Pediatric RESEARCH

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REVIEW ARTICLE

Do preterm girls need different nutrition to preterm boys? Sex-specific nutrition for the preterm infant

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Boys born preterm are recognised to be at higher risk of adverse outcomes than girls born preterm. Despite advances in neonatal intensive care and overall improvements in neonatal morbidity and mortality, boys born preterm continue to show worse short- and long-term outcomes than girls. Preterm birth presents a nutritional crisis during a critical developmental period, with postnatal undernutrition and growth-faltering common complications of neonatal intensive care. Furthermore, this preterm period corresponds to that of rapid in utero brain growth and development, and the developmental window relating to foetal programming of adult non-communicable diseases, the prevalence of which are associated both with preterm birth and sex. There is increasing evidence to show that from foetal life, boys and girls have different responses to maternal nutrition, that maternal breastmilk composition differs based on foetal sex and that early neonatal nutritional interventions affect boys and girls differently. This narrative review examines the evidence that sex is an important moderator of the outcomes of preterm nutrition intervention, and describes what further knowledge is required before providing nutrition intervention for infants born preterm based on their sex.

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IMPACT:

- This review examines the increasing evidence that boys and girls respond differently to nutritional stressors before birth, that maternal breastmilk composition differs by foetal sex and that nutritional interventions have different responses based on infant sex.
- Boys and girls born preterm are given standard nutritional support which does not take infant sex into account, and few studies of neonatal nutrition consider infant sex as a potential mediator of outcomes.
- By optimising early nutrition for boys and girls born preterm, we may improve outcomes for both sexes. We propose future studies of neonatal nutritional interventions should consider infant sex.

INTRODUCTION

Although very preterm infants are dependent upon nutrition via intravenous or enteral delivery, the evidence base for optimal nutrient intakes is limited and based on consensus agreement.[1] Despite this, early neonatal nutrition is recognised as a potentially modifiable contributor to adverse neonatal, childhood and adult outcomes in infants born preterm. Early macronutrient intakes and postnatal growth patterns are associated with both neurodevelopmental outcomes and long-term metabolic risk, and there is increasing recognition that not only quantity but quality of growth is important during what may be a critical period for developmental programming.[2] Both male and female infants are vulnerable to nutrition deficits, but may have different nutritional needs.[3] If this is the case, there is potential for universal nutrition intervention to have different effects for boys and girls born preterm, inducing harm if nutrition is inadequate or supporting good outcomes if nutritional needs are met. Infant biological sex (not gender, which is a perception of self that may not align with sex and is not applicable to the foetus/neonate) may thus be an important factor to consider when providing nutrition to newborn infants.

SEX DIFFERENCES IN NEONATAL OUTCOMES

The increased vulnerability of boys born preterm has been recognised for nearly 50 years.[4] Large observational studies of data from international neonatal networks show that overall morbidity and mortality rates for infants born preterm are improving, and that these improvements have been faster in boys than in girls.[5,6] However, preterm boys remain at higher risk than girls for neonatal mortality and morbidities,[6–9] and for later neurodevelopmental impairment.[10–12] Male sex is also a significant predictor of metabolic syndrome in adults born at very low birth weights.[13]

FOETAL SEX EFFECTS

The biological factors underlying male vulnerability are yet to be fully elucidated, but foetal sex mediates differences in pregnancy outcomes beginning in the first trimester. Sex differences in body size are present during the first trimester of pregnancy[14] and there are sex differences in metabolism starting from the blastocyst stage of embryonic development,[15] suggesting that males may be more responsive to growth-promoting influences, and therefore

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more susceptible to inadequate nutrient supply. Pregnancies with a male foetus are more likely to be affected by metabolic and cardiovascular complications[16] and are more likely to be of shorter gestation.[17] Animal studies reveal that, during pregnancy, maternal nutritional stressors provoke sexually dimorphic responses in the foetus.[18] In rat models, maternal undernutrition resulting in foetal growth restriction leads to hypertension only in the male offspring, with evidence of reduced antioxidant capacity only in growth-restricted male pups after weaning.[19] Ovine models utilising a similar mechanism of maternal undernutrition-induced foetal growth restriction have demonstrated differential expression of genes involved in glucose homoeostasis between growth-restricted male and female fetuses,[20] and reduced liver weight and epigenetic changes affecting expression of the hepatic glucocorticoid receptor only in growth-restricted male offspring.[21] In both sheep and baboon models, male fetuses show a greater decrease in growth trajectory for the same degree of maternal nutritional insult, and in baboons, only males respond to this stressor by altering their body composition, increasing production of brown (thermogenic) fat stores.[22]

