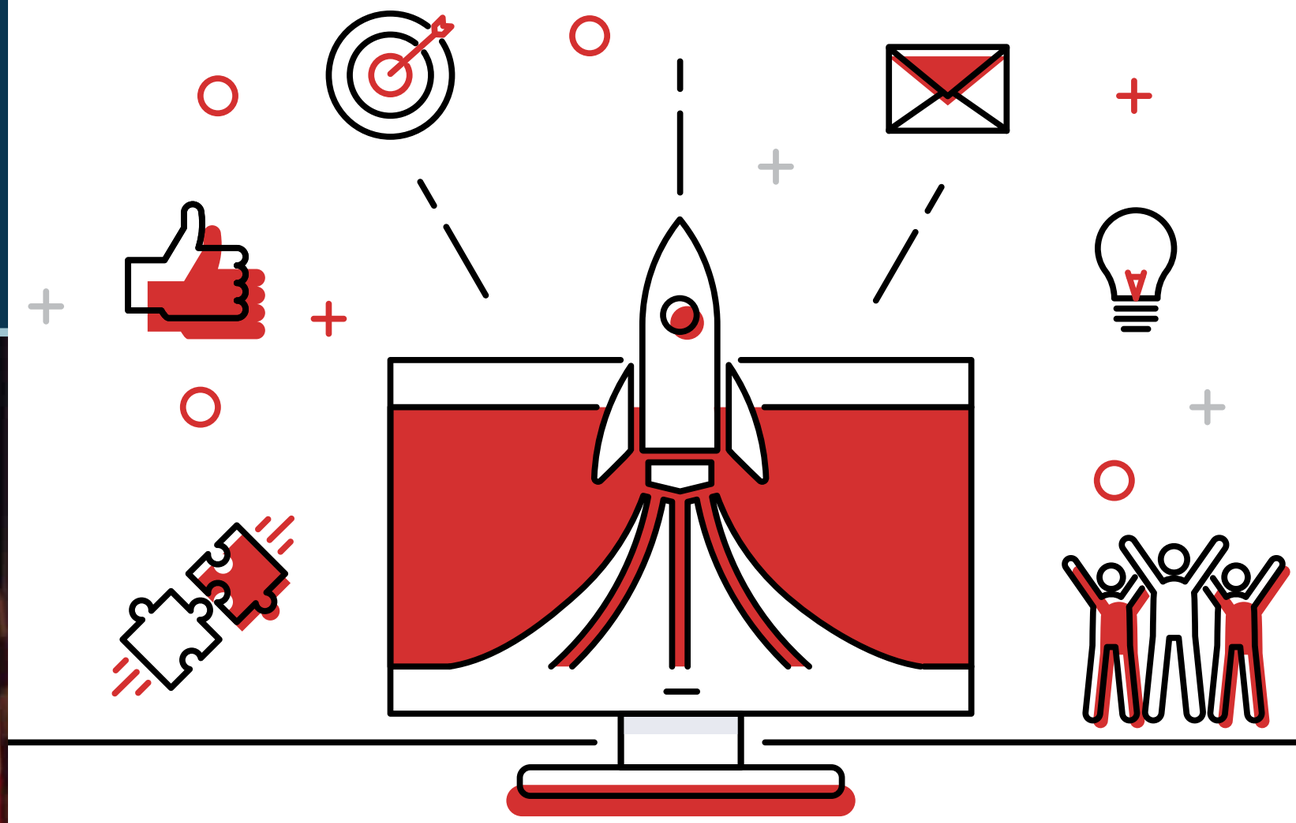


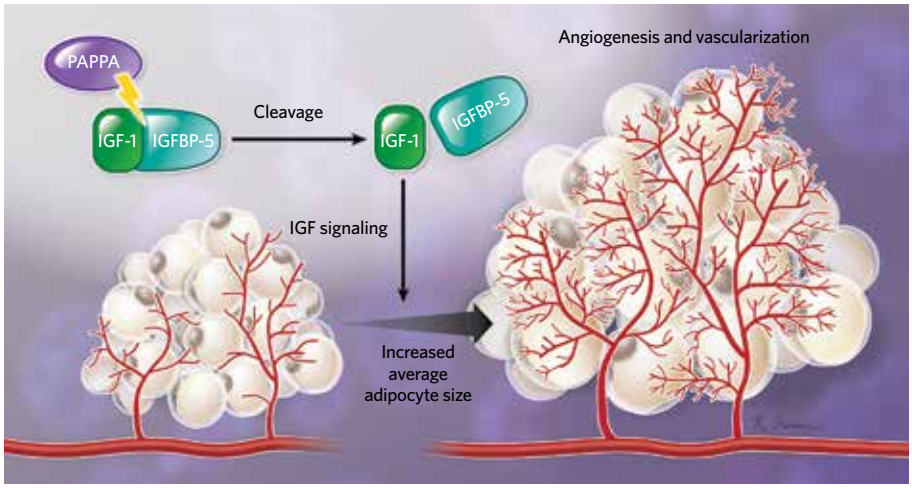
# The Literature

PHYSIOLOGY

## Fat Change

THE PAPER

R. Rojas-Rodriguez et al., "PAPPA-mediated adipose tissue remodeling mitigates insulin resistance and protects against gestational diabetes in mice and humans," *Sci Transl Med*, 12:eaay4145, 2020.




