ANTIOXIDANTS & REDOX SIGNALING
Volume 6, Number 1, 2004

Forum Review

Role of Redox in Fetal Development and Neonatal Diseases

PHYLLIS A. DENNERY

ABSTRACT

In the cell, reducing and oxidizing molecules modulate the redox state. In embryonic and fetal growth, increased oxidative stress may be detrimental, but an oxidized state can also be beneficial. This is because redox may also affect key transcription factors that can alter gene expression during development. In addition, redox may impact on placentation and amniotic membrane integrity during pregnancy. Lastly, diseases of prematurity, such as necrotizing enterocolitis, retinopathy of prematurity, and chronic lung disease, may be modulated by redox in the premature. Because antioxidant therapies have not necessarily modified the outcome of these diseases, some debate exists as to this. Nonetheless, sufficient evidence suggests a role for redox throughout embryonic, fetal, and postnatal development. This evidence will be explored here. *Antioxid. Redox Signal.* 6, 147–153.

INTRODUCTION

THE REDOX STATE is modulated by a complex interaction of reducing and oxidizing molecules that work in concert to define the cellular milieu (59). Increased oxidative stress has been implicated in many disease processes in early life. However, maintaining an oxidized state is useful in many circumstances, including fetal growth and development. The balance of oxidizing and reducing forces is key to ensuring normal fetal development and normal organogenesis. Furthermore, changes in these states occur in the transition to birth and also may be aggravated in circumstances dictated by premature birth. During fetal development, the maturation of the oocyte and the formation of the embryo require energy in the form of ATP, NADH/NADPH, and oxygen (31). Oxygen is needed to convert ADP to ATP. Oxygen consumption in the mitochondria results in the formation of reactive oxygen species, in particular the superoxide radical and the hydroxyl radical (62). In most circumstances, overproduction of these radicals is unfavorable (18, 28, 31, 78), leading to metabolic disturbances and deregulation of events in development. However, a certain amount of oxidative stress is required in key aspects of embryonic development (18, 31, 54) (Fig. 1). In this article, redox factors that influence fetal development, fetal growth *in utero,* and postnatal tissue injury will be reviewed (Table 1).

EFFECT OF REDOX ON TRANSCRIPTION FACTOR ACTIVATION

Redox may also affect development by modifying key transcription factors that can alter gene expression in the embryo. These factors include hypoxia-inducible factor (HIF-1), nuclear factor-κB (NF-κB), activator protein-1 (AP-1), and p53. The transcription factor HIF-1 is activated in hypoxic states (9, 29). This activation results in increased transcription of various genes that could impact on vascular development such as vascular endothelial growth factor (VEGF) (20). NF-κB is an important regulator of cytokine and antiapoptotic gene expression (19, 30, 44, 46). Overexpression of NF-κB could result in decreased apoptosis and increased proinflammatory state. AP-1 is exquisitely sensitive to oxidative stress (27, 66, 79). It is found on the promoter of several antioxidant enzymes. Modulation of AP-1 could further modify cellular redox status and thus alter embryonic development. The apoptotic factor p53 is expressed in conditions of DNA damage and is in-

Department of Pediatrics, University of Pennsylvania, Division of Neonatology, Children's Hospital of Philadelphia, Philadelphia, PA.

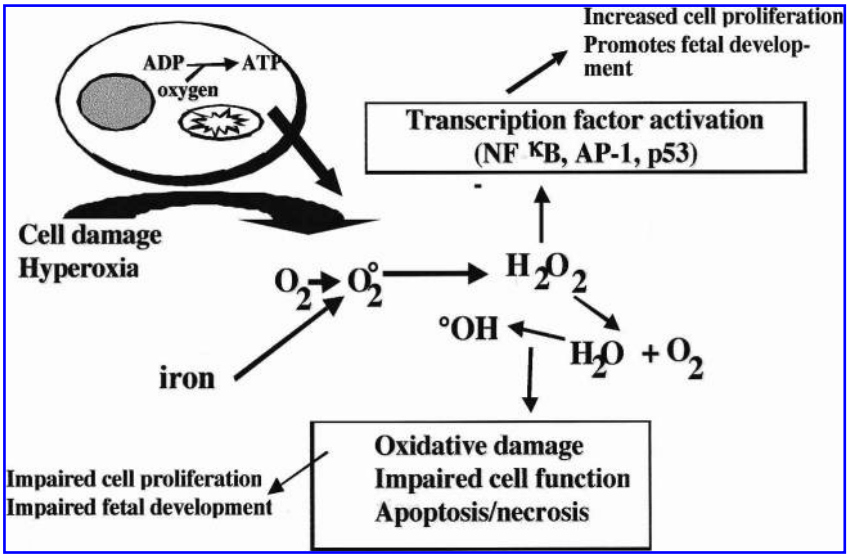

FIG. 1. Role of redox in fetal development. Cellular respiration results in the consumption of oxygen in the mitochondria. This leads to release of reactive oxygen species such as superoxide ($O_2^{\cdot}$), hydrogen peroxide (H_2O_2), and the hydroxyl radical ($^{\cdot}OH$). In situations of increased oxidative stress such as hyperoxia and in damaged cell, these reactive oxygen species can lead to the activation of various transcription factors with both positive and negative effects on the cell. These effects are further exacerbated by the presence of iron.

volved in triggering a cascade of proapoptotic events such as the liberation of Bcl-2, Bcl-xL, and Bax (apoptosis-related proteins derived from B-cell lymphoma) from the mitochondrial membrane (2, 65, 71). This results in release of caspases 3 and 9 and subsequent DNA fragmentation. Because p53 is a cell-cycle checkpoint protein, it leads to growth arrest. This protein is also able to induce apoptosis (65). This could also significantly alter embryonic development (10). Overall, changes in key transcription factors regulated by redox could significantly alter the embryo because a delicate redox balance must exist to allow for proper growth and development.

