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COMMENT

A striking result from antenatal exposure to *N*-acetylcysteine

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The journal is publishing an interesting report of women at risk of infection-associated chorioamnionitis, by giving antioxidant treatments just prior to the preterm delivery.[1] This trial required 7 years to complete in a single center to enroll just 67 patients because of demanding criteria for enrollment. To identify women at risk for preterm delivery between 24 and 34 weeks, they applied the new NICHD workshop definition of chorioamnionitis as Triple I.[2] This definition requires an amniocentesis to measure a number of biomarkers of infection and/or culture to identify live organisms. Amniocentesis for women at risk of prematurity to rule out infection is seldom done on most perinatal services in the United States. A return to amniocentesis for preterm labor would be a big boon for perinatal research. The amniocentesis was done as part of standard of care at Yale. The trial stopped with 67 of the 140 planned enrollments because several of the authors shifted to institutions. Nevertheless, the study has been well done to test the hypothesis that a maternal infusion of *N*-acetylcysteine as an antioxidant would benefit the fetus by decreasing death and intraventricular hemorrhage (IVH) and perhaps bronchopulmonary dysplasia (BPD). They and others had developed some rodent data that pregnant rats given endotoxins had fewer stillborns if they received *N*-acetylcysteine.[3] Thus, for their clinical trial, the primary outcome of this trial was of death and a long list of short-term outcomes—severe IVH, ROP, NEC, PVL, and BPD—the normal three- letter-word abbreviations of the list of complications common to the very preterm infants. They also made measurements with maternal and cord blood for inflammatory cytokines and indications of oxidant stress. I would like to have seen measurements of isoprostanes, perhaps the best biomarker for oxidant stress.[4]

Dosing and exposure to *N*-acetylcysteine was by maternal infusions using an FDA-approved dosing strategy for acetaminophen toxicity[5]—a loading infusion of 150 mg/kg over 1 h, then a 50 mg/kg infusion for 4 h; if delivery had not occurred, then the drug was continued for the next 16 h at 100 mg/kg. I have included a table of outcomes as they are so stiking (Table 1).

Neonatal transition was improved with less resuscitation needed and better APGAR scores. Neonatal outcomes were improved with a decrease in BPD from 38 to 9%, a remarkable result seen with no known therapy. A second benefit was decreased IVH. Even more remarkable was that the infusion of *N*-acetylcysteine was for only 4.9 h. The other major interventions that decrease death in very preterm infants, such as surfactant and antenatal steroids, do not decrease BPD.

Something magical is going on here. I will review briefly the use of antioxidants in neonatal medicine for the context focusing on BPD as that was their major beneficial outcome. An RCT of the treatment of infants with *N*-acetylcysteine infusion for the first week of life did not improve any outcomes.[6]

Ola Saugstad[7] proposed, many years ago, that the three-letter words for complications in very preterm infants were all associated with oxidant stress. BPD is the poster child for oxidant stress-associated disease as multiple models of BPD in rodents and baboons involve only high oxygen exposure causing inflammation and a BPD phenotype. Infection also causes oxidant stress. The problem is that in multiple animal models of BPD, targeted therapies, such as cytokine receptor blockade, vitamin D, growth factors, and small-molecule weight antioxidants,[8] can reverse much of the alveolar simplification and pulmonary vascular disease in the rodent models, but have not translated to any new therapies.[8] The exception is postnatal corticosteroids that are used routinely to treat lung disease progression to severe BPD.[9] So it is fair to say that postnatal antioxidant treatments have not proved particularly useful as a clinical strategy.

One exception with a curious outcome are the two studies by Jon Davis using human recombinant superoxide dismutase given into the airspace of preterm infants.[10] There were no short-term benefits and no effect on BPD, their primary outcome. In contrast, on follow-up at 1 year of age, the children exposed to the recombinant superoxide dismutase had less airway disease;[11] thus, the identification of a benefit was very delayed.

Another approach for a combined nutritional antioxidant treatment to decrease BPD is the trial of giving women who have delivered infants prematurely 23–29 weeks gestational age supplements with docosahexaenoic acid (DHA) as an oral supplementation and have them provide milk to supplement the infants.[12] DHA is a polyunsaturated fatty acid supplementation. DHA decreased lung injury from oxygen in animal models. Previously, direct supplementation of these very preterm infants with DHA also did not decrease BPD.[13] The supplementation with the human milk feeding is a chronic treatment to 36 weeks of gestation, which did not decrease BPD. DHA supplementation in these two trials may have increased BPD; thus, the record for antioxidants decreasing BPD clinically is not positive.

The most interesting trial from Cindy McEvoy[14] and published in 2014 established the concept of maternal treatment with an antioxidant for fetal benefit. They identified women who were smoking and in early pregnancy. They offered help with stopping smoking, but if they intended to keep smoking, they were randomized to 500 mg/day Vit C or placebo. Soon after delivery, they measured pulmonary function, and the newborns exposed to Vit C had better pulmonary function and compliance than the smokers given a placebo ($P < 0.006$). At 1 year of age, compliance relative to the Vit C treatment group was still improved ($P < 0.05$) as was clinical wheezing. In contrast to the *N*-acetylcysteine exposure, the antioxidant Vit C was an average of a 18-week exposure.

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Table 1. Results with infusions of *N*-acetylcysteine for women with infection-associated chorioamnionitis defined by Triple I.

