Inositol: A Nonglucose Carbohydrate Found in Human Breast Milk

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Expanded Commentary from the Faculty

Inositol is a naturally occurring 6-carbon sugar alcohol found in mammalian tissues. It is formed through the reduction of glucose through the polyol pathway. *Myo*-inositol is the most predominant stereoisomer found in biological tissues and is an essential nutrient for the growth and survival of all cells. Inositol is found in breast milk in relatively high concentrations (1200 µmol/L), and has the third-highest concentration of carbohydrate, with lactose and free glucose being highest.[1] Inositol plays a critical nutritional role in fetal development—as early as the first trimester of pregnancy—and in early neonatal health.[2,3] The fetus and/or placenta are able to produce inositol endogenously from glucose.[4]

Critical for Fetal and Neonatal Development

Inositol has several biological functions. It regulates cell osmolality and is essential for phosphoinositide-mediated cell signaling and glycoprotein formation.[5] It is also an important component of phospholipid surfactant production the form of phosphatidylinositol.[6] It is essential to the formation of the neural system. Interestingly, inositol is found in high concentrations in tissues with cells that do not divide rapidly, such as the central nervous system, skeletal muscle, and cardiac muscle.

Inositol Concentrations During Fetal and Postnatal Life

Inositol concentrations are elevated during embryonic and fetal life, and decline postnatally, such that plasma concentrations in preterm neonates are higher than in term neonates, and plasma concentrations of inositol in term neonates are higher than in the adult.[7,8] It is an important precursor for membrane phospholipids and is significant in the formation of the neuro system, and for surfactant production in the lung.

Studies in human pregnancies have suggested endogenous production of inositol by the fetus. This was shown in studies that measured inositol concentrations in the maternal plasma compared to umbilical cord arterial and venous concentrations. This study found that inositol concentrations were highest in the fetal umbilical artery. A second study used stable isotope tracers of inositol that were infused into the maternal circulation, and by sampling umbilical-cord blood it was shown again that the fetus was the producer of inositol.[9,10] Additional studies using stable isotope tracers demonstrated that in late-preterm and term neonates, they were able—in the first few days of life—to produce inositol endogenously at rates that exceed the intake from human breastmilk.[2]

Causes of Higher Inositol Levels

Despite endogenous inositol production by the fetus and neonate, there is a relatively high concentration of inositol in human breast milk, with the highest concentration in preterm milk compared to term human milk.[1,2,6,8] There is also some limited evidence that placental insufficiency and intrauterine growth restriction (IUGR) may result in increased fetal inositol concentrations compared to a normally grown

fetus or neonate. Markedly increased concentrations of inositol were found in the plasma of a fetal sheep model of placental insufficiency in IUGR, and likewise, high inositol concentrations have been demonstrated in the urine of human IUGR neonates.[11,12] The significance of higher than normal inositol concentrations in this condition has yet to be determined.

Causes of Insufficient Inositol Levels

At birth, inositol concentrations are higher in preterm infants compared to term infants. After birth, the concentrations of inositol are influenced by nutritional intake. Inositol is present in human milk and is supplemented in preterm formulas, and to a lesser extent, in term formulas, but is not present in parenteral nutrition. Preterm infants who are unable to receive human milk and/or preterm formula and do not endogenously produce adequate amounts of inositol, therefore, are at risk of becoming deficient.[8,13]

Potential Risks from Deficiency

Preterm infants who do not receive enteral intake of inositol and are unable to produce inositol endogenously are at risk for deficiency. Neonates with respiratory distress syndrome (RDS) may have low inositol concentrations, and infants with low levels of inositol may result in a more severe course of RDS.[3,14] Preterm infants with low inositol concentrations are also at risk for retinopathy of prematurity (ROP), which can result in loss of vision or blindness.[3,13,15] Reduced maternal inositol concentrations have been associated with increased incidence of spina bifida in the fetus during pregnancy.[16]

Inositol Supplementation

Inositol is found in human milk with the highest concentration in human preterm milk. Inositol is added to preterm formulas at about 40 mg/100 calories and, to a lesser extent, in term formulas at 5 mg/100 calories. This is in reference to the content of inositol in human preterm milk, which is about 22 mg/100 calories. Inositol is not typically included in standard intravenous (IV) parenteral nutrition. Intravenous and enteral supplementation of inositol have been used in previous randomized control trials.[3] Inositol supplements to preterm infants have been used in research protocols only, and can be given either intravenously or enterally.