REDOX IN IMPLANTATION OF THE EMBRYO

In order for implantation to occur, the oocyte must migrate along the oviduct to the uterus. The oviductal oxygen level is 40% less than atmospheric level, and the uterine oxygen level is even lower; therefore, the oocyte migrates to a progressively lower oxygen gradient as it enters into the uterus (17, 25). This reduced oxygen gradient is important for appropriate implantation. Once implantation has occurred, embryonic development can proceed.

TABLE 1. EFFECTS OF REDOX IN THE FETUS AND NEONATE

Oocyte	Promotes implantation
Blastocyst	Promotes formation of fluid-filled cavity
Pregnancy	PIH, IUGR, PROM
Neonate	CLD, NEC, ROP

CLD, chronic lung disease; IUGR, intrauterine growth restriction; NEC, necrotizing enterocolitis; PIH, pregnancy-induced hypertension; PROM, premature rupture of membranes; ROP, retinopathy of prematurity.

REDOX IN EMBRYONIC GROWTH

Low oxygen tensions promote embryonic development *in vitro* (8, 32, 52). Conversely, it has been shown that increased generation of reactive oxygen species delays embryonic development (8, 15, 28). However, inclusion of antioxidants into embryonic cultures showed varied responses. For example, overexpression of copper-zinc superoxide dismutase (CuZn-SOD) impaired syncitiofibroblast formation and resulted in lower levels of human chorionic gonadotropin, a key hormone for embryonic development (23). Furthermore, in the blastocele, an early embryo, hydrogen peroxide causes apoptosis of the inner cell mass and results in the formation of a fluid-filled cavity, which is an important event in embryonic development (53, 55).

ROLE OF REDOX IN PLACENTATION AND PREGNANCY-INDUCED HYPERTENSION

In addition to its role in embryonic development, the redox state is also key to several processes during pregnancy. Hypoxia and consequent oxidative stress can cause an increase in epinephrine and vasoconstriction leading to decreased fetal growth (35). Furthermore, increased oxidative stress has been linked to pregnancy-induced hypertension, a condition of increased blood pressure in the later half of pregnancy, which is often associated with intrauterine fetal growth retardation

(37, 74, 76). Conversely, decreased oxidative stress also has adverse effects. Investigators have shown that induced CuZn-SOD overexpression results in decreased placental development (24). Additionally, placentas of patients with Down's syndrome are abnormally formed (4), perhaps due to the overexpression of CuZnSOD, resulting from an extra copy of chromosome 21 (23, 24).

There are isoforms of superoxide dismutase (SOD) in the placenta, and these may serve to regulate the reactivity and bioavailability of nitric oxide (51). Because the blood flow in the placenta is devoid of autonomic regulation, it relies on paracrine and autocrine factors (1). Blood flow to the placenta is essential in providing adequate nutrition and oxygen to the developing fetus. In conditions where there is abnormal vascularization to the placenta, growth retardation, and/or preeclampsia, a condition that is associated with pregnancy-induced hypertension occurs with ensuing deleterious consequences (1, 41). A study by Myatt *et al.* (48) looked at normotensive pregnant patients and compared them with patients with preeclamptic and intrauterine growth retardation (IUGR) as to the distribution of SOD isoforms in the villous vasculature. In both groups, the distribution of manganese SOD (MnSOD) was observed mostly in the villous vasculature, suggesting that SOD plays a significant role in regulating blood flow to the fetus. Despite a lack of difference in MnSOD between normal and preeclamptic and IUGR pregnancies in this study (48), several other investigators have noted increased lipid peroxidation in pregnancy-induced hypertension (40, 75, 81). In one study, four indices of lipid peroxidation in the serum were measured in patients with pregnancy-induced hypertension or IUGR toward the later third of pregnancy. These patients were then treated with vitamin C to prevent oxidative damage. This resulted in improved fetal growth and decreases in markers of oxidative stress over the course of a 10-day treatment. However, the response was mixed in that some parameters of lipid peroxidation, namely lipid hydroperoxides, increased initially after treatment with vitamin C (38).

ROLE OF REDOX IN PREMATURE RUPTURE OF MEMBRANES (PROM)

Another effect of redox in the fetus is damage to fetal membranes. Reactive oxygen species can alter collagen, and this can lead to PROM and potentially to premature birth. The mechanism by which this can occur is twofold. It may be that reactive oxygen species result in increased expression of genes that cause the degradation of collagen within the membranes, such as matrix metalloproteinase (MMP) (73, 80). In fact, this may be the mechanism by which infection contributes to PROM by causing up-regulation of such genes and decreased expression of MMP inhibitors, such as tissue inhibitor of metalloproteinase (TIMP) (45). Furthermore, polymorphisms in the MMP-9 promoter are associated with increased incidence of PROM (16), demonstrating the importance of this molecule in membrane integrity. Another mechanism by which reactive oxygen species can mediate PROM is through increased superoxide ion causing increased calcium and arachidonic acid release, leading to increased lipid peroxidation and cellular damage (47, 50). Overall, oxidative stress modifies placental function and subsequent fetal well-being.

