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LACTOFERT tablet: A comprehensive nutrient support to boost reproductive health in women

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ABSTRACT

Infertility can be defined as a lack of pregnancy after one year of regular unprotected intercourse. Approximately 15%-20% of couples of reproductive age are infertile, which can be attributed equally to both male and female factors.

Nutritional supplements may play an important role in optimizing fertility health, leading to improved conception rates, particularily in cases of menstrual irregularity or unexplained infertility.

LACTOFERT, A Female fertility tablet offers powerful & potent use in the management & optimization of reproductive health in women

INTRODUCTION

Infertility can be defined as a lack of pregnancy after one year of regular unprotected intercourse. Approximately 15%-20% of couples of reproductive age are infertile, which can be attributed equally to both male and female factors.

Recent research on the role of reactive oxygen species (ROS) in human infertility has received a great deal of interest from the scientists and medical practitioners [1-3].

Reactive oxygen species (ROS)

Reactive oxygen species (ROS) are oxygen derived molecules, which are formed a sinter mediary products and are a class of powerful oxidants in the human body. ROS include superoxide anion ($O^{-}2$), hydrogen peroxide (H2O2) and hydroxyl radical (OH.). Some cells posses' specific mechanisms to produce ROS that are required for cellular functions in low concentrations [4]. Aerobic environment is a constant source of ROS through in vivo mechanisms such as electron leakage during biologic oxidations, and by physical activation of oxygen by external agents such as irradiation, e.g. UV sunlight. ROS are characterized by their ability to react with any molecule they come in contact and modify it oxidatively. The modification may result in structural and functional alterations and impair many cellular processes. Depending on their tissue concentration they can either exert beneficial physiologic effects (e.g. play role in fertilization process) or pathological damage to cellular components, including lipids, proteins and nucleic acids [5].

Antioxidant Defense system against ROS

Organisms have developed efficient protective mechanisms against excessive accumulation of ROS. ROS are neutralized by an elaborate antioxidant defense system consisting of enzymes such as catalase, super oxide dismutase and glutathione peroxidase/reductase, and numerous non-enzymatic antioxidants such as vitamin C, vitamin E, vitamin A, pyruvate, glutathione, taurine and hypotaurine [6]. In a healthy body, pro-oxidants and antioxidants maintain a ratio and a shift in this ratio towards pro-oxidants gives rise to

oxidative stress. This oxidative stress may be either mild or severe depending on the extent of shift. Whenever ROS levels become pathologically elevated, antioxidants begin to work and help minimize the oxidative damage, repair it or prevent it altogether. The male and female genital tracts are rich in both enzymatic and non-enzymatic antioxidants [7-10].

Vitamins C and E act as chain-breaking antioxidants and thus prevent the propagation of peroxidative process.

ROS AND CELL INJURY

Lipid peroxidation

ROS can attack polyunsaturated fatty acids in the cell membrane leading to a chain of chemical reactions called lipid peroxidation. Fatty acid break down results in the formation of various oxidatively modified products, which are toxic to cells and are finally converted into stable end products. The spermatozoa membrane contains large amounts of poly unsaturated fatty acids [11], which maintain its fluidity. Peroxidation of these fatty acids leads to the loss of membrane fluidity and a reduction in the activity of membrane enzymes and ion channels. As a result, the normal cellular mechanisms that are required for fertilization are inhibited. It is possible to measure the extent of peroxidative damage by estimating the stableend products of lipid peroxidation such a small on dial dehyde [5].

DNA damage

Susceptibility of DNA to oxidative damage is indicated by the presence of oxidatively modified substances like 8-hydroxy-2-deoxyguanosine.

Deoxyribonucleic acid bases and phosphodiester backbones are sites that are susceptible to peroxidative damage. High levels of ROS mediate the DNA fragmentation that is commonly observed in thespermatozoa of infertile men [12, 13]. Normally, sperm DNA is protected from oxidative insult by its specific compact organization and by antioxidants in the seminal plasma. Spermatozoa are unique in that they cannot repair DNA and depend on the oocyte for repair after fertilization [14]. Various types of DNA abnormalitiesoccur in sperm that have been exposed to ROS artificially. These abnormalities include base modification, production of base-free sites, deletions, frame shifts, DNA cross-links and chromosome all rearrangements [15, 16]. Patients with high levels of oxidative stress in their seminal fluid were found to have sperm with multiple single and double DNA strand breaks [17]. A biomarker for oxidative DNA damage, 8-hydroxy-2-deoxyguanosine, can be used to determine the extent of ROS-induced DNA damage.

