HHS Public Access

Author manuscript

J Pediatr. Author manuscript; available in PMC 2024 April 01.

Published in final edited form as:

J Pediatr. 2023 April ; 255: 17–21. doi:10.1016/j.jpeds.2022.11.021.

The critical need to address sex as a biological variable in neonatal clinical studies

Krithika Lingappan, MD, MS, Ph.D.,
Department of Pediatrics, Children's Hospital of Philadelphia, Philadelphia, USA.

Pradeep Alur, MD,
Department of Pediatrics, University of Mississippi Medical Center Jackson, MS, USA.

Eric Eichenwald, MD
Department of Pediatrics, Children's Hospital of Philadelphia, Philadelphia, USA.

Keywords

Prematurity; gender; sexual dimorphism; sex-specific; newborn

Introduction

Despite improved neonatal care and increased overall survival of preterm neonates, male sex has been identified as a risk factor associated with mortality in preterm neonates [1–4]. Even though male preterm neonates have shown faster declines in mortality, respiratory distress syndrome (RDS), and bronchopulmonary dysplasia (BPD), they still have a significantly higher risk of mortality before hospital discharge, RDS, necrotizing enterocolitis (NEC), late-onset sepsis, severe intra-ventricular hemorrhage (IVH), severe retinopathy of prematurity (ROP), and BPD compared with preterm female neonates [5]. Similar results of increased mortality in premature male neonates have been reported from neonatal cohorts from Korea, Canada, Japan, Austria, and Switzerland [3,6–9]. In one meta-analysis, 26 of the 32 studies showed increased mortality in premature males, while 6 reported no sex difference [10].

The increasing evidence of the role of sex as a biological variable in disease outcome, pathophysiology, and response to therapy has highlighted the gap in neonatal clinical and translational trials. This commentary highlights studies that have demonstrated sex-specific differences in outcomes. We acknowledge that other studies not discussed here, fail to demonstrate sex differences in the outcomes discussed here. However, most neonatal studies are not adequately powered to detect sex-specific differences in key outcomes, which likely leads to underreporting of these critical interactions. We then dissect how these observations may result from sex differences at baseline or with adaptation or response to common

Corresponding Author: Krithika Lingappan, MD, MS. Ph.D. lingappank@chop.edu. Address: 3401 Civic center Blvd, Philadelphia, PA, 19104. Phone Number: 215-590-1653. Fax Number: 215-590-3051.

Conflict of Interest
The authors have no conflict of interest to disclose.

neonatal therapies such as antenatal and postnatal steroids, and indomethacin. We argue that these data raise the critical need to assess therapeutic responses stratified by biological sex. Biological sex should be recognized as an essential factor that can drive susceptibility, pathophysiology, response to therapy, and outcomes in clinical and translational studies in neonatology.

Sex-specific differences in key neonatal outcomes:

Respiratory distress syndrome (RDS), bronchopulmonary Dysplasia (BPD), and long-term respiratory morbidities:

Respiratory morbidity, including the development of BPD, is common in preterm neonates with a long-term impact on quality of life. A propensity score matching study reported that the incidence of RDS, BPD, and moderate to severe BPD in extremely low birth weight males was significantly increased after adjusting for multiple confounding factors [11]. Males had higher rates than females for conventional ventilation, high-frequency ventilation, ventilation after CPAP, inhaled nitric oxide, steroids for BPD, and surfactant needed at any time [5]. Among extremely premature neonates who developed early hypoxic respiratory failure, female sex was associated with intact survival [12]. Male sex was associated with higher odds of home oxygen use from the California Perinatal Quality Care Collaborative data among infants diagnosed with BPD [13] and was an independent risk for tracheostomy, and among infants who received a tracheostomy, male sex was an independent predictor of mortality [14]. In the recently published longitudinal study results from the United Kingdom, deterioration in lung function trajectories was associated with the male sex [15]. Hospital readmissions were also skewed towards boys in early childhood [16,17].

