Impact of Oxidative Stress on Obstetric Outcome

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Abstract

Pregnancy is a condition that is vulnerable to all kinds of stresses resulting in changes of physiological and metabolic functions. Normal pregnancy induces profound changes in maternal anatomy and physiology that involve metabolic processes to support fetal growth and development. Physiological reactive oxidative stress levels play an important regulatory role through various signalling and transduction pathways in embryogenesis, embryonic implantation and fetoplacental development. In women, reactive oxidative species plays a role in remodelling of uterine tissue, implantation of embryo, settelement of villi and development of blood vessels that are characteristics of gestation. Oxidative Stress(OS) is a state characterized by an imbalance between pro-oxidant molecules including reactive oxygen and nitrogen species and antioxidant defences. Oxidative stress is involved in various pathological conditions such as abortion, preeclampsia, hydatiform mole, fetal teratogenecity, preterm labour, intrauterine growth restriction; all of which lead to an immense burden of maternal and fetal morbidity and mortality. Antioxidant supplementation may be effective in controlling the production of reactive oxidative species.

Keywords: Pregnancy; Placenta; Oxidative stress; Preeclampsia; Antioxidants; Therapeutic approach.

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Introduction

In healthy body Reactive Oxygen Species (ROS) and antioxidants remain in balance. When balance is disrupted towards an overabundance of ROS, oxidative stress occurs. Oxidative stress influences the entire reproductive lifespan of a woman.

Ultrasound imaging has enabled events during early pregnancy to be visualized in vivo for the first time. As a result, new understanding of the early materno-fetal relationship has emerged and with it, new insight into the pathogenesis of these disorders due to oxidative stress.

In this article we emphasize the role of oxidative stress in various physiological functions in pregnancy. Oxidant status of the cell modulates angiogenesis, which is highlighted in this review: The review comprehensively explores the literature for the role of oxidative stress in obstetrics conditions such as abortion, hydatidiform mole , embryopathy, preeclampsia, IUGR , preterm labour and adverse neonatal outcomes. We capture the role of antioxidants to reduce oxidantive stress in various obstetrics pathological disorders.

Oxidative Stress in Pregnancy

Pregnancy is confronted with aggressive episodes of progressive and periodic changes in metabolic and physiological profile. Consequently, remarkable and dramatic events occur during this period for sustaining mother and fastening the growth and

maintenance of fetus.[1]

Pregnancy is accompanied by a high energy demand of many bodily functions and an increased O_2 requirement. The O_2 tension within the placenta rises three fold between 10- 12 weeks of gestation as the maternal circulation is established, and this is associated with burst of oxidative stress in the trophoblast. Recently, it has been demonstrated that the maternal circulation starts in the periphery of the placenta where trophoblast invasion is shallowest, and subsequently extends to the centre. Oxidative stress is greatest in the periphery and results in localized degeneration of syncytiotrophoblast.[1]

Nitrous oxide (NO) is also locally produced by the placenta and together with other reactive nitrogen species, contribute to potential oxidative stress in presence of transition metals. The placenta is also rich in macrophages favouring the local placental production of free radicals, including reactive chorione species (RCIS) in which free iron is also implicated. Placental macrophages in the presence of infection are a source of NO,tumor necrosis factor and other cytokines that alter mitochondrial alterations and production of free radicals . Micronutrient deficiencies can reduce immunity even further , enhancing these alterations.[1]

Pregnancy is characterized by dynamic changes in multiple body systems resulting in increased basal oxygen and energy consumption in different organs including the fetoplacental unit. Initially the placenta has a hypoxic environment but with maturity, its vascularization develops which changes it to an oxygen rich environment. The placenta is rich in mitochondria, highly vascular, consumes about 1% of the basal metabolic rate of the pregnant woman and is exposed to high maternal oxygen.[2]

Extremes of body weight have been shown to negatively affect fecundability of females and adversely affect fetuses and embryos through oxidative mechanisms. Lifestyle factors such as maternal smoking, alcohol cosumption and recreational drug use stimulate production of unfavourable amounts of ROS leading to oxidative stress, which renders physiological processes of female reproduction and the fetus vulnerable to oxidant-induced damage. Exposure to environment pollution can also give rise to excessive oxidative stress during pregnancy and has increasingly raised concern about the impact of pollutant exposure on maternal and fetal health.[1]

Defence mechanisms against free radical damage are also enhanced as pregnancy progresses. The body, on account of susceptibility to oxidative insult is naturally provided with an efficient antioxidant system. Early, at midgestation and at term, show progressive increments in free radical scavengers such as bilirubin and glutathione as well as in the specific activities of SOD, catalase and glutathione peroxidase and reductase. Glutathione peroxidase in erythrocytes and platelets and extracellular SOD activity have also been found to increase progressively throughout gestation up to the third trimester, possibly as a response to increased presence of O_2.[2]

The placental tissues, in particular the syncytiotrophoblast contain low concentrations and activities of the main antioxidant enzymes,and so are highly vunerable to attack from reactive oxidative species.[1]