Study Results

Inositol supplementation increases plasma concentrations of inositol in preterm infants. It also increases the amount of saturated phosphatidylcholine surfactant in newborns. Randomized controlled trials of inositol supplementation for preterm infants born less than 32-weeks gestation were conducted in the 1980s and 1990s by Hallman and Friedman, et al. Results were summarized in a 2015 Cochrane Review, written by Hewlett, et al. The following results were shown in preterm infants who were supplemented with inositol [2,3,17]:

- Reduced neonatal mortality
- Reduced incidence of respiratory distress syndrome
- Reduced incidence of severe intraventricular hemorrhage (grade 2 or higher)
- Markedly decreased incidence and severity of ROP
- Inositol supplementation in preterm infants was not associated with any serious adverse events

Phelps, et al, performed a more recent pharmacokinetic study in preterm infants less than 29-weeks gestation evaluating the effects of a 10, 40, and 80 mg/kg/day of supplemental *myo*-inositol compared to placebo. Results demonstrated that increased plasma inositol concentrations were observed 2 weeks after initiation in the supplementation groups compared to placebo, with concentrations declining and

converging among all groups by 6 weeks. Concurrent increased concentrations of inositol in the urine were found, though this was not associated with an osmotic diuresis. The half-life of inositol was found to be about 8 hours. Adverse events were common in this group of extremely preterm infants, however, fewer adverse events were found in the inositol supplementation groups, though not significantly.[13]

Our [Brown, et al] research group showed that utilization rate of inositol in late-preterm and term neonates (greater than 34-weeks gestation) was higher than what would be obtained by ingestion of inositol in human milk, suggesting inositol must be synthesized endogenously in significant quantities to meet the infant's daily requirement.[2,4,18] Whether extremely preterm infants can produce inositol in sufficient quantities has not been studied. However, the 4 randomized control trials discussed by Hewlett, et al, that examined inositol supplementation in preterm infants, would suggest that an extremely preterm infant is at risk of becoming inositol deficient.

Why More Research is Needed

In clinical practice, inositol concentrations are *not* measured routinely, thus we do not know the true magnitude of infants who may be inositol deficient. There is an ongoing multicenter randomized controlled trial (NCT01954082) "Inositol to reduce retinopathy of prematurity" in the United States. This study is designed to follow up on the previous smaller randomized controlled trials (RCTs) that show a very promising effect of inositol on morbidities in preterm infants, such as ROP. There is some evidence of increased inositol concentrations in the plasma and urine of IUGR infants, though the significance of this is not understood. It is also hypothesized that elevated inositol concentrations could play a role in later life insulin resistance, as well as the risk for metabolic disease in adulthood.

Neural Tube Defects Prevention

Animal studies strongly suggest a potential role for inositol to prevent neural tube defects (NTD). Rodent embryos develop NTD when cultured in inositol deficient conditions. Inositol also prevented NTD in a genetic mouse model that is predisposed to develop NTDs.[16]

Separately, a pilot study randomized women with a previous NTD pregnancy to folic acid supplementation, which is the standard care, plus or minus inositol supplementation. Though it was a very small study, the results showed promise that a combination of folic acid and inositol supplementation started prior to pregnancy might decrease the incidence of NTD. There were no adverse events associated with maternal inositol supplementation. The results encourage a larger scale randomized controlled trial of inositol for NTD prevention.[19]

Considerations for inositol supplementation:

- Inositol is present in human milk with its highest concentration in preterm human milk.
- Inositol is supplemented in preterm formulas; however, it is not present in standard intravenous parenteral nutrition formulations.
- There is some evidence inositol supplementation in pregnant women may decrease the incidence of neural tube defects.
- More studies on inositol and its role in neonatal nutrition are needed to better define the effect and safety of inositol supplementation, and for potentially promising effects on morbidities because of inositol deficiencies.

Discussion Guide

- When is inositol supplementation beneficial?
- Are there specific cohorts of infants who might benefit more from inositol supplemented formula than others? For example, preterm vs full-term infants.
- Should this information prompt a change in our current practice?
- What are the barriers to adopting these clinical pearl considerations in our institution?
- Are there other concerns or issues we haven't talked about?

Suggested Readings and Resources

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