**SIGNAL BOOST:** Pregnancy triggers a remodeling of fat tissue, according to findings from researchers at the University of Massachusetts. In the team's proposed mechanism, pregnancy-associated plasma protein A (PAPPA), which is produced in the placenta and elsewhere in a pregnant person's body, acts on insulin-like growth factor binding protein-5 (IGFBP-5), freeing up the insulin-like growth factor-1 (IGF-1) that typically binds to it. IGF-1 signaling subsequently triggers fat remodeling, including the expansion of blood vessels (angiogenesis) into the tissue (vascularization). These changes are likely to be important for maintaining insulin-driven regulation of glucose levels in the blood, the researchers conclude, although the mechanism for this is not clear.

A fetus needs fuel, and a mother's body undergoes big physiological changes during pregnancy to make sure it gets it. One change is a reduction in insulin sensitivity, meaning that cells become less responsive to insulin signals telling them to take up glucose from the blood. In 5 percent to 9 percent of US pregnancies, cells become so resistant to insulin that they become significantly less effective at keeping blood glucose levels down. Mothers who have this temporary condition, known as gestational diabetes mellitus (GDM), may have an elevated risk of type 2 diabetes and other diseases later in life—as may her children.

Several years ago, Raziel Rojas-Rodriguez, then a PhD student in Silvia Corvera's lab at the University of Massachusetts, discovered differences in the fat, or adipose tissue, of pregnant people with and without GDM. Although increases in fat mass are normal during pregnancy, people with GDM had larger fat cells surrounding their organs, and, according to genetic assays, lower expression of certain genes involved in insulin signaling in their fat tissue than did pregnant people without GDM. The researchers wondered if there might be a link between fat remodeling during pregnancy and the development of insulin resistance.

To investigate, they focused on pregnancy-associated plasma protein A (PAPPA), which is produced mainly by the placenta and helps regulate insulin signaling and increases in the blood throughout pregnancy. In vitro assays revealed that PAPPA plays a role in remodeling human fat tissue and promotes vascularization. Compared with pregnant wildtype mice, pregnant mice lacking PAPPA had more fat around their livers and reduced insulin sensitivity, Rojas-Rodriguez says.

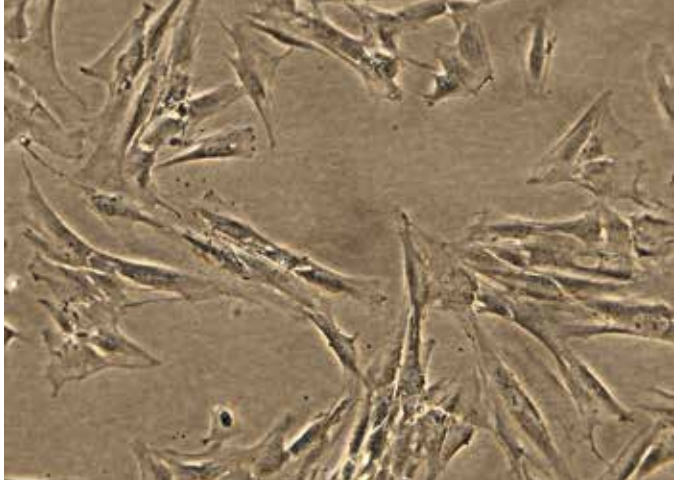
The researchers also examined hospital data from 6,361 pregnant people who took PAPPA tests (the protein is also used to diagnose fetal aneuploidy) in the first trimester and glucose tests in the third. The team found that, even when controlling for BMI and age, low PAPPA was associated with elevated GDM risk, suggesting the protein may protect against the condition.

The University of Southern California's Thomas Buchanan, who was not involved in the study, says the findings offer new insight into adipose tissue remodeling during pregnancy and into the role of PAPPA. He says the relationship between PAPPA levels and GDM is unclear because there may be confounding factors influencing a person's GDM risk that aren't captured in this study, and because the PAPPA-knockout mice don't recapitulate all the characteristics of human pregnancy. For example, although the knockouts showed reduced insulin sensitivity compared with wildtypes, they paradoxically had enhanced glucose tolerance.