Apoptosis

ROS may also initiate a chain of reactions that ultimately lead to apoptosis. Apoptosis is a natural process in which the body removes old and senescent cells; it is a process of programmed cell death. In humangerm cells, apoptosis may help remove abnormal germ cells and prevent their overproduction. Multiple extrinsic and intrinsic cell factors control the process of apoptosis [3]. The process of apoptosis may also be accelerated by ROS-induced DNA damage and ultimately may lead to a decline in sperm count [6].

MEASUREMENT OF OXIDATIVE STRESS

Oxidative stress can be estimated directly or indirectly. The direct measurement of ROS is by using electron spin resonance method and is used sparingly in reproductive medicine. Indirect tests measure oxidatively modified products. Chemiluminescence is a common method used and is based on emission of light on chemiluminescent reaction between ROS and reagent (luminal/lucigenin). The amount of light emitted is quantified and measured by a lumino meter.

Lipid peroxidation end products like malondialdehyde, lipid hydroper oxides, and conjugated dienes are commonly used to assess the oxidative stress.

Other methods are measurement of protein and DNA oxidation products, and changes in status of antioxidants. Flow cytometry is also being used to measure the individual ROS radicals [18].

ROS-TAC score

It is a concept to represent the oxidative stress status of individual more accurately. This score accommodate for the variations in both ROS and TAC (total antioxidant capacity) values [19]. Fertile men tend to have high ROS-TAC scores where asinfertile men generally have significantly

lower scores. ROS levels can also be measured directly in neat semen, thereby offering yet another measure of oxidative stress.

Role of Oxidative Stress in Male Infertility

The presence of free radicals in the spermatozoa was reported by MacLeod 50 years ago [20]. Because spermatozoa lack cytoplasmic enzymes, they often are unable to prevent oxidative damage by these free radicals. This is one of the features that make spermatozoa highly susceptible to peroxidative damage. Most cytoplasmic enzymes are extruded during the final stages of the sperm maturation process, which enables sperm to attain their characteristic morphology [21]. Nature compensated for this deficiency by providing an array of antioxidants in the seminal plasma.

Sources of ROS

Morphologically abnormal spermatozoa and leukocytes are the major sources of ROS in the male reproductive tract. Even though mature spermatozoa may not produce pathologically significant levels of ROS, oxidative damage may occur in the epididymis and seminiferous tubules where they are in close contact with the immature, ROS producing spermatozoa and leukocytes [22].

ROS production is elevated in patients who have a large percentage of spermatozoa with excess residual cytoplasm in the mid piece [22]. Excess residual cytoplasm contains enzymes such as glucose-6-phosphate dehydrogenase and creatine phosphokinase, which are linked with generation of ROS and defective sperm function. ROS may be generated at the level of plasma membrane (NADPH-oxidase system) (23) or mitochondria (NADH-dependent oxido-reductase) [24].

Human spermatozoa generate O2 [25], which spontaneously or enzymatically dis mutates to H2O2. In the presence of metal ions (iron)-O2((and H2O2together produces the more harmful oxidant, OH.. Neutrophils and macrophages are the major source of oxidants in the reproductive tract [26, 27]. During inflammation and infection, activated leukocytes can produce significantly high era mounts of ROS than non-activated leukocytes [28]. The ROS production in leukocytes is through NADPH oxidase enzyme. Even though ROS is released as part of defense mechanism in to there productive tract, it can damage surrounding spermatozoa, especially when antioxidant systems are overwhelmed. The importance of leukocyte contamination in producing ROS is well observed in Percoll-washed spermatozoa where a small number of leukocytes produce ROS. Increased levels of seminal leukocytes may also stimulate human spermatozoa to produce ROS. Such stimulation may be mediated via direct cell-cell contact or by soluble products released by leukocytes [27].

Mechanism of loss of sperm function by ROS

ROS may affect the quality and number of spermatozoa reaching the ovum in the female reproductive tract. In addition, ROS impair the fertilization process by preventing the initiation of sperm-oocyte fusion events (14). Finally, ROS can impair embryo development and affect the health of offspring by damaging sperm DNA (16).

Impairment of standard semen parameters

Motility is a very important attribute unique to spermatozoa in entire human cells. Motility is indispensable to the spermatozoa, as it has to travel the female reproductive tract to reach the site of fertilization. Studies found that levels of ROS correlate with motility of spermatozoa [30, 31]. In-vitro studies showed that the impaired motility maybe a temporary event or permanent phenomena.

