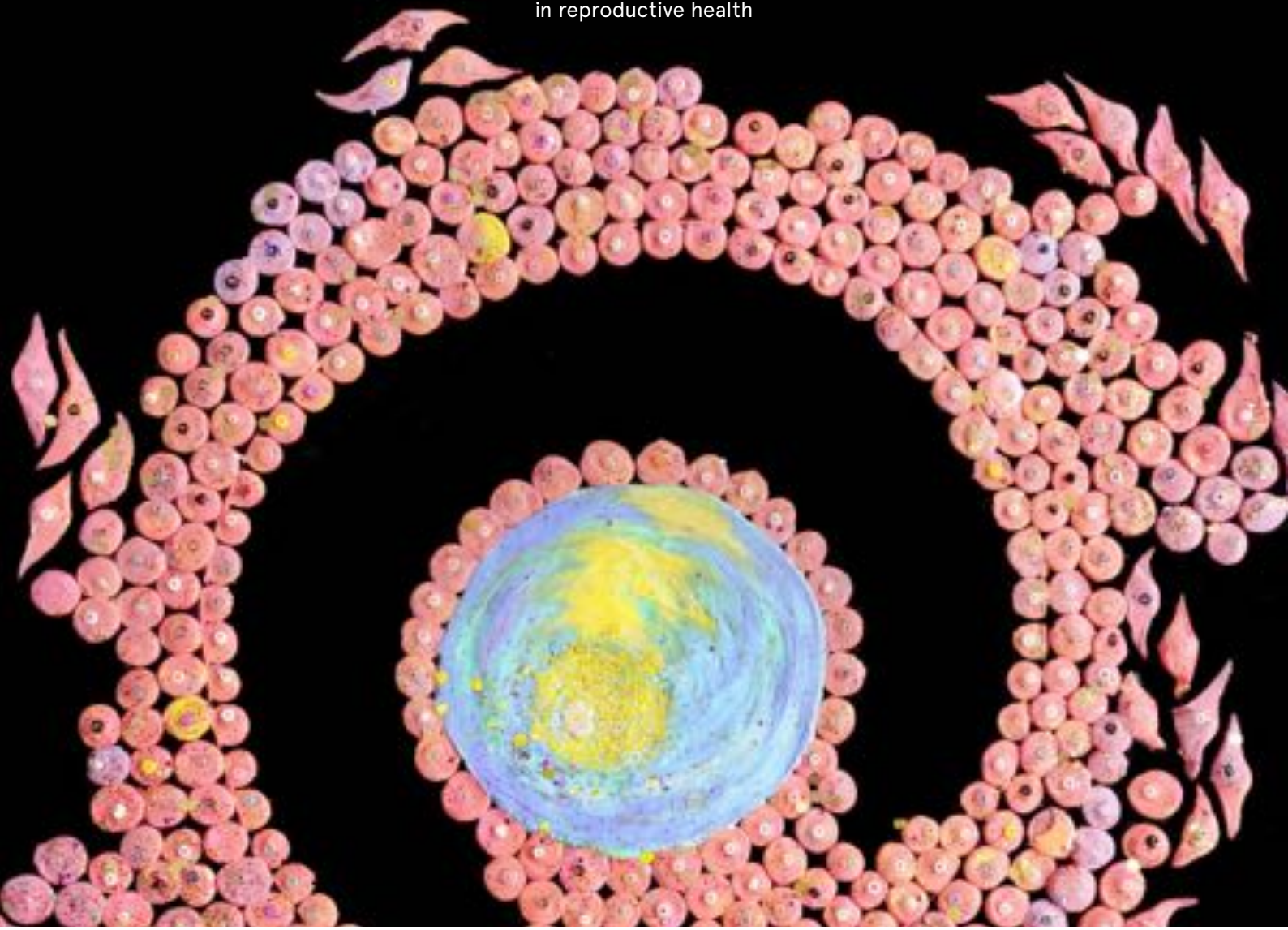
THE REPRODUCTIVE
HEALTH REPORT

Volume 001

December 2022

REPRODUCTIVE BIOLOGY TODAY

Where we are and where we need to go
in reproductive health



The Myth of IVF · The Menopause Conundrum · The Reproductive Longevity Dispatch
The Problem with Academic Publishing · The Unbearable Lightness of Data

AthenaDAO

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Reproductive Health Report
Volume 1
December 2022

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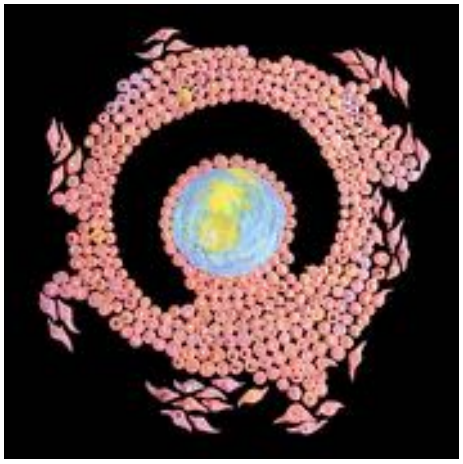

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AthenaDAO

AUTHOR
Laura Minquini

When we were in the process of conceptualizing AthenaDAO — a collective working to fund women's health research — a close female friend asked if there was even a need for such a thing.

This is the norm, not the exception; women have an overestimation of what science and technology have been able to do for our health.

Infertility? We think we have tracking apps for the more straight forward cases or IVF when more complicated.

