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Oxidative Stress and Antioxidants: Preterm Birth and Preterm Infants

Robert A. Knuppel[1], Mohamed I. Hassan[1], James J. McDermott[2], J. Martin Tucker[3] and John C. Morrison[3]
[1]*Departments of Obstetrics and Gynecology and Newborn Medicine, DuBois Regional Medical Center, DuBois, PA,*
[2]*Glen Allen, VA,*
[3]*Department of OB/GYN, University of Mississippi Medical Center, Jackson, Mississippi,*
USA

1. Introduction

1.1 General

It is agreed by all physicians that preterm labor is comprised of regular uterine contractions, usually <5 minutes apart, that results in cervical change occurring before the 37th week of pregnancy. (Elliott, 2011) Often times, preterm labor can be successfully treated with tocolytic drugs, but when such treatment results in early delivery particularly (<32 weeks) it is devastating for the family, the physician, and society in general. According to statistics in the United States preterm birth occurred in 12.6% of deliveries in 2007. (Goldenberg, 2008) Indeed, up to 75% of all perinatal mortality and half of the neurologic disadvantaged children can be traced to simply delivering before term. Adequate nutritional status of women before becoming pregnant, during the pregnancy, and after delivery, reduces adverse outcomes for both mother and baby. (Kontic & Vucinic, 2006) The absence of appropriate micronutrients lead to maternal complications such as preterm labor (PTL), iron deficiency anemia, preterm premature rupture of the membranes (PPROM), preeclampsia, intrauterine growth restriction (IUGR), as well as small for gestational (SGA) infants, and congenital malformations. (Scholl, 2008) Oxidative stress has been implicated in the development and pathogenesis of a number of diseases in neonates and especially those delivered prematurely. Newborns, and in particular preterm neonates, have less protection against and are very susceptible to free radical oxidative damage. (Saugstad, 2003)

Good nutrition is vital to the health of the mother and baby. Unfortunately, the typical American diet exceeds the recommended daily allowance of meat, grains, and fats by approximately 20% and is as much as 40-60% deficient in dairy, fruit, and vegetables. (Kaiser & Allen, 2002). Pregnancy involves rapidly dividing cells, not only in the fetus, newborn and placenta, but also in the maternal compartment (such as red cell mass and the growing uterus). Pregnancy is one state where there is almost certainly a need for additional antioxidants to combat this stress. (Kaiser & Allen, 2002) Oxidative stress

during pregnancy yields free radicals and other oxidative molecules exceeding the available antioxidant buffering capacity in the mother and growing fetus. This results in cellular damage, which is associated not only with PTL and delivery, but also preeclampsia, PPROM and IUGR as well as several serious post delivery issues for the premature infant. (Joshi et al., 2008) If not buffered, the excess of free radicals attack the endothelial lining cells of blood vessels and many organ systems by acquiring electrons from nucleic acids, lipids, proteins and carbohydrates, thus denaturing DNA in these cells. (Burton & Jauniaux, 2010) Free radicals may affect normal placental growth and cause abortions or stillbirths, while at the same time resulting in a number of chromosomal abnormalities. (Stein et al., 2008) Oxidative stress can also cause preeclampsia by disrupting the body's vasodilatation signaling process, allowing maternal blood pressure to rise, and disrupting placental blood flow. (Buhimschi et al., 2003) Oxidative stress is also related to alterations in the genetic metabolic detoxification through the cytochrome P450 1A1 gene as well as others. (Agarwal et al., 2005) When these genes are over expressed in an environment of excess radicals PTL results, which can lead to early delivery. This chapter will highlight the conditions and diseases of the mother, fetus, placenta as well as the newborn and discuss studies how micronutrients supplementation may help restore balance to the oxidative pathways.

1.2 Oxidative stress

Oxidative stress occurs when the rate of free radical production exceeds the rate of removal (or buffering) by the cellular defense mechanisms. (Burton & Jauniaux, 2010) As mentioned previously, oxidative stress has been associated with PTL and early deliveries as well as preeclampsia, PPROM and IUGR as well as many conditions and diseases in the preterm infant. (Buhimschi et al., 2003; O'Donovan & Fernandes, 2004) As shown on Figure 1, the reactive oxygen and nitrogen species will cause cytotoxic damage to proteins, lipids or DNA, unless the enzymatic and nonenzymatic antioxidants are able to balance their adverse effects. Free radicals works in many ways, for example, iron-mediated formation of ROS leading to DNA and lipid damage appears to result from an exaggeration of the normal function of iron; which is to transport oxygen to tissues, resulting in iron-induced free radical damage to cellular DNA. Free radicals are released by macrophage and neutrophil activation associated with infection and inflammation. The free radicals of interest are frequently referred to as Reactive Oxygen Species (ROS) because the most biologically important free radicals are predominantly derived from oxygen (oxygen free radicals). (Saugstad, 1996) ROS is a collective concept that includes not only superoxide anion and hydroxyl radicals but also radicals such hydrogen peroxide, which is derived from molecular oxygen (Fig. 1). ROS may be generated by different mechanisms, such as the normal electron transport chain in mitochondria and fatty acids, prostaglandin metabolism, ischemia-reperfusion, hypoxia, hyperoxia, neutrophil and macrophage activation (inflammation), the endothelial cell hypoxanthine-xanthine oxidase system (adenosine triphosphate degradation), increased free circulating transition metals, and the Fenton reaction (ferrous to ferric iron). (Shoji & Koletzko, 2007) Reactive Nitrogen Species (RNS) also damage cellular DNA and also disrupt nitric oxide signaling which controls vasodilatation (Fig. 1) Both ROS and RNS are simply molecules that have been charged with extra electron and therefore are very unstable. (Agarwal et al., 2005)

As the placenta is growing, fetus and mother require increased blood flow as pregnancy progresses and damage to the endothelial cell lining of the blood vessel wall is particularly serious. For example, as shown in a cartoon (Figure 2a), blood vessels normally use nitric oxide (NO) signaling to initiate vasodilatation. There are circumferential muscle cells around the blood vessel wall that control additional blood flow by dilating the vessel itself. Figure 2b, notes that vasodilatation (by relaxing the muscle cells in the vessel wall) leads to increased blood flow needed for the growing uterus and fetus. (Edemann & Schiffrin, 2004) Excessive free radicals in the blood will disrupt the ability for the vasodilatation signaling process (Fig. 2a); thus, vasoconstriction occurs leading to diminished blood flow to the uterus and placenta, which can result in PTL, preeclampsia and/or IUGR. (Stein et al., 2008) Severe oxidative stress may trigger chromosomal abnormalities that may lead to fetal demise. Oxidative stress can also effect the process in reverse by decreasing the body's ability to detoxify oxygen radicals. (Blondi et al., 2005) For example, the Cytochrome P450 A1A gene (CYP1A1), Glutathione S-transferases μ1 (GST m1), and 01 (GSTT1) all can interfere with the detoxification process. The ROS can also trigger a cascade of fatty acids (such as arachidonic acid) which lead to preterm contractions, cervical dilatation and birth before 37 weeks as well as inciting vasoconstriction leading to preeclampsia and IUGR. (Joshi et al., 2008) The key treatment process is to balance the impact of free oxygen and nitrogen radicals by supplying antioxidants from the diet and/or by micronutrient supplementation.