SEX DIFFERENCES IN NEONATAL BODY COMPOSITION AND METABOLISM

Although in humans, body composition is frequently reported to diverge between the sexes during puberty,[23] studies in term neonates show that these differences in body composition are in fact present at birth, with female sex a strong predictor of body fat percentage in term newborns undergoing air displacement plethysmography.[24] A more recent study of 440 healthy term infants using air displacement plethysmography found fat mass was not different between boys and girls, but the boys had significantly more lean mass.[25] In infants born preterm, improved neurodevelopmental outcomes are associated with gains of fat free mass, but are not shown to be associated with gains of fat mass.[26] Percentage fat mass at term equivalent age is higher in extremely compared to very preterm infants[27] and is associated with increased blood pressure values in childhood.[28] Adipose tissue is a target of interest when considering long-term metabolic risk, as oestrogen-mediated differences in fat deposition are thought to contribute to differences in adulthood metabolic risk between the sexes,[23] and an interaction between sex, gestational age at birth and adiposity has been described in preschool age children[29] and young adults born very preterm.[30] Animal models have been used to explore the hypothesis that interactions between sex, foetal growth and postnatal diet may alter long-term metabolic risk profiles, with growth-restricted lambs weaned to an obesogenic diet demonstrating increased visceral-to-subcutaneous adiposity ratios only in females.[31]

The effect of even brief nutritional manipulations during critical developmental windows may alter life-long metabolic risk via sex-specific genetic changes, as demonstrated in a randomised trial of macronutrient supplementation in term-born lambs.[32] Male lambs who received a nutritional supplement for just 2 weeks after birth had altered gene expression in pancreatic cells compared to same-sex controls when tested at 4 months of age. Glucose tolerance was also altered, with supplemented male lambs showing poorer glucose tolerance, and supplemented female lambs better glucose tolerance, than their same-sex unsupplemented control groups. In very preterm human infants being managed for hyperglycaemia, girls show almost double the endogenous insulin secretion than boys for the same blood glucose concentration.[33] Higher variability of endogenous insulin release and stronger correlations between blood glucose concentrations and insulin secretion rates in girls suggest that they may display greater metabolic flexibility, and thus may be able to adapt more rapidly to their postnatal nutritional environment than boys born preterm.

SEX DIFFERENCES IN STUDIES OF NUTRITIONAL INTERVENTIONS

Only a few preterm studies have reported growth and neurodevelopmental outcomes by sex, with most suggesting boys need higher nutrition. Poindexter et al.[34] found lower intravenous amino intake in the first 5 days after birth was associated with a smaller head circumference (cm) at 18 months in extremely low birth weight (ELBW, <1000 g) boys but not in girls. Others have reported lower intravenous energy and amino acid intake in the first 2 weeks after birth is associated with lower weight velocity (g/kg day) in the first 5 weeks only in preterm boys.[35,36] Van den Akker et al.[37] reported more very low birth weight (VLBW, <1500 g) boys, but not in girls, who received higher amino acids in the first week after birth had a normal neurodevelopmental outcome at 2 years corrected age (CA). Mental Development Index scores in the relatively small group of surviving girls with a normal neurodevelopment, however, appeared to be lower following the higher amino acid intake intervention.