Menopause? It is considered part of aging — a tale as old as time. In fact, one can't help but wonder how many women at the turn of the century diagnosed with "hysteria" were just experiencing the worst symptoms of aging ovaries.

Even today, we women can only depend on (while not even fully agreeing on) hormone replacement therapy (HRT) to relieve the effects of

hormonal decline, a "natural" phase in female health that creates havoc in our body—aging that feels at odds with being in one's prime.

This is one of the great mysteries — but not the sole mystery — of women's health. Most women are unaware of the inefficient and limited solutions at our disposal.

Women do not realize that the reason they have to rely on social media, Google searches, and whatever information they can find through online communities is because we are not treating women's health and research with the proportional importance that half of the world's population deserves.

Numerous whitepapers and reports have been written about the lack of funding and research in women's health. I highly recommend reading The Global Consortium for Reproductive Longevity's whitepaper "The Unspoken Truth" for the science, and The WHAM Report for the shocking data.

Rather than trying to replicate efforts, we wanted to contribute to the conversation from a different perspective. First, by establishing a baseline of where reproductive aging biology is today with a report on some of the first-ever conferences that happened this year for the field. And to highlight some of the particular problems the field faces when it comes to academic publishing and data collection.

We also wanted to call attention to the scientists, clinicians, and researchers who are worthy of the loyalty and support our culture extends to celebrities. They do not easily have millions at their disposal for funding research, nor do the media care to give them space to share insight into their work. With multiple PhDs and labs at some of the most famous academic institutions in the world, a photo posted on social media is trivial—but that's not to say it's not deserved or shouldn't be offered up.

These are people, who thanks to their passion and commitment to advancing science, are working to answer questions that can lead to better health outcomes for our mothers, sisters, daughters and every woman you care for. You need to know who they are, what they are doing, because everything starts with scientific research.

We have only just scratched the surface, especially as some of the areas of research we are focusing on such as endometriosis and Polycystic Ovary Syndrome (PCOS) were written in the context of other conditions. We hope to continue to have more reports, knowing how many more subjects, areas of science and experts there are to learn about and from.

Join our mission at AthenaDAO to help turn the tide in women's health research.

Laura Minquini

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THE MENOPAUSE CONUNDRUM

by **Leanne Delap**

AN INTERVIEW WITH DR. JENNIFER GARRISON

What if menopause were canceled?

Dr. Jennifer Garrison, a scientist in the field of reproductive longevity, says that interviewers often ask her this question. It sounds sensational, but detracts from the real message she is trying to broadcast: women's health, and in particular women's reproductive health, has been ignored by science and medicine for too long. She wants to know why ovaries age faster than the rest of a woman's body and is excited about the health improvements the answer to that question could bring for women of all ages. It could also, she says, teach us about the mysteries of aging, and the secrets to healthy longevity.

AUTHOR
Leanne Delap

INTERVIEW
Dr. Jennifer Garrison

ILLUSTRATION
Si Maclennan

"My goal is to have this be top of mind for every single person on the planet," says Dr. Garrison, who is co-founder and director of the Global Consortium for Reproductive Longevity & Equality and an assistant professor at the Buck Institute for Research on Aging near San Francisco. "We are talking about half of the population: if we can understand why ovaries age prematurely, I think we can shed light on all aspects of aging." This, she explains, would have profound economic impacts, "because of the health risks of menopause, the cost of medical care, and the loss of productivity that happens for many women at perimenopause."

Perimenopause symptoms can have a dramatic impact on a woman's ability to function, she says. At the Buck Institute, Dr. Garrison runs a research lab where: "We are trying to understand how a breakdown in homeostatic circuits in the brain drive systemic aging." A chemist and neuroscientist by training, she explains the large picture by how she looks at the small picture. "I've always been fascinated by neuropeptides, and how the brain uses these bioactive peptides as a mode of communication." She likens the system to the brain's Wi-Fi.

"I think about every piece of reproductive function as being controlled by the brain." Fertility and healthy aging "depend on neuronal pathways that both instruct and listen to feedback from reproductive tissues through a complex orchestra of hormonal signaling." Understanding how that conversation changes with age, she says, could also give insights into fertility and reproductive health in young women.

She wants to make it clear that the goal is to provide women the opportunity to choose if and when they have biological children, and to maintain their health into old age. This mission however, can be mischaracterized with headlines about canceling menopause. People often react, she says, by saying "I don't want to have periods until I'm 70! I don't want to have a baby at 60!" The key point to understand is that having a baby requires far more than functioning ovaries.

It all comes down to being honest about a reality women have to contend with: "When ovaries stop producing hormones, that increases health risks, cognitive decline, dementia, metabolic changes, depression and osteoporosis." Menopause, she adds, quadruples your risk of cardiac events. "It makes a woman's body age faster than men," because of this, she says, "women spend a significantly longer portion of their lives in poor health."

Understanding what factors cause menopause, and the related health outcomes that come with it, is a way into the future still. "In the short term, we need to redefine the diagnostics we have, rethink the field and change the narrative in terms of biomarkers." We also need to define a more comprehensive view of reproductive health span.

Ovarian aging is affected by a lot of factors, including genetics, BMI, environmental factors, therapies and health conditions. Progress, she says, lies in doing research to get at the underlying causes of reproductive decline in women. To tackle this issue, the GCRLE is providing much needed research funding to scientists all over the world, and building the ecosystem around female reproductive longevity. Meanwhile, Dr. Garrison says advocacy is key: "We need to galvanize and empower an army to help us direct funding and attention to this critical issue."