ROLE OF REDOX IN DISEASES OF PREMATURITY

A popular theory is that many of the common diseases of prematurity could result from increased reactive oxygen species and decreased antioxidant defenses (63). At birth, all newborns transition from a relatively hypoxic to a relatively hyperoxic environment (22). In many other circumstances, the oxidative burden of the premature or sick infant is enhanced. Premature newborns are relatively deficient in antioxidant enzymes and factors due to lack of placental transfer of antioxidant enzymes until the third trimester of pregnancy (21). Also, inadequate nutrition and increased exposure to oxygen radicals via intravenous lipids (33, 43, 49) may contribute to oxidative tissue injury. Furthermore, exposure to a relatively higher oxygen concentration to alleviate respiratory distress (21, 39, 63) or multiple blood transfusions resulting in the liberation of iron-derived radicals (11, 34, 77) may promote the development of oxygen radical-mediated diseases such as chronic lung disease (CLD), retinopathy of prematurity (ROP), and necrotizing enterocolitis (NEC).

ROP is characterized by excessive neovascularizaton of the retina. It is commonly found in premature infants, especially in the most immature (67). VEGF is up-regulated due to increased activation of HIF-1 (67) with repeated episodes of desaturation (58) or activation of other oxidant responsive transcription factors with increased exposure to high concentrations of oxygen (36). This results in the proliferation of tortuous vessels and traction on the retina with the potential for detachment.

NEC is the final common pathway for bowel injury in the immature gut. It occurs in 10% of premature infants. Inflammation and infection, increased solute load of formula (5), and/or and ischemia (7) lead to submucosal injury, extravasation of air in the intramural space, and potential bowel perforation. Oxygen radicals can alter inflammation in the gut and can lead to activation of platelet activating factor (5), which results in increased coagulation and subsequent microthrombus formation in small vessels.

Despite documentation of increased oxygen radicals in animal models and infants with diseases such as ROP or NEC, it has been difficult to correlate the severity of illness with antioxidant capacity (60) or the amount of oxygen radicals produced (5, 14). Interestingly, in a few studies, providing increased antioxidant defenses did not necessarily alleviate disease processes, suggesting more complex etiologies (67, 68).

In the remaining discussion, oxidative stress in the neonatal lung is discussed. There, also, the role of oxidative stress is debatable.

REDOX IN NEONATAL LUNG DISEASE

Many (up to 70%) premature infants will develop CLD or bronchopulmonary dysplasia. This condition is thought to re-

sult from ventilator-related trauma, inflammation, and oxygen radicals (69–72). The latter two are interrelated because inflammatory cells release oxygen radicals with the oxidative burst (3). Prolonged exposure to high concentrations of oxygen can also aggravate CLD. Furthermore, reduced antioxidant defenses compound the problem. Many studies have looked at indices of oxidative stress in infants destined to develop CLD and demonstrated an association with increased lipid mediators such as eicosanoids [in particular, 15-hydroxyeicosatetraenoic acid (15-HETE)] (69). This was further substantiated by the correlation of increased lipid peroxidation as measured by exhaled ethane and pentane on the fourth day of life with poor outcome (CLD and/or death) in a small study of premature infants (56). Neonates exposed to higher inspired oxygen (>40%) and to mechanical ventilation had increased protein oxidation in the bronchoalveolar lavage fluid (26). Infants who developed CLD also had increased oxidation of Clara cell secretory protein (57). In sum, the role of oxidative stress is validated by the above referenced studies, which help explain why neonates exposed to high-inspired oxygen have a higher incidence of CLD. It is felt that oxidative stress results in activation of lung matrix collagenases (64), proinflammatory gene products, and vascular proteins such as VEGF, resulting in aberrant lung development and maturation. Other studies contradict the role of oxidative stress in neonatal disease. In a prospective trial of 25 premature infants, increased polyunsaturated fatty acids (precursors of lipid peroxides) in the tracheal aspirate correlated with a decreased incidence of CLD (61). This is in agreement with one theory that polyunsaturated fatty acids are scavengers of free radicals and that they protect against oxidative stress (68). Furthermore, mean levels of lung lipid peroxidation, as determined by thiobarbituric acid-reactive substances, were similar in premature and term infants as were levels of CuZnSOD and MnSOD (70), suggesting that the concept of lowered antioxidant defenses in prematures is invalid. Furthermore, in a recent study, although protein carboxyls and malondialdehyde were higher in tracheal aspirates of preterm infants weighing <1,500 g, this did not correlate to the development of CLD. It did, however, correlate to myeloperoxidase, suggesting a link with neutrophil activation (6). In all of these studies, it is important to note that tracheal aspirates may not necessarily reflect the oxidative status more distally in the airways.

