
Role of Ayurveda in Improving Reproductive Health by Combating Oxidative Stress

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ABSTRACT

Introduction: Oxidative stress (OS), a state characterized by an imbalance between pro-oxidant molecules including reactive oxygen and nitrogen species, and antioxidant defenses. Oxidative stress plays a pivotal role in the pathogenesis of subfertility in both males and females. Adverse effect of oxidative stress on sperm quality and functions is well established. In female imbalance between prooxidants and antioxidants can lead to a number of reproductive diseases such as endometriosis, Polycystic ovary syndrome and unexplained infertility. Extremes of body weight, cigarette smoking, alcohol use, environmental pollutants, faulty diet use can promote free radical production, which could affect fertility. In Ayurveda oxidative stress could be understood as Ama formation. Agni (digestive fire) Mandhya can lead to formation of Ama that is causative factor for myriad of diseases in body which could hamper reproductive health and finally lead to infertility.

Aims: To explore the potential of Ayurvedic therapeutics in combating oxidative stress and improving reproductive health.

Objectives: Evidence based exploration of Ayurvedic therapies like Panchkarma, Garbhadhan vidhi, Rasayan & Vajikaran in reducing oxidative stress.

Methodology: Various research studies and Ayurvedic literature have been explored to establish the role of Ayurveda in improving reproductive health by reducing oxidative stress.

Discussion: Oxidative stress at the level of reproductive organs can be reduced by using ayurvedic Rasayan and Vajikaran therapies, because of its proved antioxidant properties. In the same way impact of oxidative stress on Assisted reproductive techniques (ART) can be addressed by using ayurvedic therapies.

Results: The insight in this subject established the potential of Ayurveda in improving fertility by reducing oxidative stress.

Conclusion: Ayurvedic therapeutics by rectifying metabolism and cellular health can improve reproductive health and aid modern techniques like ART and other therapies used in infertility for better outcome.

Key words: Oxidative stress, Ama, Rasayan, Vajikaran, Reproductive health.

INTRODUCTION

Oxidative stress (OS), a state characterized by an imbalance between pro-oxidant molecules including reactive oxygen and nitrogen species, and antioxidant defenses. Free radical species are unstable and highly reactive. They become stable by acquiring electrons from nucleic acids, lipids, proteins, carbohydrates or any nearby molecule causing a cascade of chain reactions resulting in cellular damage and disease. There are two major types of free radical species: reactive oxygen species (ROS) and reactive nitrogen species (NOS). The three major types of ROS are: superoxide (O₂^{•-}), hydrogen peroxide (H₂O₂), hydroxyl (OH[•]). The superoxide radical is formed when electrons leak from the electron transport chain. The

dismutation of superoxide results in the formation of hydrogen peroxide. The hydroxyl ion is highly reactive and can modify purines and pyrimidines and cause strand breaks resulting in DNA damage. Some oxidase enzymes can directly generate the hydrogen peroxide radical. The formation of reactive nitrogen species is by conversion of L-arginine to L-citrulline by nitric oxide synthase (NOS). The two common examples of reactive nitrogen species are nitric oxide (NO) and nitrogen dioxide.

With an unpaired electron, NO, which is a highly reactive free radical, damages proteins, carbohydrates, nucleotides and lipids and, together with other inflammatory mediators, results in cell and tissue damage, low-grade, sterile inflammation and adhesions ROS have been implicated in more than 100 diseases There is growing literature on the effects of OS in female reproduction with involvement in the pathophysiology of preeclampsia, hydatidiform mole, free radical-induced birth defects and other situations such as abortions. Numerous studies have shown that OS plays a role in the pathophysiology of infertility and assisted fertility. There is some evidence of its role in endometriosis, tubal and peritoneal factor infertility and unexplained infertility.

Antioxidants

Under normal conditions, scavenging molecules known as antioxidants convert ROS to H₂O to prevent overproduction of ROS. There are two types of antioxidants in the human body: enzymatic antioxidants and non-enzymatic antioxidants.

Enzymatic antioxidants

Enzymatic antioxidants are also known as natural antioxidants, they neutralize excessive ROS and prevent it from damaging the cellular structure. Enzymatic antioxidants are composed of superoxide dismutase, catalase, glutathione peroxidase and glutathione reductase, which also causes reduction of hydrogen peroxide to water and alcohol.