Speaking about the future, and the possibilities the research could lead to, gets Dr. Garrison excited. As a scientist she is very careful with her words. But when she answers a question about how women can help make this vision come true, she proposes an army.

THE REPRODUCTIVE LONGEVITY DISPATCH

A DEEP DIVE INTO CURRENT RESEARCH TRENDS IN REPRODUCTIVE AGING AND LONGEVITY

by **Dr. Maria Marinova, Nidhi Parekh, Laura Minquini, Dr. Jordan Baechle, Victoria Dmitruczyk and Ariella Coler-Reilly**

It happened June 2022, in Palm Springs, California; the first-ever scientific conference focusing on reproductive aging and longevity saw researchers from around the globe meet at the FASEB Reproductive Aging Conference. Co-organized by Dr. Jennifer Garrison, founder of the Global Consortium for Reproductive Longevity & Equality), the meeting of minds marked an increasing number of similar conferences, preceded by events including the Asia Centre for Reproductive Longevity and Equality (ACRLE) in Singapore, as well as the Aging Research and Drug Discovery (ARDD) held in Copenhagen earlier this year.

Our Health and Our Aging Ovaries: A Labyrinth

Age: 35.

That is young.

But, for women with ovaries, 35 is *actually* the start of *getting old*. So no, age — 35 — is not just a number.

At age 35, the ovaries — home to all of our eggs — begin to age at a faster rate than the rest of our body. As the ovaries age, our eggs also decrease in quantity and quality, severely affecting fertility. The field of reproductive aging focuses on this problem: understanding this aging process to improve fertility and menopause-related health risks.

While eggs are the ovary's most precious resource, the ovary also has another vital function: estrogen production. A lynchpin in every female's body, estrogen is needed for the healthy functioning of multiple organ systems in our body, which all suffer greatly when menopause hits. Menopause affects neuronal, cardiovascular and musculoskeletal systems, among many others. The aim of reproductive longevity is to target the underlying processes of reproductive aging, either by slowing down aging or reversing it. From research in this area comes positive impacts affecting the management and treatment of women's health conditions, including the field of reproductive aging and fertility.

Reproductive Longevity: Where Are We Today?

Despite the effect of ovarian aging on fertility and other health-related conditions, in *all* people with ovaries, little is understood about the aging ovaries. Meaning, to this day, we have limited understanding of why ovaries age so quickly, same goes for the processes behind the aging and to top off this stack of unknowns, cellular and molecular mechanisms that lead to aging ovaries and related health problems remain unexplained. Why are we at a standstill? Limited funding is book ended by popular belief that reproductive aging is a "natural progression" of female aging.

With the first ever Reproductive Aging Conference only just debuting this summer in Palms Spring, it's clear the field is still in its infancy. It's also apparent that researchers are in search of each other as a means of seeding awareness in their field. The conference made room for researchers to provide insights to better understand our bodies during this rapid period of decline, speaking of it in terms of it being a molecular switch, possibly an environmental trigger, or perhaps a threshold of damage that is reached? Or is reproductive aging a combination of it all?

Below, we share insights gathered from the conferences on research in the field, direct from the experts.

Is Ovarian Aging Genetic?

A person's individual genetics can provide major clues of ovarian aging and the rate at which age-related decline ensues. In other words, you may have certain genes that put you at risk of early ovarian aging, early menopause, and menopause-related health changes. After all, it's no secret that we all enter menopause at different ages.

Research in animals reveals that the loss of a single gene can cause a 30-40% increase in ovarian reserve (the number of dormant eggs). Dr. Humphrey Hung-Chang Yao, of the National Institute of Health, presented the notion that, like animals, our genes can predict the number of eggs we are born with, which is highly variable in people with ovaries. Moreover, Dr. Karen Schindler, Rutgers University, showed that certain genetic variations in animal models were found to be linked to accelerated egg-quality decline with age.

Dr. Yousin Suh from Columbia

University found that specific gene variants in your DNA involved in senescence (process by which cells decay), DNA repair and metabolism, all of which are aging associated processes, were found to be different in people who are going into menopause earlier or later in life.

You might be thinking at this point that if you drew the short straw (genetically) there is nothing you can do about it. Luckily, that's not necessarily the case. Genes are not to be thought of as a combination of destiny and polygenic risk score (a panel of genetic variants that predict risk for disease), particularly not alone. When alone, genes, are in fact a poor predictor of early menopause. Certain lifestyle factors, like smoking or drinking, must be considered when examining egg quality.

Currently, personal Anti-Mullerian Hormone (AMH) levels can be a useful marker to inform about the ovarian reserve, but a single reading of just one factor is not something you can entirely rely on, and more accessible and robust biomarkers are needed. You can even ask your mother when she entered menopause. It may be a good cost-effective clue for you until such findings are translated to accessible clinical or at-home tests.

How Is Reproductive Longevity Being Researched?