2. Maternal/fetal antioxidant issues

As previously noted, pregnancy itself places a burden of excess and unstable radicals on maternal tissues as well as those of the developing fetus and placenta. The subsequent inability to vasodilate (or direct vasoconstriction) caused by these reactive species result in diminished blood flow and can lead to PTL, PPROM, preeclampsia, and primary IUGR (or secondary due to the preeclampsia). There have been many strategies to address this excess of oxidative radicals over the last 20 years, particularly supplementation of one or two micronutrients in the hopes of reducing these serious maternal/fetal disorders. Such therapy is 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. Clinically, the hypothesis is that if vasoconstriction is reduced there would be less early deliveries both from PTL and PPROM as well as from indicated deliveries due to preeclampsia and severe fetal growth restriction.

2.1 Preterm birth/preterm premature rupture of the membranes

Recently Kramer et al., (2009) illustrated the linkage between antioxidant vitamins and spontaneous preterm birth. In this case control study blood samples were taken from a large prospective multicenter cohort (n=5337) at 24-26 weeks' gestation. Aliquots were analyzed in women with spontaneous preterm birth (n-207), and compared with two term controls per case (n=443). They were analyzed for carotenoids, retinol and tocopherols as well as long chain fatty acids. The findings revealed that high plasma concentrations of alpha and beta-carotene as well as lycopene were all associated with reductions in spontaneous preterm birth with a positive dose response across all groups. In the United States the majority of dietary alpha-carotene and nearly 40% beta-carotene is supplied by carrots,

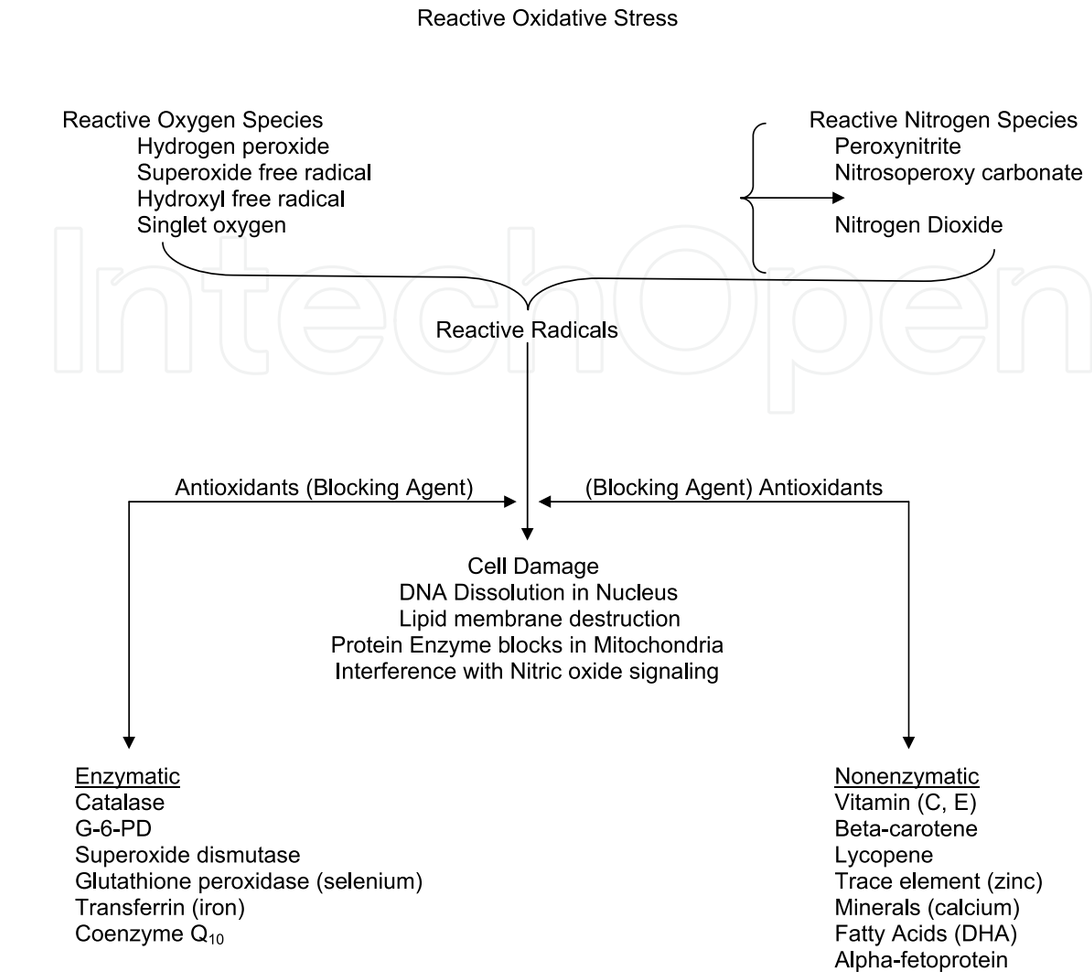

Fig. 1. Oxidative stress and various antioxidants.

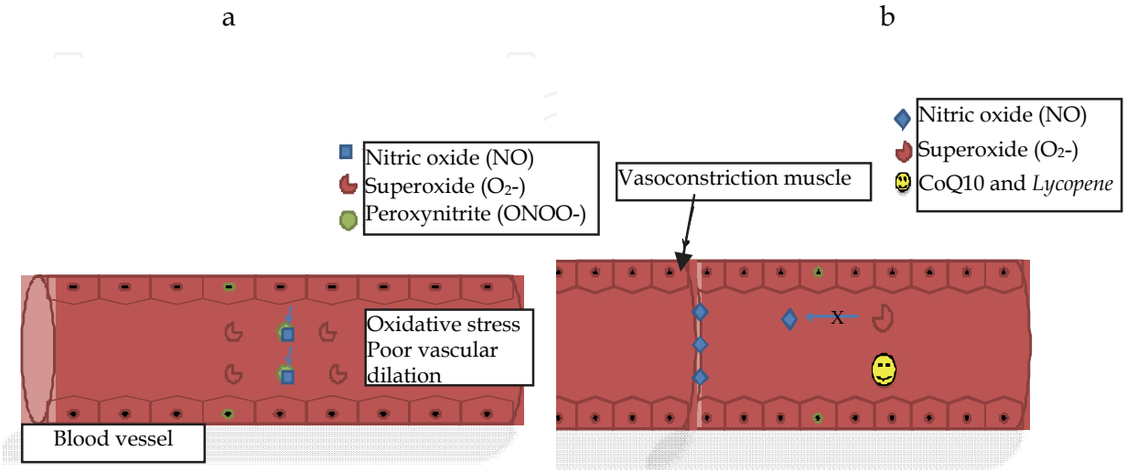

Fig. 2. A: Effect of free radicals on vascular endothelium; B: Effect of antioxidants blocking free radicals to allow normal vasodilation.

whereas almost all the lycopene (80%) is provided by tomato and tomato products; two sources low in the normal diet. (Clinton SK, 1998) Therefore, there appears to be a need for supplementation as many women studied in this and other investigations have low plasma levels of carotenoids and lycopene.

