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RESEARCH ARTICLE

A REVIEW ON THE ROLE OF OXIDATIVE STRESS IN FEMALE INFERTILITY.

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Abstract

Oxidative stress result from imbalance between free radicals formation and antioxidant defence in the body. It is a process that influences entire reproductive cycle of a woman from gametogenesis, fertilization, pregnancy and embryo development. Both ROS and RNS act as signal molecules in physiological and pathological processes of female reproductive tract. Several in vitro and in vivo studies on reproductive organs lead to observation that free radicals attack and oxidize membrane macromolecules which when accumulate, amplify tissue damage and cell death. Structural identification and characterization of compounds of plant origin capable of either boosting the endogenous antioxidants or scavenging these radicals accumulating in reproductive cells is needed to minimize the dangerous effects and explore the relationship between oxidative stress and female infertility. Nowadays, scientists are on investigations on the role of oxidative stress on the current events of infertility and development of therapeutic approaches for limiting infertility aggravated by oxidative stress. There is strong evidence of increased free radical generation in pregnancy which leads to oxidative stress. This article reviews the role of ROS and RNS in both physiological and pathological processes leading to female infertility.

Introduction:-

Complex interaction between oxidants and antioxidants modulate various physiological processes in the body via oxidative stress. Reactive radicals are neutralized into stable compounds in the body by antioxidants. Under stress conditions however, free radicals attack membrane proteins, carbohydrates and lipids initiation cascade of reactions to attain stability (Dean *et al*., 1997). The consequence of these reactions are alterations in various cellular activities exerted by enzyme inhibition, lipid damage, inhibition of protein synthesis, DNA protein cross links and ATP depletion. Free radicals generated under controlled conditions are however, important in cell homeostasis as key signal molecules in multiple physiological processes and in excess, precipitate pathological events (Wiseman and Halliwell, 1996). In female reproductive system, free radicals generation and oxidative stress have been proven to be involved in follicular and endometrial growth, oocyte maturation, embryo development, ovarian steroidogenesis, ovulation, menstrual cycle and fertilization process (Madamanchi *et al.*, 2005). This paper highlights briefly the role of oxidative stress and the mechanism in which oxidative stress leads to female infertility.

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Patho-physiology of oxidative stress in female reproduction:-
Excessive free radicals formation in antioxidants deficient cells lead to oxidative stress implicated in the modulation of endometriosis, uterine wall and steroidogenesis by modifying gene expressions via transcription factors (Ishikawa, 1993). It also play roles in maintaining normal reproductive functions and pathogenesis of female infertility (El Mouatassim *et al.*, 1999). Nowadays, scientists are on investigations on the role of oxidative stress on the recurrent events of pregnancy loss and referred it as multifactorial involving environmental and genetic factors.

Angiogenesis and oxidative stress:-
Angiogenesis involves formation of new blood vessels from pre-existing ones and takes place in oxygen deficient tissues which, invariably triggers induction of angiogenic factors. Angiogenesis, is considered key a factor for maintenance of endometrium, development of embryo, growth and development of follicles, and cyclical regeneration of endometrium after menstrual cycle (Geva and Jaffe, 2000; Bausero *et al.*, 1998; Gordon *et al*., 1996). It is a process which ensures continuous supply of blood and nutrients. During angiogenesis, released cytokines from fetal and maternal interface support embryo implantation in the endometrium and prevent implantation failure (Choi *et al.*, 2003). Female secondary sex hormones especially oestrogen promotes endothelial growth factors in preparation of endometrium for implantation and fertilization (Albratech *et al.*, 2003).The main mechanism of ROS generation in angiogenesis involves the catalytic action of NADPH oxidase which induce expression of vascular endothelial growth factors (VEGF) signalling angiogenesis and endothelial NADPH oxidase triggering the release of cytokines.

In the endometrium, increased formation of ROS causes shedding and degeneration of endometrium via activation of cyclooxygenase and transcription factor NF kappa β. These actions increase prostaglandin F2 α leading to menstrual blood flow (Sugino *et al.*, 2001). Studies by Sugino *et al.* (1996) on changes in activity of superoxide dismutase in human endometrium throughout the menstrual cycle connected the increased ROS generation to decreased expression of SOD enzyme in the late secretory phase. Moreover, activation of macrophages in the peritoneal fluid during endometrial shedding may increase generation of ROS and play roles in the etiology and pathogenesis of endometriosis. This was confirmed from studies by Shanti *et al.* (1999) who found an increased levels of auto antibodies related to oxidative stress in women with endometriosis. Lysophosphatidyl choline, which is a chemotactic factor for T-lymphocytes and monocytes was expressed in women with endometriosis based on studies by Murphy *et al.* (2000). The expression of lysophosphatidyl choline might suggest involvement of minimally oxidized low density lipoprotein in peroxidation of endometrial wall (Murphy *et al.*, 2000).