Oxidative Stress and Placenta

In humans, normal placentation begins with proper trophoblastic invasion of the maternal spiral arteries and is the key event that triggers the onset of these placental activities.[3] The placental vasculature undergoes changes to ensure optimal maternal vascular perfusion. Prior to the unplugging of the maternal spiral arteries by trophoblastic plugs, the state of low O_2 tension in early pregnancy gives rise to normal, physiological hypoxia. During this time, the syncytiotrophoblast is devoid of antioxidants, and thus, remains vulnerable to oxidative damage. Between 10 and 12 weeks of gestation, the trophoblastic plugs are dislodged

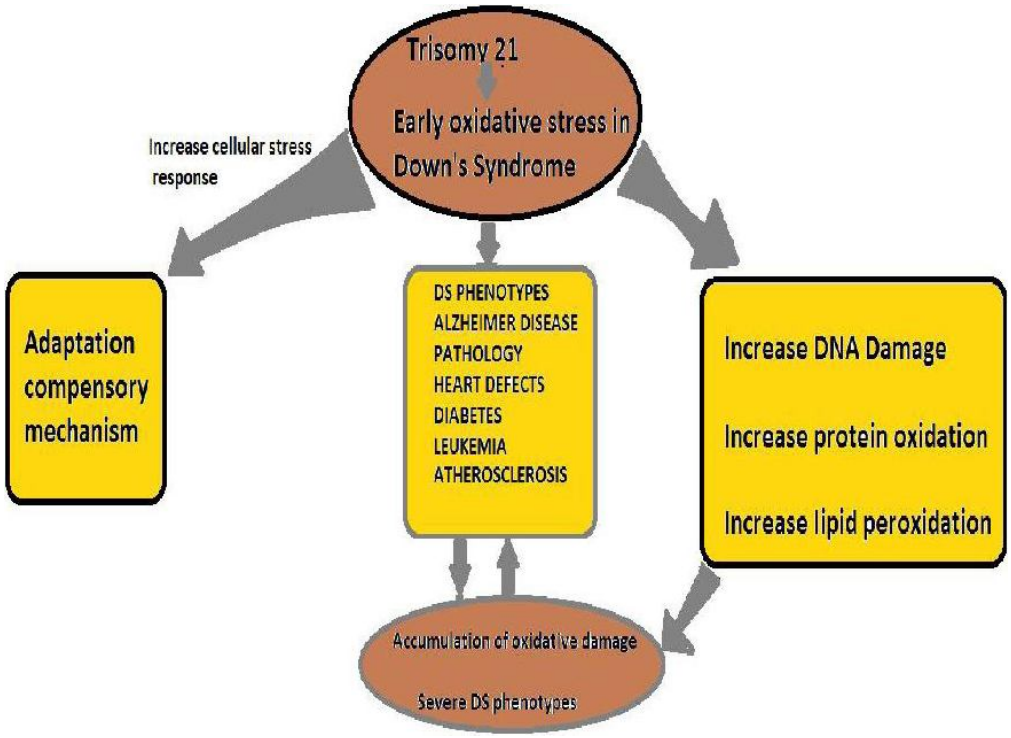
from the maternal spiral arteries, flooding the intervillous space with maternal blood. This event is accompanied by a sharp rise in O_2 tension, marking the establishment of full maternal arterial circulation to the placenta associated with an increase in ROS, which leads to OS. At physiological concentrations, ROS stimulate cell proliferation and gene expression. Placental acclamatation to increased O_2 tension and OS at the end of the 1st trimester up-regulates antioxidant gene expression and activity to protect fetal tissue against the deleterious effects of ROS during the critical phases of embryogenesis and organogenesis.[3]

The early gestation placenta is poorly protected against oxidative damage, as the antioxidant enzymes Cu, Zn-SOD and Mn-SOD are not expressed by the syncytiotrophoblast until approximately 8–9 weeks of gestation (Watson *et al*, 1997). Premature perfusion of this space during this first 10 weeks of development increases the risk of pregnancy loss (Jauniaux *et al*, 2000). The low oxygen environment during early placental development is essential for normal placental angiogenesis, and this angiogenesis is promoted by hypoxia-induced regulation of angiogenic factors, as vascular endothelial growth factor and placental growth factor. The other protective system is formed by antioxidant enzymes, playing a key role in the response of trophoblast to the burst of perfusion by maternal blood. With the increase of oxygen saturation and oxidative stress, the activity in intervillous space, the placenta employs a number of physiologic adaptations (Burton, 2009). Levels and activity of antioxidant enzymes: catalase, glutathione peroxidase, manganese and cooper, zinc superoxide dismutase are increased within placental tissues. This response is evolved as a defense mechanism to reduce harm to placental tissues exposed to this burst of oxidative stress.[4]

Oxidative Stress and Down Syndrome

Oxidative stress occurs in Down's syndrome Pathogenesis and progression due to a deregulation of gene/protein expression associated with Trisomy is characteristics of oxidative stress. Increased production of