Lycopene is a cyclic carotenoid with 11 conjugated double bonds and is found in relative few foods; therefore, requires supplementation during pregnancy. (Clinton SK, 1998) It has long been known that low levels of this carotenoid has been associated with cancers of the digestive tract, cervix, breast, skin, bladder, prostate, as well as cardiovascular diseases. (Helzlsouer, 1989) The oxidative pathways connecting low lycopene to preterm birth and PPROM have not been fully studied, but have been linked by several investigators. (Luo et al., 2006; Masters et al., 2007) Lycopene has been linked to a decrease in preterm birth by Sharma et al., (2002) who entered 251 primagravida women in a prospective randomized control trial in the second trimester. One hundred sixteen women received lycopene (2mg twice daily) while 135 women received placebo (both until delivery). Gestational age as well as mean birth weight were significantly higher in the active treatment group. The results also showed that preeclampsia (8.6% versus 17.7%), as well as IUGR (12% versus 23.7%), were lower among lycopene treated patients. The high number of double bonds in the lycopene structure is hypothesized to be responsible for the very potent antioxidant effects noted in this study. Compared with other carotenoids such as vitamin C and E, lycopene appears to be a more potent antioxidant particularly with complications such as PTL, and PPROM.

2.2 Antioxidants and preeclampsia

As noted above, lycopene was shown by Sharma et al., (2002) to reduce the incidence of PTL and preeclampsia compared to placebo treated patients. Similarly, there appears to be new interest in coenzyme Q10 (CoQ10) which is a vitamin like 1, 4-benzoquinone that, like lycopene, has a very potent antioxidant action. CoQ10 is an essential component of oxidative phosphorylation at the mitochondrial level, which helps stabilize cell membranes by acting as an antioxidant. (Crane, 1997) CoQ10 plays a well known preventive role in cardiovascular disease, cancer, as well as muscular and mitochondrial disorders. (Langsjoen et al., 1994; Folker et al., 1997; Bresolin et al., 1988) In 2003, Teran EP et al., hypothesized, because of the antihypertensive effect of CoQ10, that it might be helpful in reducing maternal preeclampsia. Teran studied a small number of normal pregnant women, non-pregnant women, and pregnant women with preeclampsia. He found that plasma levels of CoQ10 were significantly higher in normal pregnant women in comparison to non-pregnant women. However, CoQ10 levels were noted to be even lower in women with preeclampsia compared to the non-pregnant state. Pregnant women with preeclampsia had approximately ½ of the levels of CoQ10 as compared to normal pregnant women. Teran's group hypothesized that coenzyme Q10 could help regulate nitric oxide vasodilation and possible lead to less preeclampsia as well as IUGR and thus indirectly lead to less preterm birth. More recently the same investigators (Teran et al., 2009) conducted a randomized control trial with 197 women of whom 47 developed preeclampsia. The treatment group took 100mg of CoQ10 twice per day versus placebo in control women. Of the 47 women who developed preeclampsia, 30 (25.6%) were in the control group compared to only 17 (14.4%) in the CoQ10 group (p=0.03, RR 0.56 CI 0.33-0.96). Again, larger babies and less

IUGR were noted amongst CoQ10 treated patients. The results indicated that CoQ10 protection of the essential components of mitochondrial complexes as well as its protective effect on vascular endothelium in the placenta might be responsible for these positive findings. Tiano et al., work (2007) also mirrors this conclusion.

More recently Boutet et al., (2009) supported the protective effect hypothesis by showing a rise in glutathione peroxidase (an antioxidant) in those given lycopene and CoQ_{10}. This was particularly true in preeclampsia and demonstrates that both the fetus and mother are affected during preeclampsia. They showed that glutathione peroxidase controls lipid peroxidation in cell membranes which is also a function of lycopene and CoQ_{10}. As shown on Figure 2b, the lycopene and CoQ_{10} also degrade superoxide, thus preventing depletion of nitric oxide in the blood. This allows successful vasodilatation particularly in the placenta as well as the maternal organs. In turn, this could clinically lead to a reduction in preterm birth due to PTL and/or preeclampsia. (Endermann & Schiffrin, 2004). IUGR and PPROM could also be reduced. Landmesser et al., (2000) also showed that CoQ_{10} increased levels of extracellular superoxide dismutase (SOD), a major antioxidant enzyme system of endothelial cells lining vessel walls, which scavenge oxygen radicals and allow endothelial dependent dilation to occur in the conduit arteries. In this randomized study (Landmesser et al., 2000), CoQ_{10} supplementation versus placebo, increased superoxide dismutase and led to relaxation of the arteries. In addition, VO_2 and O_2 pulse pressure was greater in placebo treated patients, rather than those receiving CoQ_{10}.

In summary, the dietary supplements CoQ_{10} and lycopene prevents a wide range of radicals from degrading nitric oxide and damaging various organs. With better balance the nitric oxide is able to signal vasodilatation where needed, such as an increase in uterine blood flow during pregnancy to establish the placenta. Clinically, this could lead to a decrease in preeclampsia, IUGR, PTL, and PPROM.

2.3 Vitamin C and E

CoQ10 and lycopene have demonstrated very positive effects relative to reducing and perhaps preventing preeclampsia. However, other known antioxidants such as vitamin C and E have not been proven to be effective in published studies. For example, Poston et al., (2006) performed a randomized placebo control trial involving 2410 patients at high risk for preeclampsia from 25 hospitals. They supplemented 1000mg vitamin C and 400 IU vitamin E versus placebo from the second trimester of pregnancy until delivery. They studied the incidence of low birth weight, small for gestational age infants, and preeclampsia. The incidence of small for gestational age infants and maternal preeclampsia were identical and paradoxically the numbers of low birth weight infants were higher in the treatment group than in the control group (28% vs. 24%). Similarly, Xu et al., (2010) studied the supplementation of the same vitamins in 27 centers vs. placebo amongst 2363 women. They found no reduction in preeclampsia, but surprisingly a small, non-significant increase, in the number of growth restricted babies and perinatal death. Current studies to address these conflicting results are underway.

2.4 Omega-3 fatty acids (Docosahexaenoic Acid-DHA)

The supplementation of various omega-3 fatty acids, which have been shown to have a positive effect on the development of the fetal central nervous system and retina, has also

been correlated with a greater gestational age at birth. (Gallagher, 2004) There are over 20 fatty acids, but only the omega-3 and omega-6 polyunsaturated fatty acids cannot be manufactured by the body; thus they must be accumulated by the fetus from placental transport. (Bell 1997) The omega-3 fatty acids are essentially derived from linolenic acid and they produce eicosanoids which have anti-inflammatory and immunosuppressant properties. In contrast, omega-6 fatty acids promote inflammation and blood clotting (Adam et al., 2003). In large amounts omega-6 fatty acids lead to production of arachidonic acid (prostaglandins), which stimulate the preterm labor cascade, weaken fetal membranes and reduce placental blood flow. Unfortunately, in the typical United States diet there is a ratio of 20:1 of omega-6 versus omega-3, when the ratio should be between 1:1 and 4:1. A recent review by Greenberg et al., (2008) offers a nice description of how to meet omega-3 fatty acid needs during pregnancy. Basically, these methods involve increasing the amount of fish in the diet (two servings per week), which results in omega-3 fatty acid levels of 100-250mg per day of DHA.