Lucas et al.[38] randomised 424 preterm babies (birthweight < 1850 g) 48 h after birth to be fed either a standard infant formula (1.45 g/100 mL protein and 68 kcal/100 mL) or a preterm infant formula (2.0 g/100 mL protein and 80 kcal/100 mL with higher amounts of sodium, calcium, phosphorus, copper, zinc, vitamins, carnitine and taurine) for about 4 weeks after birth. The preterm formula group had better growth and neurodevelopment at 18 months CA[38] but at 8 years, measures of IQ between the groups were no longer different. When analysed by sex, the beneficial effect of preterm formula on Motor Development Index scores was significant for boys but not for girls.[39] Differences in the effect of enriched infant formula vs. standard term formula on growth also have been reported in a randomised controlled trial (RCT) of small for gestational age (SGA) term infants,[40] with length growth (in cm) at 9 months significantly greater in girls who had enriched formula than in boys.

In a study of 125 infants (birthweight ≤ 1750 g, gestational age ≤34 weeks) fed either a term or preterm infant formula after hospital discharge until 6 months CA to compare body composition using dual energy X-ray absorptiometry,[41] increased lean mass and fat mass were detected in those fed preterm formula, with significant sex differences in body composition. Boys had a greater bone area and bone mineral mass than girls and at discharge, term, 6 months and 12 months lean mass was higher in boys than in girls. A systematic review and meta-analysis of randomised and quasi-RCTs on the impact of macronutrient supplements on later growth of children born preterm, found in toddlers, that supplemented boys had greater length/height than unsupplemented boys but no differences in girls,[42] but no significant associations between sex and supplementation on weight or head circumference in toddlers, or on body mass index in childhood. This may indicate boys require higher nutritional intake than girls to support optimal linear growth and body composition. In another small study of normally developing teenagers born preterm, a 4-week nutritional intervention to increase enteral protein and energy content commencing shortly after birth was associated with structural brain changes in teenage boys only, where magnetic resonance imaging studies of the brain showed increased volumes of the caudate nuclei in boys but not in girls fed the same nutrient-enhanced diet.[43]

There is a perception that boys grow less well as a result of being less well.[44] However, in a recent cohort study of 434 ELBW babies, no difference in *z*-score change from birth to 36 weeks CA was found between sexes,[45] although there was a trend towards fewer boys than girls achieving expected length growth (defined as *z*-score change from birth to 36 weeks CA between −0.8 and 0.8). In this cohort, there was no significant difference in the number of boys and girls classified as unwell and the estimated nutritional intakes of boys and girls did not differ. Similarly, in an earlier cohort of 478 babies (<30 weeks' GA or 1500 g at birth), we

Table 1. Recommendations for future research.

Selected recommendations from the Institute of Medicine report "Exploring the biological contributions to human health: Does sex matter?"[65]
Avoid the conflation of sex and gender
Report sex interactions, or design studies where results can be analysed by sex
Where possible, utilise both sexes in animal studies
Report the sex of all cell lines (including placentas)
Encourage and support interdisciplinary research on sex differences

also found no significant difference between sexes in *z*-score change for weight, length or head circumference from birth to 36 weeks' CA.[3] Alur et al.[46] found despite similar energy and protein intake during transition from intravenous to enteral nutrition, energy intake was correlated with weight (percentile change) only for ELBW girls but not boys. This group also reported ELBW boys require less energy and protein than ELBW girls to maintain weight >10th centile at discharge. Breastmilk volume was been used to estimate nutrient intakes; therefore, the conclusion can only be that boys required less breastmilk volume to maintain weight >10th centile at discharge, which is not necessarily an appropriate measure of growth.[47]

When considering inconsistent findings in these studies, two important aspects should be taken into account. In the more recent studies,[3,45,46] enteral intake was predominantly breastmilk rather than infant formula, with minimal or no pooled donor milk involved. Therefore, nutritional intakes for breastmilk were estimated, often using different references,[48] and assumed to be the same for boys and girls, which may not be the case. Furthermore, growth in the studies mentioned above has been assessed in various different ways, e.g. cm, g/kg/day, weight remaining above the 10th centile at discharge or percentile change. As sex-specific differences in foetal growth rates are well recognised,[49,50] the assessment of growth by *z*-score change between two time points, which adjusts for sex and gestational age at the time of measurement, gives a more accurate assessment of growth differences by sex than the growth assessment methods used previously and this may also explain the inconsistency in growth findings by sex.