Corvera says that this seems to be because muscle tissue in these mice consumed unusually large volumes of glucose. "We don't know why," she says. "It may be that the mice are moving more." Tissue-specific knockouts could help narrow in on what's happening where, she adds. Rojas-Rodriguez, now a postdoc at Tufts University, says the team would like to measure PAPPA longitudinally during pregnancy and notes that the protein may have use as a biomarker. "Obviously this will need more studies," she says, "but there is a potential of this protease to be used in the diagnosis of gestational diabetes."

—Catherine Offord

MOUSE MOMS: When obese female mice exercised during pregnancy, their young grew up to be healthier than pups born to sedentary obese moms.



HANDY CELLS: Endometrial stromal fibroblasts, one of the endometrial cell types which expresses *HAND2*

PHYSIOLOGY

# Familial Fitness

**THE PAPER**

R.C. Laker et al., "Exercise during pregnancy mitigates negative effects of parental obesity on metabolic function in adult mouse offspring," *J Appl Physiol,* 130:605–16, 2021.

Obesity is a risk factor for numerous diseases, including cancer and type 2 diabetes. This risk extends to future generations, as parental obesity can leave epigenetic marks in egg and sperm cells that affect the metabolic health of offspring formed from those germ cells. "The health status of the parents matters," says Zhen Yan, a physician scientist at the University of Virginia who studies exercise physiology.

Yan's group had previously studied how exercise before and during pregnancy affected the adult offspring of female mice with diet-induced obesity. Maternal exercise improved glucose tolerance in their offspring, and also curbed DNA hypermethylation—an epigenetic change that can reduce expression of particular genes—of the promoter of *PGC-1α*, a gene expressed in the adult progeny's skeletal muscle, that encodes a key metabolic regulator.

In a new study, Yan and his colleagues investigated whether exercise started during pregnancy is enough to improve offspring health in mice. The adult male progeny of obese mothers that never exercised had higher insulin and glucose levels in adulthood compared with the male offspring of sedentary non-obese mothers. But when obese mothers exercised, their offspring did not show hypermethylation of *PGC-1α* and had normal metabolic health. The researchers also found that maternal exercise compensated for the negative effects of obese fathers on offspring health, preventing a pattern of glucose intolerance in their adult pups, though paternal obesity didn't affect *PGC-1α* methylation levels, suggesting a different mechanism is involved.

"I think this work is really interesting. . . . Looking at maternal and paternal influence, in general, is important," says Kristin Stanford, a physiologist at the Ohio State University who wasn't involved in the work. How maternal exercise during pregnancy counters the effects of parental obesity remains an open question, as well as how the findings might apply to humans. —Jack J. Lee

GENETICS

# Jumpstarting Labor

**THE PAPER**

M. Marinić et al., "Evolutionary transcriptomics implicates *HAND2* in the origins of implantation and regulation of gestation length," *eLife*, doi:10:e61257, 2021.

Scientists don't fully understand the molecular mechanisms that conclude human pregnancies. Simply put: "We don't know how women go [into] labor," says Mirna Marinić, a developmental biologist at the University of Chicago, adding that pregnancy in animal models is often too different from that of humans to be very informative.

Still, understanding how differences between animal and human pregnancies arise could provide novel insights into how labor is triggered. Marinić and her team compared gene expression profiles in the endometrial tissue that forms the maternal-fetal barrier across 27 species—including 18 live-birthing mammals, the egg-laying platypus, and eight other egg-laying animals—to look for shifts in gene expression associated with the evolution of different reproductive strategies.

The analyses revealed 149 genes that had evolved to be expressed in the endometrial tissue of placental mammals, and of those, a transcription factor called *heart- and neural crest derivatives-expressed protein 2* (*HAND2*) stood out. The gene is known to play a role in prepping the uterine lining for implantation and suppressing estrogen signaling; reexamining published data, the team found that *HAND2* expression decreases throughout human gestation. The researchers then knocked out *HAND2* in human endometrial cells and identified changes in the expression patterns of genes associated with premature birth and protecting the fetus from the mother's immune system, strongly pointing to a role for *HAND2* in initiating labor.

"This is really exciting, because it's leading us to genes that might be important," says Rachel Freathy, a genetic epidemiologist at the University of Exeter who was not involved in the study. Freathy identifies genomic regions involved in preterm birth, and says she was excited by the researchers' experimental approach. "It was a great bridge from the kind of work that we do that brings up associations to actually getting to the mechanisms in the right tissues." —Christie Wilcox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# Darby Saxbe: Parenthood on the Brain

Associate Professor of Psychology and Founding Director of the Center for the Changing Family, University of Southern California

BY SHAWNA WILLIAMS

Darby Saxbe got her start in psychology research early. A self-described "nerdy kid," she did a study in seventh grade in which she gave left-handed people who wrote with a "hooked" posture and right-handed people a visual test to compare their perception in their left and right visual fields "I've always been sort of curious [about] what makes people different from each other," she explains.

