State of the Science: Preclinical & Clinical NR Research (Reproductive Health)

QUOTE ON DESIGNED COVER: *"NAD deficiency is one of the many known causes of adverse pregnancy outcomes, but its prevalence in the human population and among pregnant women is unknown." (Dunwoodie et al., 2023)* [1]

Executive Summary

Nicotinamide adenine dinucleotide (NAD+) is an essential molecule found in every cell, playing a central role in numerous cellular processes, including energy production, DNA repair, and mitochondrial function. Extensive research underscores the importance of NAD+ in cellular health, with emerging evidence highlighting its role in supporting reproductive health, particularly in counteracting age-related declines. Naturally, NAD+ levels decline with age, which can impact the health and function of reproductive cells and tissue, and potentially pregnancy outcomes.

Reproductive health and fertility are fundamental for conceiving and maintaining a healthy pregnancy. They encompass factors like hormonal balance, egg and sperm quality, and overall reproductive function. As individuals age, particularly women, both fertility and reproductive health naturally decline. Women can experience a decrease in egg number and quality, while men can see a gradual reduction in sperm quality, including lower motility and count. The loss of NAD+ with age is believed to contribute to the degeneration of reproductive cells, such as oocytes (eggs) and sperm, both of which heavily rely on mitochondrial health and energy production. Given that NAD+ is involved in cellular energy production throughout the body, it is uniquely positioned to support the metabolic demands required for reproduction, fertility, and pregnancy.

The therapeutic potential of NAD+ in reproductive health continues to unfold, with promising preclinical research suggesting that maintaining healthy NAD+ levels could be a novel approach to supporting reproductive cells and fertility. Ensuring adequate NAD+ levels may help address common challenges during reproductive stages, support fetal development, and promote healthier pregnancy outcomes.

For instance, in conditions like polycystic ovary syndrome (PCOS), which is characterized by inflammation and mitochondrial dysfunction, restoring NAD+ levels has been linked to reduced oxidative stress and improved cellular health in ovarian cells [2]. Similarly, research in animal models has shown that increasing NAD+ levels—particularly through supplementation with **nicotinamide riboside (NR),** an NAD+ precursor—can reverse age-related ovarian damage, improve egg quality, support fetal development, and enhance sperm quality and quantity [3–7]. Although much of this research has been conducted in preclinical models, ongoing clinical trials are expected to provide further insights into the potential benefits of increasing NAD+ for reproductive health. These trials are exploring outcomes such as milk production during lactation, egg quality in women undergoing IVF, and overall fertility, which could offer valuable insights into the broader reproductive health benefits of NAD+.

Overall, maintaining healthy NAD+ levels is emerging as a key factor in supporting reproductive health. As research progresses, boosting NAD+ levels may become an essential strategy for addressing a variety of reproductive health challenges, offering a new avenue for supporting fertility and overall reproductive well-being.

Ex Vivo/Clinical Studies

Publication	Intervention	Objective	Key Outcomes
Wang et al. 2021 [2] NAD+ Deficiency and Mitochondrial Dysfunction in Granulosa Cells of Women with Polycystic Ovary Syndrome	**Nicotinamide Riboside**	To investigate the relationship between NAD+ and inflammation in polycystic ovary syndrome (PCOS) patients. PCOS is an endocrine disorder characterized by ovulation dysfunction. Granulosa cells (GCs) support and create the microenvironment necessary for oocyte (egg cell) development.	• In the GCs of PCOS patients, NAD+ levels were decreased, accompanied by increased inflammation, oxidative stress, and mitochondrial dysfunction. • NR administration restored NAD+ levels, reduced oxidative stress, and improved mitochondrial function in the GCs.

Ongoing Clinical Trials		
Trial Registry	**Intervention**	**Objective**
NCT04614714 Milk Volume Outcomes Following Oral Nicotinamide Riboside Supplementation in Mothers of Extremely Preterm Infants (MOONRISE) CERP ChromaDex External Research Program	**Nicotinamide Riboside**	To determine the effect of maternal NR supplementation on expressed milk volume and other markers of metabolism.
ACTRN12621001699853 The ENHANCE Study: The Effects of Nicotinamide Riboside Supplementation on the Egg Quality of Women of Advanced Age Undergoing IVF CERP ChromaDex External Research Program	**Nicotinamide Riboside**	To investigate the effects of NR on the egg quality of women of advanced age undergoing in vitro fertilization (IVF).
ChiCTR2200056972 Comparing Nicotinamide Ribose with Vitamin E to Improve Fertility in Elderly Women: A Single-Center, Randomized, Parallel Trial	**Nicotinamide Riboside & Vitamin E**	To investigate and compare the effects of NR and vitamin E alone on improving fertility in elderly patients with low ovarian reserve.

