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Response to Therapeutic Interventions in the NICU: Role of Sex as a Biological Variable

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Abstract

Sex as a biological variable plays a critical role in the pathophysiology of specific diseases and can have a potential impact on the response to therapies and disease outcomes. Sex-specific differences have been reported in prematurity-related outcomes, suggesting that preterm infants exhibit differences in biological predisposition or resilience to disease. Furthermore, striking differences in response to common neonatal therapies such as antenatal and postnatal steroids, indomethacin, and other nonpharmacologic agents raise the critical need to assess therapeutic responses stratified by biological sex. Very few clinical and translational studies in neonates report outcomes by sex, even though most account for biological sex at enrollment. Sex-specific differences in the newborn may arise from baseline or adaptive differences in male and female preterm neonates. In the current era of precision medicine and the increasing interest in tailoring risk-based therapy to patients, data from neonatal clinical studies should be disaggregated by sex and reported for informing studies with a larger sample size or meta-analyses.

INTRODUCTION

The male disadvantage in neonatal mortality and major morbidities in preterm neonates is a well-established finding in the clinical and epidemiologic literature. (1)(2)(3)(4) Sex-specific differences in neonates may arise from sex chromosome–based, hormonal, imprinting, or epigenetic mechanisms. (3) Differences in susceptibility to injury or in repair mechanisms after injury could underlie sex-based differences. Biological mechanisms related to cell death, oxidative stress, and drug metabolism are very different between males and females. (5)(6)(7)(8) Despite this, very few clinical and translational studies report outcomes by sex, even though most adjust for biological sex at enrollment.

SEX BIAS IN PREMATURITY-RELATED OUTCOMES

Male sex has been identified as a risk factor associated with mortality in many studies, despite improved neonatal care and increased overall survival of extremely premature neonates. A meta-analysis published in 2018 demonstrated that 26 of the 32 studies showed an association between male sex and mortality. (9) The National Institute of Child Health and Human Development (NICHD) and the Neonatal Research Network (NRN) extremely preterm birth outcome model is used for counseling parents about the incidence of mortality and morbidity of their preterm infant. (10) The model was developed based on data from nearly 5,000 preterm infants born at hospitals within the NICHD NRN between 2006 and

2012, and was subsequently validated in 51,000 infants born between 2006 and 2012, and 26,000 infants born between 2013 and 2016, at hospitals participating in the Vermont Oxford Network. (10) This model uses fetal sex as one of the variables that modify outcomes. In this model, female sex independently increases the odds of survival and survival without neurodevelopmental impairment between 22 and 25 weeks' gestational age. (10)

Male sex is linked not only with a higher risk of mortality, but also with neonatal morbidities associated with preterm birth. A systematic review and meta-analysis of cohort studies (41 included studies exploring the association between sex and complications of prematurity) published in 2021 (11) identified male sex to be associated with mortality as well as necrotizing enterocolitis (NEC), severe intraventricular hemorrhage (IVH), bronchopulmonary dysplasia (BPD), and use of postnatal steroids. Supporting these findings, the male bias in mortality and severe neonatal morbidities has been shown in several national cohorts and registries. In 2018, the Vermont Oxford Network, in a study including more than 205,000 infants born in the United States over 11 years, reported that male preterm neonates (<30 weeks' gestation) showed faster declines in mortality, respiratory distress syndrome (RDS), and BPD, but males still had a significantly higher risk of mortality before hospital discharge, RDS, NEC, late-onset sepsis, severe IVH, severe retinopathy of prematurity (ROP), BPD, pneumothorax, and survival with morbidities compared with females. (12) The Korean Neonatal Network reported the male bias in mortality in infants with a birthweight greater than 500 g. (13) The Canadian Neonatal Network (based on data from 2006–2017) reported a decrease in difference in mortality between male and female premature neonates but a persisting male bias in mortality, BPD, severe brain injury, ROP stage 3 or greater, NEC, and the composite outcome of mortality or one of the major morbidities. (14) The Neonatal Research Network of Japan reported higher mortality, BPD, NEC, IVH, mortality, and the composite outcome in premature male neonates based on data from 2003 to 2012. (3) Similar results were reported in Austrian and Swiss cohorts. (15)(16) An interesting twin study examining the hypothesis of the "male disadvantage" extending to the female cotwin reported that females overall had lower risks and females with a male cotwin had lower mortality, severe IVH/periventricular leukomalacia, and composite outcome (death or major neonatal morbidity) compared to the male cotwin and same-sex pairs. (17)