It has been shown the intake of fresh fish increases birth weight by prolonging gestation. (Olsen et al., 1995) The same investigators showed that fish oil supplementation had the same affect (Olsen, 2000). In one study, five Australian maternity hospitals enrolled 2399 women <21 weeks' of gestation to determine if taking fish oil in the latter half of pregnancy reduced maternal depressive symptoms and improved developmental outcomes in the offspring. (Makrides, 2010) While there was no reduction of postpartum depression symptoms, the treated patients had a lower incidence of both preterm birth and low birth weight infants, which resulted in fewer admissions to the neonatal intensive care unit and a 67% reduction in infant death. (Makrides, 2009) In an accompanying editorial, Oken & Belfort, (2009), suggest supplementing 100-200mg of DHA in addition to diet, which seems to be appropriate. Unfortunately, one need only remember as a child, taking cod liver oil, to know that fish oil supplementation is accompanied by halitosis, gastric upset, and in some cases nausea and vomiting, thus limiting patient compliance. As previously mentioned, most women normally do not consume enough fresh fish to meet the daily requirement and therefore, DHA supplementation is important.

More palatable supplementations are available to increase DHA in the diet. Omega-3 fatty acids have been found in algeal sources which are equivalent to the DHA levels found in fresh fish. (Arterburn et al., 2007; Arterburn, 2008) Indeed these algeal supplements containing DHA have been found to raise the plasma erythrocyte omega-3 fatty acid levels. (Otto, 2000) More recently Hawthorne et al., (2007) revealed that supplementation of this form of DHA in orange juice significantly improved the plasma phospholipid levels in children. (Hawthorne, 2007) Similarly, Smuts, (2003) revealed that supplementation of algeal DHA in eggs resulted in an extension of gestational age in the treated groups in a randomized clinical study. In summary, supplementation of omega-3 polyunsaturated fatty acids, particularly (DHA) is important for the developing fetus and newborn. Since fresh fish is not a staple of most American diets, algeal supplementation in the form of prenatal vitamins, containing DHA is important. Both the March of Dimes and The American College of Obstetricians and Gynecologist concur; recommending 100-200mg supplementation of DHA. Since DHA supplementation as well as other antioxidants, may be contained in prenatal vitamins a comparison of common micronutrient supplements is available are listed on Table 1.

	RDA (FNB 2009)	PreQue 10	OB complete 400	PreNexa[3]	Prenate DHA[4]	Vitafol OB+DHA[5]	Citranatal Assure[6]	Gesticare DHA[7]	OB Complete One[8]	Prenate Essentia[9]	Citranatal Harmony[10]	Prefera OB One[11]	Neevo DHA[12]	Concept DHA[13]
Administration	---	2 tablets once daily or 1 tablet twice daily	Once daily	Once daily	Once daily	2 pills once daily	2 pills once daily	2 pills once daily	Once daily	Once daily	Once daily	Once daily	Once daily	Once daily
Antioxidants														
CoQ10 (co-enzyme Q-10)	0	100 mg	0	0	0	0	0	0	0	0	0	0	0	0
Lycopene	0	10 mg	0	0	0	0	0	0	0	0	0	0	0	0
Vitamins														
Vitamin A (Beta-Carotene)	0.75-0.77 mg	2500 IU	0	0	0	2700 IU	0	0	0	0	0	0	0	0
Vitamin B_1 (Thiamine Monoitrate)	1.4 mg	2 mg	2 mg	0	0	1.6 mg	3 mg	3 mg	2 mg	0	0	0	0	2 mg
Vitamin B_2 (Riboflavin)	1.4 mg	3.4 mg	3.4 mg	0	0	1.8 mg	3.4 mg	3 mg	4 mg	0	0	0	0	3 mg
Vitamin B_6 (Pyridoxine HCl)	1.9 mg	0	25 mg	25 mg	25 mg	2.5 mg	25 mg	50 mg	30 mg	25 mg	25 mg	50 mg	25 mg	25 mg
Vitamin B_{12} (Cyanocobalamin)	26 mcg	2 mcg	26 mcg	0	12 mcg	12 mcg	0	8 mcg	50 mcg	12 mcg	0	12 mcg	50 mcg	12.5 mcg
Folate/fFolic aAcid	0.6 mg	1 mg	1.2 mg	1.2 mg	1.0 mg	1.0 mg	1.0 mg	1.0 mg	1.0 mg	1.0 mg	1.0 mg	1.0 mg	1.0 mg	1.0
Vitamin D_3 (Cholecalciferol)	200 IU	240 IU	800 IU	170 IU	200 IU	400 IU	400 IU	410 IU	1200 IU	200 IU	400 IU	400 IU	400 IU	0
Vitamin C	80-85 mg	60 mg	100 mg (as ascorbic acid with calcium ascorbate and calcium theonate)	25 mg	85 mg	70 mg	120 mg	120 mg	70 mg	85 mg	0	25 mg	40 mg	25 mg
Vitamin E (d-alpha tocopherol)	22.35 IU	30 IU	30 IU (as Hypersorb vitamin E)	30 IU	10 IU	30 IU	30 IU	30 IU	30 IU	10 IU	30 IU	10 IU	30 IU	0
Niacin (Niacinamide)	18 mg	0	10 mg	0	0	18 mg	20 mg	20 mg	10 mg	0	0	17 mg	0	1.8 mg

Minerals															
Copper	1 mg	2 mg	1 mg	0	0	2 mg	2 mg	0	1 mg	0	0	0	0	0	2 mg
Zinc (Zinc Oxide)	11-12 mg	25 mg	25 mg	0	0	25 mg	25 mg	15 mg	15 mg	0	0	15 mg	0	0	10 mg
Iron	27 mg	30 mg	40 mg (as Ferronyl and Ferrochel)	30 mg	27 mg	65 mg	35 mg	27 mg	40 mg (ferronyl) 10 mg Sumalate (elemental iron)	28 mg (ferrous fumarate)	27 mg (carbonyl iron)	22 mg Polysaccharide Iron Complex 6 mg as HIP (heme iron polypeptide)	27 mg (ferrous fumarate)	17.5 mg (ferrous fumarate) 17.5 mg Polysaccharide Iron Complex
Calcium	1000-1300 mg	0	0	160 mg	140 mg	100 mg	125 mg	200 mg	25 mg (DimaCal) & 25 mg calcium carbonate	140 mg	100 mg	0	75 mg	0	
Magnesium (Magnesium Oxide)	350-400 mg	20 mg	0	0	45 mg	25 mg	0	0	25 mg	45 mg	0	0	0	5 mg	
Selenium (as Sodium Selenate)	0	15 mcg	0	0	0	0	0	0	0	0	0	0	0	0	
Purified Fish Oil															
Docosahexaenoic Acid (DHA)	NA	100 mg	≥320 mg	265 mg	300 mg	250 mg	300 mg	250 mg	300 mg	300 mg	250 mg	200mg	250 mg	156 mg	
Other Omegas									≥40 mg	40 mg					
Other Micronutrients															
Iodine (Potassium Iodide)	0.22 mg	0	0	0	0	0	150 mcg	150 mcg	150 mcg	150 mcg	0	175 mcg	0	0	
Choline (Choline Bitartrate)	450 mg	0	0	0	0	0	0	55 mg	0		0	0	0	0	

Table 1. Prenatal micronutrient supplements.