Reactive Oxygen Species in ovary:-
Significant evidence demonstrate the presence of reactive oxygen species (ROS) such as hydrogen peroxide (H_2O_2), superoxide radical (O_2), hydroxyl radical (OH) in mammalian ovary and their biomarkers such as superoxide dismutase, glutathione peroxidase, gamma glutamyl synthetase and lipid peroxides that play roles in maintaining normal ovary functions (Behrman *et al*., 2001; Evans *et al.*, 2004; Guerin *et al.*, 2001). These biomarkers play roles in development of follicles and regulate processes involved in oocyte maturation, steroidogenesis and folliculogenesis (Suzuki *et al.*, 1999). Studies by Shiotani *et al.* (1991) on immunohistochemistry of antral follicles revealed the presence of antibody to Ad4-binding protein, which is a steroidogenic transcription factor that causes transcription of enzymes involved in steroidogenesis. This suggests a close association between steroidogenesis and oxidative stress.

Another important role of ROS in the pathophysiology of female infertility include the inhibition of progesterone secretion by hydrogen peroxide. Vega *et al.* (1995) demonstrating the effect of hydrogen peroxide on progesterone and estradiol observed a significant reduction in the quantity of both progesterone and estradiol hormones on addition of H_2O_2 to culture of human chorionic gonadotropin (HCG), which suggest inhibition of steroidogenesis. The study also revealed the expression of superoxide dismutase (SOD) by HCG which may have important role in maintenance of corpus luteum and prevention of miscarriage during pregnancy. It is worthy of note that oxidative stress biomarkers help to maintain low levels of hydro-peroxides inside the follicle, ensure continuous processes of gametogenesis and maintain fertilization process of zygote formation.

Nitric oxide synthase in female reproduction:-
In mammalian body, coordination involves an interplay of nervous and endocrine systems. Endocrine roles involve complex interaction of autocrine, paracrine and endocrine action leading to formation of viable oocyte, maturation of follicles and granulosa cells and processes associated with ovulation and luteinisation. These paracrine, autocrine

and steroid hormones act through complex multiple signalling involving both *cGMP* and *cAMP* pathways. These effects produce NO via *cGMP* as vaso-relaxant and generation of peroxynitrite from interaction of NO with superoxide radicals that increases nitrosation and oxidative stress burden of several reproductive organs (Hanafy *et al.,* 2001). Generally, NO is produced by nitric oxide synthase during the enzymatic conversion of arginine to citrulline. The enzyme is present in the endothelial cells, neuronal cells and denoted as eNOS, nNOS and iNOS for inducible nitric oxide synthase respectively. Generally, NO helps in reproductive functions (positive and negative) of the female mammals in the following important ways:

1. NO produced by eNOS and nNOS provides a media for the increased supply of blood to endometrium, an event that ensures embryo development and maintain pregnancy.
2. The NO generated by inducible NO synthase is important in destruction of pathogens and abnormal cells in the body but may destroy normal host tissue and cells. i.e NO produced by macrophages in response to entry of microbes kills abnormal cells and pathogens, helpful in reproductive functions but may damage normal host cells and tissue especially in the expression of inducible NO synthase.
3. In the fallopian tube, deficiency of NO may contribute to oviduct motility dysfunction, retention of ovum and delayed sperm motility attributed to decrease relaxant effect on smooth muscles. High levels of NO in the fallopian tube on the other hand, are highly cytotoxic to microbes and sperm, thus inhibiting normal sperm motility for fertilization (Rosselli *et al*., 1999).
4. Inducible NO produced by inducible NOS play roles in the development of theca and stromal cells of the ovary which are important in the preparation of endometrium for implantation. Its presence in the endometrial vessels was shown by Tseng *et al.* (1996) while examining endometrium and myometrium for NOS expression
5. NO play roles in controlling the contraction of uterine, relaxation of uterine and oviduct muscles especially during pregnancy in the presence of progesterone. This role was examined by (Ho *et al*., 1997) who, in their studies, found a significant decrease in NO with increase in the contraction of uterine during proliferative and pre-ovulatory phases. Contrary to this action however, a positive correlation between NO and long term heavy bleeding was observed in studies by (Arumugam and Dip, 1995). This action suggests the involvement of NO in the pathophysiology of menorrhagia.
6. High NO levels in the peritoneal fluid of macrophages during infections could interfere with the processes of ovulation, gamete transport, oocytes fertilization by sperm and embryo development which, in turn cause infertility (Ho *et al*., 1997). These high levels indicate involvement of NO and other ROS in the pathogenesis of infertility. Moreover, studies by Polak *et al.* (2001) found higher levels of NOS enzyme activity in peritoneal macrophages produced in response to immune stimulation. These high levels of NO adversely affect sperm motility, implantation and oviduct functions suggesting that reduced levels of NO blocks NO effects in improving fertility in women.
7. Various cytokines are secreted by endometrial cells, macrophages and other immune cells which stimulate endothelial NO synthase release. On the event of O.S, these abnormal immune responses might stimulate macrophages to persistently produce large amount of NO and inhibit implantation. Thus contribute to infertility (Ota *et al*., 1999).
8. NO is a regarded potential factor involved in folliculogenesis and steroidogenesis in the ovary. Its role in this capacity is that it activates various iron containing enzymes and binds to the heme containing enzyme guanylate cyclase, which forms cGMP. Studies by Sugino *et al.* (1996) revealed high plasma concentrations of NO during ovulation. Another striking finding to explain the effect of NO on steroidogenesis in ovaries was a study by Van Voorhis *et al.* (1994) which demonstrated high levels of endothelial NO synthase expression in human corpus luteum in the mid and early luteal phase and less quantity in the late luteal phase.