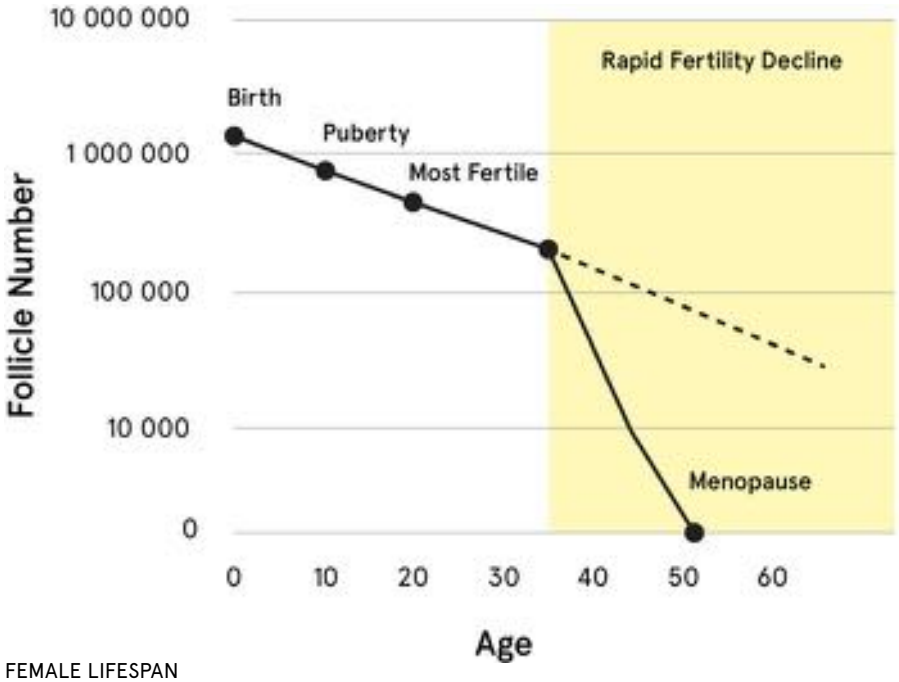
Before reproductive longevity research reaches humans, interventions are tested in mammals and lower life forms like worms, which, surprisingly, have similar fertility-related molecular pathways to humans. Although mice are a great model organism to study fertility issues in people, some research, like menopause, cannot be accurately translated from mice to people. Why? Because mice don't naturally undergo menopause. Research in these animal models help us uncover solutions that may help prevent or slow down ovarian aging and provide advance solutions for use in humans.

To improve our collective understanding of reproductive longevity and ovarian aging, efforts are being made in the field to develop models in which research can be undertaken. Notably Dr. Bérénice Benayoun, from the University of Southern California, is creating age-relevant mice models to enhance the translatability of studies that examine and intervene in reproductive system decline.

New technologies are also being developed to culture the female reproductive organs or tissues ex-vivo (outside the body). Notable studies are being done by Dr. Haiyang Wang of the National University of Singapore, who focuses on developmental competence of mammalian oocytes. These technologies will facilitate science research of female health and can be potentially applied to clinical practices, such as IVF and egg freezing.

The Key to Preventing/ Reversing Ovarian Aging

There is currently a big body of work behind some of the treatments and drugs (discussed below) in the field of aging, which if we're lucky, can be repurposed to promote reproductive longevity and prevent ovarian aging. Please note, these drugs have either been tested within animal models or in clinical trials for age-related diseases



FEMALE LIFESPAN
AND HEALTHSPAN

in humans, and have yet to be tested specifically for reproductive longevity in humans.

1. Senolytics, or molecules that selectively eliminate senescent cells

A few talks and posters at the FASEB Reproductive Aging conference suggest that senescent cells (often called "zombie cells'') contribute to ovarian aging.

Senescent cells are cells that permanently stop dividing and functioning, but don't undergo the natural process of cell death. These cells secrete inflammatory signals that drive chronic inflammation, which is implicated in many chronic age-related conditions. The accumulation of senescent cells has been associated with ovarian aging, in addition to ovarian and uterine fibrosis, preeclampsia, and trisomy 21. The use of senolytics or molecules that selectively eliminate senescent cells, has been discussed as a viable strategy against these problems.

Dr. Amanda Kallen, from Yale University, presented research showing potential of senolytics in female reproductive aging in animal models. Such drugs are currently being tested in clinical trials for other diseases, but the beauty of longevity drugs is that most work across tissues because the molecular networks between them are shared.

2. Collagen-breaking enzymes and anti-fibrotics

Inflammatory signals from senescent cells (and other sources) can lead to an accumulation of collagen deposits which contribute to stiffening and fibrosis of the ovaries. Some research suggests that this could further age the ovaries.