SEX-SPECIFIC DIFFERENCES IN RESPONSE TO THERAPY

We will highlight the existing state of knowledge on differences in response to therapies in male and female preterm neonates in the following sections. Though many of these studies have reported outcomes by sex, the data across many studies are conflicting. These could be attributed to factors in study design, sample size, statistical analysis, and reporting of study data. A summary of the studies, outcomes, and disaggregated data by sex is provided in the Table.

Antenatal Steroids

Antenatal steroid administration before preterm labor significantly improves neonatal outcomes by promoting lung maturation and surfactant production, thereby decreasing the incidence of RDS, IVH, and neonatal mortality. The scientific basis underlying the physiologic and biochemical effects of antenatal steroids in the lung have been well-established. (18) Studies in human and preclinical models have reported on sexually dimorphic effects of antenatal steroids, which are summarized below.

Sex-specific benefits of antenatal glucocorticoids have been demonstrated in multiple clinical studies. A meta-analysis of 8 studies comprising a total of 1,109 males and 968 females found that sex-specific benefits for preventing RDS were unique to the type of antenatal corticosteroid administered. (19) Betamethasone had greater benefit in males (relative risk [RR], 0.29; 95% confidence interval [CI], 0.15–0.57) while dexamethasone was more beneficial in females (RR, 0.51; 95% CI, 0.32–0.81). (19) A prospective observational study in 389 patients (232 male, 157 female) by Ramos-Navarro and colleagues found multiple sex-specific benefits with the administration of maternal betamethasone in preterm male neonates with gestational age of less than 29 weeks. (20) Sexually dimorphic outcomes after antenatal corticosteroid administration included decreased intubation in the delivery room, surfactant administration, mechanical ventilation in the first 3 days after birth, and mortality, as well as greater survival without abnormal cranial ultrasound findings in male neonates who had received antenatal corticosteroids compared to those who did not. (20) In extremely premature male neonates born between 26 and 29 weeks' gestation, the incidence of moderate and severe BPD was decreased in the antenatal steroid-exposed males compared with untreated males. (20) No statistically significant effects were observed in any of the studied outcomes in females (between treated and nontreated females). (20) This may be due to a lower sample size in the female subgroup, which has a lower susceptibility to the development of the disease. Thus, a larger sample size would be needed to detect a statistically significant therapeutic effect.

Not all studies show similar sex bias in the therapeutic effect of antenatal steroids. Opposite results were seen in a cohort of 94 premature neonates (27–34 weeks' gestation) who received betamethasone, where a benefit of decreased RDS was more pronounced in females compared to males. (21) Another study found that maternal glucocorticoids were beneficial in reducing BPD in all studied groups except in extremely low-birthweight males (<1,000 g birthweight). (22) An analysis of 11,714 extremely preterm infants born in England determined that while antenatal corticosteroids were beneficial for both sexes, as measured by decreased mortality, lower risk of grade 3–4 IVH, and shorter duration of mechanical ventilation, there was a female advantage with lower mortality in the antenatal steroid-treated group (20.2% in males vs 16.9% in females, $P<.001$). (23) Female infants who did not receive antenatal steroids had an odds ratio (OR) for mortality of 1.81 (95% CI, 1.35–2.44). However, for female infants who received antenatal steroids, the OR was 0.55 (95% CI, 0.41–0.74). In contrast, among males, the OR was 1.36 (95% CI, 1.03–1.77) for those who did not receive antenatal steroids, and 0.74 (95% CI, 0.57–0.96) for those who received antenatal steroids. (23)