Growing up in the college town of Oberlin, Ohio, it was easy to envision a career in academia, but Saxbe wasn't completely sold. When she enrolled at Yale University in 1995, she originally majored in English. After realizing that career prospects for would-be English professors weren't promising, she gravitated back toward psychology, and graduated with a double major. She moved to New York, working for tech startups and as a freelance writer, but the crash of the dot-com economy in the early 2000s led her to press the restart button on her career by going to graduate school.

She applied to a lab at the University of California, Los Angeles, that was launching an intensive study of the everyday lives of dual income heterosexual couples. Rena Repetti, who heads the lab, recalls that in her admission interview, Saxbe "came across as not only very intelligent, clearly, and very accomplished, but full of energy, full of ideas."

In the lab, Saxbe proved "an absolute joy to work with," Repetti says, displaying an impressive ability to "put different strands of research and different research literatures together in novel ways." Saxbe excels, Repetti adds, at combining biological, psychological, and social research. "I don't know of anyone, literally, who combines those three strands together as well as she does."

As part of Repetti's study, Saxbe monitored cortisol levels in the saliva of participants and compared it to people's self-reported marriage quality. Levels of cortisol, a stress hormone, normally peak in the morning and then decline. If an individual's levels instead remain high, it can indicate burnout or chronic stress. Saxbe found that women in lower-quality marriages tended to have less decline in cortisol levels throughout the day compared with their counterparts in happy marriages, while no such relationship existed for men (*Health Psychol*, 27:15–25, 2008).

Saxbe earned her PhD in clinical psychology in 2009 and went on to a year-long internship at a veteran's hospital before beginning a postdoc at the University of Southern California (USC) with psychology researcher Gayla Margolin. There, Saxbe continued to pursue her interest in family relationships and cortisol levels, while adding neuroimaging to her toolkit. Using MRI, she scanned the brains of adolescents between 15 and 18 years old as the teenagers viewed videos of either themselves, their parents, or unfamiliar peers displaying positive and negative emotions. Their patterns of brain activation were different depending on whether they were viewing unfamiliar people or viewing themselves or their parents, she found, and the particulars of those differences correlated with whether adolescents engaged in risk-taking behaviors such as shoplifting or drug use (*Soc Neurosci*, 10:592–604, 2015).

Saxbe had her two children just before and during her postdoc, and that experience aroused an interest in the changes wrought by the transition to parenthood, she says. After starting her own lab at USC in 2013, Saxbe began a study on expecting couples, focusing particularly on fathers. Men in couples expecting a child completed questionnaires and had their hormone levels measured and their brains scanned before and after the birth of their child, and underwent observation with their babies. Saxbe says that she's interested in the wide variability—among both individuals and cultures—in fathers' level of involvement in parenting. In addition, Saxbe notes, "if they are showing changes to their biology or to their brain, it suggests that you don't need to be pregnant to undergo some of those changes to your physiology." That study recently wrapped up data collection.

"What's very unique about what she's done is . . . making a very compelling case that childbirth is a life event with implications for the health of all family members involved," says Margolin, who echoes Repetti's praise of Saxbe's facility for interdisciplinary work. An example, she says, is Saxbe's 2020 launch of the USC Center for the Changing Family, which pulls together faculty and trainees from different schools at the university with the idea of "getting people to talk to each other across different fields and make connections." ■

UNIVERSITY OF SOUTHERN CALIFORNIA

# Science Moms Call for Change

The organizers behind a Mothers in Science conference say that it's time academia provide more support to researchers who are pregnant or caring for children.

BY AMANDA HEIDT

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At first glance, this year's inaugural Mothers in Science conference would have looked familiar to anyone who has attended a professional event in the last year: it was remote due to the pandemic, speakers fidgeted with their mute buttons, and more than one person revealed themselves to be wearing sweatpants.

But throughout the daylong event, held on May 8, it would quickly have become clear that this event was something unique. Ryan Watkins, a planetary scientist and program manager at NASA, spoke from her home in St. Louis, framed by a virtual background of a human landing capsule. Towards the end of her presentation, a disembodied hand pierced the capsule's window; in reality, the arm belonged to her youngest daughter, who was home sick. Watkins finished her presentation on the barriers faced by mothers in science, technology, engineering, math, and medicine (STEMM) while doling out snacks to the toddler on her lap.

On Twitter, parents shared photos of their children attending the conference alongside them, and presenters opened talks by commiserating about the challenges of balancing work and family. Aaron Clauset, a computer scientist at the University of Colorado Boulder, had his three daughters with him and needed his speaking time changed to accommodate their schedules.