Several reports of sex-specific differences in long-term respiratory outcomes of premature neonates highlight the importance of biological sex in the recovery response of the injured preterm lung. Male sex was associated with a significant decrease in forced expiratory volume (at 0.5 s) and forced expiratory flows at 75% of forced vital capacity (FEF 75) at one year of age [18]. In other studies, males saw impairment in long-term lung function [19]. Among school-aged children (11–14 years of age), who were born extremely preterm, airway function parameters were significantly worse in males [20]. No differences in respiratory morbidities by sex were reported in another long-term study, with females requiring supplemental oxygen longer compared to males [21].

Neurological morbidity and neurodevelopmental outcomes:

In-hospital predictors of Neurological Outcomes: In several large national registries, male sex was a risk factor for severe IVH among preterm neonates [22,23]. In a very large cohort of preterm neonates with RDS, female sex decreased the risk of all IVH and severe IVH [24]. A longitudinal observational study conducted at 16 Neonatal Research Network centers to characterize the outcomes of extremely preterm neonates younger than 27 weeks gestational age showed that male sex was associated with non-hemorrhagic ventriculomegaly, which in turn is associated with increased odds of neurodevelopmental impairment among extremely preterm neonates [25].

Neuroimaging and long-term Neurodevelopmental Outcomes: White matter abnormalities on brain MRI in ex-preterm neonates at 35 to 39 weeks postmenstrual age [26] and 8 years of age [27] were skewed towards the male sex. Long-term neurodevelopmental outcomes also display a strong sex bias in preterm neonates [28,29]. Motor function at five years was negatively associated with male sex [30]. Preterm females had better developmental and neurological scores than preterm boys at nine years of age. [31]. In premature neonates without severe brain injury, males were at a higher risk for developmental coordination disorder than females [32]. In a cohort of 342 VLBW neonates, deteriorating and persistently delayed gross motor trajectories were significantly higher in male infants [33]. The influence of socio-economic variables that predict neurodevelopmental outcomes may also be sex-specific. In a Swedish study, high parental education predicted higher cognitive and language scores in girls [34].

Retinopathy of prematurity (ROP): The overall incidence of ROP is similar in male and female premature neonates; however, the severity of the disease shows a male bias in many studies [35]. In a retrospective study (2009–2015), male sex was identified as a risk factor in multivariate analysis for severe (treatment-requiring) ROP [36]. Similar results were reported in a Danish, Canadian, Dutch, and a multi-national cohort of preterm neonates [37–44]. Visual impairment, measured by visual acuity in preterm neonates, also shows sex-specific differences. Among 114 extremely premature neonates (< 25 weeks of GA), normal visual acuity (defined as visual acuity >0.8 in at least one eye) was higher in girls, whereas visual impairment (visual acuity<0.33) was significantly higher in boys [45].

Long-term cardiovascular health: Preterm neonates are also at greater risk for long-term adverse cardiovascular and metabolic consequences in later life [46]. A systematic review and meta-analysis (27 studies included) identified that preterm birth is associated with higher blood pressure in adult life, and women born preterm are at a greater risk than men [47]. Similar findings were reported in another cohort with preterm-born females having higher blood pressure than males [48], suggesting susceptibility in female preterm neonates to adverse cardiovascular health long-term.

Prenatal and postnatal biological mechanisms contributing to sex-specific differences:

Baseline Differences:

Many organs follow different trajectories of development and maturation based on the fetal sex. For example, fetal lung pathways, including surfactant synthesis, exhibit sexual dimorphism [49,50], possibly due to exposure to gonadal hormones during development. However, irrespective of sex hormones, mammalian cells show intrinsic sex-specific differences and respond differently to various stressors [51]. Genes on the X and Y chromosomes can be differentially expressed between male and female cells because of X-chromosome inactivation, gene dosage, or genomic imprinting [52].

Adaptation Differences:

Various biological mechanisms are activated during the adaptation of the neonate to preterm birth that may differ between the male and female preterm neonate. For example, compared to the relatively hypoxic in-utero environment, extremely premature neonates are born into a relatively hyperoxic postnatal environment and may need supplemental oxygen to maintain normal oxygen saturations. Thus, these conditions can expose the premature neonate to conditions leading to oxidative stress at the cellular level. In a prospective cohort study, female preterm infants had less oxidative stress, decreased oxidation of DNA and proteins, and better clinical outcomes than male infants, independent of antenatal steroids [53]. Female premature neonates had higher levels of plasma glutathione peroxidase and glutathione reductase, key enzymes essential for the synthesis and regeneration of glutathione [54]. Differences in immune function between male and female neonates may also modulate the pathophysiology of disease processes in the preterm infant [55]. Microvascular dysregulation due to decreased sympathetic activation in preterm male neonates may increase their risk for hypotension and circulatory failure in the immediate postnatal period with the need for greater respiratory and circulatory support [56–58].