Sex bias in adverse effects of therapies also requires attention, as the risk-benefit ratio needs to be adjusted for each patient in clinical medicine. There are concerns about altered postnatal growth after exposure to multiple courses of antenatal steroids. (24) Interestingly, in a twin study, when exposed to prenatal betamethasone, female-only and mixed-sex twin pairs showed a greater occurrence of growth restriction compared with male-only pairs. (25) Even among the mixed-sex twin pairs, the growth restriction effect was only evident in female fetuses, with no impact observed in males. (25)

The biological mechanisms mediating sex-specific responses to antenatal steroids are not well understood. The placental glucocorticoid "barrier," constituted by the enzyme 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD_2), plays a crucial role in regulating the transfer of maternal glucocorticoids to the fetus. 11β-HSD_2 protects the developing fetus from excessive maternal glucocorticoids in mammals. Its function involves the rapid inactivation of physiologic glucocorticoids in the placenta. Stark et al (26) collected placentae and umbilical cord arterial plasma from 43 women giving birth between 24 and 36 weeks' gestation who had received antenatal steroids. They reported higher umbilical arterial cortisol and placental 11β-HSD_2 activity in preterm female neonates compared to male. (26) The authors speculated that the acute increase in expression of placental 11β-HSD_2 following antenatal corticosteroids protects the female fetus from excess glucocorticoid exposure and enables appropriate adrenal responses to physiologic stressors postnatally. (26) Interestingly, following a single course of antenatal betamethasone between 23 and 34 weeks' gestation, term females had lower 11β-HSD_2 protein levels and enzyme activity compared to males, pointing to the sex-specific and different long-term effects of antenatal steroids on placental 11β-HSD_2 expression. (27) Glucocorticoid mediated, sex-specific differences in mediators of vascular tone could also underlie the sex-specific differences in therapy response. When born within 72 hours of betamethasone administration, preterm female infants had higher urinary normetanephrine levels that were inversely related to baseline microvascular blood flow and severity of illness. (28)

In summary, one may speculate that sex as a biological variable modulates the therapeutic benefits of antenatal steroids based on different susceptibilities to lung injury, distinct drug pharmacokinetics related to placental transfer, or innate biological resilience to the development of the disease.

Postnatal Steroids

Administration of postnatal steroids to preterm neonates with evolving or established BPD remains contentious due to the tradeoff between immediate benefits and long-term outcomes and difficulties in identifying the responder patients within the eligible cohort of neonates. (29) Ventilator-dependent preterm neonates at high risk of developing BPD often receive postnatal steroid therapy. However, the response to this treatment varies, with only some infants showing improved outcomes. The question remains whether biological sex influences the therapeutic response to postnatal steroids. A meta-analysis found that preterm males were more likely to receive postnatal corticosteroids (RR, 1.234; $P<.001$). (11) A higher likelihood of male exposure was similarly observed in a French cohort, possibly

because the primary indication for administration was severity of lung disease, pointing to greater disease severity in preterm male neonates. (30)