Figure 1: Down Syndrome and Oxidative Stress



reactive oxidative species is also accompanied by mitochondrial dysfunction, which occurs in Down Syndrome cells as early as from embryonic life.Mitochondria represent both a principal source as well as target of free radicals, which in turn cause structural damage and activate signalling pathways associated with aging and age-related diseases. Both oxidative stress and mitochondrial dysfunction are prominent features of Down's syndrome.[5]

Although the genetic alterations are responsible for the major clinical presentation of the diseases,additional environmental factors seem to play an important role in determining the severity of multiple phenotypes.[6] Trisomy affects gene/protein expression that results in increased oxidative stress conditions and impaired mitochondrial function. These alterations occur early in Down's Syndrome as demonstrated by studies performed on fetal brain and amniotic fluid from Down's Syndrome pregnancy and play an important role in neurodegeneration.[6]

Although most Down's syndrome patients have senile plaques early in life and even in the fetus, it is only very later on ,that they may develop Alzheimer Diseases. Identification of common pathways together with specific differences of the neurodegenerative process occurring both in Down's Syndrome and Alzheimer disease currently represents an intense field of research. Among proposed hypothesis,oxidative stress is receiving much attention and may be considered a bridge between oxidative stress and Alzheimer disease.[6] Using antioxidant nutrients to scavange oxygen-derived free radicals may modulate some of complications of Down's Syndrome.[6]

Oxidative Stress and Early Pregnancy Loss

Overwhelming placental OS has been proposed as a causative factor of spontaneous abortion. As mentioned earlier, placentas of normal pregnancies experience an oxidative burst between 10 and 12 weeks of gestation. This OS returns to baseline upon the surge of antioxidant activity, as placental cells gradually acclimate to the newly oxidative surroundings. In cases of miscarriage, the onset of maternal intraplacental circulation occurs prematurely and sporadically between 8 and 9 weeks of pregnancy in comparison to normal continuous pregnancies. In these placentas, high levels nitrotyrosine, and markers of apoptosis have been reported in the villi, suggesting oxidative damage to the trophoblast with subsequent termination of the pregnancy. Antioxidant enzymes are unable to counter increases in ROS at this point, since their expression and activity increases with gestational age. When OS develops too early in pregnancy it can impair placental development and/or enhance syncytiotrophoblastic degeneration, culminating in pregnancy loss.[3]

The activity of serum prolidase, a biomarker of extracellular matrix and collagen turnover, has been observed to be decreased in patients with early pregnancy loss. Its levels were also shown to negatively correlate with increased OS, possibly accounting for the heightened placental vascular resistance and endothelial dysfunction secondary to decreased and dysregulated collagen turnover.[3]

Oxidative stress can also affect homeostasis in the ER. Persistence of endoplasmic OS can further sustain ER stress, eventually increasing decidual cell apoptosis and resulting in early pregnancy loss. Apoptosis of placental tissues may result from OS-induced inflammatory processes.[3]

Oxidative Stress and Recurrent Pregnancy Loss

RPL has been reported to affect around 1%-5% of couples attempting pregnancy. The majority of the pregnancy losses are early, usually before 12 weeks of gestation. In about fifty to sixty percent of miscarriages, etiology remains unknown, while endothelial damage, impaired placental vascularisation, and immune malfunction are some of the proposed factors to play a role in idiopathic abortion. Abnormal placenta due to various causes leads to oxidative stress and syncytiotrophoblast dysfunction; which ultimately leads to pregnancy loss. In early

stages of pregnancy increase in leukocyte count is observed, causing increased production of superoxide radical. Elevated generation of ROS has been demonstrated with recurrent pregnancy loss. In pregnant women significant elevation of lipid peroxides and plasma glutathione and lower levels of vitamin E, vitamin C and beta- carotene are reported to be associated with recurrent miscarriages. Similarly lower concentration of α- tocopherol, total thiols and glutathione are observed in patients with unexplained abortions. A study has reported evidence of higher prevalence of hyperhomocysteinemia in women with recurrent pregnancy loss (RPL).[7]

Oxidative stress and Trophoblastic Disease

Oxidative stress and Complete Hydatiform Mole

In the study conducted by Muge Harma and Mebmet from Turkey, they found that the oxidative/antioxidant balance shifted towards oxidative status, namely increased oxidative stress was present in patients with Complete Hydatiform Mole compared with healthy pregnant control subjects. Supplements with antioxidant vitamin C and B may prove useful in the treatment of complete hydatiform mole).[8]

Oxidative stress and Embryopathy

Physiological levels of redox may be important for embryogenesis. Overproduction of OS is detrimental for the embryo, resulting from impaired intracellular milieu and disturbed metabolism. OS can be generated in the sperms and leucocytes and on spermmediated oocyte activation and on the activation of the embryonic genome. Oxidative phosphorylation, NADPH oxidase, and xanthine oxidase are predominant sources of ROS generation in oocytes and embryos.[9]