Common Interventions with sex-specific effects:

Randomized allocation in trials achieves equal enrollment of male and female neonates in most circumstances. However, some interventions may not have a statistically significant treatment effect in the entire cohort, but when analyzed by sex, they may show benefits in male or female neonates. This may be more likely if the intervention has opposite effects on male and female neonates, which may be helpful in one sex and harmful to the other. It is important to consider the limitations of subgroup analyses due to limited statistical power leading to a false negative result and multiple comparisons leading to false positives [59].

Antenatal Steroids:

One of the most administered drugs to pregnant persons in preterm labor is antenatal steroids for their overwhelming positive effects on increasing survival in preterm neonates. However, sex-specific differences in response to this therapy have been reported. Following a single course of maternal betamethasone, placental 11β-hydroxysteroid dehydrogenase type 2 decreased in females and increased in males. Decreased 11β-HSD2 may lead to increased placental transfer of maternal cortisol in female neonates, thus postnatally improving survivability [60]. In infants born within 72 h of antenatal glucocorticoid exposure, urine normetanephrine levels were higher in females, which was, in turn, inversely correlated with microvascular blood flow at 24 hours and illness severity scores [61]. In a meta-analysis of eight studies, no effect of neonatal sex was seen on reducing RDS or other outcomes in response to antenatal steroids. However, males showed a reduction in the incidence of RDS with betamethasone while females with dexamethasone [62]. In another prospective study with 710 preterm neonates, male but not female preterm neonates had decreased mortality and acute respiratory morbidity following antenatal betamethasone [63]. In a study by Van Marter *et al.*, maternal glucocorticoid therapy reduced the incidence of BPD in female preterm neonates but only in >1 kg male preterm neonates [64].

Postnatal steroids:

Postnatal steroid therapy is often administered to ventilator-dependent preterm neonates at a high risk of developing BPD. Some babies have a favorable response to postnatal steroids, while others do not. In one study, preterm female neonates who were ventilator-dependent at ten days of age and treated with postnatal dexamethasone (1-week course) had better pulmonary outcomes than males at 28 days and a shorter duration of supplemental oxygen[65]. An individual patient data metanalysis of randomized controlled trials testing the efficacy of the prophylaxis of early adrenal insufficiency using low-dose hydrocortisone on survival without BPD during the first week of life in preterm infants showed female infants>25 weeks' gestation and chorioamnionitis exposure had a lower risk of developing bronchopulmonary dysplasia (BPD). The odds of surviving to 36 weeks without BPD was 1.40 (CI-0.97–2.02) (p=.074) in males compared to girls was 1.52 (95% CI- 1.02–2.26) (p=.038) [66]. The PREMILOC study enrolled neonates less than 28 weeks of gestation to receive either intravenous low-dose hydrocortisone or placebo during the first ten postnatal days. A significantly increased rate of bronchopulmonary dysplasia-free survival was reported in females with no differences in similarly treated male premature neonates [67].

Prophylactic Indomethacin:

Post-hoc analysis from two of the biggest trials on the use of indomethacin to prevent IVH in preterm neonates suggested that the drug may be beneficial only in male preterm neonates and potentially harmful in female preterm neonates [68,69]. Male neonates had higher odds of successful ductal closure following treatment with indomethacin [70]. Similar sex-specific differences have been reported with non-pharmacologic interventions, including delayed cord clamping [71–73], oxygen [74,75], CPAP [76], blood transfusion [77–79], and nutritional interventions [80,81].