SEX DIFFERENCES IN BREASTMILK

In human infants, maternal breastfeeding is the ideal form of nutrition and is associated with a range of beneficial neurodevelopmental and metabolic outcomes in both term and preterm populations.[51] There is evidence both from animal[52] and human[53,54] studies that the composition of breastmilk may differ by offspring sex. Interestingly, maternal breastmilk has been reported to supply more lipid (39%) and energy (24%) to boys,[54] but this needs further investigation. Macronutrients are not the only components of breastmilk observed to show sex-specific differences; breastmilk immunoglobulin content, glucocorticoid concentrations, hormone content and the composition of the milk microbiome[55,56] are also reported to vary with sex. If hormones such as IGF, glucocorticoids, etc., differ by offspring sex, this also could impact growth.[57] In fact, if breastmilk composition is different depending on offspring sex, this may explain both the absence of a difference in growth between sexes in studies where enteral nutrition was predominantly breastmilk[3,45,46] and also explains the growth differences in studies where boys and girls received interventions involving the same intravenous nutrition or infant formula of known composition.

Gut immaturity may limit the delivery of enteral feeds for very preterm infants in early life, and breastmilk alone may not meet their high nutritional requirements for growth. Macronutrient supplementation of maternal breastmilk for preterm infants is commonplace, but few studies have reported sex-specific outcomes, an issue planned to be addressed in an upcoming individual patient data meta-analysis.[58] A large randomised trial of docosahexaenoic acid (DHA) supplementation to preterm infants in the postnatal period up until term-equivalence reported associations between high (1%) DHA content and mental development index scores in girls only at 18 months' corrected age.[59] Long-term follow-up again revealed a relationship between DHA supplementation and outcome only in girls; however, the relationship at 7 years was that of a negative association between higher DHA supplementation and parent-reported executive function and behaviour.[60]

FUTURE RESEARCH

Current protocols for the management of nutritional delivery in preterm neonates do not take infant sex into account. A standardised approach to early nutrition has been shown to deliver macronutrient contents approaching the recommended daily intakes.[61] Despite receiving equal nutrition, boys are at higher risk of postnatal faltering growth,[62,63] indicating a one-size-fits-all approach may not optimise outcomes for boys and girls with different, and potentially competitive, nutritional needs. Boys and girls born preterm appear to have different responses to nutritional interventions during the critical developmental period following preterm birth, and the biological mechanisms that may underpin these differences are present from early foetal life. If preterm infants need sex-specific intravenous nutrition solutions, breastmilk fortifier or breastmilk substitutes to optimise their growth and development, this is potentially an inexpensive and easily implemented intervention to improve health outcomes, especially for boys born preterm. However, the determination of what those nutritional interventions should be, and the ability to translate this emerging evidence to clinical practice, is hampered by the post hoc nature of many of the analyses relating sex to the effects of early nutrition, and the failure of many studies to consider sex as an important variable in infants' responses to nutritional interventions, not merely as a potential confounder. This lack of pre-specified, sex-specific analysis is in no way unique to neonatal research,[64] but if we are to provide nutritional interventions that optimise neurodevelopmental and metabolic outcomes for every infant born preterm, it is vital that the potentially competing nutritional needs of the sexes are accurately delineated. Future research into neonatal nutrition should follow the recommendations set out by the Institute of Medicine in its 2001 report "Exploring the biological contributions to human health: Does sex matter?",[65] as detailed in Table 1.

CONCLUSION

Nutrition is a potential modifier of adverse neurodevelopmental and metabolic outcomes in infants born preterm. There is increasing evidence of important differences between boys and girls in responses to foetal nutritional insults; neonatal body composition; breastmilk composition; and responses to early life macronutrient intakes and long-term metabolic risk profiles.

However, few studies of neonatal nutritional interventions consider infant sex as an important variable, and pre-specified sex-specific analyses are rare. Planned studies of neonatal nutritional interventions should consider that boys and girls may have different and competing nutritional needs.

AUTHOR CONTRIBUTIONS

A.C.T. authored the first draft and C.J.O., J.M.A. and B.E.C. critically reviewed and edited the manuscript. All authors approved the final version of the manuscript for submission.

ADDITIONAL INFORMATION

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