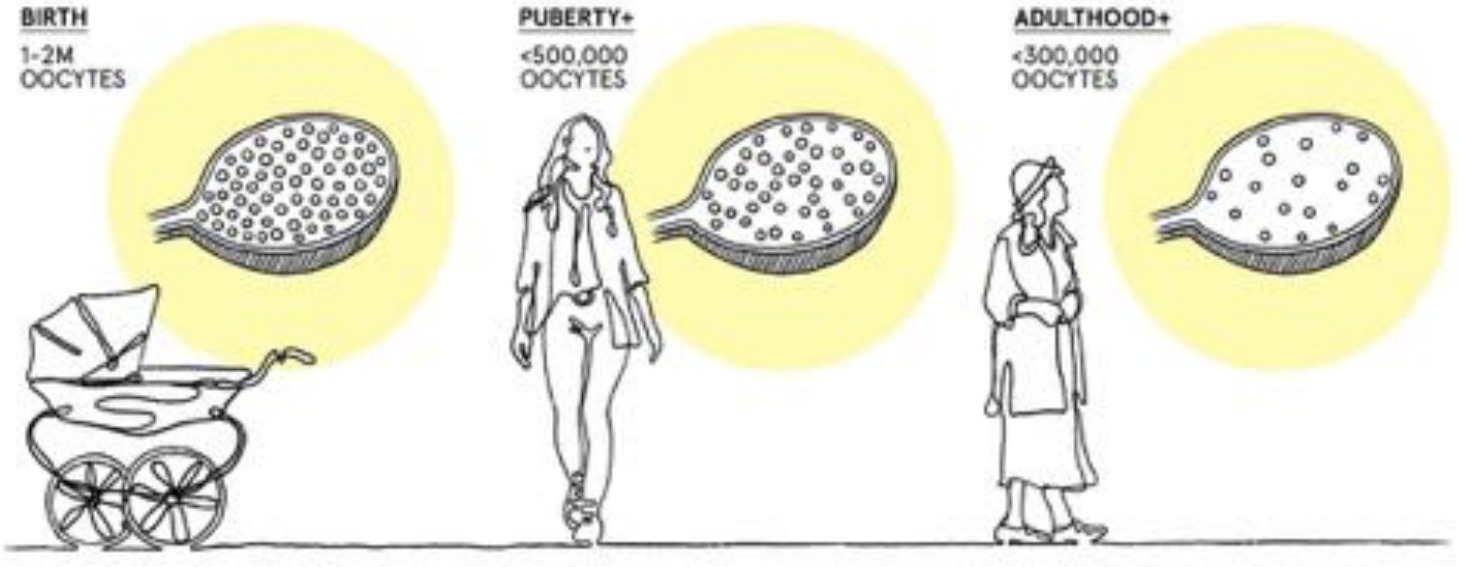
Dr. Francesca Duncan, of Northwestern University, presented experimental treatments where collagen-breaking enzymes and anti-fibrotics, helped alleviate aging indications commonly found in ovarian aging, PCOS (polycystic ovarian syndrome) and after chemo/radiation. Similarly, Dr. Rebecca Robker, from the University of Adelaide used anti-fibrotic drugs, such as pirfenidone, to cause a strong increase in ovulation.

3. Rapamycin

Rapamycin is one of the most popular interventions in aging research. It is an off-patent drug which is already used in medical practice (in high doses) for the prevention of organ rejection in transplantation patients. Rapamycin holds tremendous promise for ovarian aging because there is evidence that it can mitigate age-related damage, but it might also be useful for suppression of oocyte activation (or the transition from a dormant primordial oocyte to a growing/active one) which would protect the egg reserve we are born with. This dual role means rapamycin could work by preserving ovarian reserve, while also delaying aging in the ovarian environment.

Dr. Kara Goldman, of Northwestern University, showed rapamycin protects the fertility of chemotherapy-treated animal models. More specifically, her research suggested that early life 4-week rapamycin treatment in mice doubled their reproductive lifespan.

With this astonishing data Dr. Goldman demonstrated one of the strongest effects to date within the field. Imagine, the existence of a drug—already used in humans for years—re-evaluated as a treatment for other health issues. The potential



OOCYTES VS. AGE

is huge; an ongoing clinical trial for rapamycin treatment in women who have unsuccessfully gone through IVF by Dr. Yousin Suh, from Columbia University, could be further proof of this.

4. NAD supplements

Another increasingly popular longevity molecule, NAD, is also studied by multiple research labs. NAD is ubiquitous throughout the molecular networks of the cell and important for all parts of the body but it is shown to decline with age. Researchers (like Dr. Lindsay Wu, University of New South Wales, Dr. Karen Schindler, Rutgers University, and Lauren Haky, Verdin Lab, Buck Institute for Research on Aging) are modulating NAD metabolism to see if boosting its production (or slowing its destruction) is a potential solution for reproductive aging.

5. Diet and nutrition

Diet and nutrition affects many areas of health, and reproductive longevity is no different. Currently, a few tested dietary modifications are currently being researched in animals. Dr. Carlos Ribeiro from the Champalimaud Foundation found that a lack of certain amino acids (which are the building blocks of proteins) reduces fertility in animals while increasing NaCl (salt) improves it. Increasing breakdown or avoiding Branched-Chain Amino Acid (BCAA) accumulation also shows evidence in extending reproductive lifespan. Similarly, alpha - ketoglutarate improves reproductive health, as shown by Dr. Chen Lesnik from Princeton University.

With all this data, the big question remains: how does it all come together to affect fertility and reproductive health in humans? More science-backed information on optimizing diet for fertility, pregnancy or preserving reproductive longevity is required.

Aging, including reproductive aging, is a complicated phenomena involving many pathways in the body. Currently, no treatments are available to delay or prevent reproductive aging and promote reproductive longevity, but research is ongoing.

Reproductive Health Education

In summing up all three conferences—FASEB Reproductive Aging, ACRLE, and ARDD—there has been significant progress being made in the field of reproductive longevity, even though the field is still in its infancy. Moreover, the above-mentioned conferences did fantastic at bringing researchers from different fields together to discuss common goals, forging a commitment to improve research in the field and enabling conversation on the best practices to facilitate adoption and information flow to patients. As more and more people begin to take note of women's health, so will we foster forward thinking sessions about new frontiers in the field, always bringing the conversation back to you.

While there is room for further progress in the area, there appears to be a strong need to empower people with educational materials relating to ovarian aging and how it relates to fertility decline and an increased risk of other health conditions. It is important we increase public engagement and make sure the coming innovations – to improve fertility for late-life reproduction and prevent/delay health complications relating to aging ovaries (like menopause) are available to everyone. Additionally, we need to incentivize collaboration and dialogue between academic scientists, clinicians and industry/biotech leaders that go beyond current models.

At AthenaDAO, we're doing just that: creating the foundation for social interaction and networking among researchers and patients in this growing field. By empowering the general public to make informed decisions about their health and wellbeing, we are spreading the word—information that will travel on through to media and news outlets who bear the true responsibility in educating people on a central issue affecting every woman's health. The time has arrived, the conversation has started.