Recommendations for reporting outcomes by biological sex:

Biological sex should be recognized as an essential factor driving susceptibility, pathophysiology, outcomes, and response to therapy in clinical and translational studies in neonatology. We have highlighted in this commentary that the sex-specific effects of interventions in the neonatal population are prevalent and need to be acknowledged and addressed in future studies. Sex as a biological variable must be considered during data collection, analysis, and reporting. Even though powering the studies to look at the primary outcome in each biological sex may not be possible in every circumstance, at a minimum, the data from studies should be disaggregated and reported by biological sex. The interaction of treatment and sex should be assessed by appropriate statistical methods and reported. These reports should be interpreted cautiously, considered exploratory and hypothesis-generating, and should not inform clinical change. But this is critical so that these results can be further investigated in more extensive studies. Ideally, a priori, sex, and treatment interaction should be accounted for during study design and power analysis. Raw data from clinical studies should be reported stratified by biological sex to facilitate the planning of future studies and meta-analyses [82–84].

Sources of Financial Assistance:

NIH/NHLBI grants: R01-HL146395 and R01HL144775 to KL.

References

[1]. Brothwood M, Wolke D, Gamsu H, Benson J, Cooper D. Prognosis of the very low birthweight baby in relation to gender. Arch Dis Child 1986;61:559–64. [PubMed: 2425752]

[2]. Stevenson DK, Verter J, Fanaroff AA, Oh W, Ehrenkranz RA, Shankaran S, et al. Sex differences in outcomes of very low birthweight infants: the newborn male disadvantage. Arch Dis Child Fetal Neonatal Ed 2000;83:F182–5. [PubMed: 11040165]

[3]. Ito M, Tamura M, Namba F, Japan NRN of. Role of sex in morbidity and mortality of very premature neonates. Pediatr Int 2017;59:898–905. [PubMed: 28477387]

[4]. O'Driscoll DN, McGovern M, Greene CM, Molloy EJ. Gender disparities in preterm neonatal outcomes. Acta Paediatr 2018;107:1494–9.

[5]. Boghossian NS, Geraci M, Edwards EM, Horbar JD. Sex Differences in Mortality and Morbidity of Infants Born at Less Than 30 Weeks' Gestation. Pediatrics 2018;142. 10.1542/PEDS.2018-2352.

[6]. Hwang JH, Jung E, Lee BS, Kim EAR, Kim KS. Survival and Morbidities in Infants with Birth Weight Less than 500 g: a Nationwide Cohort Study. J Korean Med Sci 2021;36:1–9.

[7]. Garfinkle J, Yoon EW, Alvaro R, Nwaesei C, Claveau M, Lee SK, et al. Trends in sex-specific differences in outcomes in extreme preterms: progress or natural barriers? Arch Dis Child Fetal Neonatal Ed 2020;105:F158–63.

[8]. Steurer MA, Adams M, Bacchetti P, Schulzke SM, Roth-Kleiner M, Berger TM. Swiss medical centres vary significantly when it comes to outcomes of neonates with a very low gestational age. Acta Paediatr 2015;104:872–9. [PubMed: 26014127]

[9]. Kiechl-Kohlendorfer U, Simma B, Urlesberger B, Maurer-Fellbaum U, Wald M, Wald M, et al. Low mortality and short-term morbidity in very preterm infants in Austria 2011–2016. Acta Paediatr 2019;108:1419–26. [PubMed: 30817025]

[10]. Vu HD, Dickinson C, Kandasamy Y. Sex Difference in Mortality for Premature and Low Birth Weight Neonates: A Systematic Review. Am J Perinatol 2018;35:707–15. [PubMed: 29241280]

[11]. Su Z, Lin L, Fan X, Jia C, Shi B, Huang X, et al. Increased Risk for Respiratory Complications in Male Extremely Preterm Infants: A Propensity Score Matching Study. Front Endocrinol (Lausanne) 2022;13.

[12]. Kaelber DC, Russell Localio A, Ross M, Leon JB, Pace WD, Wasserman RC, et al. Early Hypoxic Respiratory Failure in Extreme Prematurity: Mortality and Neurodevelopmental Outcomes. Pediatrics 2020;146.

