Bronchopulmonary Dysplasia in Preterm Infants – Understanding the Physiological Changes in AA and DHA during Gestation

This article at a glance

- Bronchopulmonary dysplasia is a form of lung injury caused by assisted ventilation and oxygen support compounding an incomplete development of lung tissue observed in very early and low birth weight preterm infants.
- In a study of fetal fatty acid (LCPUFA) accretion during the third trimester of pregnancy, the level of...
arachidonic acid contained in phosphatidylcholine (AA-PC) was found to be more abundant in cord blood than in the maternal circulation, and fetal docosahexaenoyl-PC (DHA-PC) level started exceeding maternal levels after week 33.

- **Bronchopulmonary dysplasia severity was associated with a low AA-PC to DHA-PC ratio in cord blood of very immature infants born before week 28. In particular, higher cord blood levels of DHA-PC were associated with more severe bronchopulmonary dysplasia in these neonates.**

- **This study points at specific requirements for individual long-chain polyunsaturated fatty acids (LCPUFA) for optimal lung development during a specific time period, of relevance to dietary habits during pregnancy and to preterm infant nutrition.**

Bronchopulmonary dysplasia is a form of chronic lung disease that occurs with relatively high incidence in low birth weight preterm infants. With some variation between prenatal care units, a typical incidence can be on the order of 30% of preterm infants with birth weights of < 1000 g. Bronchopulmonary dysplasia develops as a result of parenchymal tissue injury caused by the vitally-needed mechanical ventilation and use of oxygen that is superimposed on a lung tissue that is less developed than it would be at term, and characterized by a pro-inflammatory state resulting from immaturity. In the weeks before term birth, in particular from week 33 onwards, lung tissue undergoes marked
development, with the formation of future gas-exchanging alveoli and the formation of the adjacent vasculature. The “pre-alveolized” and minimally vascularized lung of very immature infants is highly susceptible to lung injury. The development of milder ventilation techniques, treatment with surfactant, and prenatal glucocorticoid therapy has contributed to a lower incidence of bronchopulmonary dysplasia in preterms, and has permitted a shift towards lower incidence in preterms born at later gestational length. On the other hand, the survival of preterms with earlier gestational age has increased, rendering more surviving preterms at risk of bronchopulmonary dysplasia.

Bronchopulmonary dysplasia can also occur in neonates with respiratory distress syndrome, or develop over the course of the first weeks after birth for unclear reasons, but possibly related to infections in utero. Histologically, it is characterized by unusual abnormalities of the bronchioles, such as metaplasia, a decrease in alveolar number, and formation of cysts, and an incomplete vascularization of lung tissue. A marked inflammatory response with granulocyte sequestration in the lung and formation of cytokines and transforming growth factor-β also typifies bronchopulmonary dysplasia. The disorder can lead to substantial structural remodeling of lung and airway tissue, such as scarring and replacement of normal branched alveolar respiratory surface with consequences for impaired lung function into adulthood. A significant proportion of infants with bronchopulmonary dysplasia recover nearly fully with only small losses in expiratory flow capacity,
There are no effective treatments available and emphasis has been much on prevention, promoting optimal lung growth and keeping neonates safe from infections. Effective treatments for bronchopulmonary dysplasia are furthermore difficult to develop since these should not also interfere with the still developing alveolar septation and vascular growth. A growing mechanistic understanding of bronchopulmonary dysplasia has allowed increased attention to approaches that augment the resistance of the immature preterm lung tissue towards mechanical and hyperoxic lung injury, for example through the use of nutritional support that boosts antioxidant enzyme systems and anti-inflammatory responses. In addition, knowledge about the progressive increase in lipid accumulation occurring alongside a relative decrease in protein accretion during the third trimester, and the detrimental effects of the interruption of placental LCPUFA accretion following preterm birth, has generated interest in evaluating the importance of fatty acid and lipid requirements in fetal development during the third trimester.