Excessive ROS causes ATP to deplete rapidly resulting in decreased phosphorylation of axonemal proteins and cause transient impairment of motility [32]. Peroxidative damage to the sperm membrane and axonemal proteins appears to be the cause of permanent impairment in sperm motility. ROS appears to play a role in the apoptosis of spermatozoa by activating caspases. Under normal conditions, abnormal sperm undergo apoptosis, which minimizes their presence in the semen. These verity of oligozoospermia has been correlated with excessive levels of ROS [33]. ROS may stimulate the process of apoptosis, resulting in the death of spermatozoa and decreased sperm count [6]. Patients with a low sperm count have a reduced chance of initiating a pregnancy.

Impairment of sperm-oocyte fusion

A minimal amount of ROS is required for the normal sperm-oocyte fusion. Spermatozoa and oocyte has inbuilt mechanism to prevent excessive production of ROS at the time of sperm-oocyte fusion, this may be by the release of SOD

(superoxide dismutase) [35]. If there is anabnormality in the production of SOD, ROS generation can continue uninterruptedly and damage both spermatozoa and oocyte. The affect of ROS on sperm fertilizing capacity cannot be quantified by measuring routine semen parameters. It is possible that the levels of ROS needed to impair sperm-oocyte fusion events are lower than those required to affect sperm motility. The inability of sperm to fuse with an oocyte appears to be due to the effects of ROS on the sperm membrane. The lipid peroxidation process results in loss of membrane fluidity due to disorganization of membrane architecture and reduction in the activity of membrane enzymes and ion channels. As a result, spermatozoa are unable to initiate the necessary biochemical reactions associated with acrosome reaction, zona pellucida binding and oocyte penetration [36, 37].

Sperm DNA damage

Sperm DNA contributes the half of genomic material to the offspring. Thus, normal sperm genetic material is required for fertilization, embryo and fetus development and postnatal child well being [16, 38]. A recent study showed decreasing likelihood of pregnancy with increasing levels of 8-hydroxy-2-deoxyguanosine, an indicator of oxidative damage to DNA [39]. The percentage of sperm with DNA damage is negatively correlated with the fertilization rate [12]. Oocytes can repair DNA damage to some extent, but when the damage is severe, embryo death and miscarriages can occur. The affect of ROS on DNA integrity has become the focus of recent attention due to widespread use of assisted reproduction techniques (ART) such as intra cytoplasmic injection (ICSI). In natural pregnancy, oxidative damage to the sperm membranemay ensure that spermatozoa with damaged DNA lose their ability to fertilize an oocyte. How ever, sperm with DNA damage can potentially be injected into an oocyte in the ICSI resulting in fertilization and pregnancy which may progress to live birth with congenital abnormalities [34].

ROS & Male infertility

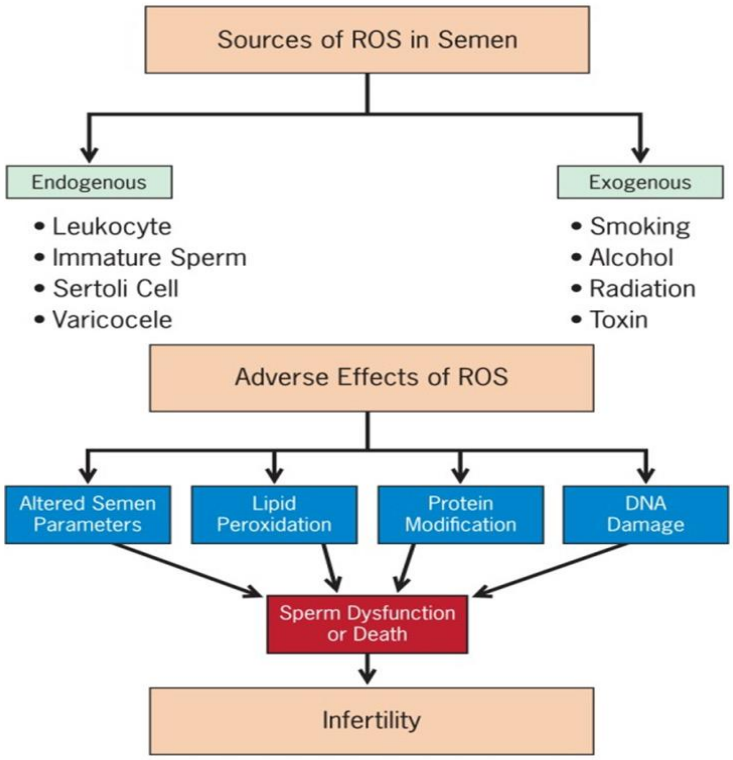


Figure 1: Common sources of excessive reactive oxygen species (ROS) in semen and their deleterious effect