To add to the confusion, antioxidant therapies to prevent CLD have been met with variable success. Interventions with antioxidant such as recombinant human SOD did not change the incidence of CLD (13, 72). Low levels of vitamin A correlated with increased CLD (12). However, in a review of trials of administration of vitamin A in preterm infants, only the smallest prematures (<1,000 g) showed a decreased incidence of CLD (67). Perhaps the lack of success of these antioxidant therapies stems from the multifactorial nature of this disease or the significant impact of inflammation on the development of CLD (71, 72). Furthermore, antiinflammatory agents can alter oxidative stress and sole use of an antioxidant may not mitigate this effect. This is suggested by decreased phospholipid peroxidation in the bronchoalveolar fluid of premature infants after administration of meter-dosed inhaled steroids for 0–12 days (82). Furthermore, preventing neutrophil influx reduced DNA damage in hyperoxia-exposed newborn rats (3). It may be necessary to administer a cocktail of antiinflammatory and antioxidant compounds to prevent CLD. Whether this approach would adversely modify lung development in the growing premature by altering lung redox (18, 42) and subsequent gene expression remains to be determined.

CONCLUSIONS

Redox plays an important role in embryonic, fetal, and neonatal development. Many examples demonstrate that increased oxidative stress may result in abnormal development, but the literature equally demonstrates that obliterating oxidative stress is deleterious to some aspects of development. Additionally, antioxidant therapies have not yet consistently modified the outcome of diseases of oxygen radicals in prematures, suggesting a multifactorial origin. Future studies with combination therapies may be more successful.

ABBREVIATIONS

AP-1; activator protein; CLD, chronic lung disease; CuZn-SOD, copper-zinc superoxide dismutase; HIF, hypoxia-inducible factor; IUGR, intrauterine growth retardation; MMP, matrix metalloproteinase; MnSOD, manganese superoxide dismutase; NEC, necrotizing enterocolitis; NF-κB, nuclear factor-κB; PROM, premature rupture of membranes; ROP, retinopathy of prematurity; SOD, superoxide dismutase; VEGF, vascular endothelial growth factor.

REFERENCES

1. Ahmed A and Perkins J. Angiogenesis and intrauterine growth restriction. *Baillieres Best Pract Res Clin Obstet Gynaecol* 14: 981–998, 2000.
2. Ashcroft M, Taya Y, and Vousden KH. Stress signals utilize multiple pathways to stabilize p53. *Mol Cell Biol* 20: 3224–3233, 2000.
3. Auten RL, Whorton MH, and Nicholas Mason S. Blocking neutrophil influx reduces DNA damage in hyperoxia-exposed newborn rat lung. *Am J Respir Cell Mol Biol* 26: 391–397, 2002.
4. Banerjee S, Smallwood A, Nargund G, and Campbell S. Placental morphogenesis in pregnancies with Down's syndrome might provide a clue to pre-eclampsia. *Placenta* 23: 172–174, 2002.
5. Bhatia AM, Feddersen RM, and Musemeche CA. The role of luminal nutrients in intestinal injury from mesenteric reperfusion and platelet-activating factor in the developing rat. *J Surg Res* 63: 152–156, 1996.
6. Buss IH, Darlow BA, and Winterbourn CC. Elevated protein carbonyls and lipid peroxidation products correlating with myeloperoxidase in tracheal aspirates from premature infants. *Pediatr Res* 47: 640–645, 2000.
7. Cassutto BH, Misra HP, and Pfeiffer CJ. Intestinal post-ischemic reperfusion injury: studies with neonatal necrotizing enterocolitis. *Acta Physiol Hung* 73: 363–369, 1989.