This honest discourse, and the empathy extended to struggling parents, is just the behavior the team behind the event, the nonprofit Mothers in Science (MIS), is working to normalize. For too long, say the organization's founders, academia has sidelined the contributions of parents, prompting many to abandon their careers. Studies report that women worldwide shoulder a disproportionate burden of household labor, and mothers specifically earn less money, are less likely to be hired or promoted, and are more likely to drop out after starting their families than fathers or childless peers are. (Little research focuses specifically on trans or nonbinary parents.) Pregnant people also face prejudice, so much so that the US Department of Education included pregnancy discrimination under its 1972 Title IX civil rights law. With a pandemic straining many working parents, the motivation is there to advocate for change—before the world returns to a normal that suits only some.

Since launching MIS in 2019, Isabel Torres—the organization's cofounder, a PhD in genetics, and a mother of four children—has seen the group swell and its influence grow, in part because women are speaking out about the challenges they face. "There's a lot of silence and stigma around motherhood, and women know . . . that it is used against us in the professional setting." Despite a subtle closing of the gender gap in recent years, Torres continues, change has been slow, and motherhood is still seen by many employers as a liability.

The conference brought together researchers studying gender disparities in academia, drawing almost 200 participants from 46 countries. During presentations and panels, scientists detailed how the system fails working mothers and pregnant people; highlighted existing solutions; and brainstormed new strategies for research and policy. "Mums are scared that everything will go back to the way it was, so our organization is really pushing for change now," Torres says of her team's decision to host the conference during the pandemic. "We hope to bring a deep change to the system, because it's so overdue."

## Work barriers

Torres's ardor stems from her own experiences as a new mother during her PhD studies at the University of Cambridge. "You go back to the lab, and you don't feel different, but you feel that people see you differently," she says. Torres was no longer as involved in research planning, and colleagues stopped inviting her out to network because they expected she was overwhelmed, she recalls. While her career goals remained unchanged, "they just assume you're no longer ambitious, that you just want an easier, more flexible job," she tells *The Scientist*. She left academia after completing her degree, and now works as a science writer and editor.

For researchers who spend long stretches in the field, however, parenthood can in fact be difficult to reconcile with career aspirations. Gemma Collins, a molecular ecologist at the Senckenberg Biodiversity and Climate Research Centre in Germany who was not at the MIS conference but has shared her parenting challenges with MIS through social media, scheduled her first pregnancy around Antarctic field seasons during her PhD work. After waiting one year, Collins decided not to postpone again. But when she contacted her funders about rescheduling her second expedition, they declined. "The fieldwork that I'd managed to get funding for, they just gave the slot to someone else," she tells *The Scientist* in a video recording. "I was gutted, and a bit bitter about it."

The decision to delay parenthood also affected Monica Malta, an epidemiologist at the University of Toronto. Initially, she wanted to start a family once she was more secure in her career. But as a postdoc approaching 40, she forwent applying for a tenure-track job and took a leave of absence to have the first of her three children via in vitro fertilization. "I think it's very common for most women in STEMM to wait . . . because our training takes a lot of time," she says, adding that many of her friends who wanted children ultimately chose work instead.

Stories such as these have played out in countless iterations, with mothers facing a number of barriers collectively called the maternal wall. Several women from STEMM backgrounds tell *The Scientist* that in addition to having colleagues assume their priorities, as happened to Torres, others had their competency questioned when, for example, they needed time to get themselves back up to speed. Still others say they have been asked, illegally, about their family planning during interviews and felt that the job depended on their answers.

**Mums are scared that everything will go back to the way it was, so our organization is really pushing for change now.**

—Isabel Torres, MIS

This kind of anecdotal evidence is common, says Torres, with women communicating through whisper networks. But research presented at the conference is providing hard data to support the experiences of exasperated mothers. In one 2019 study highlighted at the event, sociologists Erin Cech and Mary Blair-Loy investigated how people's careers changed after having children. Using data from the National Science Foundation (NSF), they found that nearly half of all new mothers leave full-time STEMM employment following the birth or adoption of their first child, while roughly one-third leave the field entirely. "The sheer size of the attrition was really striking to us," Cech tells *The Scientist*, adding that mothers rarely return even once their children enter school. "Once you're out of full-time STEMM employment, it's really unlikely that you will jump back in." The effects weren't limited to mothers: nearly one-quarter of new fathers surveyed had also left full-time employment in STEMM on becoming parents.

More recently, a study by Clauset and others, published in *Science Advances* and shared at the MIS conference, found that researchers in computer science, history, and business delay having kids by several years compared to the national average, and that respondents who self-identified as women tended to have fewer children than the average US parent. Parenthood was also linked to a sustained decline in publications for mothers—between 17 percent and 48 percent, depending on the field—compared to women who did not have children, while fathers' output changed very little, on average, compared to men who did not have children. Within computer science, mothers wrote roughly 18 fewer papers in the decade following their child's birth, a gap that would take five years to close. "I didn't really expect it to be so much," says study coauthor Allison Morgan, a computer scientist at the University of Colorado Boulder who analyzed the data for her dissertation. "It's meaningful because so many academics become parents," she adds, noting that nearly 80 percent of respondents over 40 had children.