A randomized controlled trial of postnatal dexamethasone (1-week high dose course if ventilator-dependent at 10 days; mean gestational age of 27 weeks) found a sex-specific benefit in preterm females, with better pulmonary outcomes (based on mechanical ventilation or death) at 28 days and shorter time of supplemental oxygen requirement. (31) A significant limitation was the small sample size, with 17 infants in the dexamethasone group (11 males, 6 females) and 24 in the placebo group (8 males, 16 females).(31) An individual patient data meta-analysis aimed to assess the efficacy of low-dose hydrocortisone prophylaxis in preventing early adrenal insufficiency and its impact on survival without BPD in preterm infants. Four randomized controlled trials with individual patient data were included in this study.(32) Subgroup analyses of the primary outcome (survival without BPD) revealed that female infants treated with low-dose hydrocortisone exhibited a lower risk of developing BPD. (32) The odds of survival without BPD at 36 weeks' PMA for male infants were found to be 1.40 (95% CI, 0.97–2.02; P=.074), which showed a potentially favorable trend but did not reach statistical significance. (32) In contrast, female infants demonstrated significantly better odds of survival without BPD until 36 weeks' PMA, with an OR of 1.52 (95% CI 1.02–2.26; P=.038). (32) The Early Low-Dose Hydrocortisone randomized controlled trial to improve survival without BPD in extremely preterm infants analyzed data from 521 enrolled neonates of less than 28 weeks of gestation. The neonates received either intravenous low-dose hydrocortisone or placebo during the first 10 postnatal days, with the primary outcome being survival without BPD at 36 weeks' PMA. (33) Subgroup analyses in enrolled male and female preterm neonates noted no significant response to hydrocortisone treatment in males (OR, 1.05; 0.64–1.74), but a significantly increased rate of BPD-free survival in females (OR, 2.25; 1.25–4.04). The number needed to treat to gain 1 BPD-free survival was 7 (95% CI, 4–23) in females compared to 12 (95% CI, 6–200) for the entire cohort, after adjusting for gestational age. (33) Long-term effects of postnatal corticosteroids are of concern in preterm neonates. Although early dexamethasone therapy in preterm infants to prevent BPD is not used widely, a follow-up study at 2 years' corrected age in a randomized controlled study cohort showed that dexamethasone-treated boys had significantly lower body weight and shorter height compared to controls. (34) This highlights that not only the intended benefits but also the adverse effects of pharmacotherapies may be sex-biased.

Nonsteroidal Anti-Inflammatory Drugs

Nonsteroidal anti-inflammatory drugs such as indomethacin and ibuprofen have been used for 2 primary indications, prevention of IVH and pharmacologic closure of the patent ductus arteriosus. Ibuprofen and indomethacin are nonselective cyclooxygenase inhibitors. Importantly, some studies that looked at the efficacy of prophylactic indomethacin for IVH prevention reported sex-specific differences in response to therapy. In the trial led by Ment et al, (35) female infants who received indomethacin had similar rates of IVH as the controls. However, among male infants, those randomized to receive indomethacin had 2.5 times less IVH compared with controls, and there were no cases of grade 3 or 4 IVH in the indomethacin group. Indomethacin-treated preterm males also had higher testing scores than

controls, independent of IVH prevention. The authors speculated that this effect could be due to the more pronounced anti-inflammatory effects of the drug in preterm males.

The Trial of Indomethacin Prophylaxis in Preterm Infants analyzed sex-mediated effects of indomethacin prophylaxis on severe IVH after the publication of the main findings of the study. (36) Statistical analysis was performed to test for interaction between biological sex and treatment for the primary composite outcome of death or survival to 18 months' corrected age with 1 or more of the following: cerebral palsy, cognitive delay, blindness, or deafness. There was a significant interaction between sex and treatment (P=.048), suggesting a differential treatment effect of indomethacin by sex. However, adverse indomethacin effects in girls contributed to this interaction.

Male sex was associated with increased odds (OR, 3.46; 95% CI, 1.18–10.1) of successful medical closure of the ductus and higher odds of medical closure of a hemodynamically significant ductus (OR, 5.22; 95% CI, 1.11–17.5) (37) with indomethacin. In the multicenter, noninferiority BeNeDuctus trial, comparing expectant management with early ibuprofen treatment for a patent ductus arteriosus, the composite primary outcome included death, NEC (Bell palsy stage IIa or higher), or moderate to severe BPD, at 36 weeks' PMA. (38) Subgroup analysis by sex showed a better outcome for expectant management in male infants than in female infants. (38)

Nutrition and Nutritional Supplements

Nutritional interventions and postnatal growth also have significant sexual dimorphism, with nutritional accretion being better in female preterm neonates. (39)(40) Differences in human breast milk composition based on neonatal sex (41) and differences in the neonatal microbiome (42) may play a significant role in the modulation of both short- and long-term outcomes in preterm neonates. Antibiotic exposure during the neonatal period has adverse impact on the developing gut microbiome. Neonatal antibiotic exposure led to significant growth attenuation in term boys and did not affect similarly exposed girls born at term. (43)