The mechanism of NO in steroidogenesis involves increased prostaglandin synthesis via activation of cyclooxygenase and by apoptosis (Van Voorhis *et al.,* 1994). Growth of the follicles and apoptosis are considered important processes involved in folliculogenesis and NO is involved in these processes due to vaso-relaxant effect. High concentration of NO together with superoxide produced by NO synthase may cause tissue damage and cell death when peroxynitrite is generated. The involvement of NO in the regulation of various functions of the ovary has been suggested by the expression of nitric oxide synthase in the follicles and corpus luteum and its presence in follicular fluid (Wu et al., 2003; Ekerhovd et al., 2001; Sugino *et al*., 1996). High plasma concentration of NO in the secretory and mid cycle phases of folliculogenesis suggest the harmful effect of its deficiency on implantation and pregnancy.

OS in follicular fluid may be responsible for low oxygen supply in the intracellular portion and potentiates oocyte development by increasing oocyte cytoplasmic defects rate, impaired chromosomal segregation in oocytes with poor

vascularization of follicles. Presence of OS biomarkers are responsible for increased apoptotic cell death and embryo fragmentation (Lornage, 2003).

Oxidative stress and Miscarriage:-
The placenta is covered by trophoblastic layer to enhance the flow of blood from mother into the fetus. ROS are always produced in the endometrium and their high levels cause trophoblastic invasion which has been implicated as the main cause of abortion. The mechanism might involve reduce resistance of spiral arterioles, high capacitance of the uterus causing preeclampsia and miscarriage (Lane *et al.,* 2002).

There is strong evidence of increased free radical generation in pregnancy which leads to O.S. During labour, there is increased levels of biomarkers that induce lipid peroxidation especially hydro-peroxides (Schweigert *et al.,* 2003) and up-regulation of antioxidants. How OS play roles in induction and initiation of labour is not yet understood but may involve stimulation of prostaglandin synthesis and decrease in endogenous antioxidants levels.

Antioxidants:-
These are nutrients in our food and or substances that prevent oxidative damage to our body cells by scavenging the radicals produced in our body or slow down the oxidative damage. They may be endogenous or exogenous. Endogenous antioxidants are enzymatic in nature and include superoxide dismutase, catalase, glutathione peroxidase that play various roles in preventing oxidative attack and damage to biological membranes, proteins and nucleic acids in cells. Exogenous antioxidants however, are non- enzymatic in nature and include natural antioxidants such as vitamin c (ascorbic acid), tocopherol (vitamin e), retinoids (vitamin A); plant phenolic and polyphenolic compounds such as flavonoids, coumarins, tocopherols etc; and food source antioxidants in vegetables, cereals, fruits, legumes, nuts and eggs.

There are some synthetic antioxidants that are widely used today such as Butylated Hydroxyl Anisole (BHA), and Butylated Hydroxyl Toluene (BHT).

Conclusion:-
Despite the role of certain oxidants in reproductive homeostasis, oxidant stressors are contributors of female infertility and that antioxidants are good for reproductive health has a significant impact on researches in reproductive health. Several scientists today recognize the role of vegetables and herbal products in maintaining and improving reproductive functions. Oxidative stress has been implicated in the pathogenesis of spontaneous abortion, miscarriage, endometrial degeneration and menstrual bleeding, ovarian steroidogenesis, sperm motility in female reproductive tract and fertilization. An increasing number of investigations are still ongoing to find antioxidant drugs, which not only maintains reproductive functions but also improve quality of life of people. Therefore, there is increasing interest in researches on herbal preparations and natural compounds that maintain and or improve reproductive functions.

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