## Practical solutions

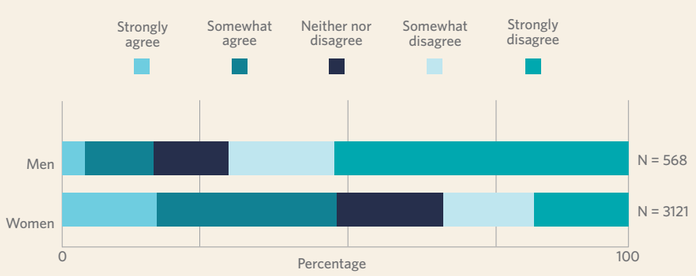
Shortly after launching MIS, Torres and her team developed their own survey to capture evidence of what they believe is a global phenomenon. The survey, which was sent to universities worldwide and publicized on social media, garnered nearly 9,000 responses from more than 120 countries. Watkins, who is also the research manager at MIS, presented preliminary results at the conference about the challenges parents face, reaffirming

what has been shown on a smaller scale in other studies, either in particular countries or within specific disciplines. This replication of existing findings on a larger scale will be important, she says, when MIS delivers its final report to various groups that help shape academic policies. The group's advocacy work "might start small, at the institution level . . . [but] ultimately we'd like to get up to government levels, finding out what representatives we can take this kind of information to," Watkins tells *The Scientist*.

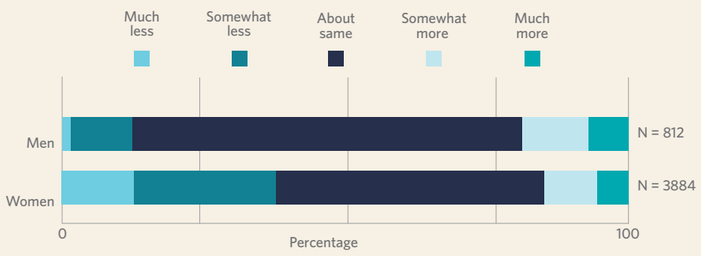
In addition to generating data that could help shape policy, the survey provided a space for parents to express their opinions about what needs fixing and share their ideas for long-term solutions. Mothers and fathers have long been frustrated by insufficient parental leave, for example, suggesting that policies addressing this issue could be powerful

**PARENTS SPEAKING OUT:** As one of their first actions after launching in 2019, Mothers in Science designed and distributed a survey about parenting in STEMM that received almost 9,000 responses from academics living in 128 countries. Participants included self-identified men, women, and nonbinary individuals living with and without children. Results from two of the questions are presented below for women and men, who accounted for around 97 percent of the respondents.

The time I stayed away from work for parental leave (with my first child) affected my professional credibility or reputation.




Since becoming a parent, have you generally been offered fewer, more, or about the same number of professional opportunities?




recruitment and retention tools. In Morgan's survey, half of the women respondents said leave policies were somewhat or very important in choosing their current job, but only 60 percent of the surveyed institutions offered paid leave.

Some funders are already playing a part in bringing about that change by offering flexible deadlines, grant extensions for parental leave, and subsidies for childcare. Deadline extensions during COVID-19 garnered more applicants who self-identified as female, and both the NSF and the National Institutes of Health (NIH) have initiatives geared towards parents, including paid leave for doctoral and postdoctoral fellows, funding for faculty to hire technicians to assist with research while academics are on leave, and annual subsidies for childcare. The NIH's Office of Extramural Research tells *The Scientist* in an email that such policies have benefited thousands of scientists, and in response to their popularity, the agency plans to expand its childcare subsidies over the next fiscal year.

For parents wanting to reclaim their careers, nonprofits are offering programs to help academics re-enter STEMM following extended absences. In the US and Canada, the American Physical Society's M. Hildred Blewett Fellowship provides funding to women for one year to cover childcare, salary, equipment, and tuition, while in the UK and Ireland, a fellowship from the Daphne Jackson Trust provides money and training to scientists of any gender resuming research after a break of two or more years.

One Trust awardee is Aisha Baba-Dikwa, now a microbiologist at the University of Manchester. She had been teaching for five years while she started her family, but missed the intellectual curiosity of conducting research. "It took a wake-up call—starting a family—to make me realize I had to go back into research, because that was my passion," she tells *The Scientist* from her car, speaking between errands with her son, now eight years old.