Oxidative stress leads to macromolecule damage, namely protein modification, lipid peroxidation, and DNA oxidation, and can lead to cell death; playing a role in fetal embyopathies. Diabetes in pregnancy is associated with suboptimal decidualization. NO plays a key role in decidualization and embryo implantation. It increases vascular permeability, vasodilatation, and blood flow in the uterus, and is a component of the decidual cell reaction. Diabetes during pregnancy is associated with embryonic dysmorphogenesis. Due to its capacity to regulate cell survival, apoptosis, differentiation, oxidative and nitrosative stresses play a significant role in embryo organogenesis. Low and high levels of NO can lead to embryonic maldevelopment, possibly due to an improper regulation of apoptotic events. During embryo and fetal development, NO has been found to be relevant in regulating differentiation of lung branching morphogenesis, cephalic morphogenesis, heart development, and nephrogenesis. Different antioxidants such as tocopherol and gluthatione ethyl ester increase expression of *PAX-3* and prevent apoptosis and the induction of hyperglycemia-induced neural tube and heart defects.[4] Deficient folate levels in the mother result in elevated homocysteine levels. The homocysteine-induced OS has been proposed as a potential factor for causing apoptosis and disrupting palate development and causing cleft palate.[9]

There is an age related decline in the number and quality of follicles in females. ROS may damage the oocytes. The age related decline in oocyte quality also results in increased incidence of congenital anomalies in children. The ageing of the oocytes affects many biochemical pathways which have a deleterious effect on pre- and post-implantation development of the embryo. The pre and postovulatory ageing of the oocytes have also been associated with congenital anomalies, behavorial alterations, and learning disabilities in later life and constitutional diseases such as diabetes mellitus, and schizophrenia.[3]

Oxidative Stress and Pre-Eclampsia

Pre-Eclampsia stems from a defect in early

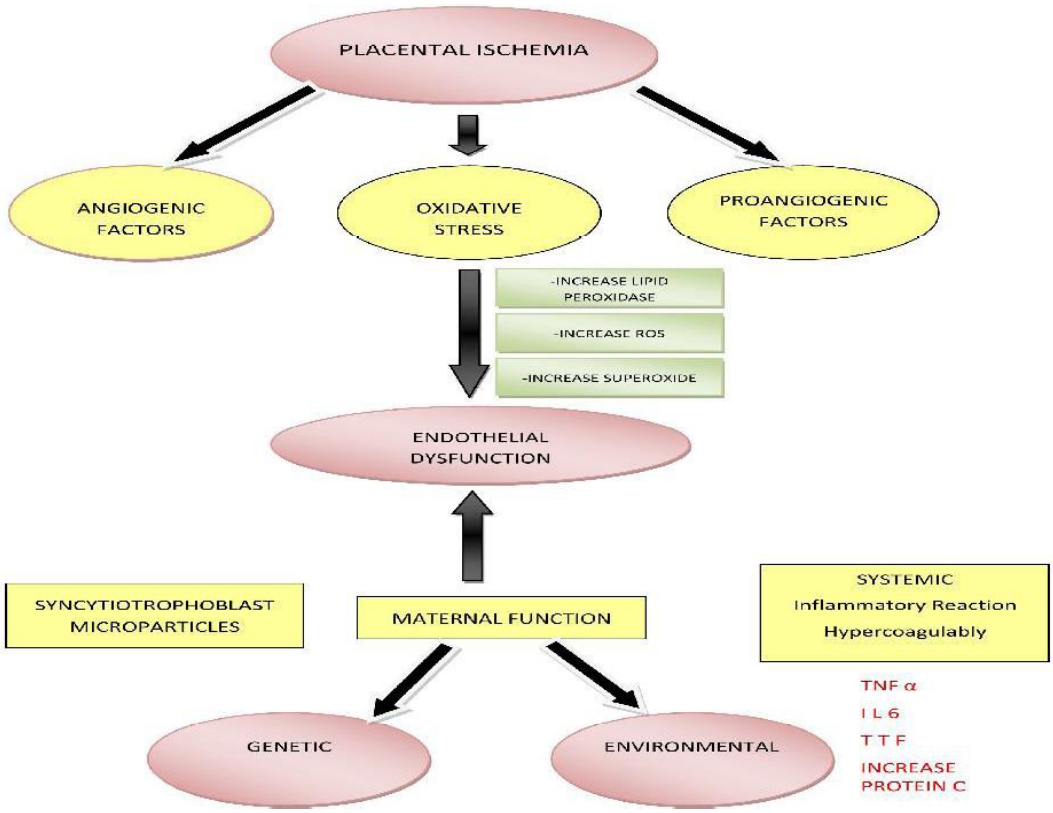
trophoblast invasion, for although invasion is sufficient to anchor the conceptus, it is insufficient to convert the spiral arteries into low resistance channels.Because the placenta and fetus continuously extract O_2, transient hypoxia will result and consequently the placenta suffers a chronic low-grade ischemia /perfusion type injury.[10]