3. Oxidative stress in preterm infants

As shown on Fig. 1, antioxidant defenses include the enzymes superoxide dismutase, catalase, and glutathione. Antioxidants cross the placenta, and include vitamins A, C, E, and CoQ_{10} as well as lycopene and DHA. Premature infants are at particular risk from oxidative stress because both endogenous and passively acquired exogenous antioxidant defense systems do not accelerate in maturation until late in the third trimester. (Finer & Leone, 2009; Baba & McGrath, 2008) 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. (Pressman, 2011) The evidence is growing that oxidative stress is the final common endpoint for a complex of events that either are genetically determined or are triggered by an in utero stressor. The newborn infant, especially those delivered prematurely, is very susceptible to free radical-induced oxidative damage. First, the premature infant is frequently exposed to oxygen therapy and hyperoxia which is richer in oxygen than the intrauterine environment exposing the infant to an excess of free radicals. (Maulik et al., 1999) Second, the antioxidant defense mechanism and its ability to be induced by hyperoxia is relatively impaired in preterm infants. (Speer & Silverman, 1998) Third, the preterm infant has an increased susceptibility to infection and inflammation, which increases oxidative stress. (Saugstad, 1988) Finally, free iron is found in the plasma and tissue of premature infants to a greater extent than in the term infants. 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). (Clyman, 1989; Archer et al., 1989; Sanderud, 1993)

3.1 Free radicals, reactive oxygen species, reactive nitrogen species and antioxidant defense

Preterm infants are at risk of unique immaturity-related neonatal diseases and a common factor in the pathogenesis of such diseases is the free radical tissue injury from oxidative stress. (Pressman, 2001) Free radicals may be generated by exposure of preterm infants to high oxygen concentrations during resuscitation and mechanical ventilation as well as by hyperoxia during the reperfusion phase of a hypoxic-ischemic brain insult, primarily in the presence of high concentrations of non-protein bound iron. (Saugstad, 1996) Small amounts of free radicals are generated continuously in living organisms and are important for normal cell reactions and cell growth. Under normal circumstances, there is a critical balance between pro-oxidant and antioxidant forces. Normally, the body's antioxidant defenses will handle free radicals, which are produced. On the other side, excessive production of ROS enhances many diseases associated with deficient antioxidant defenses and produces tissue injury in preterm infants. Many lifesaving procedures in the neonatal intensive care units may produce ROS an possible tissue damage due to the newborn's poorly developed antioxidant systems. The preterm infants are frequently exposed to excessive oxidative stress generated by the high oxygen concentrations used in neonatal resuscitation or mechanical ventilation, by inflammation and infection, and by parenteral nutrition.

As shown on Fig. 1, the antioxidant defense mechanisms are both enzymatic and nonenzymatic. (Shoji & Koletzko, 2007; Thibeault, 2000)

3.2 Enzymatic antioxidant defenses

Antioxidant enzyme activities have been shown to increase in response to oxidative stresses (Fig. 1). Antioxidant enzymes participate in a complex interaction of reducing and oxidizing molecules that defines the cellular milieu necessary for maintaining cellular, placental, fetal, and postnatal growth. (Dennery, 2004) Such enzymes have low activity in preterm infants and cannot balance excessive ROS production. The most important antioxidant enzymes are copper-zinc superoxide dismutases (SOD), which are found in cytoplasm as well as peroxisomes, and manganese SOD from mitochondria. SOD catalyzes the dismutation of superoxide anion to H2O2. Glutathione peroxidase (GPx) in mitochondria and catalase (CAT) in peroxisomes catalyze the reaction of H2O2 to molecular oxygen and water. These enzymes, together with vitamin E, play an important role in the peroxidation of polyunsaturated free fatty acids in cell membranes. (Thibeault, 2000)

In extremely low birth weight (<1500gms) infants, structural immaturity and surfactant deficiency necessitate mechanical ventilation and oxygen administration, both of which contribute to an inflammatory response. Oxidative stress in preterm infants is expressed by lower (reduced) and higher (oxidized) glutathione concentrations in plasma of preterm infants compared with term infants and lower glutathione levels in tracheal aspirates of preterm infants developing BPD. (Smith et al., 1993; Grigg et al., 1993) Glutathione peroxidase is important for removal of intracellular hydrogen peroxide and lipid peroxides, and glutathione is a direct scavenger of oxidants both intracellularly and extracellularly. Its role in lung protection is suggested by the high concentrations of glutathione in the lining fluid of lower airways and alveoli, with a transient postnatal decrease in preterm infants. (Jain et al., 1995) Many trials have incorporated enzymes in the process of prevention of tissue damage by oxygen in preterm neonates to prevent chronic lung disease. The challenge is how to introduce them into the cells or maintain them in the circulation when administered systemically. Effective therapy must be directed to the target organ and to a specific ROS or RNS. (Jankov et al., 2001; Thibeault, 2000)

3.3 Non-enzymatic antioxidant defenses

Other pathways to resist oxidative stress include the non-enzymatic pathways (Fig. 1). Nutrients such selenium, copper, and zinc may have antioxidant functions as components of antioxidant enzymes. Vitamins A, E, and C, ceruloplasmin, transferrin, glutathione (GSH), and bilirubin are considered to have antioxidant properties. Prematurity places the preterm infants at risk of ROS-induced injury because of relatively deficient uteroplacental transfer of these nutrients important to antioxidant defense. (Shah MD & Shah SR, 2009) Selenium is involved in many selenoenzymes, with GPx being the most important. Plasma selenium concentrations and Glutathione peroxidase (GPx) activity are associated with the birth weight of infants. (Trindade, 2007) Although selenium deficiency may participate in preterm diseases, the data is not sufficient to support this concept. (Darlow & Austin, 2003) The role of vitamin A likely is mediated through its action on retinol-binding protein and the retinoic acid receptor, rather than direct antioxidant effects. Serum levels of vitamin A have consistently been shown to be reduced in preterm infants. (Darlow & Graham, 2007) Vitamin C (ascorbic acid) concentrations rise in placenta and fetal liver with increasing

gestational age. A number of recent studies have suggested that supplementation with vitamin C or E may prevent teratogenic effects of maternal diabetes, but have not been consistently found to provide other measurable benefits. (Dheen et al., 2009)
Ceruloplasmin, transferrin and ferroxidase participate in the metabolism of iron, which acts as a potent oxidizing agent, so diminished function or bioavailability would be expected to increase susceptibility to oxidative stress. ROS production is enhanced by the presence of free iron. (Brion et al., 2003) Reductions in the concentrations of these non-enzymatic antioxidants may predispose the preterm infant to difficulties with increased production of ROS. Reduced transferrin and ceruloplasmin concentrations have been observed in asphyxiated preterm infants prior to the development of periventricular-intraventricular brain hemorrhage. (Lindeman et al., 2000) Glutathione depletion or inadequate synthesis has been proposed to explain developmental susceptibility of the preterm newborn to oxidative stress. Low levels in the broncho-alveolar fluid predicts the later development of BPD in intubated premature newborns. (Grigg et al., 1993) In vitro bilirubin has been demonstrated as a potent antioxidant scavenger of peroxyl radicals. In the oxidative process, bilirubin reverts to its precursor biliverdin, a nontoxic product. A direct relationship between the total antioxidant status of the newborn plasma and bilirubin concentrations was found in both preterm and term infants. (Wiedemann et al., 2003)