Join the conversations at AthenaDAO on Discord.

THE PROBLEM WITH ACADEMIC PUBLISHING

by **Dr. Polina Lishko**

IN WOMEN'S REPRODUCTIVE RESEARCH

AUTHOR
Dr. Polina Lishko

ILLUSTRATION
Si Maclennan

Reproductive biology is growing and slowly gaining popularity as a discipline, but unfortunately not at the pace that would allow this field to come out of the shadows and shed the label of a "specialized discipline." A genuine misnomer, this specialized discipline studies the physiology and pathophysiology of processes, the importance and broad significance of which apply *literally* to every human being on this planet.

And yet the field is much less represented in scientific literature compared to more popular fields such as cancer biology, neuroscience or cell biology. Just a brief PubMed search using the word "infertility" yields ~108,424 scientific peer-reviewed publications in the last 50 years. "Female fertility" search produces even more modest results (only 6,102 publications), while "reproductive physiology" shows a mere 3,360. For comparison, the search for "cancer" returns with more than 4,3 million publications within the same timeframe. "Aging" and "Alzheimer's" boast 585,106 and 206,016 publications, respectively.

What does all this tell us? Popularity of any given scientific field and its representation in academia is congruent with funding and with funding comes renowned scientists coupled with skilled trainees, which together foster growth and prosperity within said field. This calls to mind something known as the "impact factor."

Relied on by leading scientific journals, the impact factor is a metric that calculates how many times a particular scientific paper has been cited by others. If these journals publish a manuscript from a popular discipline, let's say, cancer biology, the manuscript is guaranteed to be cited by many research groups, just because there are multiple research laboratories working in this field. Likewise, these journals will be more reluctant to consider a manuscript from the field of female reproductive physiology since it may decrease their impact factor. Trigger a cursed loop: lack of publications in leading scientific journals leads to the lack of general scientific and public interest, cascading into lack of funding, brain drain and a reluctance among fresh talent to build their career in female reproductive studies. And so, the field shrinks and so worsens the cyclical effects of disinterest.

To break this cycle, intervention at any of the above levels is necessary. Better public awareness and better funding will stimulate scientific interest and fuel research. Cooperation from leading scientific journals, and their editorial boards, could turn the dial forward with calls for special issues dedicated to reproductive biology, a move that goes far to invigorating the field and provide a backdrop for scientific breakthroughs.

The outcome of all of this working together is not just new knowledge (which is, of course, priceless) but better healthcare, dramatic improvement in reproductive health, education, as well as agreement, and unity on many points that currently divide our nation.

When it comes to the abortion debate or contraception accessibility, personal views are nothing if not divisive. For many women, the question of whether they have a right over their own bodies is not even a question, the answer is crystal clear. Yet, many others who do not understand or care to understand anything about female reproductive physiology (and even less about female reproductive pathophysiology), rest on their ignorance as a means of deeming the above question debatable.

Lack of scientific research and knowledge about the female body does nothing to help further women's rights. It is harshly evident there is need for more attention focused on the field of reproductive biology. We are living in a golden age of science, a period when biotechnology, bioengineering, human genome studies and advances in medicine made possible by powerful new tools and interdisciplinary research are leading exploration into new frontiers across biological disciplines. Now is the time for women's reproductive research to come to the forefront. Breakthroughs in this field are possible in the very near future, it is simply a matter of fertilizing this field with adequate attention and effort.

THE UNBEARABLE LIGHTNESS OF DATA

AN INTERVIEW WITH DR. LA FOLLETTE

by **Laura Minquini**

DR. LA FOLLETTE

AUTHOR
Laura Minquini

INTERVIEW
Dr. Lizellen La Follette

ILLUSTRATION
Si Maclennan

Dr. La Follette believes in the potential of running small clinical studies with MDs like herself as one of the ready solutions to closing the gap in women's clinical health data.

Our first attempt to get time with the good doctor was foiled by one of her patients going into labour — fitting given our topic of conversation. Our second try at a chat was successful and produced a collection of learnings we wanted to pass on. As the discussion below demonstrates, Dr. La Follette isn't one to point to a problem and leave it at that. She is coming up with a solution to close the gap.

Laura: Let's start with a bit about you and your practice, what can you tell us?

Dr. La Follette: I have been a private practice OBGYN in the San Francisco Bay Area for 30 years. I see women of all ages and remain deeply committed to helping women and to advance science as it impacts women's lives and health.

L: You must have seen a lot of shifts in your field over the years—science is ever changing.

LF: So much of clinical medicine takes too long to actually move the ball towards better health. There have been so many wrong turns. Just take the incorrect press release of the 2000 WHI that showed estrogen was a risk for breast cancer. Fast-forward 17 years later, the only medicine that decreases breast cancer incidence and mortality is estrogen. So, for those physicians who have been withholding hormones, how have they helped their patients?

L: On that note, how would you say your ideas might help to generate

relevant women's health data with clinical studies in private practice?

LF: We need to use clinical medicine data and find pathways of health... and likely use machine learning to do so.

L: Can you give an example?

LF: Like how to recognize the 10.5% preterm delivery rate in the US before it happens; use what we have, use the PRetRM blood test from Sera Prognostics combined with the Whoop data from the 1200 volunteers who wore Whoop during their pregnancies. The data shows that about 7 weeks before delivery, these volunteers experienced a change in HRV and RHR (heart rate variability and resting heart rate). Can we combine this to help all women not have an early baby?

L: Is this cost-efficient?

LF: Cost efficient? Hmmmm.... great question. Depends on who is funding it.