Non-enzymatic Antioxidants

Non-enzymatic antioxidants are also known as synthetic antioxidants or dietary supplements. The body's complex antioxidant system is influenced by dietary intake of antioxidant vitamins and minerals such as vitamin C, vitamin E, selenium, zinc, taurine, hypotaurine, glutathione, beta carotene, and carotene. Vitamin C is a chain breaking antioxidant that stops the propagation of the peroxidative process. Vitamin C also helps recycle oxidized vitamin E and glutathione. Taurine, hypotaurine and transferrin are mainly found in the tubal and follicular fluid where they protect the embryo from OS. Glutathione is present in the oocyte and tubal fluid and has a role in improving the development of the zygote beyond the 2-cell block to the morula or the blastocyst

Oxidative Stress in Female Reproduction

Cells have developed a wide range of antioxidants systems to limit production of ROS, inactivate them and repair cell damage. OS influences the entire reproductive span of women's life and even thereafter (i.e. menopause). It has been suggested that the age-related decline in fertility is modulated by OS. It plays a role during pregnancy and normal parturition and in initiation of preterm labor. The pathological effects are exerted by various mechanisms including lipid damage, inhibition of protein synthesis, and depletion of ATP. There is some understanding of how ROS affect a variety of physiologic functions (i.e. oocyte maturation, ovarian steroidogenesis, ovulation, implantation, formation of blastocyst, luteolysis and luteal maintenance in pregnancy. ROS are a double-edged sword – they serve

as key signal molecules in physiological processes but also have a role in pathological processes involving the female reproductive tract. Since the balance is maintained by the presence of adequate amounts of antioxidants, measuring levels of the antioxidants, individually or as total antioxidant capacity (TAC), has also been examined. Superoxide dismutase (SOD) enzymes, Copper-Zinc SOD (Cu-Zn SOD) and Manganese superoxide dismutase (MnSOD) have been localized in the granulosa and thecal cells of the growing follicle. Selenium dependent glutathione peroxidase activity has been demonstrated in the follicular fluid and serum of patients undergoing IVF.

Measurement of Oxidative Stress

The presence of ROS and antioxidants in the female reproductive tract has been demonstrated by various methodologies in animal and human studies. A number of OS biomarkers have been investigated including superoxide dismutase, glutathione peroxidase, conjugated dienes, lipid peroxides, thiobarbituric acid reactive substances, glutaredoxin, oxidative DNA adducts, follicular fluid, NO and TAC. Metabolites of NO (nitrite and nitrate) in peritoneal fluid are determined by nitrate reductase and the Griess reaction. Total NO (nitrite and nitrate) levels in the serum and follicular fluid assay of NO are measured via a rapid-response chemiluminescence analyzer. Various biomarkers of oxidative stress have been determined in the placenta by immunohistochemistry or western blot analysis. Oxidative DNA adducts 8-hydroxy 2-deoxyguanosine have been studied by immunostaining in placenta, in patients with IUGR (intrauterine growth retardation) and patients with preeclampsia and IUGR. The basal levels of ROS in the leukocytes in whole blood can be determined using the dihydroethidium and dichlorodihydrofluorescein-diacetate probes.

Assisted Reproduction

Assisted reproductive technique (ART) involves the direct manipulation of the human oocytes, sperm or embryos outside the body, to establish a pregnancy. A variety of causative factors of infertility can be indications for ART, i.e. tubal factor, endometriosis, male factor and unexplained infertility. Assisted reproductive techniques offer excellent opportunities to infertile couples for achieving pregnancy. There may be multiple sources of ROS in an IVF setting including the oocytes, cumulus cell mass, or spermatozoa used for insemination. The follicular fluid microenvironment has a crucial role in determining the quality of the oocyte. This in turn impacts the fertilization rate and the embryo quality. Oxidative stress markers have been localized in the follicular fluid in patients undergoing IVF/embryo transfer (ET). Low intrafollicular oxygenation has been associated with decreased oocyte developmental potential as reflected by increasing frequency of oocyte cytoplasmic defects, impaired cleavage and abnormal chromosomal segregation in oocytes from poorly vascularised follicles. ROS may be responsible for causing increased embryo fragmentation, resulting from increasing apoptosis. Thus, increasing ROS levels are not conducive to embryo growth and result in impaired development. Current studies are focusing on the ability of growth factors to protect in vitro cultured embryos from the detrimental effects of ROS such as apoptosis. [1]

Concept of Aama in Ayurveda

Aam is broadly defined as undigested food resulting from a process that is entirely gastrointestinal. On deep evaluation, indicates that the production of Aam is a systemic process that extends to metabolic and other physiological processes in the body. Aam can be enumerated as-

- The by-product of impaired digestion.