Preclinical Studies			
Publication	**Intervention**	**Objective**	**Key Outcomes**
Ear et al. 2019 [3] Maternal Nicotinamide Riboside Enhances Postpartum Weight Loss, Juvenile Offspring Development, and Neurogenesis of Adult Offspring CERP ChromaDex External Research Program	**Nicotinamide Riboside**	To investigate whether postpartum might dysregulate maternal NAD+ and whether increasing systemic NAD+ with NR supplementation could benefit rodent mothers and their offspring.	• NR increased prolactin production, boosting lactation, with peak lactation occurring on day 14. • NR caused a more than 20-fold increase in the mammary NAD metabolome in postpartum rodents. • NR-supplemented mothers had higher levels of BDNF (brain-derived neurotrophic factor) in their milk. • The offspring of NR-supplemented mothers had higher BDNF levels in their hindbrain and exhibited qualities that reached adulthood, including reduced anxiety, increased strength, better endurance in swim tests, improved performance on balance tests, better spatial memory, increased hippocampal neurogenesis, and leaner body composition.
Yang et al. 2020 [4] Increasing Ovarian NAD+ Levels Improve Mitochondrial Functions and Reverse Ovarian Aging	**Nicotinamide Riboside**	To investigate whether NR supplementation in aged mice could increase ovarian NAD+ levels in the context of age-dependent decreases in ovarian fertility.	• NR increased ovarian NAD+ levels, leading to an increased number of ovarian follicles and ovulatory potential, as well as an increased live birth rate. • NR also reduced levels of reactive oxygen species (ROS) and abnormalities in aging mouse oocytes. • NR improved ovarian mitochondrial energy metabolism.

Kim et al. 2021 [8] A Decrease in NAD+ Contributes to the Loss of Osteoprogenitors and Bone Mass with Aging CERP ChromaDex External Research Program	**Nicotinamide Riboside**	To investigate the mechanisms that underlie age-related decreases in bone formation (osteoporosis) in aged mice.	• NR increased the capacity of stem cells to differentiate into more mature bone stem cells. • Old mice had lower NAD+ levels in their osteoblast progenitor cells (immature bone cells). • NR slowed the loss of bone mass with aging. • Mice with reduced NAD+ levels lost bone mass at a young age, suggesting NAD+ decline contributes to reduced bone formation with age.
Yang et al. 2022 [9] Metabolic and Epigenetic Dysfunctions Underlie the Arrest of In Vitro Fertilized Human Embryos in a Senescent-Like State	**Nicotinamide Riboside**	To investigate why many human embryos halt developing during IVF and to explore possible treatments to prevent this, such as NR treatment.	• Arrested human embryos entered a senescent-like state and had a reduction in key proteins. • NR partially rescued the arrested embryos, allowing them to develop into the morula stage, where the embryo is a solid ball of cells, and the early blastocyst stage, where a fluid-filled cavity begins to form.
Li et al., 2022 [10] Nicotinamide Riboside Supplementation Ameliorated Postovulatory Oocyte Quality Decline CERP ChromaDex External Research Program	**Nicotinamide Riboside**	To investigate the effects of NR treatment on maintaining mouse oocyte quality in vitro.	• NAD+ levels naturally declined in postovulatory mouse oocytes over time, but this decline was reversed with NR treatment. • NR increased NAD+ levels and reduced the occurrence of abnormal oocytes by 9%. • NR improved oocyte quality by reducing abnormal spindle formations and enhancing fertilization potential. • NR helped prevent age-related mitochondrial dysfunction in oocytes, lowering levels of ROS, DNA damage, and cell death.
Lee et al., 2023 [5] Dietary Supplementation with Nicotinamide Riboside Improves Fetal Growth Under Hypoglycemia	**Nicotinamide Riboside**	To assess the protective effects of NR supplementation on gestational hypoglycemia in female mice. Gestational hypoglycemia occurs when a woman develops low blood sugar during pregnancy.	• In control mice, NR enhanced resistance to energy deprivation and boosted gluconeogenesis, the process of producing glucose from non-carbohydrate sources. • In ovariectomized mice (mice without ovaries), NR reduced high blood sugar levels and induced gluconeogenesis. • In pregnant mice, NR prevented maternal hypoglycemia by increasing blood sugar levels. • Hypoglycemic mice supplemented with NR had higher fetal birth weights.
Li et al., 2023 Characterization of Long-Term Ex Vivo Expansion of Tree Shrew Spermatogonial Stem Cells	**Nicotinamide Riboside**	To investigate the effects of repeated cell culture transfer on the sperm-producing capabilities of the spermatogonial stem cells of tree shrews, and assess the potential protective effects of boosting NAD+ through treatment	• NR increased NAD+ levels, decreased oxidative stress, and alleviated deficiencies in mitochondrial function, DNA damage, and ATP production in spermatogonia—precursor sperm cells. However, short-term NR administration did not increase the spermatogonial stem cell population.