Applying for the Daphne Jackson Fellowship required Baba-Dikwa to submit a research proposal to potential host institutions, which provided additional funding in addition to lab space and an advisor. The money allowed her to ease back in by working in the lab part time, and her adviser trained her on new molecular tools. "It was really a drop in the deep end, as a new mother," Baba-Dikwa says. Her son was then only two years old, and her pregnancy had been difficult and draining. The fellowship gave her confidence and the experience to land the first job she interviewed for afterwards, she says. "They really give you all the tools you need as a person returning to science."

## The right moment

The proliferation of groups such as MIS signals that greater awareness, and real change, may finally be on the way. Still, breaking through cultural and structural barriers to equality and equity within STEMM will require moving "beyond the sense of this being an individual problem, where mothers must be . . . educated about how they might best game the institution," to a broader understanding of academia's failings, Cech says.

**For parents wanting to reclaim their careers, nonprofits are offering programs to help academics re-enter STEMM following extended absences.**

All scientists should reject unfair policies, initiate conversations about what parents need, and extend empathy to their colleagues with children, say Torres and Watkins. As a new mother, Watkins asked her postdoctoral advisor for space to pump breast milk, which he had simply never recognized as a need but happily granted. Collins similarly approached her male supervisors as a PhD student about setting aside an empty room for her to use. Her outdated building didn't even have a women's restroom or diaper-changing facilities at the time, and the room gave her privacy to pump in a clean and quiet space.

With conversations on these issues coming to the fore amid a broader discussion about what work will look like after the pandemic, Torres feels confident that change is coming, the success of the conference being just the latest example of a groundswell of support. "It might be slow, it might go step by step, but I think this is definitely the moment," she says. "Mothers are at the breaking point; the system is at the breaking point. I just hope we'll be able to push enough to really change the system irreversibly." ■

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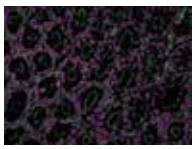

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# Pregnancy's Biomedical Futures

CRISPR and other innovations are likely to open up a wealth of new options for having children.

BY HENRY T. GREELY

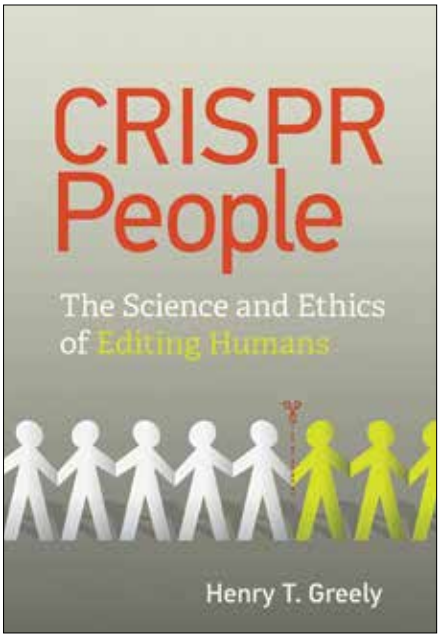
Genetic knowledge has played a direct role in pregnancy for more than 50 years, since the first use of amniocentesis to extract amniotic fluid containing fetal cells and DNA for analysis. Noninvasive prenatal testing (NIPT)—which is significantly cheaper than amniocentesis and, requiring only a blood draw, can be done earlier in pregnancy—started a decade ago and is now common. NIPT will only become better, providing more-accurate information on risk for thousands of rare genetic conditions and dozens of more-common diseases. It's just one of the technologies poised to transform pregnancy over the coming decades.

Today, bad news from prenatal testing leaves would-be parents with two options: terminate the pregnancy or prepare for the birth of an ill or at-risk child. For over 30 years, parents have been able to avoid this dilemma by turning to preimplantation genetic diagnosis (PGD). This procedure starts with in vitro fertilization (IVF), but then tests embryos before they are transferred into the uterus. For many people, choosing not to transfer an embryo destined to have a genetic disease raises less concern than aborting an already implanted embryo or growing fetus.

PGD opens yet another door. One might edit the genes of those at-risk embryos, using CRISPR or other methods, before using them to try to start a pregnancy. Infamously, Chinese scientist He Jiankui used embryo editing to make babies three years ago. In this case, rather than trying to head off genetic disease, He was attempting to confer HIV resistance by introducing mutations in *CCR5,* a gene that encodes a cell-surface receptor that the virus latches onto to infect T cells. He expected acclaim, but instead was condemned around the world and ultimately sentenced to prison. For many people, He's sin was changing the babies' DNA in ways they could pass on to their children, because changed cells in the embryo would eventually become eggs or sperm. This argument against heritable changes would also apply when the change is made to correct disease-causing mutations—or when it is used to try to "enhance" the resulting babies. Whether such germline editing should be a "line in the sand," not to be crossed, is hotly disputed.