A relatively well-studied example for the requirement of a specific LCPUFA in fetal and infant development is that of DHA in the central nervous system. Significant research is being carried out to understand the contribution of the fetal and early-life adequacy of DHA to the proper development of neural tissue and the neurocognitive faculties in childhood. How distinct LCPUFA species serve the fetal development of the peripheral organs is far less studied. Interestingly, in the cerebral cortex of the developing fetus in the third trimester and in term neonates the abundance of another LCPUFA, arachidonic acid (AA), is comparable to that of DHA.
in total lipids and in specific phospholipids. Together with its chain-lengthened product eicosatetraenoic acid (also known as adrenic acid), omega-6 LCPUFAs are nearly \textit{twice} as abundant in total lipids of the cortex of neonates as DHA. Brain phosphatidyl-inositol, although quantitatively a minor phospholipid species, is far more enriched in AA compared to DHA. Only later, during early childhood, does the concentration of DHA in cerebral cortex overtake that of AA, to remain higher well into late adulthood. AA is obtained more easily from typical foods ingested by pregnant and lactating mothers than DHA, and is \textit{produced} from dietary linoleic acid (LA) more readily than DHA is from its essential fatty acid precursor alpha-linolenic acid (ALA).

The absolute intake of AA is important, however, for the composition of infant formula given to infants that are not breast-fed. The importance of AA, in addition and in relation to DHA, to infant development has been discussed in recent Guest Articles in Fats of Life (link 1, link 2).

A recent study has investigated the temporal changes in the levels of some phospholipids carrying LCPUFA in the maternal circulation and in the fetal circulation during the third trimester of pregnancy. The study was performed by Bernhard \textit{and colleagues} from the Departments of Neonatology and Gynecology, and the Center for Pediatric Clinical Studies, Faculty of Medicine, Eberhard-Karls-University in Tübingen, Germany. The researchers obtained serum samples from 108 mothers soon after delivery, of which 94 were from singleton pregnancies. Umbilical cord plasma samples from 121 newborns were collected at birth. The various lipids measured at birth were considered to reflect the spectrum and levels of phospholipid-bound fatty acids of fetuses of equivalent ages. A temporal portrait of lipid dynamics during the last trimester of gestation was thus obtained. The fatty acid
composition of two phospholipid species, phosphatidyl-choline (PC) and phosphatidyl-ethanolamine (PE), was determined by liquid chromatography-tandem mass spectrometry. Little information on the analytical methodologies was provided. Bronchopulmonary dysplasia severity was quantified by a scoring assessment according to the categories absent, mild, moderate or severe.