The disturbance in the oxidant-antioxidant balance renders the tissue more vulnerable to free radical injury. Free radical lead to the formation of lipid peroxides which are directly involved in mediating maternal endothelial dysfunction by increasing the production of thromboxane A2 and expression of cell adhesion molecules in uteroplacental vasculature and also in maternal peripheral vasculature. In pre-eclampsia, antioxidant nutrients are utilized to a greater extent to counteract free radicals. This may provide an explanation reduced concentration of ascorbic acid in maternal circulation. This rapid decrease in antioxidant capacity would propagate lipid peroxidation leading to the the biological cascade of leucocyte inactivation, platelet adhesion and aggregation and the consequent release of vasoconstrictive agents.[10]

Ascorbate oxidizing activity and levels of known circulating markers of oxidative stress (e.g., nitrosothiols, lipid oxidation products, and antibodies to low-density lipoproteins) are increased in women with pre-eclampsia. Oxidative stress markers are also increased in the decidua, placenta, and other maternal tissues. Many studies confirm that levels of antioxidants such as vitamin C, vitamin E, and other antioxidants are reduced in the sera and placentas of pre-eclamptic women.[11]

Placenta is rich in polyunsaturated fatty acids and could serve as a rich source of lipid peroxides. Deleterious effects of free radicals include initiation of lipid peroxidation, oxidative damage of biomolecules, and cellular dysfunction, and it is proposed that these may initiate maternal vascular endothelial dysfunction and leukocyte activation, recognized features of preeclampsia. Further,

Figure 2: Pregnancy Induce Hypertension and Oxidative Stress



the production of vasoconstrictor endothelin is increased in preeclampsia. Diminution of the antioxidant response to the oxygenation stimulus results in oxidative stress that may lead to trophoblast degeneration and possibly contribute to impairment of trophoblast invasion and diminished remodeling of the spiral arteries.[12]

In a study conducted by Dr. Suresh Chari, maternal homocysteine concentration was rasied in pre-eclampsia. Increased Homocysteine may be a marker of underlying conditions that are directly related to pregnancy complications, such as subclinical vascular disease, reduced glomerular filtration rate, and inadequate plasma-volume expansion. Thus in pregnant women the vascular endothelium may be more sensitive to oxidative stress and elevated homocysteine level. This may be responsible for the development of preeclampsia.[12] Other maternal factors including activated neutrophils and imbalance between anticoagulants and procoagulants aggravate the oxidative stress.[4]

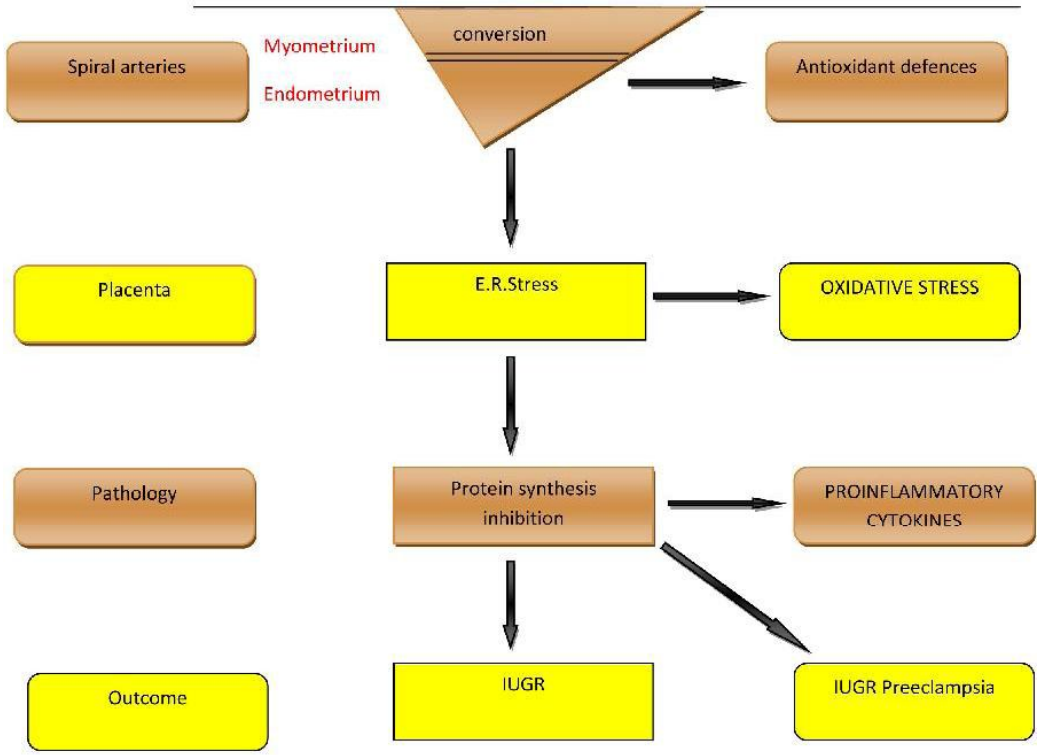
Oxidative Stress and INGR

Studies indicate that patients with IUGR develop OS because of placental ischemia/ reperfusion injury secondary to improper spiral arteriole development. Imbalanced injury and repair as well as abnormal development of the villous tree are characteristic of IUGR placentas, predisposing them to depletion of the syncytiotrophoblast with consequently limited regulation of transport and secretory function. As such, OS is recognized as an important player in the development of IUGR.