	N-acetylcysteine	Placebo infusion	*P*	Number needed to treat
Patient number	33	44	NS	
Duration of infusions to delivery (h)	4.9	3.8	NS	
Total *N*-acetylcysteine dose (g)	16.5	NA	–	
Abnormal neonatal transition[a]				
Oxygen use	13	5	0.04	
Mask CPAP with ventilation use	11	12	0.04	
Intubation, PPV, and drugs	3	12	0.04	
Odds of Apgar <7, 5 min	2	13	0.003	
Odds of Apgar <4, 1 min	2	12	0.03	
Surfactant in the delivery room	2	10	0.02	
Neonatal outcomes[a]				
Primary outcomes: composite morbidity score	16	7	0.04	3.9
Death	2	6	0.26	–
Early-onset sepsis	9	16	1.0	–
Severe IVH	2	4	0.7	4.3
Severe ROP	4	9	0.22	–
Severe NEC	5	6	1.0	–
BPD	1	10	0.006	3.4
IVH and/or death	6	17	0.01	3.1
BPD and/or death	3	13	0.01	3.4

[a]Patient numbers.

Experiments in rodents and primates demonstrate that fetal exposure to nicotine can disrupt airway development.[15] It is well documented that prenatal, even passive, smoke exposure is associated with wheezing and asthma in young children.[16] It seems to me that this excellent trial has an actionable outcome: Vit C supplementation to women who insist on smoking during pregnancy. The results of this trial are easier to accept as the science behind fetal exposure to smoking is detailed in several animal models very large and sound, and the treatment is prolonged.

There is another oxidant that fetuses are frequently exposed to well-known developmental effects: ethanol. The results of Buhimschi et al.[1] need to be repeated in a much larger multicenter trial, which I hope will be verified as this would be a major advance to decrease BPD. They comment that the benefit may be because of timing. The field has not tried antenatal interventions to decrease BPD; these results should stimulate that effort. This is important as the newer concepts about the trajectory of lung development and aging have identified prematurity and BPD as precursor diseases linked to chronic obstructive pulmonary disease and the potential for cardiovascular disease in midlife.[17]

ADDITIONAL INFORMATION

Competing interests: The author declares no competing interests.

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REFERENCES

1. Buhimschi, C. S. et al. Antenatal N-acetylcysteine to improve outcomes of premature infants with intra-amniotic infection and inflammation (Triple I): randomized clinical trial. *Pediatr. Res.* (2020). https://doi.org/10.1038/s41390-020-01106-w.
2. Higgins, R. D. et al. Evaluation and management of women and newborns with a maternal diagnosis of chorioamnionitis: summary of a workshop. *Obstet. Gynecol.* **127**, 426–36. (2016).
3. Buhimschi, I. A., Buhimschi, C. S. & Weiner, C. P. Protective effect of N-acetylcysteine against fetal death and preterm labor induced by maternal inflammation. *Am. J. Obstet. Gynecol.* **188**, 203–208 (2003).
4. Morrow, J. D. & Roberts, L. J. The isoprostanes: their role as an index of oxidant stress status in human pulmonary disease. *Am. J. Respir. Crit. Care Med.* **166**, S25–S30 (2002).
5. Riggs, B. S., Bronstein, A. C., Kulig, K., Archer, P. G. & Rumack, B. H. Acute acetaminophen overdose during pregnancy. *Obstet. Gynecol.* **74**, 247–253 (1989).
6. Ahola, T. et al. N-acetylcysteine does not prevent bronchopulmonary dysplasia in immature infants: a randomized controlled trial. *J. Pediatr.* **143**, 713–719 (2003).
7. Saugstad, O. D. Oxygen toxicity in the neonatal period. *Acta Paediatr. Scand.* **79**, 881–892 (1990).
8. Jobe, A. H. Animal models, learning lessons to prevent and treat neonatal chronic lung disease. *Front. Med. (Lausanne)* **2**, 49 (2015).
9. Doyle LW, Cheong JL, Ehrenkranz RA, Halliday HL. Late (>7 days) systemic postnatal corticosteroids for prevention of bronchopulmonary dysplasia in preterm infants. *Cochrane Database Syst Rev.* **10**, CD001145 (2017).
10. Suresh, G. K., Davis, J. M. & Soll, R. F. Superoxide dismutase for preventing chronic lung disease in mechanically ventilated preterm infants. *Cochrane Database Syst Rev*. CD001968 (2001).
11. Davis, J. M. et al. Pulmonary outcome at 1 year corrected age in premature infants treated at birth with recombinant human CuZn superoxide dismutase. *Pediatrics* **111**, 469–76. (2003).
12. Marc, I. et al. Effect of maternal docosahexaenoic acid supplementation on bronchopulmonary dysplasia-free survival in breastfed preterm infants: a randomized clinical trial. *JAMA* **324**, 157–167 (2020).
13. Collins, C. T. et al. Docosahexaenoic acid and bronchopulmonary dysplasia in preterm infants. *N. Engl. J. Med.* **376**, 1245–55. (2017).
14. McEvoy, C. T. et al. Vitamin C supplementation for pregnant smoking women and pulmonary function in their newborn infants: a randomized clinical trial. *JAMA* **311**, 2074–2082 (2014).
15. Spindel, E. R. & McEvoy, C. T. The role of nicotine in the effects of maternal smoking during pregnancy on lung development and childhood respiratory disease. implications for dangers of E-cigarettes. *Am. J. Respir. Crit. Care Med.* **193**, 486–94. (2016).
16. Gonzalez-Luis, G. E. et al. Tobacco smoking during pregnancy is associated with increased risk of moderate/severe bronchopulmonary dysplasia: a systematic review and meta-analysis. *Front. Pediatr.* **8**, 160 (2020).
17. Hurst, J. R. et al. Respiratory and cardiovascular outcomes in survivors of extremely preterm birth at 19 years. *Am. J. Respir. Crit. Care Med.* **202**, 422–32. (2020).