4. Free radical excess and neonatal organ damage

4.1 Neonatal brain injury

Brain injury in neonate can be precipitated by different mechanisms including hypoxia, hyperoxia, ischemia-reperfusion, and infection with the consequent release of oxygen free radicals and inflammatory mediators (cytokines) by activated neutrophils and macrophages. Immature brains are particularly vulnerable to oxidative stress due to poor antioxidant capabilities, high concentration of free iron and increases in unsaturated fatty acids. (Dugan & Choi, 1994) Furthermore, the inadequate scavenging ability of the immature nervous system, characterized by lower SOD and GPx activity, contributes to the accumulation of H2O2 and subsequent neurotoxicity. As H2O2 accumulates, it is exposed to free iron, resulting in generation of OH, a potent cytotoxic free radical. During brain reperfusion in a preterm infant, overload with ionic iron due to low concentrations of iron-oxidizing and iron-binding proteins may induce iron-catalyzed lipid peroxidation of the cerebral endothelial cells, resulting in vascular injury and intraventricular hemorrhage (IVH). (Lackmann et al., 1996)
The process of hypoxic-ischemic brain injury begins with the insult and extends for several hours into the recovery period (reperfusion phase of injury). With an increase in brain oxygenation in the reperfusion phase, superoxide and hydroxyl radicals are formed. (Volpe, 2001) Free radicals alter Na/K ATPase activity in cortical synaptosomal membranes, resulting in glutamate release, membrane injury, and cell death resulting in edema and seizures after 18-24 hours. (Perlman, 2006) Neonatal hypoxia can also upregulate the expression of nitric oxide (NO) synthases in the cerebral cortex, causing increased production of NO which functions as a free radical and also can trigger several neuronal cell death mechanisms, including NMDA receptor and neuronal nuclear membrane modification and transcription of apoptotic genes. (Mishra et al., 2006) Recent studies indicate that inflammatory mediators also contribute to hypoxic-ischemic brain injury, and although hypoxia-ischemia is recognized as a cause of neonatal brain injury, cytokine

mediated maternal-fetal infection (sepsis or fetal inflammatory response syndrome) also plays an important role in the pathogenesis of fetal/neonatal brain damage including early periventricular leukomalacia (PVL). (Mishra et al., 2006; Hitti et al., 2001)

There are several neuroprotective interventions and experimental models aiming at ameliorating brain injury. However, few of these interventions have been confirmed as sufficiently safe for clinical use. Further studies are necessary, but current approaches that appear safe and effective include free radical inhibitors, free radical scavengers, and mild cerebral hypothermia; the latter being the most promising. The neonatal mortality rates in extremely low birth weight infants have been reduced, but with increasing survival rate, the risk of prenatal and neonatal brain damage has not been eliminated and may be increased. (Louis et al., 2004; Marlow et al., 2005) The dilemma of determining the timing in which the potential damaging factor for the brain has occurred is a challenge for all the perinatal and neonatal specialists. In the past, acquired brain damage was mainly attributed to birth trauma, birth asphyxia, and other pathologies occurring around birth. (ACOG/AAP, 2003) With the advances in neonatal brain neuroimaging, especially MRI and MRS, cord blood nucleated red blood cells, and biomarkers for oxidative stress, it has become possible to determine a time window of the brain damage. Regarding the neonatal brain imaging, cranial ultrasound (US) has been used for many years to determine the type, extent, and evolution of brain lesions like hypoxic-ischemic encephalopathy as cerebral edema is almost always seen during the first day of life (12-18-24hrs. after birth). However, the higher sensitivity of MRI has made this study superior to cranial US in detecting early brain damage. Besides hypoxic-ischemic encephalopathy, brain MRI can also detect other lesions such as cortical-subcortical damage, diffuse cortical lesions, bilateral parasagittal lesions, brain stem lesions, cerebellar and hippocampal lesions. Brain MRI can also provide information on brain development changes such as myelination of white matter, glial cell migration and early PVL. (Childs et al., 2001) Diffusion-based MRI can provide the earliest indicators of brain damage and can be used in detecting the antenatal, perinatal, or postnatal timing of hypoxic insult. The MRI has also been used to detect fetal brain damage. (Girard et al., 2003) Nucleated red blood cell (NRBC) count indicates fetal hypoxia in both term and preterm infants. Correlations between NRBC count and cord blood pH with brain damage have been demonstrated. (ACOG/APP, 2003) For cases of intrapartum HIE cord pH is almost always <7.0. (ACOG/AAP, 2003) Also, correlations between high NRBC counts and poor neurological outcomes have been demonstrated. (Buonocore et al., 1999) Although the exact time elapsing between hypoxia and appearance of NRBC is not known, there is evidence that a period of more than 24 hours is necessary between the onset of fetal hypoxia and appearance of NRBC in blood. (Buonocore et al., 1999)

The role of oxidative stress in brain injury after fetal hypoxia has been extensively studied and demonstrated. During hypoxia, free radicals production increases with a possible decreased antioxidant defense which leads to mitochondrial dysfunction, inhibition of protein synthesis, enhanced mechanisms of apoptosis, and increased oxidative stress. (Delivoria & Misbra, 1998) Oxidative stress during fetal and neonatal hypoxia can therefore be assayed in cord blood as a marker of severe prenatal hypoxia/asphyxia. Assessment of oxidative stress is currently made by measuring advanced glycation end products from oxidation of proteins, carbohydrates, and lipids in cytoplasm, nucleus, and membranes. (Yamamoto et al., 2002) In conclusion, in addition to information provided by the obstetricians, neonatologists can have other tools of determining whether brain damage has

occurred in the prenatal, intrapartum, or postnatal period, however, each tool has its limitations.

4.2 Retinopathy of prematurity: (ROP)

Retinopathy of prematurity which is a disease limited almost exclusively to premature infants. It is characterized by abnormal vascularization of the retina, causing a range of vision impairment, and remains a major cause of morbidity for premature neonates. The discovery of the relationship between hyperoxia and the development of ROP represented a breaking point in modern neonatology. (Ashton & Cook, 1954; Campbell, 1951; Patz et al., 1952) The fetus in utero is exposed to arterial oxygen pressure of 22–24 mm Hg. After delivery, the premature infant may be exposed to a relative hyperoxia that may downregulate vascular endothelial growth factor (VEGF) production leading to vaso-obliteration of existing vessels and arrest of the vascularization. As ROP has been related to hyperoxia, reactive oxygen stress may be involved in this disease. (Shweiki et al., 1992)

As the retina develops anterior to the arrested vascularization area, there will be increased oxygen demand, which creates localized physiological hypoxia which will increase the expression of the VEGF in response to hypoxia. With maturation, the non-vascularized retina becomes increasingly metabolically active and consequently hypoxic. Hypoxia leads to more VEGF, which induces neo-vascularization of the retina, which in severe cases may result in retinal fibrosis and retinal detachment. (Darlow & Graham, 2002; Penn et al., 1994; Smith et al., 1999) Present therapy for severe ROP is mainly based on laser retinal ablation of the avascular retina. This therapy reduces the incidence of blindness by 25%. (Good, 2004) A number of antioxidants and nutrients have been or may be tested. Vitamins A and C supplementation do not seem to reduce the rate of severe ROP. (Darlow et al., 2005; Lakatos et al., 1986) D-penicillamine, however, is a powerful antioxidant and vasomodulator and there are some promising data which strongly indicate that this drug may reduce the severity of ROP.