- The accumulation of unrepelled wastes in the body.
- The first expression of aberrations in the physiological processes of the body.

Aama represents the transition from physiology to pathology. Thus, it is the precursor of inflammatory, degenerative and infective processes that eventually manifest as full-fledged diseases. The fundamental principle in Ayurveda is that by tackling *Aam* at an early stage, progression of diseases can be arrested or prevented.

Characteristic Features of Aama

- Avipakva- Improperly processed
 - Asamyuktam- unbound or not integrated.
 - Durgandham- foul smelling
 - Bahu picchilam – very sticky
 - Sadanam sarva gatranam- capable of causing weakness in the entire body or body parts.
- [2]

When we try to understand the concept of *Aama* in present context it can be easily equated with oxidative stress in the body. As *agni* in Ayurveda can be understood as digestion and metabolism, because *jathargni*, *dhatvagni* and *rasagni* assumes the presence of *agni* upto cellular level.

- Avipakvam- Due deficiency of oxygen at cellular level, free radicals can be produced from non-enzymatic reactions of oxygen with organic compounds in aerobic oxidation.
- Asamyuktam-Free radicals are atoms, molecules, or ions with at least one unpaired valence electron. They can be generated by breaking a chemical bond so that each fragment retains one electron.
- Durgandham- Bahu picchilam- As they are electron deficient, they wander in the cell for their stability and effect the biomembrane.
- Sadnam sarva gatranam- Free radicals or Reactive Oxygen Species affect the cellular metabolism in whole body and cause multisystem disorders along with infertility by reduced sperm motility, DNA damage, decreased oocyte quality and decreased fertilization rates.

Aims: To explore the potential of Ayurvedic therapeutics in combating oxidative stress and improving reproductive health.

Objectives: Evidence based exploration of Ayurvedic therapies like *Panchkarma*, *Garbhadhan vidhi*, *Rasayan* & *Vajikaran* in reducing oxidative stress.

Materia & Methods: Various research studies and Ayurvedic literature have been explored to establish the role of Ayurveda in improving reproductive health by reducing oxidative stress.

DISCUSSION

In Ayurveda the major factors that lead to *Bandhyatva* (infertility) in women are *Yoni Dosha* (Abnormalities of reproductive organs), *Shukra*, *Asrik* (sperm, ovum), *Ahar- vihar* (faulty dietary habits and lifestyle), *Akaal yog* (improper time), *Bala sankshya* (general debility) [3]. Among which faulty dietary habits lead to *Agnimandhya* and *Aam* formation i.e. generation of ROS and oxidative stress. In the management of *Bandhyatva*, various *Rasayan* and *Vajikaran* *Aushdhis* are mentioned. For the use of *Vajikaran* drug the basic principle is *Srotoshuddhi* (purification of channels). Without purification of bodily channels, results of *Vrishya yoga* (Aphrodisiac drugs) could not be attained. *Shodhan chikitsa* as *Vaman*,

