"Supporting the nitrate/nitrite/NO pathway will not only optimize NO, but it will also down-regulate oxidative stress and inflammation to support and even possibly extend fertility."
—Beth Shirley RPh CCN

Nitric Oxide and Fertility

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The latest World Health Organization (WHO) data in 2023 indicates that one in six women struggle with getting pregnant or staying pregnant.[1] There are numerous reasons for this, including toxins and environmental poisons in our air, food, and water, and not getting enough sleep or being stressed, to name just some of the factors. Many key infertility drivers have a nitric oxide (NO) deficiency at their base, such as cardiovascular concerns with improper blood flow, metabolic and blood glucose/insulin issues, polycystic ovary syndrome (PCOS), intestinal health issues, immune and autoimmune issues, mitochondrial health issues, and electromagnetic frequency (EMF) exposures.

NO is linked to almost all physiological functions of male and female aspects of reproduction, from erection and sperm health in the male to ovulation, implantation, carrying the baby to full term, and labor in the female.

Oxidative stress as a driving force behind infertility

Oxidative stress, an imbalance between prooxidants and antioxidants, may be the primary cause of male and female infertility.[2] Oxidative stress involves excess production of reactive oxidative species (ROS) and free radicals that overpower our defense capabilities.

In males, excess ROS leads to DNA damage and oxidation of lipoprotein components and oxidative stress. This adversely affects sperm functional competence, fluidity and thus mobility.[3] Oxidative stress in males has also been correlated with such adverse events as reduced fertilization, dysregulated preimplantation embryo development, recurrent pregnancy loss and even childhood mortality. It is estimated that oxidative stress at seminal level contributes up to 80% of all infertility diagnoses.[4]

In females, oxidative stress can lead to numerous reproductive diseases such as endometriosis, PCOS, unexplained fertility, as well as pregnancy complications like spontaneous abortion, recurrent pregnancy loss, and preeclampsia.[2]

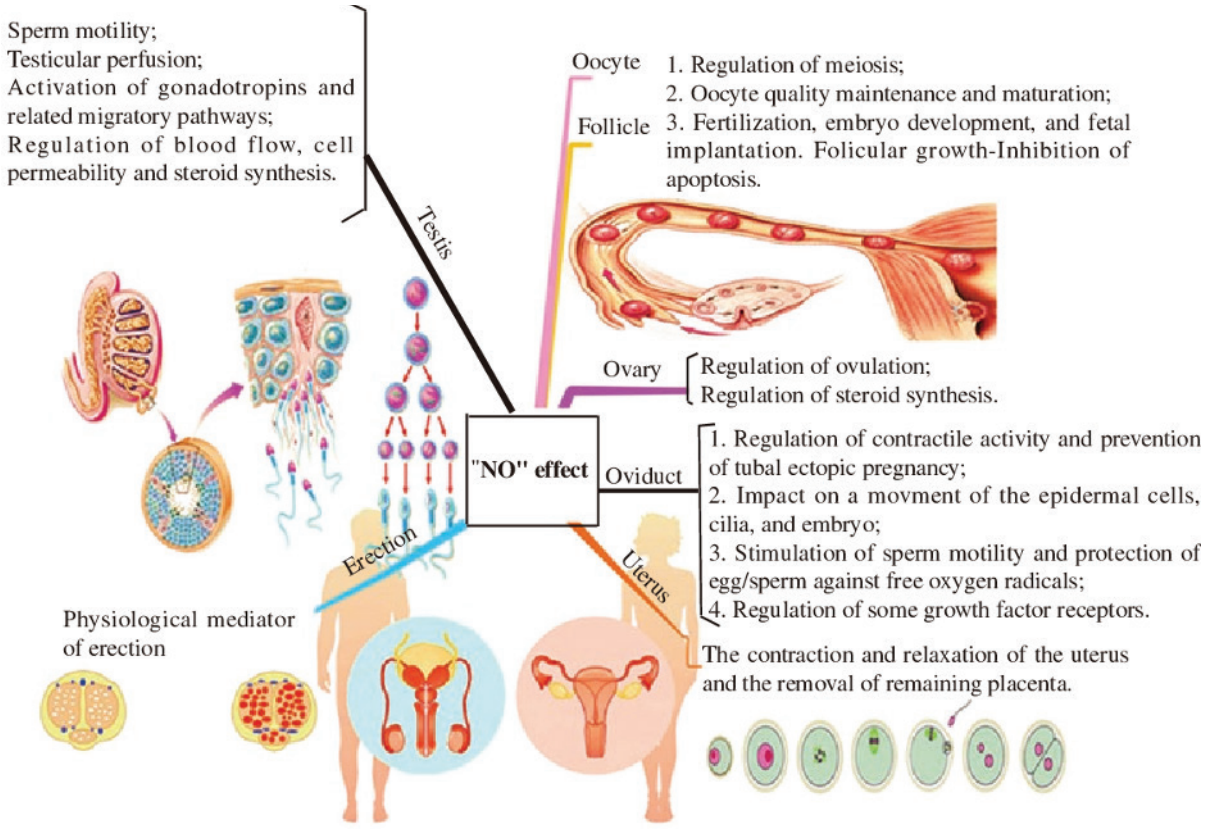
There are three main sources of superoxide production in the body. Oxidative stress is a key driver for cell damage affecting oocytes, sperm, embryos, and in fact, all facets of fertility.