In this study group, 47% of the birth cohort of very immature neonates, born in week 24-28 post-menstrual age, developed bronchopulmonary dysplasia of mostly moderate severity. Beyond week 28 post-menstrual age no cases of bronchopulmonary dysplasia were observed. The overall levels of phosphatidyl-choline (PC), but not those of phosphatidyl-ethanolamine (PE), were correlated between mother and newborn. PC is an important carrier of PUFA to the placenta, from where PUFA species are transported to the fetus, whereas PE is believed to be less important in this respect. In mothers, PC levels decreased until week 33 post-menstrual age, after which levels started to rise again. Maternal PE levels did not show this pattern and levels kept gradually increasing throughout pregnancy. In neonates at birth, PE levels in cord plasma remained approximately the same from week 24 until term at week 42, at a low concentration (approximately 9 times lower than maternal values). Total PC levels in newborn cord blood were much higher than PE levels, and were approximately 3- to 4-fold lower than in the maternal circulation, and showed a slow decrease during the third trimester.
The levels of several PC species containing specific fatty acids displayed positive correlations between maternal and fetal blood. This was the case for PC species containing oleic acid, AA, eicosapentaenoic acid (EPA) and DHA. When levels were expressed as the molar ratio of PC lipid species containing a particular fatty acid, a breakpoint in the pattern of maternal PC concentration was seen for PC-DHA; a constant ratio of fetal to maternal PC-DHA levels was observed until week 33, followed by a relative increase in fetal PC-DHA levels. This may point at an even more active placental accretion and fetal absorption (biomagnification) of DHA from week 33 until term. The increased uptake of DHA from PC-DHA was at the expense of other PC species: PC containing saturated fatty acids and LA also showed a breakpoint at week 33, but from this moment accretion (as measured from the fetus-mother molar fractional ratio) gradually decreased until week 44. A constant ratio was observed for oleic acid, AA and EPA throughout the last trimester. Interestingly, the molar ratio of AA-PC in the fetus was constantly higher than in mothers, suggesting active AA accretion throughout the last trimester. In contrast, the molar ratio of LA-PC was half that seen in mothers, suggesting a restricted placental transport of LA into the fetal circulation.
The researchers next focused on any specific changes in the levels of AA and DHA at the moment of birth of very early preterms (born between week 24 and 27 post-menstrual age) at highest risk for developing bronchopulmonary dysplasia. The ratio of AA-PC to DHA-PC in cord blood was approximately 5 in this group of preterms, whereas it was around 2 in their mothers. This ratio remained constant in mothers that delivered at any time during the third trimester, but the high cord blood ratio seen in very early preterms also gradually decreased up to week 37-41 towards the same ratio of 2. The severity of bronchopulmonary dysplasia in preterms born before week 28 was found to be inversely related to the ratio of AA-PC to DHA-PC in cord blood (and was unrelated to the ratio in maternal blood). Additional analyses indicated that the levels of AA-PC were not related to the severity of BPD, but BPD grade was higher in early preterms with higher levels of DHA-PC levels. The results suggest that, on a background of sufficient maternal-fetal AA delivery, a higher fetal ratio of AA to DHA in PC is associated with a reduced risk of developing BPD.

Taken together, this study has provided new insight into the dynamic changes in LCPUFA during the last trimester of pregnancy. DHA may be even more actively delivered to the fetus via PC from week 33 onwards. AA accretion seems to remain constant throughout the third trimester, as far as its presence in PC is reflecting AA levels in the fetal circulation. The study supports the possibility that specific peripheral organs have specific temporal requirements for sufficiency in specific polyunsaturated fatty acids. Lung and airway development in humans occurs from about 22 weeks of gestation.
gestation onwards and pulmonary growth remains active even after birth with alveolarization following vascular development. This study suggests that both AA and DHA already need to be available in sufficient amounts from week 24 onwards, with an optimal ratio of AA to DHA within PC that is dominated by AA, to allow healthy development of the lung and small airways. This requirement precedes the ramping up of maternal-fetal delivery of DHA at around week 32, likely serving higher demands for this PUFA in supporting the growth of tissues during late gestation.

This study provides the first indications that AA may be of critical importance to the proper development of the lung during a specific period of gestation. These analyses were based on a limited group of only 19 very early preterm infants and their mothers, and future studies are needed to confirm and understand its role in the developmental biology of the lower airways and lungs. As lung tissue continues its full development after birth, the optimal provision of specific nutrients that may become limiting to fetal growth, such as choline, AA and DHA, may be very important. A new randomized controlled intervention trial will address the usefulness of supplemental DHA added to a soy oil-based emulsion (devoid of AA) in the enteral feeding given to preterms born before week 29 with bronchopulmonary dysplasia. Given that it is still unknown how relatively higher levels of fetal DHA-PC during the critical period of week 24-27 postmenstrual age may predispose to bronchopulmonary dysplasia, new intervention trials that address the effect of supplemental DHA may also want to consider the insight gained in this new study by Bernhard and colleagues. This may involve supplementation with more AA than DHA in very early preterm infants, to reduce a potential inhibitory effect of DHA on the incorporation of AA into membrane phospholipids.
Guaranteeing adequate dietary intakes of both AA and DHA by pregnant women itself already in the beginning of the third trimester to enable fetal lung development may further lower the risk for bronchopulmonary dysplasia incidence and severity in neonates.


Worth Noting