8. Catt JW and Henman M. Toxic effects of oxygen on human embryo development. *Hum Reprod* 15 (Suppl 2): 199–206, 2000.
9. Chiappe-Gutierrez M, Kitzmueller E, Labudova O, Fuerst G, Hoeger H, Hardmeier R, Nohl H, Gille L, and Lubec B. mRNA levels of the hypoxia inducible factor (HIF-1) and DNA repair genes in perinatal asphyxia of the rat. *Life Sci* 63: 1157–1167, 1998.
10. Choi J and Donehower LA. p53 in embryonic development: maintaining a fine balance. *Cell Mol Life Sci* 55: 38–47, 1999.
11. Cooke RW, Drury JA, Yoxall CW, and James C. Blood transfusion and chronic lung disease in preterm infants. *Eur J Pediatr* 156: 47–50, 1997.
12. Darlow BA and Graham PJ. Vitamin A supplementation for preventing morbidity and mortality in very low birthweight infants. *Cochrane Database Syst Rev* CD000501, 2000.
13. Davis JM, Parad RB, Michele T, Allred E, Price A, and Rosenfeld W. Pulmonary outcome at 1 year corrected age in premature infants treated at birth with recombinant human CuZn superoxide dismutase. *Pediatrics* 111: 469–476, 2003.
14. DeJonge MH, Khuntia A, Maisels MJ, and Bandagi A. Bilirubin levels and severe retinopathy of prematurity in infants with estimated gestational ages of 23 to 26 weeks. *J Pediatr* 135: 102–104, 1999.
15. Eppig JJ and Wigglesworth K. Factors affecting the developmental competence of mouse oocytes grown in vitro: oxygen concentration. *Mol Reprod Dev* 42: 447–456, 1995.
16. Ferrand PE, Parry S, Sammel M, Macones GA, Kuivaniemi H, Romero R, and Strauss JF 3rd. A polymorphism in the matrix metalloproteinase-9 promoter is associated with increased risk of preterm premature rupture of membranes in African Americans. *Mol Hum Reprod* 8: 494–501, 2002.
17. Fischer B and Bavister BD. Oxygen tension in the oviduct and uterus of rhesus monkeys, hamsters and rabbits. *J Reprod Fertil* 99: 673–679, 1993.
18. Fisher JC, Kling DE, Kinane TB, and Schnitzer JJ. Oxidation–reduction (redox) controls fetal hypoplastic lung growth. *J Surg Res* 106: 287–291, 2002.
19. Flohe L, Brigelius-Flohe R, Saliou C, Traber MG, and Packer L. Redox regulation of NF-kappa B activation. *Free Radic Biol Med* 22: 1115–1126, 1997.
20. Forsythe JA, Jiang BH, Iyer NV, Agani F, Leung SW, Koos RD, and Semenza GL. Activation of vascular endothelial growth factor gene transcription by hypoxia-inducible factor 1. *Mol Cell Biol* 16: 4604–4613, 1996.
21. Frank L. Antioxidants, nutrition, and bronchopulmonary dysplasia. *Clin Perinatol* 19: 541–562, 1992.
22. Frank L and Groseclose EE. Preparation for birth into an O_2-rich environment: the antioxidant enzymes in the developing rabbit lung. *Pediatr Res* 18: 240–244, 1984.
23. Frendo JL, Therond P, Bird T, Massin N, Muller F, Guibourdenche J, Luton D, Vidaud M, Anderson WB, and Evain-Brion D. Overexpression of copper zinc superoxide dismutase impairs human trophoblast cell fusion and differentiation. *Endocrinology* 142: 3638–3648, 2001.
24. Frendo JL, Therond P, Guibourdenche J, Vidaud M, and Evain-Briona D. Implication of copper zinc superoxide dismutase (SOD-1) in human placenta development. *Ann N Y Acad Sci* 973: 297–301, 2002.
25. Gardiner CS, Salmen JJ, Brandt CJ, and Stover SK. Glutathione is present in reproductive tract secretions and improves development of mouse embryos after chemically induced glutathione depletion. *Biol Reprod* 59: 431–436, 1998.
26. Gladstone IM Jr and Levine RL. Oxidation of proteins in neonatal lungs. *Pediatrics* 93: 764–768, 1994.
27. Gomez del Arco P, Martínez-Martínez S, Calvo V, Armesilla AL, and Redondo JM. Antioxidants and AP-1 activation: a brief overview. *Immunobiology* 198: 273–278, 1997.
28. Goto Y, Noda Y, Narimoto K, Umaoka Y, and Mori T. Oxidative stress on mouse embryo development in vitro. *Free Radic Biol Med* 13: 47–53, 1992.
29. Haddad JJ and Land SC. O^2-evoked regulation of HIF-1alpha and NF-kappaB in perinatal lung epithelium requires glutathione biosynthesis. *Am J Physiol Lung Cell Mol Physiol* 278: L492–L503, 2000.
30. Haddad JJ, Olver RE, and Land SC. Antioxidant/prooxidant equilibrium regulates HIF-1alpha and NF-kappa B redox sensitivity. Evidence for inhibition by glutathione oxidation in alveolar epithelial cells. *J Biol Chem* 275: 21130–21139, 2000.
31. Harvey AJ, Kind KL, and Thompson JG. REDOX regulation of early embryo development. *Reproduction* 123: 479–486, 2002.
32. Hashimoto S, Minami N, Takakura R, Yamada M, Imai H, and Kashima N. Low oxygen tension during in vitro maturation is beneficial for supporting the subsequent development of bovine cumulus–oocyte complexes. *Mol Reprod Dev* 57: 353–360, 2000.
33. Helbock HJ and Ames BN. Use of intravenous lipids in neonates. *J Pediatr* 126: 747–748, 1995.
34. Hirano K, Morinobu T, Kim H, Hiroi M, Ban R, Ogawa S, Ogihara H, Tamai H, and Ogihara T. Blood transfusion increases radical promoting non-transferrin bound iron in preterm infants. *Arch Dis Child Fetal Neonatal Ed* 84: F188–F193, 2001.
35. Hooper SB, Coulter CL, Deayton JM, Harding R, and Thorburn GD. Fetal endocrine responses to prolonged hypoxemia in sheep. *Am J Physiol* 259: R703–R708, 1990.
36. Hosford GE and Olson DM. Effects of hyperoxia on VEGF, its receptors and HIF-2alpha in the newborn rat lung. *Am J Physiol Lung Cell Mol Physiol* 285: L161–L168, 2003.
37. Hubel CA. Dyslipidemia, iron, and oxidative stress in preeclampsia: assessment of maternal and feto-placental interactions. *Semin Reprod Endocrinol* 16: 75–92, 1998.
38. Karowicz-Bilinska A, Suzin J, and Sieroszewski P. Evaluation of oxidative stress indices during treatment in pregnant women with intrauterine growth retardation. *Med Sci Monit* 8: CR211–CR216, 2002.
39. Kelly FJ. Free radical disorders of preterm infants. *Br Med Bull* 49: 668–678, 1993.
40. Kharb S. Lipid peroxidation in pregnancy with preeclampsia and diabetes. *Gynecol Obstet Invest* 50: 113–116, 2000.
41. Kingdom J, Huppertz B, Seaward G, and Kaufmann P. Development of the placental villous tree and its conse-