Many clinical conditions were found to be associated with increased oxidative stress [33]. Infections and inflammations involving the male reproductive tract are obvious conditions associated with oxidative stress in view of excessive generation of ROS by leukocytes [40-42]. Very high percentage of spinal cord injury patients were reported to have elevated levels of oxidative stress [43, 44].

Mechanism of infertility in patients with varicoceleis poorly understood and ROS is postulated as a possible mediator [45, 46]. Elevated levels of ROS and depressed levels of TAC were associated with varicocele [47-49]. Patients who under went vasectomy reversal also had high levels of reactive oxygen species [50, 51]. A history of smoking was associated with high levels of oxidative stress [52].

ROLE OF ROS IN FEMALEINFERTILITY

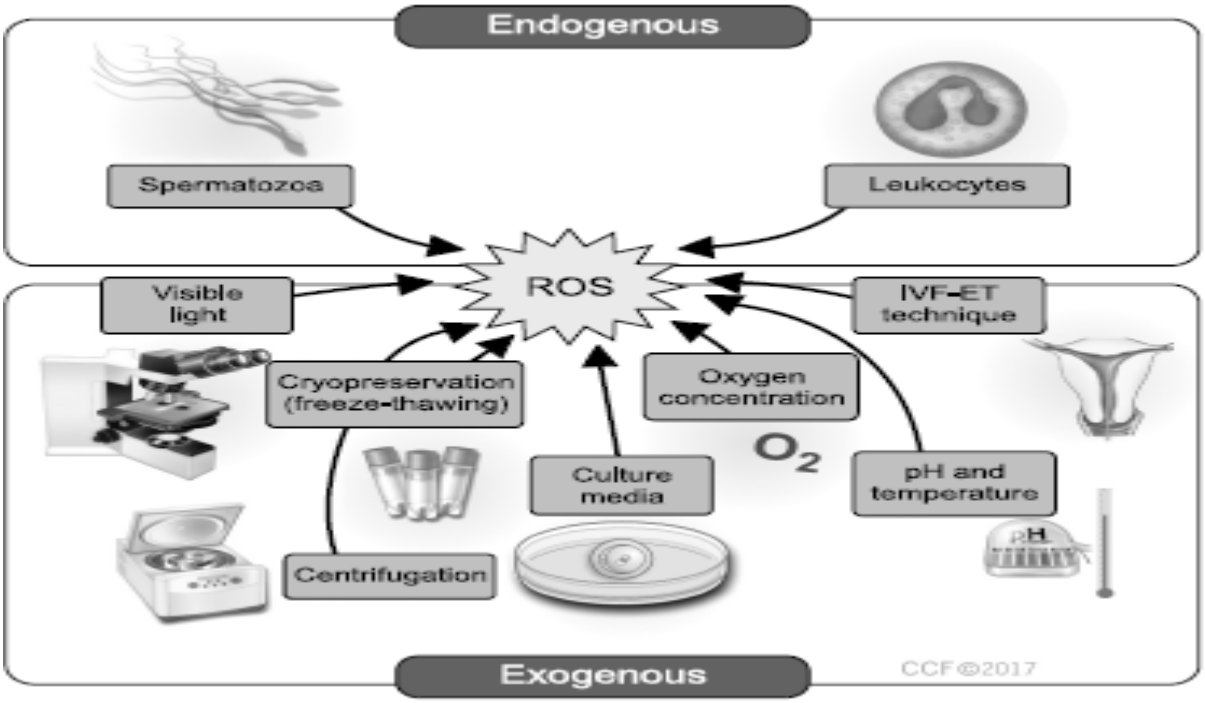


Fig. 2. Sources of reactive oxygen species (ROS) in the assisted reproduction setting. IVF-ET: *in vitro* fertilization-embryo transfer.

Many studies reported the presence of oxidative and antioxidant systems in various female reproductive tissues [53-57]. ROS appears to have physiological role in female reproductive tract in many different processes such as: oocyte maturation, fertilization, luteal regression, and endometrial shedding [58, 59]. ROS levels in follicular fluid maybe used as markers for predicting the success of in vitro fertilization (IVF) [3].