Supporting the nitrate/nitrite/NO pathway addresses each of these sources of superoxide:

1. Uncoupled nitric oxide synthase (NOS) enzyme – nitrate supports recoupling of NOS.[5]
2. NADPH oxidase — nitrate, nitrite, and NO down-regulate NADPH oxidase.[6]
3. Uncoupled mitochondrial electron transport chain (ETC) — nitrite and NO recouple ETC.[7]

By downregulating the production of superoxide, oxidative stress is inhibited, and balance can be restored. Supporting the nitrate/nitrite/NO pathway and optimizing NO protects against oxidative stress, helping to protect oocytes and sperm against oxidative damage and improving fertility and reproductive health.

Fig 1. Effects of Nitric Oxide on reproductive organs and related physiological processes.



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Nitric Oxide in male and female fertility

NO affects all stages and functions of the reproductive process in both males and females. NO donors may be useful for promoting fertility. In contrast, NO inhibitors have been shown to be useful for contraception.[3]

In both males and females, NO regulates the hypothalamus release of gonadotropin-releasing hormone (GnRH), which then travels to the pituitary for release of the gonadotropins, luteinizing hormone (LH) and follicle-stimulating hormone (FSH). LH and FSH then travel to the ovaries or testis to stimulate production of the sex hormones, estrogen, progesterone, and testosterone. These sex hormones can then modulate the release of NO through NOS.[10]

Male factors may be contributing 50% to infertility issues.[9] NO plays an important role in spermatogenesis, sperm maturation, and capacitation in keeping the sperm viable. In fact, the concentration of NO determines the sperm level. NO is also essential for erections to take place.[10]

NO plays an essential role in every aspect of female fertility including regulation of the menstrual cycle, follicular development, oocyte maturation, ovulation, luteinization, fertilization, embryo development, pregnancy maintenance, and childbirth.[10]

In pregnancy, the renal plasma flow and the glomerular filtration rate (GFR) of the kidney increases 50–80% above nonpregnant flow. NO is responsible for this renal adaptation throughout pregnancy. NO deficiency is connected to pregnancy-induced hypertension and preeclampsia. Studies in animals show that using an NOS inhibitor, like L-NAME, induced hypertension, proteinuria, and fetal growth retardation.[3]