		with NR. Tree shrews, closely related to primates, offer a valuable model for studying human-relevant spermatogenesis processes.	
Ni et al., 2023 BNC1 Deficiency Induces Mitochondrial Dysfunction-Triggered Spermatogonia Apoptosis Through the CREB/SIRT1/FOXO3 Pathway: The Therapeutic Potential of Nicotinamide Riboside and Metformin	**Nicotinamide Riboside**	To assess the therapeutic potential of NR and metformin administration in ameliorating spermatogenic failure and subfertility in mice with a Basonuclin 1 (BNC1) gene mutation, which is linked to subfertility in males and females.	• In mice with the BNC1 mutation, NR and metformin alone effectively reversed mitochondrial dysfunction, inhibited spermatogonia death, and improved testicular architecture. • NR and metformin alone also increased sperm count, motile sperm count, and progressive sperm count, improving overall sperm quality and quantity.
Warren et al., 2023 [11] The NAD Salvage Pathway in Mesenchymal Cells is Indispensable for Skeletal Development in Mice	**Nicotinamide Riboside**	To investigate the role of NAD+ in bone development using mice lacking the NAMPT gene in all mesenchymal cells (stem cells that differentiate into bone and cartilage) of the limb, and to assess whether oral NR supplementation during pregnancy can mitigate bone formation defects in offspring.	• Mice lacking the NAMPT enzyme exhibited severe limb and sternum shortening at birth, likely due to NAD+ deficiency, and died a few days after birth for reasons that were unclear. • To determine if the NAD+ deficiency was responsible for these defects, NR was administered orally to the mice during pregnancy. Prenatal NR supplementation reduced the severity of skeletal abnormalities, preventing joint malformations and promoting better development of the forelimbs, though the defects were not fully corrected. • The partial rescue of prenatal skeletal defects by NR allowed the NAMPT-knockout mice to survive and ambulate after birth.
Selli et al., 2023 [12] Nicotinamide Riboside Preserves Ovarian Injury in Experimental Sepsis Model in Rats	**Nicotinamide Riboside**	To assess the protective effects of NR administration on ovarian damage in a rat model of intestinal damage-induced sepsis.	• High-dose NR reduced inflammatory stress markers and ovarian tissue damage caused by sepsis in rats. • NR mitigated inflammation by decreasing white blood cell infiltration, markers of cell damage, and follicular cell death, which is crucial for oocyte maturation. • NR increased antioxidant enzyme activity in the ovaries.
Yang et al., 2023 [13] Deletion of Enzymes for De Novo NAD+ Biosynthesis Accelerated Ovarian Aging	**Nicotinamide Riboside**	To investigate how reduced NAD+ levels impact ovarian aging and fertility, and whether NR supplementation could enhance fertility and egg	• Middle-aged mutant mice showed lower NAD+ levels, leading to reduced fertility and dysfunction in both the ovaries and mitochondria. • NR increased ovarian NAD+ levels, partially restoring fertility in the mutant mice, as evidenced by an increased litter size.