quences for fetal growth. *Eur J Obstet Gynecol Reprod Biol* 92: 35–43, 2000.
42. Luo X, Sedlackova L, Belcastro R, Cabacungan J, Lye SJ, and Tanswell AK. Effect of the 21-aminosteroid U74389G on oxygen-induced free radical production, lipid peroxidation, and inhibition of lung growth in neonatal rats. *Pediatr Res* 46: 215–223, 1999.
43. Marshall TA and Roberts RJ. In vitro and in vivo assessment of lipid peroxidation of infant nutrient preparations: effect of nutrition on oxygen toxicity. *J Am Coll Nutr* 9: 190–199, 1990.
44. Matthews JR and Hay RT. Regulation of the DNA binding activity of NF-kappa B. *Int J Biochem Cell Biol* 27: 865–879, 1995.
45. Maymon E, Romero R, Pacora P, Gomez R, Mazor M, Edwin S, Chaiworapongsa T, Kim JC, Yoon BH, Menon R, Fortunato S, and Berry SM. A role for the 72 kDa gelatinase (MMP-2) and its inhibitor (TIMP-2) in human parturition, premature rupture of membranes and intraamniotic infection. *J Perinat Med* 29: 308–316, 2001.
46. Müller JM, Rupec RA, and Baeuerle PA. Study of gene regulation by NF-kappa B and AP-1 in response to reactive oxygen intermediates. *Methods* 11: 301–312, 1997.
47. Muller M and Sorrell TC. Oxidative stress and the mobilisation of arachidonic acid in stimulated human platelets: role of hydroxyl radical. *Prostaglandins* 54: 493–509, 1997.
48. Myatt L, Eis AL, Brockman DE, Kossenjans W, Greer IA, and Lyall F. Differential localization of superoxide dismutase isoforms in placental villous tissue of normotensive, pre-eclamptic, and intrauterine growth-restricted pregnancies. *J Histochem Cytochem* 45: 1433–1438, 1997.
49. Neuzil J, Darlow BA, Inder TE, Sluis KB, Winterbourn CC, and Stocker R. Oxidation of parenteral lipid emulsion by ambient and phototherapy lights: potential toxicity of routine parenteral feeding. *J Pediatr* 126: 785–790, 1995.
50. Nigam S and Schewe T. Phospholipase A_2s and lipid peroxidation. *Biochim Biophys Acta* 1488: 167–181, 2000.
51. Okatani Y, Watanabe K, Wakatsuki A, Tamura S, and Sagara Y. Effects of superoxide and peroxynitrite on vascular tension in the human umbilical artery. *Acta Obstet Gynecol Scand* 77: 883–888, 1998.
52. Olson SE and Seidel GE, Jr. Reduced oxygen tension and EDTA improve bovine zygote development in a chemically defined medium. *J Anim Sci* 78: 152–157, 2000.
53. Parchment RE. Programmed cell death (apoptosis) in murine blastocysts: extracellular free-radicals, polyamines, and other cytotoxic agents. *In Vivo* 5: 493–500, 1991.
54. Pierce GB and Parchment RE. Progression in teratocarcinomas. *Basic Life Sci* 57: 71–78; discussion 78–81, 1991.
55. Pierce GB, Parchment RE, and Lewellyn AL. Hydrogen peroxide as a mediator of programmed cell death in the blastocyst. *Differentiation* 46: 181–186, 1991.
56. Pitkanen OM, Hallman M, and Andersson SM. Correlation of free oxygen radical-induced lipid peroxidation with outcome in very low birth weight infants. *J Pediatr* 116: 760–764, 1990.
57. Ramsay PL, DeMayo FJ, Hegemier SE, Wearden ME, Smith CV, and Welty SE. Clara cell secretory protein oxidation and expression in premature infants who develop bronchopulmonary dysplasia. *Am J Respir Crit Care Med* 164: 155–161, 2001.
58. Reynaud X and Dorey CK. Extraretinal neovascularization induced by hypoxic episodes in the neonatal rat. *Invest Ophthalmol Vis Sci* 35: 3169–3177, 1994.
59. Rogers JM and Hunter ES 3rd. Redox redux: a closer look at conceptal low molecular weight thiols. *Toxicol Sci* 62: 1–3, 2001.
60. Rogers S, Witz G, Anwar M, Hiatt M, and Hegyi T. Antioxidant capacity and oxygen radical diseases in the preterm newborn. *Arch Pediatr Adolesc Med* 154: 544–548, 2000.
61. Rudiger M, von Baehr A, Haupt R, Wauer RR, and Rustow B. Preterm infants with high polyunsaturated fatty acid and plasmalogen content in tracheal aspirates develop bronchopulmonary dysplasia less often. *Crit Care Med* 28: 1572–1577, 2000.
62. Sanders SP, Zweier JL, Kuppusamy P, Harrison SJ, Bassett DJ, Gabrielson EW, and Sylvester JT. Hyperoxic sheep pulmonary microvascular endothelial cells generate free radicals via mitochondrial electron transport. *J Clin Invest* 91: 46–52, 1993.
63. Saugstad OD. Oxygen toxicity in the neonatal period. *Acta Paediatr Scand* 79: 881–892, 1990.
64. Schock BC, Sweet DG, Halliday HL, Young IS, and Ennis M. Oxidative stress in lavage fluid of preterm infants at risk of chronic lung disease. *Am J Physiol Lung Cell Mol Physiol* 281: L1386–L1391, 2001.
65. Schuler M, Bossy-Wetzel E, Goldstein JC, Fitzgerald P, and Green DR. p53 induces apoptosis by caspase activation through mitochondrial cytochrome c release. *J Biol Chem* 275: 7337–7342, 2000.
66. Schulze-Osthoff K, Bauer MK, Vogt M, and Wesselborg S. Oxidative stress and signal transduction. *Int J Vitam Nutr Res* 67: 336–342, 1997.
67. Smith LE. Pathogenesis of retinopathy of prematurity. *Acta Paediatr Suppl* 91: 26–28, 2002.
68. Sosenko IR, Innis SM, and Frank L. Polyunsaturated fatty acids and protection of newborn rats from oxygen toxicity. *J Pediatr* 112: 630–637, 1988.
69. Stenmark KR, Eyzaguirre M, Westcott JY, Henson PM, and Murphy RC. Potential role of eicosanoids and PAF in the pathophysiology of bronchopulmonary dysplasia. *Am Rev Respir Dis* 136: 770–772, 1987.
70. Strange RC, Cotton W, Fryer AA, Jones P, Bell J, and Hume R. Lipid peroxidation and expression of copper-zinc and manganese superoxide dismutase in lungs of premature infants with hyaline membrane disease and bronchopulmonary dysplasia. *J Lab Clin Med* 116: 666–673, 1990.
71. Sun Y and Oberley LW. Redox regulation of transcriptional activators. *Free Radic Biol Med* 21: 335–348, 1996.
72. Suresh GK, Davis JM, and Soll RF. Superoxide dismutase for preventing chronic lung disease in mechanically ventilated preterm infants. *Cochrane Database Syst Rev* CD001968, 2001.
73. Tsatas D, Baker MS, and Rice GE. Differential expression of proteases in human gestational tissues before, during and after spontaneous-onset labour at term. *J Reprod Fertil* 116: 43–49, 1999.