4.3 Chronic lung disease/bronchopulmonary dysplasia: (CLD/BPD)

The development of chronic lung disease in infancy remains a significant health problem, particularly in the premature infant. Hyperoxia is an important factor in the development of bronchopulmonary dysplasia and is associated with growth arrest and impaired alveolar septal development in the neonatal lung. (Jobe, 1999) The etiology of CLD is unknown, but many investigators have suggested that free radicals play a key role in its development. The pathogenesis of chronic lung disease/BPD is multi-factorial, and many pre- and postnatal risk factors have been identified, such as chorioamnionitis, systemic infection, inadequate resuscitation, high-inspired oxygen concentrations, barotrauma, volutrauma, and mechanical ventilation. These factor all can injure tissue through oxygen toxicity and pro-inflammatory mediators acting on immature airways and pulmonary tissue. (Saugstad, 1998)

Chemokines (interleukin [IL]-8) and other pro-inflammatory cytokines such as IL-1, IL-6, and tumor necrosis factor-alpha are produced by alveolar macrophages, airway epithelial cells, fibroblasts, type II pneumocytes, and endothelial cells of preterm infants. Activated neutrophils and macrophages release potent proteases together with many enzymes. However, free oxygen radicals inactivate the protease inhibitors (alpha-1-proteinase inhibitor), leading to an imbalance between protease and antiprotease inhibitor,

contributing to damage and excretion of elastic fiber degradation products. Oxidative stress increases both metalloproteins and their inhibitors, causing disruption of the extracellular matrix and contributing to pulmonary fibrosis. (Speer, 2004, 2006) The main source of free radicals in the lungs seems to be phagocyte activation. The increase in phagocyte number and interleukin concentrations in the broncoalveolar fluid obtained from premature infants with CLD indicates that oxygen toxicity and inflammation are involved in the development of lung injury. (Delacourt et al., 1996; Groneck et al., 1993; Pittet et al., 1997)

Several important factors contribute to augmented oxidative stress in the newborn and especially the preterm infant. First, because of immaturity, the lung of preterm infants is frequently exposed to oxygen therapy and hyperoxia. Second, the antioxidant defense and its ability to be induced during a hyperoxic challenge are impaired. Third, the preterm infant has an increased susceptibility to infection and inflammation, which increases oxidative stress. Fourth, free iron, which catalyzes the production of free oxygen radicals, can be detected in preterm infants. (Asikainen & White, 2004; Welty, 2001; Welty & Smith, 2001) Antioxidant nutrients, including inositol, glutamine, cysteine, and methionine, as well as vitamins and some trace elements have been thought to play a role in protection of lung parenchyma. (Binivale & Ehrenkranz, 2006) A trial of parenteral inositol for preterm infants who had respiratory distress showed that inositol supplementation was associated with increased survival and a lower incidence of BPD. Interventions to prevent lung oxidative injury in preterm infants require more basic clinical studies to solve the intricate oxidative mechanisms in the molecular processes and address the use of specific or groups of antioxidants. (Hallman et al., 1992)

4.4 Necrotizing enterocolitis: (NEC)

Oxidative stress is caused by an imbalance between the production of ROS and the ability to detoxify them with the help of antioxidants. The premature infant is especially susceptible to ROS-induced damage because of inadequate antioxidant stores at birth, as well as impaired up-regulation in response to oxidant stress. Several etiologic factors have been identified in the pathogenesis of NEC: immaturity, hypoxia/ischemia, hyperosmolar feedings, and bacterial colonization as well as oxidative stress. (Hsueh et al., 2002) The preterm infants are more vulnerable to NEC by an interaction of local defense, enteral feeding, bacterial colonization, inflammatory response and genetic susceptibility. The preterm infants have inadequate local nonspecific mucosal defenses, delayed gut colonization, and down-regulation of intracellular signaling that inhibit inflammatory reaction. Failure of the intestinal barrier in the preterm infants may induce an excessive inflammatory response resulting in platelet-activating factor (PAF)-induced bowel injury and high concentrations of pro-inflammatory cytokines that trigger the production of free radicals. (Martin & Walker, 2006)

The final pathway in NEC pathogenesis involves free radical injury. During hypoxia the intestine will accumulate xanthine-oxidase with excessive generation of ROS during the reperfusion period, resulting in oxidative cellular damage. This hypothesis is strongly supported by experimental studies that show protective benefit of pretreatment with antioxidants such as allopurinol, superoxide dismutase (SOD), and vitamin E. (Hsueh et al., 2002) Many strategies to prevent NEC have been investigated, but few are promising. Feeding human milk can reduce the incidence of NEC. Human milk antioxidant components include the enzymes superoxide dismutase for dismutation of superoxide

anion, catalases for degradation of hydrogen peroxide (H2O2), glutathione peroxidase for destruction of H2O2 and organic peroxides. Human milk contains other molecules including cysteine, vitamins C and E, which are scavengers of oxygen radicals. (L'Abbe & Friel, 2000; Lindmark-Mansson & Akesson, 2000)

5. Preventive and therapeutic strategies against free radical damage

Human studies have demonstrated that a delicate balance between the production of reactive oxygen species and the antioxidant defense factors is essential to prevent cell damage from the ROS/RNS. The premature infant is especially susceptible to oxidation-induced damage because of: first, inadequate concentrations of antioxidants at birth since developmental increases in antioxidant capacity occur in the latter part of gestation and; second, the ability to increase synthesis of antioxidants in response to hyperoxia or other oxidant challenges is deficient. Relative impairments in the induction of antioxidant enzymes may result in an increased risk for the development of free oxygen radical diseases of the newborn such as periventricular leukomalacia, bronchopulmonary dysplasia, and retinopathy of prematurity. (Auten & Davis, 2009) Accordingly the preventive and therapeutic strategies have focused on avoiding the reactive oxygen species as well as using antioxidants; both enzymatic and non-enzymatic.

5.1 Avoid oxidative stress

Increased production of ROS can occur as a result of many conditions affecting the mother (maternal diabetes, maternal drugs, chorioamnionitis, congenital infections), as well as the newborn infant (hyperoxia, reperfusion, inflammation). Prevention and control of maternal diabetes which if not treated, is associated with an increased production of ROS, can minimize the incidence of ROS-induced fetal structural defects. (Wiznitzer et al., 1999) Epidemiologic data have suggested a strong association between chorioamnionitis and the development of bronchopulmonary dysplasia due to increased concentrations of pro-inflammatory cytokines in human amniotic fluid and fetal cord blood, indicating a systemic inflammatory response during chorioamnionitis. Treatment of maternal chorioamnionitis may minimize the ROS-induced fetal insult. (Buhimschi et al., 2009)

Obviously, avoidance of neonatal conditions such as asphyxia, hyperoxia, and retinal phototherapy light exposure which can cause excessive release of free oxygen radicals are the best strategy in avoiding the oxidative stress in neonates. It is also important to consider the fact that infection, especially sepsis, is a significant source of oxidative stress. Accordingly, early identification and treatment of sepsis and the concept of optimal oxygenation are considered important preventive strategies. Conventional indications suggest that optimal oxygen tension should be maintained between 50-70 mmHg. (Wolkoff & Narula, 2000). A significant decrease in chronic lung disease and retinopathy of prematurity without any difference in mortality were observed in extremely low birth weight infants kept at less than 95% oxygen saturation compared to those kept at more than 95%. (Sun, 2002) Hyperoxia and oxidative stress may occur during neonatal resuscitation with a potential risk is associated with resuscitating those infants, especially preterm infants, with 100% oxygen due to more production of ROS compared to room air. (Ramij et al., 1993) Accordingly, it seems reasonable to suggest avoiding routine neonatal resuscitation with 100% oxygen. To avoid hyperoxia in a very pre-term infants (less than, 32 weeks gestation), use of an oxygen blender and pulse oximeter during resuscitation is recommended.

