Rethinking the reproductive clock: Can NAD+ preserve fertility?

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Recent research indicates that the compound NAD+ offers a promising solution to support fertility and reproductive longevity

With many women choosing to start families later in life, the need for strategies to maintain ovarian health has grown. In this article, Dr. Rebecca Crews from Renue By Science, LLC, rethinks the reproductive clock by asking if NAD+ can help preserve fertility.

Oocyte quantity and quality declines with age

Having children after the age of 30 has become increasingly common. In the U.S., 18% of all births in 2018 were to women aged 35 and older, compared to 15% in 2013, 11% in 2002, and 8% in 1990. (1) This trend reflects improvements in quality of life, including greater educational and career opportunities that offer women increased autonomy and flexibility in family planning. However, despite these advancements, women still face a limited reproductive window and declining fertility.

Peak fertility occurs around age 25, begins to decline after 30, and accelerates after 35. Women are born with a fixed number of oocytes, which form the primordial follicle pool, known as the ovarian reserve. Over time, both the number and quality of these oocytes decline, significantly impacting fertility.

Many factors contribute to ovarian reserve decline, with age-related changes as a primary driver. Notably, the hallmarks of aging are evident in the ovary even before the decline in ovarian reserve, suggesting they could be valuable targets for strategies aimed at preserving ovarian health. (2)

The primary challenge in age-related fertility decline is the quantity and quality of oocytes. While assisted reproductive technologies (ART) can help address age-related fertility issues, their success still heavily depends on the availability of high-quality oocytes.

Therefore, strategies aimed at maintaining ovarian reserve health are needed to improve fertility outcomes in older women.

Targeting NAD+ is a promising strategy for ovarian health

Nicotinamide adenine dinucleotide (NAD+) levels are known to decline with age in various tissues in both animals and humans. In mice, ovarian NAD+ levels are reduced and associated with reproductive aging. NAD+ is an essential molecule and is required in over

500 reactions in the body. NAD+ is required for energy production, participating in metabolic pathways such as glycolysis and oxidative phosphorylation, as well as in pathways related to longevity and cellular stress response.

NAD+ is important for DNA repair, mitochondrial function, cell proliferation, lipid and glucose homeostasis, and immune cell function. Several NAD+-dependent enzymes, including sirtuins, CD38, and poly (ADP-ribose) polymerases (PARPs), require NAD+ to carry out important functions that maintain cellular integrity and longevity. These enzymes have a significant role in ovarian aging and are also being investigated as therapeutic targets. (3)

NAD+ precursors improve ovarian reserve in aged mice

Supplementation with NAD+ precursors, such as nicotinamide mononucleotide (NMN) and nicotinamide riboside (NR), has been shown to increase NAD+ levels and improve ovarian aging in numerous animal studies. In aged mice, NMN enhanced oocyte quality by elevating SIRT2 levels, which play a crucial role in preventing spindle and chromosome defects – a major cause of pregnancy loss.

Additionally, NMN improved mitochondrial function and energy production while reducing inflammation in oocytes. It also prevented ovarian atrophy and maintained hormone secretion (E2, AMH, and FSH) in aged mice.

NAD+ precursors have demonstrated promising benefits for ART outcomes. NMN supplementation improved fertility in aged mice by increasing the number of healthy embryos and the success of fertilization. It also helped mice with mitochondrial DNA mutations to conceive. NR improved the quality of mature eggs and early embryos by reducing oxidative stress, improving mitochondrial function, and maintaining normal chromosome structure. (3)

Clinical trials are needed to move forward

Numerous human studies suggest that NAD+ precursors can help counteract age-related physiological decline, enhancing physical function and metabolic health by supporting cellular health and repair processes. However, the specific impact of NAD+ on ovarian aging remains unexplored in human clinical trials. While ovarian aging shares several mechanisms with other age- related conditions that have been studied, targeted research is necessary. Specifically, research is needed to evaluate NAD+’s impact on ovarian reserve quality, reproductive outcomes, hormone levels, and response to assisted reproductive technologies (ART).

Perspectives for future research

The traditional “fertility cliff” at age 35 no longer reflects modern reproductive realities. As more women delay childbearing, the need for personalized strategies to understand and maintain ovarian health grows. Research emphasizes the role of NAD+ in preserving

oocyte quality and mitochondrial function, offering a promising avenue for supporting reproductive longevity. Tailored interventions targeting NAD+ could redefine fertility care by addressing age-related ovarian decline.

Innovative diagnostics are essential for assessing ovarian aging and guiding rejuvenation strategies. Biomarkers tied to NAD+ metabolism, mitochondrial health, and oxidative stress offer insights into fertility potential. Incorporating these tools into diagnostic frameworks allows for better monitoring of interventions like NAD+ supplementation and personalized guidance to preserve ovarian function. Identifying biomarkers specific to NAD+ activity could enhance the predictive power of fertility evaluations.

Understanding NAD+ dynamics within ovarian cells is a critical step toward improving fertility. NAD+ is a central player in energy production, DNA repair, and stress responses – all essential for oocyte quality. Research into its activity across the ovarian cycle and in different cell types, such as granulosa and theca cells, could clarify its role in maintaining ovarian health. This knowledge would refine strategies targeting oxidative stress and mitochondrial function to sustain fertility.

Preclinical studies show that NAD+ precursors like NMN and NR improve ovarian function, but human trials are needed to establish optimal dosing. Tailored supplementation protocols, accounting for factors like age and hormonal status, are key to maximizing benefits and enhancing fertility outcomes. [4]

By prioritizing personalized fertility strategies, improved diagnostics, and targeted NAD+ research, we can empower women with proactive tools to preserve reproductive health and plan for the future.

References

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