Women with IUGR have been reported to have increased free radical activity and markers of lipid peroxidation. Furthermore, Biri *et al* (2007) reported that higher levels of MDA and xanthine oxidase and lower levels of antioxidant concentrations in the plasma, placenta, and umbilical cords in patients with IUGR compared to controls.

Furthermore, disordered protein translation and signalling in the placenta can also cause ER stress in the syncytiotrophoblast, and has been demonstrated in placentas of IUGR patients. ER stress inhibits placental protein

Figure 3: IUGR and Oxidative Stress



synthesis, eventually triggering apoptosis. The origin of these placental insults induced by OS and ER stress is not completely understood, but ischemia/reperfusion and hypoxiareoxygenation are considered as significant contributors.[3]

The normal fetal growth is a result of complex interaction among the three components of maternal-placental –fetal unit. Nutritional status of the mother is the most important maternal factor leading to IUGR. Malnutrition is associated with significant Oxidative Stress in small for gestational age neonates born at term to malnourished mother.[1]

Oxidative Stress and Preterm Birth

Preterm labour is devastating for the family, the physician, and society in general. Oxidative stress has been implicated in the development and pathogenesis of a number of diseases in neonates and especially those delivered prematurely.[13]

Oxidative stress is a contributing factor for tissue injury through formation of free radicals and reactive oxygen/nitrogen species leading to inflammatory cytokines which result in premature birth. Oxidative stress is likely a contributing factor in the development and severity of several newborn conditions to the extent that Saugstad (1988, 2005) has suggested the phrase "oxygen radical disease of neonatology". The idea suggests that oxidative stress affects a variety of organs, often simultaneously, causing neonatal diseases such as bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP), necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH), and periventricular leukomalacia (PVL).[13]

Of these etiologies, intrauterine infection and inflammation is considered a main contributor to preterm birth. The combination of genetics and inflammatory responses is an active area of research that could explain preterm labor in some women with common risk factors. Women in preterm labor have diminished antioxidant abilities to defend against OS induced damage. Maternal environment of increased OS and decreased antioxidants renders both the mother and fetus more susceptible to ROS-induced damage.

The concentration of Mn-SOD increases as a protective response to inflammation and Oxidative Stress. Activation of the membrane inflammatory response is observed in preterm labor. Amounts of the proinflammatory cytokines IL-1 beta, IL-6, and IL-8, have been observed in the amnion and choriodecidua of patients in preterm labor than in women in spontaneous term labor. Low maternal serum selenium levels in early gestation have been associated with preterm birth. The presented evidence implicates inflammation and suppressed antioxidant defenses in the pathogenesis of preterm labor.[3]

Metalloproteinase are a group of endopeptidase enzymes with a collagenolytic activity and are activated in preterm premature rupture of membranes. The redox balance determines the matrix metalloproteinase activity of the amniochorionic membranes. Metalloproteinase activity was found to be increased directly by superoxide anion, a byproduct of macrophages and neutrophils.[7]

Oxidative Stress and Diabetes

There are a no. of pathways that may contribute to oxidative stress observed in gestational D.M placenta.In the placenta, ROS and RNS are an important source of growth and signaling factors, and are susceptible to ROS mediated apoptosis. The placenta is endowed with many anti-oxidants,some of which are increased in gestational D.M. There is much data to indicate that maternal D.M during pregnancy may induce Oxidative stress in the newborn that may entail biochemical disturbances of the fetus. Given that the placenta provides the interface of the maternal and fetal circulations,it may play a crucial role in protecting the fetus from adverse effects of the maternal diabetic millieu.

Oxidative Stress and Anaemia

Anemia is known to promote oxidative stress due to inadequate tissue oxygen supply leading to increased free radical production and very low level of circulating red blood cells and mobile free radical scavengers which provide protection to tissues from ROS mediated damage[3] Malondialdehyde (MDA) is a product of lipid peroxidation and has been found to be elevated in conditions of oxidative stress. PUFA gets oxidized to form lipid peroxides which are unstable and undergo decomposition to form reactive carbonyl compounds. Iron is required by the enzymes involved is oxidative metabolism . At the same time it must be considered that ferrous iron used for oral iron therapy in pregnancy-itself is a potent pro oxidant and several studies have suggested that iron deficient women were more susceptible to this iron therapy induced oxidative stress.[14]