Virechan & *Basti* should be done before prescribing *Vajikaran* drugs. (4). *Vaman* is a procedure in which *Doshas* (waste products and toxins) are eliminated through upper channels i.e. mouth. Specially, the *Kapha* and *Pitta Dosh*a brought to *Amashya* (stomach and duodenum) from all over the body by specific premonitory procedures and then eliminated out by inducing the emesis. *Virechan* similarly eliminates *Pitta dosha* from body by inducing purgation. These purificatory measures reduce oxidative stress in the body and enhances the effectiveness of *Rasayn* and *Vajikaran* drugs. A study observed the increase in SOD (Superoxide dismutase) and GSH (Glutathione) levels and decrease in MDA [Malondiadehyde] levels provide the evidence of free radical scavenging activity and antioxidant sparing effect of *Sanshodhan* therapy [5]. In Ayurveda it has been mentioned that the emotional state and dietetics of mother are going to affect fetal development in utero [6]. Therefore, the expectant mother should follow proper diet along with good life style in order to prevent the factors likely to harm the fetus. The modern concept of epigenetics corroborates the ancient findings. Epigenetic modifications are chemical changes to DNA and chromatin proteins that regulate gene expression without changing the DNA sequence. Maternal nutrition during pregnancy can induce epigenetic alterations in the fetal genome, such as changes in DNA methylation. These epigenetic alterations can alter gene expression in the offspring without changing the DNA sequence. Environmental factors, such as maternal lifestyle, including diet and level of physical activity or sedentary time, may also be associated with epigenetic modifications. Maternal weight during pregnancy was also associated with altered methylation patterns in the child's DNA and later infant adiposity. Offspring in both underweight and overweight mothers were reported to have altered DNA methylation patterns. Poor diet lacking in nutrients- like iodine, iron, folate, calcium and zinc- can cause anaemia, pre-eclampsia, haemorrhage and death in mothers. They can also lead to stillbirth, low birthweight, wasting and developmental delays for children [7]. These environmental and dietary factors affect metabolism at cellular level by creating oxidative stress and DNA damage. To combat these damages and attaining healthy conception and child, preparation of body should start from *Ritukala* in which light diet [*Shali* rice, *Yavann*], strict hygiene, avoidance of coitus and specific do's and Don't are mentioned. *Garbhadhan vidhi* consists of prerequisite characteristic of couple like age, kala, name, phenotype that is ideal for healthy conception. Besides it before trying for conception the couple should undergo *Samshodhan* [biopurification), consume light diet, male should take *madhuraushdh sadhit ghrith evum kshir* and female should eat *taila masha*. *Putreshti yagya* is mentioned by Kashyapa for psychological wellbeing of couple [8]. *Rasayan* drugs like *Amalaki*, *Ashwgandha*, *Brahmi*, *Shankhpushpi*, *Guduchi*, *Yashtimadhu* etc all are having free radical scavenging, antioxidant, anti-inflammatory, chemoprotective and immunomodulatory effects. Ayurveda contains a particular group of *Rasayan* herbs, called *Vajikaran*, that deals with nourishment and stimulation of sexual tissues, improves reproductive vitality and deals with oxidative stress via antioxidant mechanism [9,10]. After conception, under *Garbhini Paricharya*, Ayurvedic literature is full of diet and lifestyle related practices that prevents oxidative stress related damage to DNA of growing fetus in the womb, as fetus in utero consumes nutrients from mother through placenta.

Based on the current findings, the presence of oxidative stress has a significant impact on the quality of gametes and embryos when performing assisted reproductive techniques (ART). Unfortunately, in vitro manipulation of these cells exposes them to a higher level of reactive oxygen species (ROS). Oxidative stress can damage DNA, lipids and proteins and can be caused by many factors, including ART drugs and their metabolic products. Here are some ways to reduce oxidative stress in ART:

- 1) Light filters: Use light filters to reduce environmental factors in an IVF laboratory.

- 2) Add antioxidants to maturation medium to reduce the risk of oxidative stress and DNA damage.
- 3) Moderate exercise
- 4) Heathy diet: Eat a heathy diet high in antioxidant- rich foods, Vitamin C, vitamin E and beta-carotene are often referred to as “antioxidant vitamins” and have been suggested to limit oxidative damage in humans.
- 5) Limit exposure to environmental pollutants with oxidizing properties and limit exposure to sun [11].

Ayurveda can help by reducing oxidative stress in the body of couple by going through *Samshodhan* before ART. Besides it *Uttarbasti* with medicated oils can improve the receptivity of endometrium for embryo implantation by reducing oxidative stress at that level.

Oral use of *Rasayan*, *Vajikaran* drugs along with healthy dietary practices as mentioned in Ayurveda can improve the outcome of ART. Yoga and meditation will improve the physical as well as mental health of couple and reduce oxidative stress. At the level of culture medium adding the extract of *Rasayan* drugs with proved antioxidant properties could be tried and explored.

RESULTS

Oxidative stress is a double-edged sword, who controls many physiological functions of body. But imbalance in production of reactive oxygen species and level of antioxidants in body leads to many diseases. High level of oxidative stress has adverse effect in reproductive health. Which is the major cause of infertility among couples. Reducing oxidative stress by following healthy diet and lifestyle can improve reproductive health and even aid in infertility management by using Artificial reproductive techniques (ART). In Ayurveda specific dietary and lifestyle guidelines are mentioned in the form of *Rajahswala Paricharya*, *Garbhadhan Vidi*, *Garbhini Paricharya*, *Rasayan*, *Vajikaran* in relation to getting healthy progeny. *Bandhyatva* management is mentioned by following *Pathya-Apathya* and *Aushdhi* etc. *Samshodhan* therapy along with *Rasayan* and *Vajikaran* have proven antioxidant action. In Ayurveda *Aama* can be correlated to oxidative stress. By following advocated dietary regimen *Agnibala* can be preserved and optimum *Agnibala* curtails the production of *Aama* i.e. reactive oxygen species (ROS).

CONCLUSION

Ayurvedic therapeutics by rectifying metabolism and cellular health can improve reproductive health and aid modern techniques like ART and other therapies used in infertility for better outcome.

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