Maternal docosahexaenoic acid (DHA) supplementation during lactation had a positive effect on the neonatal weight profile and velocity in females, with no difference seen in males. (44) In addition, males who received DHA showed lower weight and head circumference at 36 weeks' PMA compared to placebo-treated controls. Another trial of DHA supplementation to preterm neonates showed a significant sex bias by treatment interaction on measures of parent-reported executive function and behavior, with a poorer outcome in girls who received high DHA. (45)

Oxygen

The effect of treatment by sex was analyzed in a retrospective cohort of preterm neonates to assess sex-specific responses to oxygen saturation (SpO_2) targets to prevent hyperoxia during 2 epochs (high SpO_2: 92%–100% and low SpO_2: 85%–93%). (46) Interestingly, the response to lower SpO_2 targets was only seen in females with lower rates of BPD, ROP, and length of stay, and no difference was seen in boys. (46) The Neonatal Oxygenation Prospective Meta-analysis was a prospectively planned meta-analysis of individual participant data from 5 randomized controlled trials to test lower (85%–89%)

versus higher (91%–95%) SpO_2 targets, and the primary outcome was death or major disability at age 18 to 24 months. (47) The subgroup analysis by sex was performed and was reported in the supplemental data and considered exploratory. The outcome of the requirement for positive airway pressure with endotracheal tube at 36 weeks' PMA, which would equate to severe BPD, was reported by sex. When the interaction of sex and treatment was assessed for this outcome, the P value was .05, suggesting that sex as a biological variable influences the effects of therapy for the outcome. The adjusted RR in males was 1.16 (95% CI, 0.89–1.50), with a higher outcome rate in the lower SpO_2 group. In females, the adjusted relative risk was 0.78 (95% CI, 0.57–1.06) with a lower outcome in the lower saturation group. (47) The availability of these exploratory data is crucial for future meta-analyses and to cautiously weigh the risk-benefit ratio of therapy in male and female preterm neonates.

Other Therapies

Preterm neonates receive transfusions very frequently during their hospital course, with 90% of extremely preterm neonates receiving at least 1 packed red blood cell transfusion. Among infants with a birthweight of less than 1,000 g and gestational age of 22 to 29 weeks enrolled in the Transfusion of Prematures trial, female infants in the liberal group (higher pretransfusion hematocrit threshold) had the most significant degree of structural brain abnormality despite being older (higher gestational age at birth in females) than the boys in the same group. (48) In a subsequent study with the same cohort, female infants showed an increase in monocyte chemoattractant protein 1 in response to transfusions, which was also associated with worse neurocognitive outcomes. (49) This study raised the possibility of sex-specific thresholds of transfusion requirements among preterm neonates. Reporting of results or analysis of outcomes by sex was lacking in other major transfusion trials. (50)

With the emergence of cell-based therapies, the biological source of the cells or cell-based therapy (male/female and age) may have specific biological effects on the recipient. Premature neonates who exclusively received blood transfusions from older female donors had a lower risk of death or serious morbidity. (51)

STRATEGIES TO IMPROVE REPORTING OF SEX-SPECIFIC DATA IN CLINICAL STUDIES

In randomized controlled trials, great attention is paid to random allocation of subjects to the therapy and control groups, and this usually achieves equal enrollment of male and female neonates in most circumstances. The primary outcome in many neonatal trials is a composite outcome (death or BPD; death or severe neurodevelopmental impairment; etc), and most trials report the outcomes of the individual components. A few trials report outcomes disaggregated by biological sex, and some of them surprisingly show evidence of sex bias in the primary outcome or the components of the composite outcome. This may be due to greater benefit or a higher incidence of adverse effects of the therapy in one sex compared to the other. On some rare occasions, the intervention or therapy may have opposite effects in male and female neonates, where it may be helpful in one sex and harmful in the other.

In all of these examples, reporting data by sex also reduces the need for repeating the study because prior studies failed to disaggregate study participants by sex.