The microbiome, fertility, and Nitric Oxide

Microbiome health plays a pivotal role in male and female infertility, as well as in vitro fertilization (IVF) outcomes, an aspect that is often overlooked.[11] Studies show that an imbalance in the gut microbiome will alter structure and function of the intestinal barrier, leading to inflammation and oxidative stress, which in turns leads to hormone imbalances, blood glucose dysregulation, immune system dysfunction, mood disturbances such as anxiety and depression, and numerous other maladies. Supporting the nitrate/nitrite/NO pathway can play an essential role in intestinal health.[11]

In males, microbiome health has been implicated in idiopathic male infertility. There is a direct relationship between dysbiosis of the gut microbiome and male infertility.[5] Semen can transmit organisms that may become residents of the uterus and males can transmit information to their partners and their offspring through their microbiome.[11]

In the female, microorganisms live in the vagina and in the upper reproductive system, including ovaries, fallopian tubes, and uterus. Infertile women have a different microbiome than fertile women.[11]

"Seminovaginal" microbiome can influence couples' health, reproductive outcomes, and their offspring's health.[11]

Supporting the nitrate/nitrite/NO pathway plays a significant role in a healthy microbiome and a healthy GI tract. NO is critical in a healthy mucous membrane layer—our first layer of defense against pathogens—down-regulates mast cell degranulation and histamine release, down-regulates macrophage inflammatory cytokine release, reduces adherence and secretion of neutrophils, improves circulation, and decreases oxidative stress.[12] Nitrate can decrease levels of bacteria associated with poor systemic health and protects gut microbiome under inflammatory conditions. Nitrate can prevent or reduce bacterial dysbiosis and stimulate eubiosis.[13] All the microbiomes are connected, and nitrate protects the microbiome and increases microbial biomass.[14]

Tight junction (TJ) proteins play a vital role in epithelial transport and barrier integrity. Loss of these TJ proteins results in the breakdown of the barrier, a process called "leaky gut." In leaky gut, there is decreased gastric expression of the TJ proteins occludin and claudin-5. Nitrate increases these TJ proteins and protects and repairs leaky gut.[15]

Autoimmune disorders and fertility

Autoimmune disorders may underlie infertility issues.[16] There is a dynamic interplay between gut health and autoimmune conditions. Dysbiosis and leaky gut increase chronic inflammatory response and development of autoimmune diseases.[17] The gut microbiome maintains homeostasis of our immune response. Dysbiosis contributes to the TH17/T reg cell imbalance which influences proinflammatory cytokine levels like IL17.[18]

Nitrate decreases the proinflammatory TH1 and TH17 in the blood and decreases IL17 in the colon. Nitrate also increases T reg cells, which has everything to do with self-tolerance and controls autoimmunity.[18]

Oxidative stress with excess production of ROS is rampant in autoimmune diseases.[19] Supporting the nitrate/nitrite/NO pathway down-regulates oxidative stress.

Raynaud's phenomenon is associated with leaky gut and numerous autoimmune conditions. Raynaud's has been associated with infertility and pregnancy complications.[20] Raynaud's has vascular spasms that restrict blood flow to the extremities and can be treated successfully by optimizing NO.[21]

Mitochondrial health, Nitric Oxide, and fertility

Mitochondria, being the powerhouse of the cell, are key players in ATP generation as well as the resultant ROS production from mitochondrial respiration. Mitochondrial health is essential for healthy sperm and oocytes and their further development. Mitochondrial dysfunction can not only influence fertility and embryo viability, but it also regulates transgenerational inheritance.[22]

Each sperm has approximately 50–75 mitochondria, which produce energy for sperm's movement and fertilization.[23] By contrast, oocytes have between 100,000–200,000 mitochondria, because the development of oocytes and early embryos are solely dependent on mitochondrial ATP production.[22]

Nitrate, nitrite, and NO mediate and regulate mitochondrial function.[24] Mitochondria even have their own form of NOS called mtNOS, which shows how essential NO is in mitochondrial function.