Whenever there is imbalance in the levels of ROS and antioxidants- damage can occur to oocytes and embryos through various pathological mechanisms. Oxidative Stress can affect the female fertility potential in number of ways. It may affect the ovulation, fertilization, embryo development and implantation. The sources of ROS in Graafian follicle may be macrophages, neutrophils and granulosa cells. Follicular fluid contains high levels of antioxidants, which protect oocytes from ROS-induced damage. Significantly lower selenium levels were detected in follicular fluid of patients with unexplained infertility compared with those with tubal infertility or couple swith male factor infertility [60]. Another study reported that baseline TAC levels were higher in follicles whose oocytes fertilized successfully (61).Elevated levels of ROS in peritoneal fluid may be the cause of infertility in some women who do not have any other obvious cause. Elevated levels can damage the ovum after its release from the ovary, the zygote/embryo and spermatozoa are very sensitive to oxidative stress.

Studies have compared ROS levels in peritoneal fluid between women undergoing laparoscopy for infertility evaluation and fertile women undergoing tubal ligation. ROS level sin the peritoneal fluid were significantly higher in the patients with idiopathic infertility compared with the fertile women [57, 62]. High levels of malondialdehyde and low levels of antioxidants in the peritoneal fluid were reported in patients with unexplained infertility compared to controls [63].

Oxidative stress& its role in endometriosis

Oxidative stress is postulated as one of the possible mechanism of endometriosis. [64]. The endometrial tissue has multiple cells like macrophages, red blood cells, which can generate ROS. Studies of women with endometriosis have suggested that peritoneal macrophages are responsible for increased production of ROS or increased expression of xanthine oxidase in endometrial cells [65, 66]. High levels of oxidatively modified substances in peritoneal fluid and ectopic endometrial tissue were reported [67]. Altered expression of defensive anti oxidantenzymes and low levels of vitamin E were reported in patients with endometriosis [68].

Effect of ROS on Embryo Growth

Oxidative stress appears to have a detrimental effect on the development of embryo. ROS may originate from embryo metabolism and from the surrounding environment [71, 72]. ROS not only alters most types of cellular molecules but also induces early embryonic developmental block and retardation [56]. High levels of ROS and apoptosis were reported in fragmented embryos compared to non-fragmented embryos [73].

Effects of Oxidative stress on in-vitro fertilization

DNA damage induced by oxidative stress has important clinical implications in the context of assisted reproduction. Spermatozoa selected for ART most likely originate from an environment experiencing OS, and a large percentage of these sperm may have damaged DNA (2). There is a strong possibility that spermatozoa with damaged DNA maybe used during ART [16], which can negatively affect the ART success rate and increase the risk of spontaneous abortion or offspring with genetic disorders. ROS levels in mature spermatozoa correlate significantly with the fertilizing potential of spermatozoa [77, 78]. Estimating ROS levels may help predict the success rate of assisted reproduction procedures.

ROS and Sperm Preparation

A possible source of ROS in ART media is during the preparation of semen. Sperm preparation is necessary to enhance and maintain sperm quality and function after ejaculation before the semen specimen can be used for ART procedures [79]. The production of ROS may be due to either 1) activation of spermatozoa by centrifugation process, 2) absence of antioxidantrich seminal plasma, or 3) because of minimal contamination of ROS produced by leukocytes and abnormal spermatozoa. The small amount of ROS produced may not decrease motility but can still cause DNA damage [29]. A proper sperm preparation method should be selected so as to decrease the production of ROS.

THERAPEUTIC TREATMENT STRATEGIES AGAINST ROS

In both male and female reproduction, oxidative stress appears to be due to increased generation of ROS rather than a depletion of antioxidants. It isimportant to identify the source of increased ROS generation [80]. The underlying etiological factor for abnormal leukocyte infiltration (e.g.leukocytospermia, inflammation, infection, smoking) should be determined. Patients with history of smoking should be advised to stop smoking. Any exposure to drugs, toxic substances and radiation should be checked and patients advised to stop exposure to them. Infections of there productive tract should be treated with appropriate antibiotics.

Initially, specific therapeutic options directed against the etiological cause of raised ROS should be tried. Patients with reproductive tract infection should be treated with antibiotics. Anti-inflammatory agents may help patients with persistent leukocytospermia and elevated levels of cytokines.

