Oral metabolic supplementation can reverse the reproductive clock in mice: A potential remedy to restore reproductive aging?

Introduction

It is popularly said that 'change is the only constant' and rightly so because it is the only means of survival and progress for any living species on earth. Homo sapiens are significantly unique because despite being a single species they have evolved into an indefinite number of communities, tribes, societies and nations with even more diverse religious, social and cultural practices. Depending upon the different beliefs and social mindset several topics were kept hush-hush and were seldom discussed publicly. One such crucial topic was that of the reproductive health in women, which is pivotal for the existence and survival of the entire human race but was still rarely spoken about or discussed. However, we are gradually heading towards an era of societal and mental evolution where orthodox mindsets are being challenged and age old norms are being broken to bring about healthy reforms in the society. Science has played the most important role in this because it is universal, univocal and unbiased. Women reproductive health has not only become a crucial health debate but also the focus of extensive scientific and medical research.

Changing lifestyles, stressful careers, struggle for financial stability and personal choices are often responsible for couples delaying child birth. It is perfectly acceptable for couples to choose the right stage for starting a family but the fact that several factors can negatively impact fertility is causing alarm. Diet, unhealthy lifestyles, smoking, alcohol addictions, hormonal changes, genetic and medical conditions are the important factors that can affect fertility in women. Further age is one of the most crucial factors that can negatively impact the fertility in women. The reproductive system ages faster than one realizes. A woman is born with her entire supply of eggs but as aging progresses the eggs become less viable and their quality deteriorates. There are several causes for female infertility such as ovulation problems, polycystic ovary syndrome, endometriosis, problems with the fallopian
tubes, problems with the uterus etc. Aging is a natural gradual process but its effects start manifesting earlier under conditions of stress, unhealthy diets, hormonal irregularities and disturbed lifestyles. The reproductive potential of a woman begins to decline after the age of 35-40 years and gradually diminishes up till menopause. Other difficulties for the older woman include increased risk of miscarriage and genetic abnormalities in the unborn baby.

In our previous article “Have humans finally discovered path to reverse aging: Synergistic interaction between cellular pathways is the new hope in combating old age” we had highlighted the significance of aging and elaborated the research attempts made to

Figure1: Graphical summary of the study published. The oral administration of NMN restores reproductive aging in oocytes. Source: Cell Reports 2020 (1).
unravel the molecular cascades. In the current article we shall cite and discuss the latest research endeavor made to improve the fertility rates in female mice and reverse the aging process in the eggs. This study was carried out by a team of researchers at the University of Queensland and the promising results hold relevance for human beings which have made it feature as popular news (1).

The facts and relevance of the study
Reproductive aging in mammalian females is a gradual and an irreversible process which is associated with declining oocyte (egg) quality. The quality and viability of oocytes is the rate-limiting factor to fertility. The oocytes in the ovary of humans are laid down during in utero development, where they form a finite pool that does not undergo self-renewal. Therefore, oocytes are highly prone to age-related dysfunction. The molecular basis for the age related decline in oocyte quality is attributed to increased reactive oxygen species (ROS), reduced mitochondrial bioenergetics, genome instability and disturbances during meiotic chromosome segregation(2, 3). The molecular basis of this age related chromosome mis-segregation in oocytes is still unknown and thus this area remains beyond therapeutic correction. The metabolite nicotinamide adenine dinucleotide (NAD+/NADH) is a prominent enzyme substrate and redox cofactor that is necessary for energy metabolism, epigenetic homeostasis and DNA repair. As age progresses levels of this essential cofactor decline in somatic tissues and reversing this decline through treatment with metabolic precursors for NAD+ has gained interest as a treatment for improving health in aged individuals. The current study demonstrates that deteriorating oocyte quality is also associated with declining levels of nicotinamide adenine dinucleotide (NAD+) (4). Figure 1 summarizes the crux of the study via a graphical abstract.

Mouse was chosen as the experimental model organism because it shows similar reproductive aging that occurs in humans. In mice the fertility starts to decline around 8 months of age due to oocyte defects. Hyperspectral microscopy imaging techniques that exploit the autofluorescence of NADH and NADPH were used to detect and measure the levels of the metabolic cofactor. Twelve-month-old females were treated with NMN in drinking water (2 g/L) for 4 weeks, following which mature metaphase-II (MII) oocytes were recovered and subjected to multispectral microscopy imaging of autofluorescence to determine the relative abundances of native fluorophores. It was clearly observed that NAD(P)H levels declined in oocytes from aged animals as compared to young (4- to 5-week-old) animals. Further NMN treatment increased and replenished NAD(P)H levels in oocytes from aged animals (1). The experiments were extended to ovarian tissues to determine whether this trend occurred across the entire ovary or was it confined to oocytes alone. Mass spectrometry results showed that there was no decline in whole ovary NAD(H) levels with age, further confirming that it the oocytes which are specially subject to an age-related decline in NAD+. Experiments further confirmed that the quality of oocytes could be improved by
treatment with the NAD+ metabolic precursor nicotinamide mononucleotide (NMN). Mice were fed with low doses of NMN in their drinking water over four weeks which rejuvenated the oocyte quality in aged animals, leading to restoration in fertility and significant increase in live births during a breeding trial. This effect was recapitulated by transgenic over expression of the NAD+-dependent deacetylase SIRT2, though deletion of this enzyme does not impair oocyte quality (1). NMN supplementation can reverse the adverse effect of maternal age on developing embryos representing an opportunity to rescue female reproductive function in mammals. Figure 2 shows the imaging data depicting the NMN content in oocytes of mice.

Figure 2: Multispectral imaging data showing NAD(P)H content in oocytes from young (4- to 5-week-old) and aged (12-month-old) mice treated with low doses of NMN in drinking water for 4 weeks. Source: Cell Reports 2020 (1).

Current and future prospects

Increasing maternal age is the biggest barrier in family planning and reproductive aging in
oocytes is a major hurdle to pregnancy for older women. Despite the enormous demand, there are yet no clinically viable strategies to either preserve or rejuvenate oocyte quality during aging. The oocyte quality is defined by the capacity of the oocyte to support meiotic maturation, fertilization, and subsequent embryonic development. Poor egg quality has become the single biggest challenge facing human fertility in developed countries. As more women are embarking on pregnancy later in life there is an increasing demand for assisted reproduction technologies (ARTs) such as in vitro fertilization (IVF), which is invasive, is expensive, carries health risks and has a limited success rate. Further IVF cannot improve egg quality, so the only alternative for older women at present is to use eggs donated by younger women. The results of the present study report a novel non-invasive treatment using oral administration of NAD+ boosting agents which could maintain or restore the quality and number of eggs and restore reproductive function. This novel approach would be far less invasive than IVF and alleviate the biggest barrier to pregnancy for older women. The study shows promising potential and its credibility shall be further validated once the clinical trial testing is accomplished in humans. Till then we believe and hope that ‘age will continue to remain just a number’ and in times to come women will have better reproductive health and the right to choose motherhood even later in life. On that note we sign off by saying that maternal age and reproductive health in women are no longer hushed topics instead proving to become focal points of biological research, open discussions and medical interventions.

References


