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Treating "ovarian aging" has two opposite but equally exciting goals.

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Josh Johnson, Ph.D.

University of Colorado School of Medicine, Department of Obstetrics and Gynecology

Interventions to treat ovarian aging are on the horizon

A recent conference this spring (1) featured research presentations and some lively discussion about how different scientists are approaching female reproductive aging. Intervention strategies are in development that will impact ovarian aging in ways that would have sounded impossible just a few years ago. These strategies are exciting and represent enormous technical achievement(s). We can say that these interventions have the goal of improving ovarian "performance," but a closer look reveals two separate, or at least "separable" goals.

Important measures of health like heart function, bone and muscle strength, and cognitive function can be compromised when ovaries stop working at the time of menopause (2). The first type of intervention will keep ovaries functioning longer, and delay those consequences of menopause. That will help individuals stay healthier longer. *Here, slowing ovarian aging means, literally, delaying the time that ovaries will stop working.*

The second type of intervention promises to help those interested in having (genetic) children reach that goal. In this second case, egg "quality"(3) and/or access to more eggs inside the ovary (4) needs to be improved. *Calling this second strategy "slowing ovarian aging" refers to making sure that eggs are "good" longer...here we are trying to slow down how quickly eggs "go bad." We can also try to gain access to remaining eggs inside the ovary that tend not to grow on their own.* There may be those for whom extending the duration of ovarian function **and also** improving their chances of conceiving a child overlap, but as will be seen, it is useful to consider these goals separately.

Treatment of ovarian aging by improving ovarian "performance" I: slowing things down

First, consider the desired interventions that will "slow down" ovarian aging. This work will be done at the level of the number of remaining ovarian follicles. It is the overall pattern of follicle loss that's being targeted, and we describe that pattern in some detail in a previous blog post (5), and a few publications (6-8). Briefly here, it is the number of remaining follicles in the ovary and how quickly they are being depleted that control how much longer a woman's ovaries will function.

If we imagine a woman's ovarian reserve of primordial follicles as the water level in a bucket, both the starting water level, and, how quickly drips are leaving the bucket control how much longer water remains. Here, having some water left means that her ovaries are still functioning!

The "slow down" strategy means that either a) the loss of primordial follicles from the reserve needs to be slowed (slower "drips"), or, b) additional primordial follicles need to be added to the reserve...and any new follicles that are added have to behave normally! It's easy to understand the impact of slowing the drip rate, and this is being attempted using pharmaceutical or even natural compounds that slow down follicle loss. Adding **more** water to the bucket (more primordial follicles to the ovaries) is worth exploring a little more.

So, scientists are now sharing impressive examples of producing new follicles *from a person's own cells* by engineering stem cells. Modifying and treating those stem cells to develop into egg cells and other cells of ovarian follicles can now be done reproducibly, and new follicles can be "loaded" into tissue like the normal ovarian tissue they would normally be found within. Engineered tissue containing brand-new follicles is then attached surgically to the ovary, and their growth and survival is being monitored. All that should be left is being able to produce enough follicles to "raise the water level in the bucket" so that the ovary functions longer and supports health longer. That is, *if* those new follicles function normally. If we add new follicles and they're lost faster than normal follicles, the ovary might not function for a longer time after all. The groups attacking the problem in this way are up to this challenge, and it shouldn't take too long to work out how the new follicles perform in terms of how long they stick around.

Note that nothing we've covered so far has anything at all to do with how good the eggs in the follicles are, or whether the new follicles contain eggs that are good enough to produce a healthy baby. This brings us to the second strategy to "slow ovarian aging".

Treatment of ovarian aging by improving ovarian "performance" II: increasing egg quality

Improving the eggs that you've got

Keeping ovaries working longer as discussed above may be much less important to some people than having a baby. Increasing the number of eggs available for attempts at conceiving a baby could be their top priority. By this, I mean that eggs inside the ovary could be improved so that the chances of conceiving "at home" are better, or, people could be treated so that eggs in the ovary are improved, and larger numbers of good eggs could be retrieved in the clinic for *in vitro* fertilization.