After treating the primary cause (such as varicocele), patients can be advised to take antioxidant supplementation. Antioxidants can be started directly when a specific etiology cannot be identified (idiopathic infertility).

Male infertility

Pathophysiology of male infertility

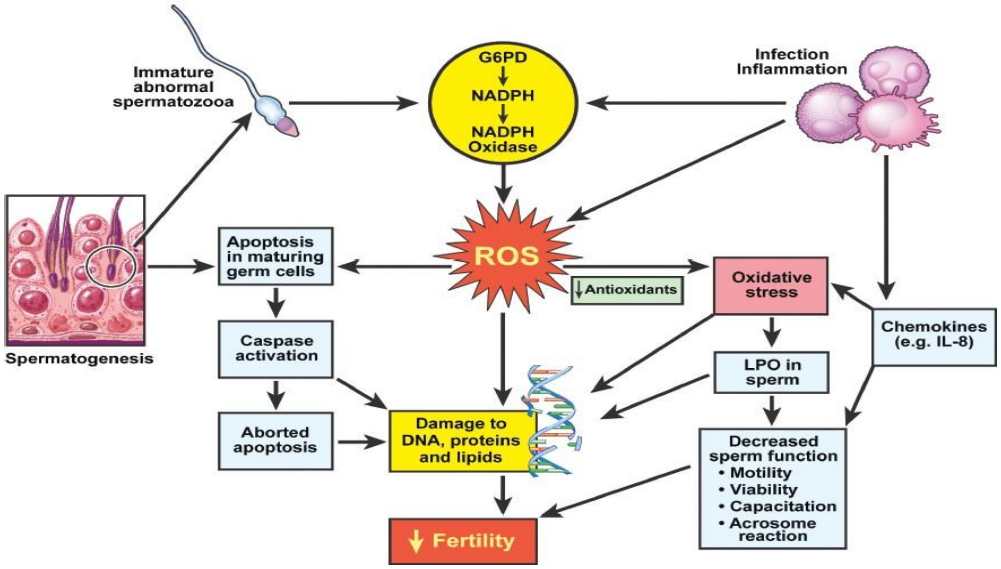


Fig 8: Pathophysiology of Male Infertility

Oxidative stress is an important aspect in male infertility

- Infertile men have very high levels of semen ROS
- Spermatogenesis is very sensitive to oxidative stress
- Protects sperm from oxidative damage
- Significantly improves sperm quality. Increases sperm count. Concentration, Motility, Morphology

Semen analysis should be repeated after a full spermatogenic cycle in those men showing large number of abnormal spermatozoa with excessive cytoplasm in the mid piece during a routine analysis. This can help distinguish between a temporary disturbance in spermatogenesis and a permanent defect in spermatogenesis.

Varicocelectomy may remove an unknown stimulus of ROS generation. Even though there is no definitive consensus on the use of antioxidants, many in vitro and in vivo studies have shown that they improve semen quality and fertility [80]. Some studies showed improvement in terms of pregnancy rate after antioxidants supplementation.

Oral vitamin E is an antioxidant favored by many researchers and clinicians. Oral administration of 300 mg twice a day of vitamin Ein a randomized double blind placebo control led trial showed significant improvement of pregnancy rates (21%; 11/52) in infertile (asthenozoospermic)patients, while resulting in lack of pregnancies in the placebo group. This study also found significant improvement in sperm motility, and reduced lipidper oxidation levels after vitamin E supplementation [81].

A combination of vitamin E and selenium inoligo as the note ratozoospermic (OAT) patients resulted in significant improvement in sperm motility, viability and morphology [82].

Treatment may be more appropriate if antioxidants are given to the patients with raised ROS levels.

The combination therapy of vitamins A plus E and essential fatty acids significantly reduced ROS and improved pregnancy rates [84].

Oral administration of 200 mg of Vitamin C, 200 mg of Vitamin E and 400 mg of GSH for 2months significantly improved serum levels of antioxidants and relatively decreased sperm DNA damage [13].

Female infertility

There are few studies on the role of antioxidants in female infertility (89, 90). Both the studies reported higher pregnancy rate with vitamin C supplementation compared to the control group. In vivo antioxidants may be helpful in infertile women

who smoke, as history of smoking is associated with high levels of oxidative stress [55].

Use of antioxidants in IVF media appears to be useful in improving the pregnancy rates. Higher implantation and pregnancy rates were found when antioxidant supplemented media was used rather than standard media without antioxidants [91].