[13]. Ejiawoko A, Lee HC, Lu T, Lagatta J. Home Oxygen Use for Preterm Infants with Bronchopulmonary Dysplasia in California. J Pediatr 2019;210:55–62.e1. [PubMed: 30987778]

[14]. Han SM, Watters KF, Hong CR, Edwards EM, Knell J, Morrow KA, et al. Tracheostomy in Very Low Birth Weight Infants: A Prospective Multicenter Study. Pediatrics 2020;145.

[15]. Bisquera A, Harris C, Lunt A, Zivanovic S, Marlow N, Calvert S, et al. Longitudinal changes in lung function in very prematurely born young people receiving high-frequency oscillation or conventional ventilation from birth. Pediatr Pulmonol 2022;57:1489–96. [PubMed: 35388626]

[16]. Gäddlin PO, Finnström O, Wang C, Leijon I. A fifteen-year follow-up of neurological conditions in VLBW children without overt disability: relation to gender, neonatal risk factors, and end stage MRI findings. Early Hum Dev 2008;84:343–9. [PubMed: 17936525]

[17]. Klitkou ST, Iversen T, Stensvold HJ, Rønnestad A. Use of hospital-based health care services among children aged 1 through 9 years who were born very preterm - a population-based study. BMC Health Serv Res 2017;17.

[18]. Voynow JA, Feng R, Ren CL, Dylag AM, Kemp JS, McDowell K, et al. Pulmonary function tests in extremely low gestational age infants at one year of age. Pediatr Pulmonol 2022;57:435–47. [PubMed: 34779149]

[19]. Sanchez-Solis M, Garcia-Marcos L, Bosch-Gimenez V, Pérez-Fernandez V, Pastor-Vivero MD, Mondéjar-Lopez P. Lung function among infants born preterm, with or without bronchopulmonary dysplasia. Pediatr Pulmonol 2012;47:674–81. [PubMed: 22170860]

[20]. Harris C, Zivanovic S, Lunt A, Calvert S, Bisquera A, Marlow N, et al. Lung function and respiratory outcomes in teenage boys and girls born very prematurely. Pediatr Pulmonol 2020;55:682–9. [PubMed: 31910333]

[21]. Collaco JM, Aherrera AD, McGrath-Morrow SA. The influence of gender on respiratory outcomes in children with bronchopulmonary dysplasia during the first 3 years of life. Pediatr Pulmonol 2017;52:217–24. [PubMed: 27362897]

[22]. Mohamed MA, Aly H. Male gender is associated with intraventricular hemorrhage. Pediatrics 2010;125. [PubMed: 20672932]

[23]. Kent AL, Wright IMR, Abdel-Latif ME, Bowen J, Bajuk B, Vincent T. Mortality and adverse neurologic outcomes are greater in preterm male infants. Pediatrics 2012;129:124–31. [PubMed: 22184652]

[24]. Doshi H, Moradiya Y, Roth P, Blau J. Variables associated with the decreased risk of intraventricular haemorrhage in a large sample of neonates with respiratory distress syndrome. Arch Dis Child Fetal Neonatal Ed 2016;101:F223–9. [PubMed: 26394896]

[25]. Pappas A, Adams-Chapman I, Shankaran S, McDonald SA, Stoll BJ, Laptook AR, et al. Neurodevelopmental and Behavioral Outcomes in Extremely Premature Neonates With Ventriculomegaly in the Absence of Periventricular-Intraventricular Hemorrhage. JAMA Pediatr 2018;172:32–42. [PubMed: 29181530]

[26]. Parikh NA, Sharma P, He L, Li H, Altaye M, Priyanka Illapani VS, et al. Perinatal Risk and Protective Factors in the Development of Diffuse White Matter Abnormality on Term-Equivalent Age Magnetic Resonance Imaging in Infants Born Very Preterm. J Pediatr 2021;233:58–65.e3. [PubMed: 33259857]

[27]. Reiss AL, Kesler SR, Vohr B, Duncan CC, Katz KH, Pajot S, et al. Sex differences in cerebral volumes of 8-year-olds born preterm. J Pediatr 2004;145:242–9. [PubMed: 15289777]

[28]. Synnes A, Luu TM, Moddemann D, Church P, Lee D, Vincer M, et al. Determinants of developmental outcomes in a very preterm Canadian cohort on behalf of the Canadian Neonatal Network and the Canadian Neonatal Follow-Up Network n.d.