My new book, *CRISPR People: The Science and Ethics of Editing Humans*, tells this story of human germline genome editing in depth, including He's experiment and the many problems with it. But if the process of editing the DNA of embryos is eventually shown to be safe and effective, it might end up being adopted, especially as we continue to improve our understanding of genetics. As we learn more about the effects of genetic variations, gene editing technologies will have more to offer. Most of us look forward to this when it involves disease, while the (distant) prospect of "enhancement" of traits such as height or intelligence causes very mixed feelings.

Now, consider that we may soon be able to make eggs and sperm from stem cells derived from a person's skin. This technique, which has already worked in mice and is being researched with human cells, offers hope to people who cannot have their own genetic children because they lack functional sperm or eggs, as well as a potential pathway for LGBTQ couples who want to have children who are biologically their own. If the technique becomes an easy source of human eggs, it may also allow people to bypass the uncomfortable, risky, and expensive process of harvesting eggs for IVF, which could lead to a vast expansion of the use of PGD.




*MIT Press, February 2021*

Finally, in several decades, one might be able to make a living uterus outside the body using stem cells and, by mechanically giving it blood with oxygen, nutrients, and the right hormones, use it to gestate a baby. This not-exactly-artificial womb could transform pregnancy entirely, and with it, the lives of billions of people.

Some of these developments will come to pass, some will not, and some things that I have neither discussed nor dreamt of will happen. While these advances could bring great benefit, they could also be abused, creating in real life the familiar dystopias of the breakdown of family structures, state control over parental decisions, or genetically stratified societies. We need to watch these biomedical possibilities to make sure they deliver a better tomorrow. ■

*Henry T. Greely is Professor of Law, Professor by Courtesy of Genetics, and Director of the Center for Law and the Biosciences at Stanford University. Read an excerpt from* CRISPR People *at the-scientist.com.*

# Birth of Midwifery, Circa 100 CE

BY LISA WINTER

Around 100 CE, a Greek physician of the Roman Empire known as Soranus of Ephesus wrote several books on medicine, compiling the knowledge of the day into volumes on anatomy, disease, surgery, and pharmacology, among other subjects. His most enduring work, *On Midwifery and the Diseases of Women*, covered female reproduction from conception through newborn care, including new solutions to old problems. It would remain the gold standard for obstetrics and gynecology until significant scientific strides were made during the Enlightenment 1,500 years later.

Prior to Soranus's writings, childbirth wasn't viewed as an event that "needed medical intervention in terms of helping a baby come out," explains physician and medical writer Randi Hutter Epstein. Laboring mothers were attended by midwives who themselves had given birth and gained knowledge through experience. Doctors were rarely involved in the birthing process, even in complicated cases, because gynecology was considered beneath them. But Soranus argued that, in addition to being clean and literate, midwives should be trained in basic medicine in order to properly care for an expectant mother and her child.

Soranus's book was divided into four sections, the first of which dealt with midwifery, menstruation, contraceptives, abortive procedures, and virginity. The others focused on newborn care, gynecological maladies, and healing herbs. His is the first known description of a technique for turning a baby whose back is covering the birth canal, a situation known as a transverse position that until that point had nearly always ended in the baby's death. By reaching into the uterus and pulling on the baby's legs to manipulate it into a breech, or feet-first, position, the delivery became merely tricky, rather than impossible.

**EASY DOES IT:** A relief carving of a midwife delivering a baby in ancient Rome. As part of the birthing process, Soranus wrote, it was the midwife's job to keep the mother calm and relaxed, even during times of examination: "The midwife should beware of fixing her gaze steadfastly on the genitals of the labouring woman, lest being ashamed, her body become contracted. . ."

Among his other innovations, Soranus developed a birthing chair with stirrups, and protocols for cutting the umbilical cord and cleaning the stump and for removing blood clots from the uterus following delivery of the placenta. He recommended an examination of the newborn to determine overall health, similar to the Apgar tests infants receive today, to determine which babies were "worth rearing."

Soranus also advised against some common practices of the day, particularly that of immediately placing a newborn in cold water to "firm it up." Soranus denounced the practice, noting that everyone is negatively affected by cold, but newborns would be especially, given that they had only known a warm uterus.

One area that hasn't aged as well is the burden Soranus placed on mothers. He asserted that even a mother's thoughts or whether she looked at the moon could influence the outcome of the birth, and wrote, "Even if a woman transgress some or all of the rules mentioned and yet miscarriage of the fetus does not take place, let no one therefore assume that the fetus has not been injured at all."

Originally written in Greek, *On Midwifery* was translated into many other languages, including Arabic, German, and Latin. Its guidelines remained standard practice through Europe and the Middle East for roughly 1,500 years, until formalized training for midwifery began and obstetrics became a recognized medical field. This brought about more interaction between midwives and doctors, and the invention of forceps allowed for babies to be extracted during difficult births, lowering infant mortality rates. ■

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