74. Walsh SW. Maternal–placental interactions of oxidative stress and antioxidants in preeclampsia. *Semin Reprod Endocrinol* 16: 93–104, 1998.
75. Walsh SW, Vaughan JE, Wang Y, and Roberts LJ, 2nd. Placental isoprostane is significantly increased in preeclampsia. *FASEB J* 14: 1289–1296, 2000.
76. Wang Y and Walsh SW. Placental mitochondria as a source of oxidative stress in pre-eclampsia. *Placenta* 19: 581–586, 1998.
77. Wardle SP, Drury J, Garr R, and Weindling AM. Effect of blood transfusion on lipid peroxidation in preterm infants. *Arch Dis Child Fetal Neonatal Ed* 86: F46–F48, 2002.
78. Wilson TM, Rivkees SA, Deutsch WA, and Kelley MR. Differential expression of the apurinic/apyrimidinic endonuclease (APE/ref-1) multifunctional DNA base excision repair gene during fetal development and in adult rat brain and testis. *Mutat Res* 362: 237–248, 1996.
79. Xanthoudakis S, Miao G, Wang F, Pan YC, and Curran T. Redox activation of Fos-Jun DNA binding activity is mediated by a DNA repair enzyme. *EMBO J* 11: 3323–3335., 1992.
80. Xu P, Alfaidy N, and Challis JR. Expression of matrix metalloproteinase (MMP)-2 and m*M*P-9 in human placenta and fetal membranes in relation to preterm and term labor. *J Clin Endocrinol Metab* 87: 1353–1361, 2002.
81. Zeeman GG, Dekker GA, van Geijn HP, and Kraayenbrink AA. Endothelial function in normal and pre-eclamptic pregnancy: a hypothesis. *Eur J Obstet Gynecol Reprod Biol* 43: 113–122, 1992.
82. Zimmerman JJ, Gabbert D, Shivpuri C, Kayata S, Ciesielski W, Miller J, Peters ME, Eissenstat RP, and Shen G. Meter-dosed, inhaled beclomethasone attenuates bronchoalveolar oxyradical inflammation in premature infants at risk for bronchopulmonary dysplasia. *Am J Perinatol* 15: 567–576, 1998.

Address reprint requests to:
Phyllis A. Dennery, M.D.
Department of Pediatrics
University of Pennsylvania
Chief, Division of Neonatology
The Children's Hospital of Philadelphia
34th Street and Civic Center Blvd.
2nd Floor, Main Hospital, Rm. 2435
Philadelphia, PA 19104

E-mail: dennery@email.chop.edu

Received for publication September 19, 2003; accepted October 20, 2003.

This article has been cited by:

1. Chunmei Lin, Jung-Min Yon, A Young Jung, Jong Geol Lee, Ki Youn Jung, Jong-Koo Kang, Beom Jun Lee, Young Won Yun, Sang-Yoon Nam. 2012. Resveratrol prevents nicotine-induced teratogenesis in cultured mouse embryos. *Reproductive Toxicology* **34**:3, 340-346. [CrossRef]
2. K. Vande Loock, R. Ciardelli, I. Decordier, G. Plas, D. Haumont, M. Kirsch-Volders. 2012. Preterm newborns show slower repair of oxidative damage and paternal smoking associated DNA damage. *Mutagenesis* **27**:5, 573-580. [CrossRef]
3. Serafina Perrone, Maria Luisa Tataranno, Gemma Stazzoni, Giuseppe Buonocore. 2012. Biomarkers of oxidative stress in fetal and neonatal diseases. *Journal of Maternal-Fetal and Neonatal Medicine* 1-15. [CrossRef]
4. Rønnaug Solberg, Serafina Perrone, Ola Didrik Saugstad, Giuseppe Buonocore. 2012. Risks and benefits of oxygen in the delivery room. *Journal of Maternal-Fetal and Neonatal Medicine* **25**:S1, 41-44. [CrossRef]
5. Fernando E Viteri. 2011. Iron endowment at birth: maternal iron status and other influences. *Nutrition Reviews* **69**, S3-S16. [CrossRef]
6. Luisa Minghetti, Agnese Suppiej, Anita Greco, Malida Franzoi, Irene Pascoli, Vincenzo Zanardo. 2011. Oxidative stress in twin neonates is influenced by birth weight and weight discordance. *Clinical Biochemistry* **44**:8-9, 654-658. [CrossRef]
7. Yan Lin, Xing-fa Han, Zheng-feng Fang, Lian-qiang Che, Jerry Nelson, Tan-hai Yan, De Wu. 2011. Beneficial effects of dietary fibre supplementation of a high-fat diet on fetal development in rats. *British Journal of Nutrition* 1-9. [CrossRef]
8. Anna Lewinska, Ewa Macierzynska, Agnieszka Grzelak, Grzegorz Bartosz. 2011. A genetic analysis of nitric oxide-mediated signaling during chronological aging in the yeast. *Biogerontology* . [CrossRef]
9. Giuseppe Buonocore, Serafina Perrone, Maria Luisa Tataranno. 2010. Oxygen toxicity: chemistry and biology of reactive oxygen species. *Seminars in Fetal and Neonatal Medicine* **15**:4, 186-190. [CrossRef]
10. Nagwa A. Meguid, Ahmed A. Dardir, Eman M. El-Sayed, Hanaa H. Ahmed, Adel F. Hashish, Afaf Ezzat. 2010. Homocysteine and oxidative stress in Egyptian children with Down syndrome. *Clinical Biochemistry* **43**:12, 963-967. [CrossRef]
11. H. Arthur Woods. 2010. Water loss and gas exchange by eggs of Manduca sexta: Trading off costs and benefits. *Journal of Insect Physiology* **56**:5, 480-487. [CrossRef]
12. Serafina Perrone, Maria Luisa Tataranno, Simona Negro, Mariangela Longini, Barbara Marzocchi, Fabrizio Proietti, Francesca Iacoponi, Serena Capitani, Giuseppe Buonocore. 2010. Early identification of the risk for free radical-related diseases in preterm newborns. *Early Human Development* **86**:4, 241-244. [CrossRef]
13. Joern R. Steinert , Amanda W. Wyatt , Ron Jacob , Giovanni E. Mann . 2009. Redox Modulation of Ca2+ Signaling in Human Endothelial and Smooth Muscle Cells in Pre-Eclampsia. *Antioxidants & Redox Signaling* **11**:5, 1149-1163. [Abstract] [Full Text PDF] [Full Text PDF with Links]
14. Ashok Agarwal , Sajal Gupta , Lucky Sekhon , Rani Shah . 2008. Redox Considerations in Female Reproductive Function and Assisted Reproduction: From Molecular Mechanisms to Health Implications. *Antioxidants & Redox Signaling* **10**:8, 1375-1404. [Abstract] [Full Text PDF] [Full Text PDF with Links]
15. Kelly F. Portes, Cecília M. Ikegami, Joselito Getz, Ana P. Martins, Lucia Noronha, Luciana F. Zischler, Giseli Klassen, Anamaria A. Camargo, Silvio M. Zanata, Estela Bevilacqua, Lia S. Nakao. 2008. Tissue distribution of quiescin Q6/sulfhydryl oxidase (QSOX) in developing mouse. *Journal of Molecular Histology* **39**:2, 217-225. [CrossRef]
16. Hiromichi Shoji, Yuichiro Yamashiro, Berthold KoletzkoOxidative Stress and Antioxidants in the Perinatal Period **20070778**, 71-92. [CrossRef]

17. S PERRONE, M LONGINI, C BELLIENI, G CENTINI, A KENANIDIS, L DEMARCO, F PETRAGLIA, G BUONOCORE. 2007. Early oxidative stress in amniotic fluid of pregnancies with Down syndrome. *Clinical Biochemistry* **40**:3-4, 177-180. [CrossRef]
18. Giuseppe Buonocore, Serafina Perrone, Luisa De Marco, Carl Valerio BellieniBiomarkers of hypoxic brain injury 699-718. [CrossRef]
19. Kumuda C. Das . 2005. Thioredoxin and Its Role in Premature Newborn Biology. *Antioxidants & Redox Signaling* **7**:11-12, 1740-1743. [Abstract] [Full Text PDF] [Full Text PDF with Links]
20. Ashok Agarwal, Sajal Gupta, Rakesh Sharma. 2005. Oxidative stress and its implications in female infertility – a clinician's perspective. *Reproductive BioMedicine Online* **11**:5, 641-650. [CrossRef]
21. Kumuda C. Das . 2004. Redox Control of Premature Birth and Newborn Biology. *Antioxidants & Redox Signaling* **6**:1, 105-107. [Citation] [Full Text PDF] [Full Text PDF with Links]