[29]. Hintz SR, Kendrick DE, Vohr BR, Poole WK, Higgins RD. Gender differences in neurodevelopmental outcomes among extremely preterm, extremely-low-birthweight infants. Acta Paediatr 2006;95:1239–48. [PubMed: 16982497]

[30]. Leversen KT, Sommerfelt K, Rønnestad A, Kaaresen PI, Farstad T, Skranes J, et al. Prediction of neurodevelopmental and sensory outcome at 5 years in Norwegian children born extremely preterm. Pediatrics 2011;127.

[31]. Gäddlin P-O, Finnström O, Wang C, Leijon I. A fifteen-year follow-up of neurological conditions in VLBW children without overt disability: Relation to gender, neonatal risk factors, and end stage MRI findings 2007.

[32]. Zwicker JG, Yoon SW, MacKay M, Petrie-Thomas J, Rogers M, Synnes AR. Perinatal and neonatal predictors of developmental coordination disorder in very low birthweight children. Arch Dis Child 2013;98:118–22. [PubMed: 23264434]

[33]. Su YH, Jeng SF, Hsieh WS, Tu YK, Wu YT, Chen LC. Gross Motor Trajectories During the First Year of Life for Preterm Infants With Very Low Birth Weight. Phys Ther 2017;97:365–73. [PubMed: 28339607]

[34]. Månsson J, Fellman V, Stjernqvist K. Extremely preterm birth affects boys more and socio-economic and neonatal variables pose sex-specific risks. Acta Paediatr 2015;104:514–21. [PubMed: 25620552]

[35]. Holmström G, van Wijngaarden P, Coster DJ. Genetic susceptibility to retinopathy of prematurity: the evidence from clinical and experimental animal studies. Br J Ophthalmol 2007;91:1704–8. [PubMed: 18024814]

[36]. Chan H, Cougnard-Grégoire A, Korobelnik JF, Delyfer MN, Touboul D, Coste V, et al. Screening for retinopathy of prematurity by telemedicine in a tertiary level neonatal intensive care unit in France: Review of a six-year period. J Fr Ophtalmol 2018;41:926–32. [PubMed: 30442486]

[37]. Slidsborg C, Jensen A, Forman JL, Rasmussen S, Bangsgaard R, Fledelius HC, et al. Neonatal Risk Factors for Treatment-Demanding Retinopathy of Prematurity: A Danish National Study. Ophthalmology 2016;123:796–803. [PubMed: 26854038]

[38]. Thomas K, Shah PS, Canning R, Harrison A, Lee SK, Dow KE. Retinopathy of prematurity: Risk factors and variability in Canadian neonatal intensive care units. J Neonatal Perinatal Med 2015;8:207–14.. [PubMed: 26485554]

[39]. Lundgren P, Kistner A, Andersson EM, Pupp IH, Holmström G, Ley D, et al. Low birth weight is a risk factor for severe retinopathy of prematurity depending on gestational age. PLoS One 2014;9.

[40]. van Sorge AJ, Termote JUM, Kerkhoff FT, van Rijn LJ, Simonsz HJ, Peer PGM, et al. Nationwide inventory of risk factors for retinopathy of prematurity in the Netherlands. J Pediatr 2014;164.

[41]. Lai YH, Tseng HI, Yang SN, Hsu HT, Chen HL. Neonatal intensive care unit-specific screening criteria for retinopathy of prematurity. Kaohsiung J Med Sci 2012;28:601–6. [PubMed: 23140768]

[42]. Araz-Ersan B, Kir N, Akarcay K, Aydinoglu-Candan O, Sahinoglu-Keskek N, Demirel A, et al. Epidemiological analysis of retinopathy of prematurity in a referral centre in Turkey. Br J Ophthalmol 2013;97:15–7. [PubMed: 23125061]

[43]. Weintraub Z, Carmi N, Elouti H, Rumelt S. The association between stage 3 or higher retinopathy of prematurity and other disorders of prematurity. Can J Ophthalmol 2011;46:419–24. [PubMed: 21995985]