Antioxidants, especially vitamin C, can improve the blastocyst development rate in a mouse embryo model [92].

In ART procedures, sperm preparation techniques separate mature spermatozoa and thus minimize the interaction between ROS producing cells in semen (e.g. leukocytes, immature abnormal spermatozoa)and normal spermatozoa. Density gradient separation and swim-up methods are commonly used sperm preparation methods. Adding antioxidants to the sperm preparation media may help prevent ROS induced damage and preserves the quality of spermatozoa during ART procedures.

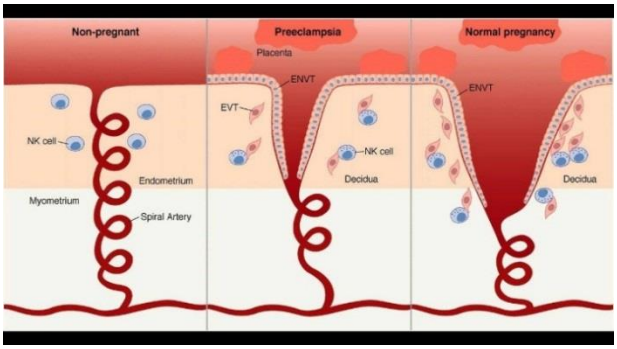
Composition of LACTOFERT tablet

- L-arginine 100 mg
- L-Carnitine-L-Tartrate 250 mg
- Zinc (as Zinc Sulphate) 6 mg
- Vitamin E 5 mg
- Vitamin C 20 mg
- Selenium 20 mcg
- L-Glutathione (Reduced) 25 mg
- Coenzyme Q1050 mg
- Vitamin B120.5 mcg
- Astaxanthin 10% 20 mg
- Lycopene 10% 20 mg
- DHEA 25 mg.
- L-Arginine100 MG

PHARMACOLOGICAL ACTION OF EACH INGREDIENTS

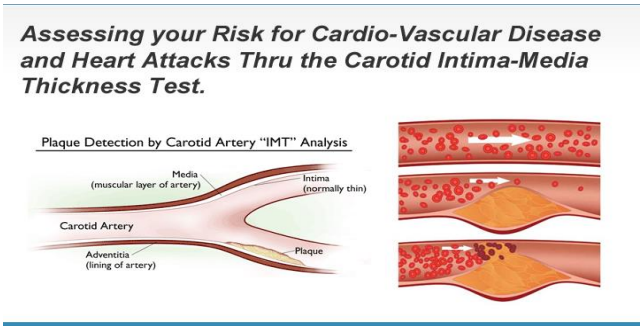
L-Arginine

Supplementation during pregnancy with a medical food containing L-arginine and antioxidant vitamins reduced the incidence of pre-eclampsia in a population at high risk of the condition.93 Antioxidant vitamins alone did not have a protective effect for prevention of pre-eclampsia. Development of blood vessels, and vascular endothelial growth factor protein expression in the endometrium.94 L-Arginine supplementation may be detrimental to embryo quality and pregnancy rate during controlled ovarian hyper stimulation cycles.



L-Carnitine-L-Tartrate

The study was performed to evaluate the effects of carnitine administration on carotid intima-media thickness (CIMT) and inflammatory markers in women with polycystic ovary syndrome (PCOS), carnitine administration for 12 weeks to participants with PCOS had beneficial effects on CIMT and plasma NO.



Zinc (as Zinc Sulphate)

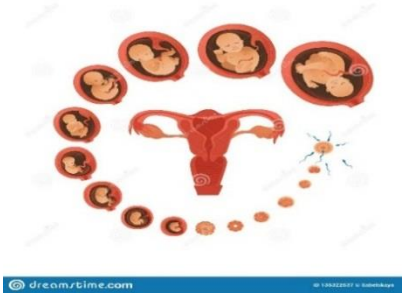
Zinc plays critical roles during embryogenesis, fetal growth, and milk secretion, which increase the zinc need for pregnancy and lactation. Increased needs can be met by increasing the dietary zinc intake, along with making homeostatic adjustments in zinc utilization [95].

Vitamin E 5mg

Vitamin E has received much attention in recent years due to its ability to improve reproductive health. Vitamin E has been reported to exert beneficial effects as an antioxidant against the reproductive disorders. Hence, it is highly recommended for women to consume [96].

Glutathione

Glutathione is the body's major antioxidant which helps in preserving all other antioxidants.. It has been confirmed that it plays an important role in maintaining the biological value of germ cells, and it has been implicated in the fertilization process and early embryo development.