		quality in middle-aged mice with genetic mutations.	• NR also increased ovarian reserve and improved the quality of oocytes in the mutant mice.
Thompson et al., 2023 [14] Nicotinamide Riboside, an NAD + Precursor, Protects Against Cardiac Mitochondrial Dysfunction in Fetal Guinea Pigs Exposed to Gestational Hypoxia	**Nicotinamide Riboside**	To evaluate whether NR supplementation could reverse mitochondrial dysfunction in fetal guinea pig hearts caused by gestational hypoxia, a condition that reduces oxygen supply to the fetus and disrupts heart and placental mitochondrial function, impairing growth and organ development.	• Hypoxia reduced fetal body weight and placental NAD+ levels, while increasing placental weight and mitochondrial dysfunction. • NR restored body weight, mitochondrial function, and placental NAD+ levels in hypoxic fetuses, and also elevated liver NAD+ levels in both normoxic (normal oxygen) and hypoxic fetuses. • NR also prevented the reduction in fetal heart weight in males and normalized the increase in fetal brain weight in females.
Arslan et al., 2024 [15] Nicotinamide Mononucleotide and Nicotinamide Riboside Reverse Ovarian Aging in Rats Via Rebalancing Mitochondrial Fission and Fusion Mechanisms	**Nicotinamide Riboside & Nicotinamide Mononucleotide**	To evaluate the effectiveness of NR supplementation and nicotinamide mononucleotide (NMN) administration alone in reversing ovarian aging and improving egg production by restoring mitochondrial function in middle-aged rats.	• NR and NMN treatment enhanced both the quantity and quality of follicles, as well as the corpus luteum, which is vital for fertility hormone production. • NR and NMN treatment in middle-aged rats boosted gene expression related to mitochondrial fusion, which is essential for protecting oocytes and follicles. • NR and NMN supplementation raised SIRT1 levels in the ovaries, helping to delay ovarian aging by promoting key enzymes. • NR and NMN restored the balance of LH and FSH hormones, which are often disrupted during ovarian aging.
Liu et al., 2024 [16] Maternal Administration of Acetaminophen Affects Meiosis Through its Metabolite NAPQI Targeting SIRT7 in Fetal Oocytes	**Nicotinamide Riboside & Nicotinamide**	To assess the potential effects of maternal administration of acetaminophen on fetal oocyte development in mice and assess the potential of NR and nicotinamide (NAM) supplementation to reverse these adverse effects.	• Acetaminophen caused a dose-dependent delay in chromosomal development of fetal oocytes, disrupted DNA damage repair in oocytes, and led to a significant reduction in NAD+ levels in the ovaries. • Both NR and NAM effectively reversed the acetaminophen-induced delay in chromosomal development in the ovaries of mice. However, NR was slightly more effective than NAM, as it better rescued genes crucial for meiosis (cell division).
Li et al., 2024 [17] The NAD+ Precursor Nicotinamide Riboside Protects Against Postovulatory Aging In Vitro	**Nicotinamide Riboside**	To determine if NR administration could prevent postovulatory aging (POA) of oocytes during in vitro culture and improve the success rates of	• NR effectively reduced signs of aging-related decline in oocyte quality by lowering levels of reactive oxygen species, enhancing mitochondrial function (demonstrated by increased ATP production), and correcting the positioning of essential cellular components known as cortical granules.

		artificial reproductive technology (ART). POA is a significant challenge, especially for older women, as it reduces egg quality and lowers the chances of successful pregnancies through ART.	• NR also helped restore the proper arrangement of spindles and the alignment of chromosomes, while lowering DNA damage in the oocytes.
Jahan et al., 2024 [18] **NAD+ Depletion is Central to Placental Dysfunction in an Inflammatory Subclass of Preeclampsia**	**Nicotinamide Riboside**	To investigate the role of NAD+ depletion in placental function and inflammation-driven preeclampsia (PE), and to evaluate whether boosting NAD+ with NR administration can mitigate the harmful effects of inflammation in PE, using human placenta, a human trophoblast cell model, and a rat model of PE.	• In both human and rat placentas affected by PE, NAD+ levels were lower, and the activity of NAD-consuming enzymes was elevated, resulting in mitochondrial dysfunction and increased oxidative damage. • In a human trophoblast cell model, NR treatment restored NAD+ levels, reduced protein damage, and improved mitochondrial function. • In a rat model of PE, NR treatment reduced blood pressure, decreased placental inflammation, and improved both placental and fetal weight, leading to increased fetal survival.
Xu et al., 2025 **Nicotinamide Riboside Supplementation Alleviates Testicular Aging Induced by Disruption of Qprt-Dependent NAD+ De Novo Synthesis in Mice**	**Nicotinamide Riboside**	To investigate the role of NAD+ in sperm production in mice lacking the quinolinate phosphoribosyl transferase (Qprt) gene, which is essential for NAD+ production in spermatocytes (cells in the testes that produce sperm).	• In mice lacking the Qprt gene, NR treatment increased NAD+ levels in immature spermatocytes and the testes. • NR also increased testicular weight and sperm count, reduced programmed cell death, protected the development of sperm cells, and altered the expression of X and Y sex chromosomes.
Zhu et al., 2025 [19] Nicotinamide Riboside Supplementation Ameliorates Ovarian Dysfunction in a PCOS Mouse Model	**Nicotinamide Riboside**	To investigate the impact of NR supplementation on ovarian function in a mouse model of PCOS.	• NR prevented a decrease in ovarian NAD+ levels, normalized estrous cycle irregularities, and improved ovulation potential in PCOS mice. • NR protected against ovarian fibrosis and improved mitochondrial function in stromal cells (connective tissue cells) within the ovaries of PCOS mice. • NR improved oocyte quality by increasing mitochondrial function, supporting early embryonic development, and reducing

			mitochondrial clustering, oxidative stress, and spindle abnormalities in fertilized oocytes from PCOS mice.

*The **ChromaDex External Research Program (CERP)** is an essential component of ChromaDex's R&D Program. Through CERP, ChromaDex material and technical expertise is freely provided for exceptional preclinical and clinical, investigator-initiated research projects. Additionally, CERP funds research studies supporting ChromaDex's business needs. Please visit https://www.chromadex.com/research/cerp/ for more information.*

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