Multiple steps can be considered during the design, analysis, and reporting of clinical trial data to give due diligence to the role of sex as a biological variable. A study design with biological sex as a factor (each sex is equally provided the therapy being evaluated) is an appropriate way to examine sex differences in response to treatment. Next, testing within each sex to look for differences between control and intervention arms is not sufficient to report sex-specific differences. Also, comparing males and females within the experimental arm without taking controls into account is the wrong approach. A statistically appropriate approach would be to use 2-way analysis of variance to detect a statistically significant interaction between sex and treatment.

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ABBREVIATIONS

11β-HSD2	11β-hydroxysteroid dehydrogenase type 2
BPD	bronchopulmonary dysplasia
CI	confidence interval
DHA	docosahexaenoic acid
IVH	intraventricular hemorrhage
NEC	necrotizing enterocolitis
NICHD	National Institute of Child Health and Human Development
NRN	Neonatal Research Network
OR	odds ratio
PMA	postmenstrual age
RDS	respiratory distress syndrome
ROP	retinopathy of prematurity
RR	relative risk
SpO_2	oxygen saturation

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EDUCATION GAPS

Sex as a biological variable plays a crucial role in infant outcomes related to prematurity, with preterm male neonates having a higher risk of many morbidities compared with female preterm infants. Many studies also show sex-specific differences in response to therapies used for prematurity-related conditions. This article underscores the need to consider the role of sex as a biological variable in the design of clinical trials, raises awareness of existing knowledge of sex-specific differences, and provides directions for future reporting of study results.

OBJECTIVES

After completing this article, readers should be able to:

1. Describe the sex-specific differences reported in outcomes in preterm neonates.
2. Describe the current evidence on sex-specific differences in response to specific pharmacotherapies in preterm neonates.
3. Identify the need to consider sex as a biological variable in designing, reporting, and reviewing neonatal clinical studies.

Summary

Sex-specific differences in disease pathophysiology and drug pharmacokinetics may underlie some of the different responses to therapies among male and female preterm neonates. Male sex increases the risk for mortality and for the development of many morbidities related to prematurity. An elevated baseline risk of developing an outcome should change the risk-benefit ratio of a therapy under consideration. An elevated baseline risk of a major morbidity could make a tradeoff of a drug-related adverse effect acceptable. However, many clinical trials do not report outcomes by sex, even though all attempts are made to enroll an equal number of male and female neonates at randomization. Reporting outcomes of clinical and therapeutic trials by sex would be crucial, and assessing the interaction between biological sex and treatment would discern if there is a potential role of biological sex in different responses to therapy. Effect size and 95% CI should also be reported in both sexes. The clinician should realize that these data should be considered as a subgroup analysis and preliminary as the study was probably not powered a priori to answer the question of differences by biological sex. Conducting improper statistical analyses to report sex-based differences is inappropriate and risks the reporting of misleading information. However, reporting these data transparently with the original report would facilitate a meta-analysis if a sex-specific signal is potentially found for a therapeutic agent. In the age of precision medicine and attempts to tailor the right therapy for the right patient, considering sex as a biological variable during the design, execution, analysis, and reporting of therapeutic trials is a critical need.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Know the prenatal and postnatal risk factors for bronchopulmonary dysplasia/chronic lung disease and be aware of various preventive strategies.

Table.