NO regulates the binding to and the release of oxygen from hemoglobin and thus the supply of oxygen needed for mitochondrial respiration.[25] NO binds with cytochrome C oxidase (COX) leading to a partial reversible inhibition of mitochondrial respiration and may control the production of ROS without negative effects on ATP production.[26] Nitrate decreases proton leak across the inner mitochondrial membrane, which could account for as much as 25% of the resting energy expenditure.[24]

Nitrite and NO increase mitochondrial biogenesis by activating AMP-activated protein kinase (AMPK) and SIRT1, which activates peroxisome proliferator-activated receptor-gamma coactivator (PGC)-1alpha, a critical regulator of energy metabolism. In fact, treatment with NO donors has been shown to increase mtDNA.[24]

Telomeres, pregnancy, and the nitrate, nitrite, NO pathway

Telomere erosion and dysfunction is one of the hallmarks of aging.[27] Telomers shorten because of the effects of ROS, which easily oxidize and deplete them. Sperm and oocytes have higher telomere length than regular somatic cells. As women age, this adversely affects telomerase activity and decreases length of telomeres, and this increases not only infertility but also frank ovarian insufficiency. However, in sperm, telomere length increases with advancing paternal age, which may be the reason men can keep their fertility into later life.[28]

Supporting the nitrate/nitrite/NO pathway and optimizing NO activates telomerase activity, increases telomere length, and inhibits cellular senescence and cellular aging.[29] This action supports the idea of enabling women to extend their fertility longer and increase their chances of having a healthier baby.

Psychological stress, Nitric Oxide, and fertility

Stress and adrenal dysfunction negatively affect fertility and reproduction in both males and females. Activating the hypothalamic-pituitary-adrenal (HPA) axis increases corticotrophin-releasing hormone (CRH), which inhibits GnRH and in turn, LH and FSH release. This affects sex steroid hormone release in the ovaries and testes. Glucocorticoids inhibit LH and ovarian estrogen and progesterone secretion.[30] In males, psychological stress impairs semen quality. Under adrenergic activation during stress, there is increased vasoconstriction, which decreases testosterone production and decreases spermatogenesis.[31]

Glucocorticoids inhibit NOS production of NO. These steroids increase ROS production by the mitochondria, as well as ROS produced through the actions of NADPH oxidase and xanthine oxidase. Oxidative stress uncouples NOS, increasing superoxide production. When NOS is uncoupled, it becomes a superoxide generator, not an NO producer, so oxidative stress increases even more. Cortisol, a glucocorticoid, decreases synthesis of tetrahydrobiopterin (BH4), which is the essential cofactor to keep NOS coupled and functioning. Cortisol also decreases membrane transport of arginine.[32] In addition, cortisol increases blood glucose levels and hemoglobin A1C, which increases oxidative stress. Hemoglobin A1C binds tightly with NO, interfering with NO's bioavailability.[33]

Cortisol is a catabolic hormone. Consequently, stress causes inflammation and damage to all cells including those in the GI tract, increasing dysbiosis and leaky gut. Optimizing the nitrate/nitrite/NO pathway protects against the deleterious effects of stress on the GI tract.[34]

Polycystic ovary syndrome

Polycystic Ovary Syndrome (PCOS) is one of the most common endocrine disorders in reproductive women, with a prevalence of up to 20% and with almost 2/3 of those women not ovulating on a regular basis causing infertility. As women age, PCOS morphs into more of a metabolic disease that encompasses insulin resistance, impaired glucose tolerance, type 2 diabetes (T2D), dyslipidemia, hypertension, and cardiovascular disease.[35]

NO mediates all these conditions associated with PCOS. These conditions produce an NO-deficient state. In insulin resistance and T2D, there is increased oxidative stress. Increased oxidative stress leads to NOS uncoupling. PCOS increases asymmetric dimethylarginine (ADMA) synthesis, which uncouples NOS, increasing oxidative stress as well as decreasing arginine bioavailability for the NOS enzyme. ADMA is a biomarker for oxidative stress and endothelial dysfunction.[36] High blood glucose, seen in PCOS, promotes cellular senescence and decreases telomerase activity.[36]