I suppose here that it is useful to note that in our "bucket of water" analogy, there are some drops of water leaving the bucket that are good, and others that are not good. The drops will leave the bucket just the same, but we need to think about how to increase the number of drops that represent eggs that are good enough to give rise to a healthy baby. In this case, we are neither adding more water to the bucket, nor slowing down the rate of drops lost over time.

So it is currently common for clinics to make suggestions about how one can improve their chances of conceiving if lifestyle etc. (9) Many of these suggestions are backed up by very solid clinical and experimental evidence. For example, it is quite well-understood how chemicals in cigarette smoke can directly and indirectly damage eggs. Further, it is well-established that the numbers of eggs produced during IVF cycles is lower, and smoking corresponds to greater numbers of cancelled IVF cycles(10).

New medical interventions are improving IVF success at the level of improved egg quality. CoQ10 (11), NMN (12). Early days.

More eggs to choose from

When ovaries get close to running out of eggs (stated another way, when the ovarian reserve declines past a threshold) and only a few thousand primordial follicles remain, the number of growing follicles also declines. This means that fewer and fewer follicles are present that might survive and grow large enough to produce a mature egg. This can happen to people that are quite young, and the problem is that there aren't a lot of eggs available. If conception isn't happening at home, and IVF is to be attempted, even hormonal stimulation leads to very few eggs to choose from. How could we "slow down ovarian aging" and increase the numbers of good eggs?

Even later, numbers of primordial follicles can be present in the ovary that aren't growing. This might be up to 1000 non-growing follicles that are present, but not "accessible." Stimulating those last remaining follicles to grow is a way to increase the number of eggs that could be used for

conception, too. So the separate goal here is to increase the chances of producing a good egg or eggs, giving that person a chance at conceiving a healthy baby.

Similar-sounding goals with opposite outcomes (for now)

Having expanded on each of the two types of intervention above, we can now address the point that they will actually result in exactly opposite outcomes! Ready?

Each of our intervention strategies will "treat" ovarian aging. In the first case, the goal is helping ovaries function longer by keeping numbers of primordial follicles high. In the second case, however, the goal of accessing more follicles so that they grow and stay alive can lead to more good mature eggs for patients! Accessing more primordial follicles means they will be removed from the ovarian reserve, though, and the impact of getting more eggs will be having fewer primordial follicles left. The overall impact then, will be that ovaries will run out of follicles at least slightly sooner. The trade-off of increasing the number of eggs available to use for conception may be highly desirable even though menopause is will arrive somewhat earlier can be considered on a case-by-case basis.

Final thoughts

The reason for this post is that when we discuss treating "ovarian aging" it is very important to think precisely about the goal in mind. If the goal is to support health by keeping ovaries functioning longer, slowing the rate of follicle loss, or, adding new follicles are the ways to go. If the goal is to increase the chances of conceiving a child by improving egg quality, it may be necessary to access and use some number of the remaining follicles...unless a combined approach is used.

There may be future "combined approach" treatments that both slow follicle loss *and* improve egg quality, or that can favor one process and can be "switched" to favor the other when needed. After all, the ultimate goal is keeping people healthy while also supporting the target of their giving birth to their own healthy genetic children if desired. At least to me, it's worth taking a moment to consider what we mean by "slowing ovarian aging" so that we can think clearly about these goals.

LINKS AND REFERENCES

1. 2023 Reproductive Aging Conference, Chicago, April 30-May 3, 2023
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3. egg quality

4. access to more eggs Akt/Pten Hsueh, Liu
5. Johnson and Lawley, Blog Post 25, "How random is ovarian aging?"
6. PeerJ
7. BOR
8. JMB
9. Lifestyle modification to improve egg quality
10. Smoking and eggs retrieved
11. Juriscova CoQ10
12. Wu NMN