A Summary of the Studies, Outcomes, and Disaggregated Data by Sex

Therapy/Intervention	Study Type	Outcome	Sex-specific Benefit or Harm	Reference No.
Antenatal glucocorticoids	Meta-analysis (8 studies)	RDS	Benefit of betamethasone in males (RR 0.29; 95% CI 0.15–0.57)	
			Benefit of dexamethasone in females (RR 0.51; 95% CI 0.32–0.81) (1,109 males, 968 females)	19
Maternal betamethasone	Observational, prospective study	Multiple	Benefit in males (< 29 weeks), none in females	
			Delivery room intubation: OR 0.382 (0.201–0.726)	
			Mechanical ventilation: (first 3 days after birth) OR 0.304 (0.139–0.668)	
			Surfactant administration: OR 0.355 (0.167–0.755)	20
			Survival: OR 2.377 (1.076–5.247) (232 males, 157 females)	
			Moderate/severe BPD: OR 2.59 (1.010–6.641) (177 males, 122 females) Benefit in females	
	Prospective study	RDS	Incidence of RDS 29.1% (14/48) in males vs. 8.6% (4/46) in females	21
Maternal glucocorticoids	Nested in another randomized control trial	BPD	No benefit in extremely low birthweight (<1 kg) males (107 males, 88 females)	22
Postnatal dexamethasone (1-week course, if ventilator dependent at 10 days)	Randomized controlled trial	Pulmonary outcome at 28 days	Benefit in females Better pulmonary outcome at 28 days	
		Supplemental oxygen	Shorter time of supplemental oxygen (19 males, 22 females)	31
Low-dose hydrocortisone	Individual patient data meta-analysis	Survival without BPD at 36 weeks' PMA	Benefit in females OR (Females): 1.52; 95% CI: 1.02-2.26 (457 females, 525 males)	32
	Randomized controlled trial	Survival without BPD in extremely preterm infants	Benefit in Females OR (Females): 2.25 (1.25 to 4.04) (280 males, 241 females)	33
Indomethacin (for prevention of intraventricular hemorrhage)	Randomized controlled trial	IVH at postnatal day 5	Benefit in males RR in males 0.34 (*P*=.007)	
			Also noted benefit in cognitive testing in males (235 males, 196 females)	35
Indomethacin (for survival without neurosensory impairment)	Randomized controlled trial	Death before corrected age of 18 months OR one or more of the following: cerebral palsy, cognitive delay, hearing	Probable negative effect in females, lower risk of severe IVH in males	

Therapy/Intervention	Study Type	Outcome	Sex-specific Benefit or Harm	Reference No.
		loss requiring amplification, and bilateral blindness	Death OR (Females): 1.59; 95% CI: (1.01–2.52) Severe IVH OR (Males): 0.54; 95% CI: (0.31–0.94) (585 males, 558 females)	36
Ibuprofen (expectant management vs. early treatment for a patent ductus arteriosus, the BeNeDuctus trial)	Randomized controlled trial	Death, NEC (Bell palsy stage IIa or higher), or moderate to severe BPD, at 36 weeks' PMA	Benefit of expectant management in males Males: 44.3% in expectant management and 74.3% in early ibuprofen. ARD: one sided 95% CI (−30; −17) Females: 48.5% in expectant management and 52.2% in early ibuprofen. ARD: 1-sided 95% CI (−3.8; +10.5) (140 males, 133 females)	38
DHA supplementation in preterm infants	Randomized controlled trial	Neonatal growth profile	Benefit in females, ? harm in males Higher mean weight from birth to 36 weeks' PMA in females Higher weight velocity in females Decreased weight and head circumference at 36 weeks' PMA in males (275 males, 253 females)	44
	Randomized controlled trial	Neurodevelopmental outcome at 7 years	Harm in females Poorer executive function and conduct problems in girls in the high DHA group (324 males, 280 females)	45
Oxygen saturation targets (sex-specific differences with oxygen saturation targets 92%–100% vs 85%–93%)	Retrospective cohort study	Various neonatal morbidities	Lower oxygen saturation targets beneficial in females, no effect in males Lower rates of BPD, ROP and length of stay in females (241 males, 256 females)	46
Transfusion (for anemia of prematurity based on a liberal or restricted transfusion threshold)	Randomized controlled trial	Brain MRI indices	Harm in females enrolled in the liberal group Greater structural brain abnormalities in females in the liberal transfusion group (30 males, 36 females)	48

ARD=adjusted risk difference; BPD=bronchopulmonary dysplasia; CI=confidence interval; DHA= docosahexaenoic acid; IVH=intraventricular hemorrhage; MRI=magnetic resonance imaging; NEC=necrotizing enterocolitis; OR=odds ratio; PMA=postmenstrual age; RDS=respiratory distress syndrome; ROP=retinopathy of prematurity; RR=relative risk.