Oxidative Stress and Neonatal Outcomes

Elevated oxidative stress has been reported in term infants with fetal distress and in preterm infants. Preterm infants are highly susceptible to free radical damage because of low antioxidant reserves. Both enzymatic and nonenzymatic scavenging antioxidants are deficient in preterm infants. OS adversely affects fetal outcomes in preterm infants, and in term infants, it is associated with fetal distress. Significantly elevated concentrations of 8-iso-prostaglandins F2α, a product of lipid peroxidation, were detected in cord blood from singleton pregnancies complicated by moderate or thick meconium-stained liquor. Management of oxidative stress with amnioinfusion may be beneficial in patients with meconium stained liquor because it lowers lipid peroxide levels, a marker of oxidative stress. Oxidative stress may have a role in programming embryo and fetal development in-utero.[7]

Oxidative Stress and Therapeutic Approach

The body, on account of susceptibility to oxidative insult, is naturally provided with an efficient anti-oxidant system.A series of enzymes also act as scavenging systems including superoxide dismutase (SOD), catalase and glutathione peroxide. These enzymes are the first line of defence against ROS and are referred to as primary antioxidants. Many anti-oxidant defence systems depend on micronutrients themselves, proteins provide amino-acids for synthesis of antioxidant defence systems. Because of the strenous nutritional demands of the growing fetus, pregnancy represents a nutritionally perilous state for every pregnant women, as she provides nutrients to support her child's rapid growth in addition to supplying her own metabolic needs.[1]

The antioxidant vit.E is known to have multiple actions in addition to prevention to prevention of lipid peroxidation) (i.e.inhibition of NADPH) oxidase activation and the inflammatory response. In view of the abnormally low plasma vit. C concentrations in pre-eclampsia, a combination of vit. C and E is a promising prophylactic strategy for prevention of pre-eclampsia.[1] Antioxidants like glutathione, vit. C, vit. E are crucial to all stages of pregnancy, as they provide protection against oxidative stress that can cause congenital malformations and miscarriage. Glutathion and other antioxidants have been demonstrated to be vital in preventing oxidative stress in pregnant women with inflammation or conditions like Diabetes and preeclampsia in many studies.

Antioxidants can protect the embryonic development in a diabetic environment.[1]

Oxidative stress leads to focal collagen damage in the fetal membranes and result in preterm labor. Antioxidant supplementation has been investigated in preterm labor and preeclampsia for beneficial effects.[3] Clinical trials in pregnant women have shown that increasing the amount of lycopene, and CoQ10, as well as DHA, seems to reduce the burden of the maternal fetal disorders. However, many of the market leaders in

prenatal micronutrients supplementation include many of these antioxidant vitamins, minerals, and trace elements.[13] Strategies are directed at decreasing the numbers of reactive oxygen/nitrogen species by supplementing vitamins A, C or E in hopes of reducing vasoconstriction and/or organ damage.[13] Antioxidants improve the outcome of pregnancy by decreasing radical related tissue damage.

Breast Feeding

Some studies have suggested that increased ROS could be scavenged by feeding human milk. Human milk is recognized as the optimal form of nutrition during the neonatal period, providing nutrients and a variety of components (minerals, vitamins, and enzymes) that can work as antioxidants. Human milk antioxidant components include the enzymes superoxide dismutase for dismutation of superoxide anion, catalase for degradation of hydrogen peroxide (H_2O_2), glutathione peroxidase for destruction of H_2O_2 and organic peroxides. Human milk contains other molecules including cysteine, vitamins C and E, which are scavengers of oxygen radicals. (Ledo *et al*, 2009; Tsopmo & Friel, 2007) Further work may identify micro supplements which could be added to breast milk or formula to address the need for more antioxidants.[13]

Discussion

Excessive ROS production and resulting oxidative stress may contribute to aging and several diseased states affecting female reproduction. The imbalance of the oxidative agents and antioxidants have been proposed as a causative agents of RPL and several pregnancy related disorders , most notably pre-eclampsia, IUGR, gestational D.M, preterm labour.

Pregnancy is a state of oxidative stress arising from increased placental mitochondrial activity and production of free radicals. The locus of the catabolism, metabolism and oxidative reactions within the cells is mitochondria. Excessive production of ROS may occur at certain windows in placental development and in pathologic pregnancies; overpowering antioxidant defences and deleterious outcome.

Newborns and in particular preterm neonates, have less protection against and are susceptible to free radical oxidative damage. Although free radical injury is well recognized in neonatal disease pathogenesis, a clear definition of its degree of participation, the precise mechanisms and the specific radicals involved in early disease need to be established. Although research is promising, further studies for early identification of infants at risk from oxidative stress and development of safe and effective antioxidant strategies to prevent or minimize oxidative damage is required.

Adequate nutritional status of women before becoming pregnant, during the pregnancy and after delivery reduces adverse outcomes for both mother and baby. The absence of appropriate micronutrients lead to maternal complications such as preterm labour, iron deficiency anaemia, preterm premature rupture of membranes, pre-eclampsia, as well as small for gestational age infants and congenital malformations. By using antioxidant nutrients to scavange O_2 derived free radicals may modulate some of the complications of Down's Syndrome. The antioxidant supplementation, avoidance of different environmental factors as polluted comestibles may lead to decrease of infertility rate and incidence of pregnancy related disorders.