Another preventive strategy is avoiding or at least minimizing the barotrauma and volutrauma caused by mechanical ventilation in preterm infants with respiratory distress syndrome. Barotrauma, volutrauma and oxygen toxicity, during mechanical ventilation, are important factors in the pathogenesis of CLD with the release of multiple pro-inflammatory cytokines and increased production ROS and RNS that are destructive to lipids, proteins and DNA, within the pulmonary cells. Avoidance of the use of pure oxygen during resuscitation as well as avoidance of mechanical ventilation with the use of early surfactant and nasal continuous positive air pressure (CPAP) may reduce respiratory tissue damage. (Schult et al., 2003)

5.2 Antioxidant therapy

The use of antioxidants to suppress or at least minimize the molecular damage by ROS and or RNS could be considered in situations in which hyperoxia is expected. Antioxidants could be both enzymatic and non-enzymatic factors that scavenge various oxidants.

5.2.1 Antioxidant enzymes

Antioxidant enzymes include copper-zinc superoxide dismutase (CuZnSOD), and manganese SOD can catalyze the dismutation of superoxide anion to H2O2. Supplementation with an aerosol-delivered SOD mimetic improved alveolar development in a baboon model of severe BPD caused by prematurity, hyperoxia, and mechanical ventilation. (Chang et al., 2003) Another antioxidant enzyme is the Glutathione peroxidase (GPx) which is also important for removal of intracellular hydrogen peroxide and lipid peroxides, and glutathione is a direct scavenger of oxidants both intracellularly and extracellularly. Its role in lung protection is suggested by the high concentrations of glutathione in the lining fluid of lower airways and alveoli, with a transient postnatal decrease in preterm infants. (Jain et al., 1995) Many trials have been made to incorporate enzymes in the process of prevention of tissue damage by oxygen in preterm neonates to prevent diseases like chronic lung disease. The challenge is how to introduce them into the cells or maintain them in the circulation when administered systemically. Effective therapy must be directed to the target organ and to a specific ROS or RNS. (Jankov et al., 2001; Thibeault, 2000)

5.2.2 Non-enzymatic antioxidants

Non-enzymatic antioxidants include glutathione, thioredoxin, vitamins A, C, and E, melatonin, polyphenols, certain trace elements, and others. As previously mentioned, vitamins A, C, and E are important factors in normal physiology as well as antioxidant defense. The role of Vitamin A is mediated by acting on retinol-binding protein and the retinoic acid receptor. However, serum levels of vitamin A have consistently been shown to be reduced in preterm infants thus increasing their risk for chronic lung disease. (Darlow & Graham, 2007; Debier & Larondelle, 2005) Although vitamin concentrations can be increased in the serum of preterm animal models, this has not resulted in a significant reduction in ROS-induced injury. (Berger et al., 1998; Brion et al., 2003) Studies has shown that Melatonin can reverse oxidant/antioxidant imbalance in damaged lung tissue in neonatal rats and thus it may have a promising beneficial factor on hyperoxia-induced lung disease in human neonates with chronic lung diseases. (Jan et al., 2007; Mollaoglu et al., 2007; Pignone et al., 2006)

5.2.3 Hypothermia

During hypoxia-ischemia, an overproduction of free radicals has been suggested to cause oxidative stress, with harmful effects on cells and tissues. Recent studies have shown therapeutic systemic cooling or hypothermia therapy may exert protective effects against oxidative stress. Term infants were randomly selected for treatment with moderate whole body hypothermia versus standard supportive care after perinatal asphyxia. Total hydroperoxide as a biomarker of oxidative stress, and C-reactive protein as a marker of inflammation, were monitored. The slower increase and lower peaks of total hydroperoxides and the C-reactive protein in the hypothermic group support the hypothesis that hypothermia may reduce the post-asphyxic oxidative stress. (Perrone et al., 2010)

5.2.4 Breast feeding

Another preventive strategy against ROS is the advocacy of breast feeding for all infants as 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 (H2O2), glutathione peroxidase for destruction of H2O2 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.

6. Conclusion

A physiologic redox state is essential for normal human development. However, pregnant women, their growing fetus as well as preterm newborns are highly susceptible to oxidative stress because they often are exposed to hyperoxia, infectious/inflammatory conditions, and high concentrations of nonprotein- bound iron, which can contribute to increased production of free radicals. It has been shown unequivocally that during pregnancy and in the preterm newborn, there are lower levels of antioxidant factors, which result in an imbalance between oxidant and antioxidant factors that actually trigger free radical injury. Several studies have shown that in women with such an imbalance, preeclampsia, preterm labor, intrauterine growth restriction, and preterm premature rupture of the membranes, can result. Also, investigations have suggested that oxidative stress is involved in the pathogenesis of neonatal diseases such as periventricular leukomalacia, intraventricular hemorrhage, and bronchopulmonary dysplasia, retinopathy of prematurity and necrotizing enterocolitis. Clinical trials in pregnant women have shown that increasing the amount of lycopene, and CoQ_{10}, as well as DHA, seems to reduce the burden of the maternal fetal disorders listed above. Single supplementations of vitamins A, C, E, have not shown salutary results. However, has shown on Table 1, many of the market leaders in prenatal micronutrients supplementation include many of these antioxidant vitamins, minerals, and trace elements. Also, clinical trials have provided indirect evidence supporting the concept that free radicals play a key role in the pathogenesis of neonatal diseases. 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 every disease need to be established. While well accepted in obstetric practice, the impact of antioxidant therapy in the neonatal period remains under investigation. Although research is promising, further studies for early identification of infants at risk from oxidative stress and the development of safe and efficient antioxidant strategies to prevent or minimize oxidative damage are required.

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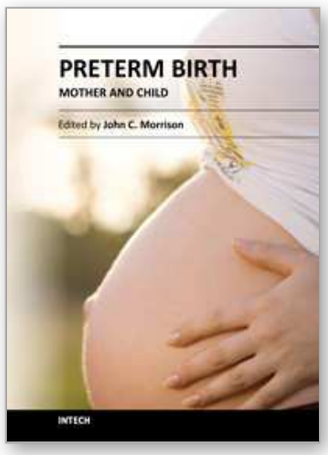

Preterm Birth - Mother and Child

Edited by Dr. John Morrison

ISBN 978-953-307-828-1
Hard cover, 368 pages
Publisher InTech
Published online 27, January, 2012
Published in print edition January, 2012

While there are many studies and books regarding preterm birth, both the obstetric and in the neonatal/pediatric literature, what is missing is the integration of data from obstetrics through neonatal course and into pediatrics as the neonate transverses childhood. A continued dialogue between specialties is essential in the battle against preterm birth in an attempt to relieve the effects or after-effects of preterm birth. For all of our medical advances to date, preterm birth is still all too common, and its ramifications are significant for hospitals, families and society in general.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Robert A. Knuppel, Mohamed I. Hassan, James J. McDermott, J. Martin Tucker and John C. Morrison (2012). Oxidative Stress and Antioxidants: Preterm Birth and Preterm Infants, Preterm Birth - Mother and Child, Dr. John Morrison (Ed.), ISBN: 978-953-307-828-1, InTech, Available from: http://www.intechopen.com/books/preterm-birth-mother-and-child/oxidative-stress-and-antioxidants-preterm-birth-and-preterm-infants

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InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
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InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
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