Embryo Development Circle

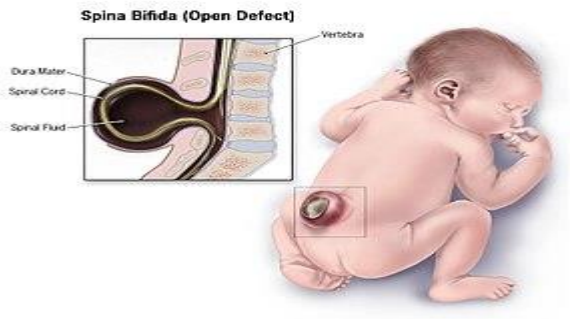
CoQ10

Pretreatment with CoQ10 increases ovarian response to stimulation and improves oocyte and embryo quality in young low prognosis patients with diminished ovarian reserve. There is a possible beneficial effect on clinical pregnancy and live birth rates [97]. The age-related decline in oocyte quality and quantity could be reversed by the administration of CoQ10. And also, mitochondrial and reproductive phenotypes observed in the old females including reduced ATP production and increased meiotic spindle abnormalities, resulting in infertility. Ovarian reserve in the oocyte-specific *Pdss2*-deficient animals was diminished, leading to premature ovarian failure which could be prevented by maternal dietary administration of CoQ10 [98].

B12 in pregnancy

Early detection of a vitamin B12 deficiency before becoming pregnant and prevention of maternal micronutrient deficiencies in the periconceptional period is a possible path to avoid some complications during pregnancy and reduce health problems in the infant.

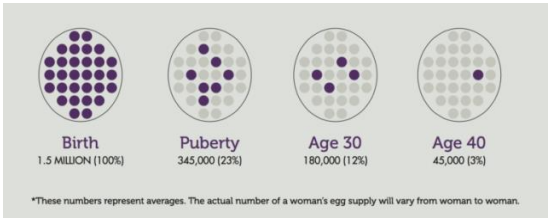
Women with the lowest B12 levels had 5 times the risk of having a child with a neural tube defect compared to women with the highest B12 levels. [99]



B12 levels during pregnancy are associated with increased risk of preterm birth, particularly in B12-deficient women. [100]

Astaxanthin

Astaxanthin exhibits free radical scavenging, singlet oxygen quenching, and antioxidant activities which could probably positively affect animal and human health. [101]



DHEA

DHEA supplementation seems to improve the ovarian environment where follicle maturation takes place, and appears to function by acting on the androgen receptors that are expressed on the granulosa cells and ovarian stroma, resulting in increasing antral follicle counts and AMH levels, and therefore ovarian reserve. [102]

Lycopene

Women in the lycopene supplementation group had significantly lesser incidence of growth restricted babies and had a significantly better perinatal outcome compared to women in the placebo group. lycopene supplementation does seem to help in reducing the incidence of intra-uterine growth restriction. [103]

Vitamin C

The regular supplementation of ascorbic acid to pregnant women proved to reduce hospitalization rate during pregnancy and provide overall mother-to-child health benefit, also to be safe as no patient complained or withdrew from the study due to side effects. Our results indicate the benefit of adding vitamin C in the guidelines of multivitamin supplementation to pregnant women [104]

Selenium

As the interpretation of maternal selenium status is hampered in pregnancy, due to numerous physiological changes, we suggest to use clinical infant outcome in order to establish selenium cut off levels in pregnancy. In a Norwegian population of healthy pregnant women, a low maternal selenium status was associated with a lower psychomotor score at 6 months and an increased risk of infant infection during the first 6 weeks of life.

Dosage: BID

Indications: Preconception, Poor ovarian response, Diminished Ovarian Reserve, Neural tube defects, IUGR, IVF, Embryogenesis.

Contra-Indications

Known contraindications to any ingredients of the supplement. The drug may interact with Anti-Epileptic Drugs. Avoid consumption of Alcohol

Safety

- It is generally well tolerated and has no severe adverse effect.
- It has an excellent safety record in both animal & human investigations.

Side-Effects

Epigastric pain/tenderness, heartburn, diarrhea and nausea vommiting etc.

Special Precautions

Take with or directly after meals to lessen the possibility of gastrointestinal upset.

Storage Conditions

- Store in a cool & dry place below temperature 25^{o}C, protected from light.
- Keep out of reach of children.

Storage Life Is 2 Years

The preparation should not be used after the expiry date.

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