Reference values for ROS and NOS, minimum safe concentrations or physiologically beneficial concentrations have yet not been defined. Interventions for overcoming oxidative stress in conditions such as abortions, pre-eclampsia, preterm labour and gestational diabetes and IUGR are still investigational. Further investigations are necessary to find a sensitive biochemical marker in early pregnancy to permit interventions in order to prevent pre-eclampsia.

The inability to vasodilate (or direct vasoconstriction) caused by ROS result in diminished blood flow and can lead to preterm labour, PPROM, pre-eclampsia and IUGR. Treatment is directed at decreasing the number of ROS/RNS by supplementary vit. A, C, E in the hope of reducing vasoconstriction and or organ damage clinically the hypothesis is that, if vasoconstriction is reduced, there would be less early deliveries, both from preterm labour, PROM, as well as deliveries due to pre-eclampsia and severe IUGR.

Pregnant women with HIV infection, selenium deficiency or micronutrient deficiencies like vit. C or vit. A, were found to have adverse clinical outcomes in large prospective studies. There is increasing argument for increasing selenium intake in these patients. There is emerging enthusiasm in the use of antioxidants natural or synthetic. Small molecules that mimic antioxidant enzymes are the new tools being developed in the antioxidant armamentarium. These are cell membrane permeable unlike the natural superoxide dismutase. Antioxidants targeting cellular organelles like mitochondria are also being investigated.

References

1. Ashma Rana. Oxidative stress in pregnancy-Role of anti-oxidant. *Obst and Gynaec Today.* 2004; IX(12).
2. Imran A Siddiqui, Anila Jaleel, Waleed Tamimi, Hanan MF Al Kadri. Materno-Fetal Medicine Role of oxidative stress in the pathogenesis of preeclampsia. *Arch Gynecol Obstet.* 2010; 282: 469–474. DOI 10.1007/ s00404-010-15386.
3. Ashok Agawal, Anamar Aponte-Mellado, Beena J Premkumar, Amani Shaman and Sajal Gupta. The effects of oxidative stress on female reproduction: a review. *Reproductive Biology and Endocrinology.* 2012; 10: 49. doi:10.1186/ 1477-7827-10-49
4. Levente lázár, Dr. Volodymyr Lushchak (ed.). The role of oxidative stress in female reproduction and pregnancy. ISBN; 978-953-51-0552-7.
5. Pinar E Coskun and Jorge Busciglio. Oxidative stress and Mitochondrial dysfunction in Down's Syndrome: Relevance to Aging and Dementia. *Current Gerontology and Geriatric Research.* vol.2012 Article ID 383170,7pages.doi:10-1155/2012/383170
6. Marzia Perluigi and Allan Butterfield. Oxidative stress and Down Syndrome: A Route toward Alzheimer-like Dementia. *Current Gerontology and Geriatric Research.* vol.2012, Article ID 724904,doi:10.1155/2012/724904.
7. Sajal Gupta, MD, Neena Malhotra, MD, Dipika Sharma, MD, Anjali Chandra, MD, Agarwal Ashok. Oxidative stress and its role in female infertility and assisted reproduction: clinical implications. *International Journal of Fertility and Sterility.* 2009; 2(4): 147-164.
8. Muge Harma, Mebmet Harma, Ozcan Erel. Increased oxidative stress in patients with hydatiform mole. *Swiss Med Weekly.* 2003; 133: 2003,133.
9. Sajal Gupta, Lucky Sekhon, Nabil Aziz, Ashok Agarwal. The impact of oxidative stress on female reproduction and art: an evidence-based review in: Antonis makrigiannahis, botros risk. Juan Garcia Vetarco, Hassan. New York: Cambridge Up; 2008, 178-86.
10. Eric Jauniaux Lucillus Poston, Graham Burton. *Human Reproduction Update.* 12(6): 747-755.
11. JB Sharma, A Sharma, A Bahadur, N Vimala, A Satyam, S Mittal. Oxidative stress markers and antioxidant levels in normal pregnancy and pre-eclampsia. *International Journal of Gynecology and Obstetrics.* 2006; 94: 23 – 27.
12. Dr Suresh Chari, Dr Madhur Gupta, Dr Sunita Ghike. correlation of homocysteine and oxidative stress in patients with preeclampsia. Journal of Recent Advances in *Applied Sciences (JRAAS)* 2011; 26: 1-5. ISSN 0970-1990
13. Robert A Knuppel, Mohamed I Hassan, James J McDermott, J Martin Tucker and John C Morrison. Oxidative Stress and Antioxidants: Preterm Birth and Preterm Infants, Preterm Birth - Mother and Child, Dr. John Morrison (Ed.). 2012. ISBN: 978-953- 307-828-1.
14. Sujata Maitra, Anitha M, Vishwanath HL, Sreelatha R and Some Gowda. Iron and Oxidative Stress in Pregnancy in Anemic Indian Women. *Asian J Med Res.* 2012; 1(1).