Clinical medicine is messy and complex just as humans are. We need more people versed in this kind of data analysis to find any conclusions of clinical relevance that can't be decided by a bunch of VCs who want immediate results, but rather a commitment to finish the studies and spend money on the analysis... and time. Using our current system of grant applications from the NIH or the like is not cost efficient either, but at least the NIH won't pull the plug for messy data.

L: Would the sample size be big enough for the data to be relevant?

LF: Any sample size could be big enough, if you start with a pilot and then expand it should look like there is a finding. I have 10,000 patients in my EMR. That's plenty.

L: Makes sense. How can this data be shared?

LF: Data could be shared in a publication, as well as poster or lecture at a relevant symposium on Women's Health.

L: That seems simple enough. The question is then, why is this currently not already done?

LF: A few reasons. Most doctors are not in private practice with this kind of data. You need a spot/doctor/clinic that keeps track of this data, then asks a question and uses this data to see if with machine learning, there is an answer.

L: And there isn't general interest in this?

LF: Most health care systems: Kaiser, Sutter and Foundation models employ doctors who are not interested in clinical research and thus there is no motivation to ask questions. These providers are paid handsomely to see lots of patients and get out after 9-5 or a 12 hour shift. There is no interest in asking clinical questions in that set up.

L: Okay, knowing that, what could we focus on as a low hanging fruit?

LF: Low hanging fruit? A. good non-invasive genetics companies like Luna Genetics trying to get amnio grade genetics from whole trophoblasts, so every woman can be reassured — non-invasively — of the health of their unborn child. B. preterm labor brings a few things we can measure. The PreTRM test from Sera Prognostics combined with the Whoop wearable data, and then use machine learning for a preterm labor signal to act on. C. help companies who are looking at ways to protect women in labor from pelvic floor injuries, like Materna Medical [and their product] Maternal Prep. If used in labor, it can protect the pelvic floor from injury.

And finally, D. use clinical data from Edifice Health to see if there is an aging clock of inflammation that can be influenced. That's a big prospective data set from the Bay Area. The study was closed by VCs as data was messy.

THE MYTH OF IVF

The importance of understanding the real-life limits of technology and biology

AUTHOR
Lu Dong

INTERVIEW
Dr. Zhongwei Huang

ILLUSTRATION
Si Maclennan

Life as a clinician and researcher in Obstetrics and Gynaecology keeps Dr. Zhongwei Huang busy. A well-known specialist based at National University Hospital in Singapore, Dr. Huang also acts as the Deputy Director of the Asia Centre for Reproductive Longevity and Equality (ACRLE), where he performs translational research on fertility and reproductive aging.

As an IVF expert with years of experience, Dr. Huang has a catalog of achievements and challenges gathered over the course of his career. Dr. Huang, who confirms that 65% of the couples he's seeing come to him with fertility issues, shares a general timeline for the IVF procedure, while opening up about life in science and his professional journey into fertility and reproductive aging.

A couple seeking IVF treatment is first assessed based on items such as age, ovarian reserve and semen analysis. If they qualify, they will be counselled to prepare for IVF cycles, discussing financial and psychological matters. In this early stage, some couples are already deemed unsuitable for IVF, often due to advanced age i.e. women who have reached menopause are not suitable for IVF assessment. "I think the most critical factor for IVF that many couples don't know is actually their biological ages", confirms Dr. Huang. " After age 40 onwards, there will be lower chances of delivery and usually by age 45, the chance of pregnancy is very low, hence not ideal for IVF. Even if there are follicles in the ovaries, the quality of oocytes for 40 years and above may be very poor."

"IVF has become more accessible and popular nowadays, but many people still have the misunderstanding that IVF is a silver bullet for all infertility problems."

One IVF cycle starts with ovarian stimulation, which takes about 12-14 days. Daily drug injection and transvaginal scan monitoring occurs at least every few days and can be arduous. According to Dr. Huang, a big challenge in this step is to find the

right dose for each individual woman due to high variability. "We have to take extra caution treating younger women with good ovarian reserve", he says. "There's a higher risk of 3-8% of ovarian hyperstimulation syndrome, OHSS, for this group of women." OHSS is a life-threatening complication causing ovarian fluid leaks to other parts of the body, triggering symptoms including blood clots and difficulty breathing.

Once the follicles reach a target size, the next step is the ovulation trigger, followed by egg retrieval. Egg retrieval is a surgical procedure under sedation where a needle is guided through the vagina to collect the follicles via suction. Dr. Huang notes, "Of course, there will be risks associated with anesthesia and the surgery itself, such as injuries and bleeding in neighbouring tissues."

The follicles collected are then examined by embryologists to determine their maturation and quality. Based on Dr. Huang's experience, usually, 15 mature eggs would be good, but "quality can be another issue." From here, other concerns are considered during the actual fertilization step such as: Can the sperms really fertilize the eggs? Can the fertilized eggs develop into embryos? "These are the things that we have little control over and sadly the attrition rate can go even higher at this step."