Supporting the nitrate/nitrite/NO pathway encourages production of BH4 to recouple the NOS enzyme, as well as down-regulating the production of superoxide and oxidative stress underlying this NO-deficient condition. NO can prevent cellular senescence and increase telomerase activity.[37]

Supporting healthy prolactin levels

Increased serum prolactin levels decrease expression of a protein called kisspeptin, which reduces GnRH release leading to decreased pituitary release of LH and FSH. This results in hypogonadism, infertility, and amenorrhea.[37] Hyperprolactinemia has also been associated with reduced sexual desire and erectile dysfunction in males.[38] NO and NO donor molecules inhibit release of prolactin.[38,40]

Electromagnetic fields, infertility, and Nitric Oxide

Electromagnetic fields (EMFs) exposure is emerging as a powerful promoter of infertility.

EMFs emanate from power lines, computers, phones, TVs, radios, Wi-Fi, and microwave ovens. They have high penetration power and have destructive, non-thermal biological effects. EMFs can cause neuroendocrine changes by disrupting brain function and particularly hypothalamus function. This leads to disruption of GnRH release and thus a decrease in LH and FSH release. EMFs inhibit melatonin production and not only does this increase oxidative stress, melatonin influences LH and FSH release.[41] Melatonin is a free radical scavenger as well as a potent radioprotective agent.[42] EMFs activate NADPH oxidase and increase superoxide production promoting oxidative stress.[30]

Most of the studies on EMFs have been done on animals. However, there have been some cases of spontaneous abortions and fetal abnormalities in pregnant women from computer monitor use.[41] In animals, EMF inhibited ovulation, decreased the number of corpora lutea, accelerated apoptosis in the ovaries, was deleterious in the implantation period, and had negative effects on the early development of the embryo.[41]

EMFs have been shown to negatively affect sperm count, morphology, motility, and viability. Disruption of sperm mitochondria and high levels of ROS increasing oxidative stress and infertility is seen.[43]

EMFs increase oxidative stress by stimulating NADPH oxidase's production of superoxide. EMFs increase ROS and extensive electron leakage from the mitochondrial electron transport chain.[44] EMFs increase calcium influx through the voltage-gated calcium channel (VGCC). This increase of Ca2+ influx accelerates oxidative damage.[45] Increased ROS and oxidative stress uncouple NOS leading to more oxidative stress. EMFs increase the activity, concentration, and lifetime of ROS.[45]

This extensive electron leakage from the mitochondrial ETC damages and disrupts the normal cellular processes of the cell, including sperm, oocytes, and embryos.

EMFs dysregulate the hypothalamic/pituitary/adrenal (HPA) axis increasing cortisol, the stress hormone.[46] EMF exposure is considered a biological stress response.[46] There is an upregulation of the sympathetic nervous system and downregulation of the parasympathetic nervous system invoking the "fight-or flight" response.[47]

EMFs increase gastrointestinal and blood brain barrier (BBB) permeability disturbing the microbiome, which increases leaky gut and "leaky brain."[5] The health of the gut is intimately connected with infertility.

Supporting the nitrate/nitrite/NO pathway not only increases the production of NO, it decreases and scavenges production of ROS by downregulating NADPH oxidase, recoupling of the mitochondrial electron transport chain and helping to recouple the NOS enzyme. NO and NO donors inhibit the voltage-gated calcium channel (VGCC) influx of Ca2+, decreasing oxidative stress that is seen in EMF exposure.[48]

Conclusions

NO is linked to almost all functions of male and female reproduction. The inability to produce optimal NO has deleterious consequences upon every facet of infertility. Fact is, by the time we are 40, our ability to produce NO through the NOS enzyme decreases to around 50%. Any inflammatory or chronic issue will impair and uncouple NOS even more. Oxidative stress and inflammation are at the base of infertility and reproductive challenges and can be the primary cause for infertility in both males and females. Supporting the nitrate/nitrite/NO pathway will not only optimize NO, but it will also down-regulate oxidative stress and inflammation to support and even possibly extend fertility.

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