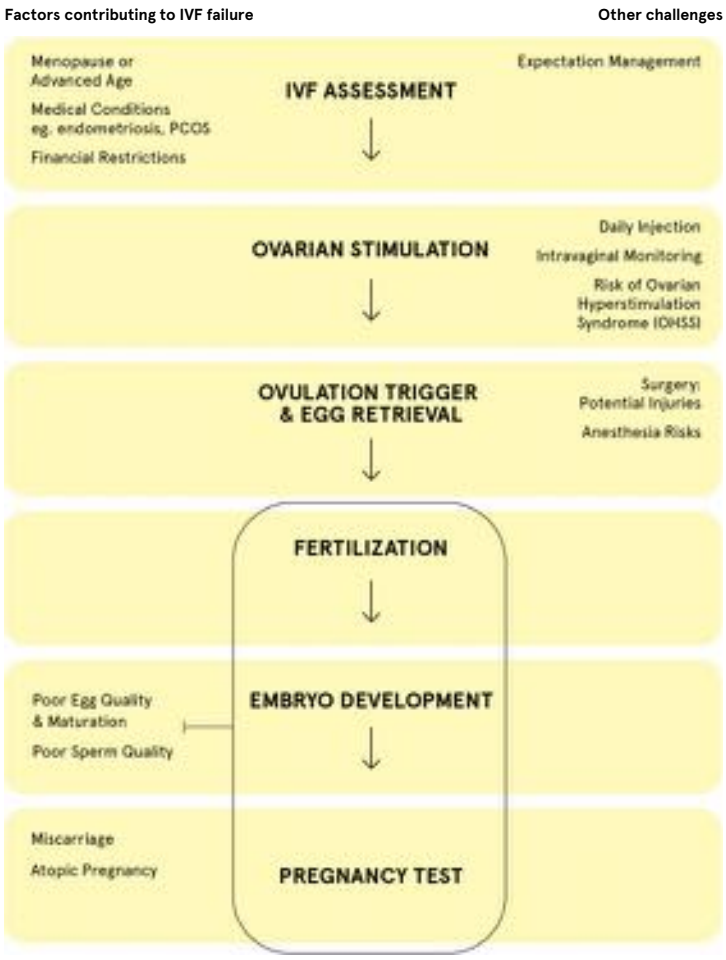
If the eggs are fertilized and develop into blastocysts successfully after about 5 days, the embryo(s) is/are transferred into the woman's uterus. "The IVF success rate is usually determined by a pregnancy test after two weeks, not more than 35%", Dr. Huang says. "Things such as miscarriage and atopic pregnancy can still happen after that, even bringing the chance of healthy births down."

In total, one cycle takes up to 6 weeks and the number of cycles needed is very couple-specific, according to Dr. Huang. The cumulative success rate increases after 3-6 IVF cycles and is dependent on the good quality of both eggs and sperm. Dr. Huang digresses, "There are just so many points with attrition rates that we can't really control much and couples can feel very disappointed. Sometimes we have to go back right from the beginning and notably, the couple's ages increase with each cycle."

As Dr. Huang shares, couples often arrive in his office with an incorrect expectation of IVF outcomes, sometimes hinged to a misunderstanding of reproductive biology. "Many couples think that they will just undergo one cycle and miraculously get pregnant," he says. "Some even still think so after they are informed of their low sperm or follicle counts." As Dr. Huang sees it, the mistake in knowledge may be rooted in popular culture. "Perhaps the media has hyped it up."

As for how Dr. Huang handles such a situation, he seeks to educate. "Manage their expectation by informing them of the attrition rate at each step", is Dr. Huang's recommendation, adding notes on how his team "educate [couples] on

DR. ZHONGWEI HUANG



FACTORS AND RISKS TO IVF

IVF FACTOID

Nurse and embryologist, Jean Mary Purdy, was part of the trio that developed in vitro fertilization, but her role was ignored for 30 years.

lifestyle management, optimizing their physical conditions." Then there's talk of building a support system, a critical component of the process. "We counsel them psychologically. They really need mental support from families, especially the partner."

Dr. Huang also shared with us his experiences with women experiencing reproductive medical conditions. According to him, while women with PCOS usually have many follicles left, his concern is the quality. In addition, these patients are at higher risk of OHSS and the dosing and procedures have to be individualized for these women.

In fact, PCOS is one of the leading causes of infertility primarily due to anovulation and also increased metabolic risks, such as diabetes, which can affect the pregnancy and health of the fetus. With regard to endometriosis, a condition resulting in scarring of the pelvis and which affects the fallopian tubes, Dr. Huang proceeds with care knowing "endometriosis can be a major cause for infertility and oocyte quality drop." As he indicates, for those with large endometriotic cysts, "ovarian reserve is further reduced as cysts may have to be removed at the expense of removing healthy ovarian tissues." This in turn, may inspire the doctor to "hesitate to even start the cycle." Given his experiences, Dr. Huang calls for more quality research on understanding the biology and pathophysiology of PCOS and endometriosis to help women living with these conditions.

After 44 years since the popularization of IVF, there remains many challenges with this procedure. In Dr. Huang's perspective, this is owing to the lack of understanding, research and funding in reproductive biology. "There remain too many unknowns with strict legislations limiting the use of discarded gametes and embryos for research."

All this could change with more research and resources in the field and lead to breakthroughs that could address the everyday problems affecting IVF. "Cryo-preservation of eggs still needs to be improved, as now not all eggs are viable after thawing", shares Dr Huang. "We need to find quality markers for eggs that better predict the outcome."

The transfer of knowledge is one step forward the doctor hopes he will see in the near future with greater public awareness around reproductive health and IVF. Education is too often, in Dr. Huang's experience, the missing component. "It's a draining process and we hope the couples could come in earlier or they know themselves better, and then we could do something earlier."

For Dr. Huang, continued research and public education brings him closer to his vision of IVF in a world where the procedure "resolves what intrauterine insemination and other assisted reproduction techniques cannot do for couples and ensures that once embryos are formed, they are able to achieve a healthy pregnancy and live birth."

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