[44]. Darlow BA, Hutchinson JL, Henderson-Smart DJ, Donoghue DA, Simpson JM, Evans NJ. Prenatal risk factors for severe retinopathy of prematurity among very preterm infants of the Australian and New Zealand Neonatal Network. Pediatrics 2005;115:990–6. [PubMed: 15805375]

[45]. Jacobson L, Hård AL, Horemuzova E, Hammarén H, Hellström A. Visual impairment is common in children born before 25 gestational weeks--boys are more vulnerable than girls. Acta Paediatr 2009;98:261–5. [PubMed: 18823297]

[46]. Markopoulou P, Papanikolaou E, Analytis A, Zoumakis E, Siahanidou T. Preterm Birth as a Risk Factor for Metabolic Syndrome and Cardiovascular Disease in Adult Life: A Systematic Review and Meta-Analysis. J Pediatr 2019;210:69–80.e5. [PubMed: 30992219]

[47]. Parkinson JRC, Hyde MJ, Gale C, Santhakumaran S, Modi N. Preterm birth and the metabolic syndrome in adult life: a systematic review and meta-analysis. Pediatrics 2013;131.

[48]. Hovi P, Vohr B, Ment LR, Doyle LW, McGarvey L, Morrison KM, et al. Blood Pressure in Young Adults Born at Very Low Birth Weight: Adults Born Preterm International Collaboration. Hypertension 2016;68:880–7. [PubMed: 27572149]

[49]. Seaborn T, Simard M, Provost PR, Piedboeuf B, Tremblay Y. Sex hormone metabolism in lung development and maturation. Trends Endocrinol Metab 2010;21:729–38. [PubMed: 20971653]

[50]. Nielsen HC. Testosterone regulation of sex differences in fetal lung development. Proc Soc Exp Biol Med 1992;199:446–52. [PubMed: 1549623]

[51]. Penaloza C, Estevez B, Orlanski S, Sikorska M, Walker R, Smith C, et al. sex of the cell dictates its response: differential gene expression and sensitivity to cell death inducing stress in male and female cells. FASEB J 2009;23:1869–79. [PubMed: 19190082]

[52]. Carrel L, Willard HF. X-inactivation profile reveals extensive variability in X-linked gene expression in females. Nature 2005;434:400–4. [PubMed: 15772666]

[53]. Vento M, Aguar M, Escobar J, Arduini A, Escrig R, Brugada M, et al. Antenatal steroids and antioxidant enzyme activity in preterm infants: influence of gender and timing. Antioxid Redox Signal 2009;11:2945–55. [PubMed: 19645572]

[54]. Hamon I, Valdes V, Franck P, Buchweiller MC, Fresson J, Hascoet JM. [Gender-dependent differences in glutathione (GSH) metabolism in very preterm infants]. Arch Pediatr 2011;18:247–52. [PubMed: 21255988]

[55]. O'driscoll DN, Greene CM, Molloy EJ. Expert Review of Clinical Immunology Immune function? A missing link in the gender disparity in preterm neonatal outcomes Immune function?

A missing link in the gender disparity in preterm neonatal outcomes. Clinical Immunology 2017;13:1061–71. [PubMed: 28972799]

[56]. Hansen Pupp I, Hellström-Westas L, Elsmén E. Preterm male infants need more initial respiratory and circulatory support than female infants. Acta Paediatr 2004;93:529–33. [PubMed: 15188982]

[57]. Corbisier De Meautsart C, Dyson RM, Latter JL, Berry MJ, Clifton VL, Wright IMR. Influence of sympathetic activity in the control of peripheral microvascular tone in preterm infants. Pediatr Res 2016;80:793–9. [PubMed: 27497044]

[58]. Stark MJ, Clifton VL, Wright IMR. Sex-specific differences in peripheral microvascular blood flow in preterm infants. Pediatr Res 2008;63:415–9. [PubMed: 18356749]

[59]. Burke JF, Sussman JB, Kent DM, Hayward RA. Stratification of risk for hospital admissions for injury related to fall: cohort study n.d.

[60]. Braun F, Hardt AK, Ehrlich L, Sloboda DM, Challis JRG, Plagemann A, et al. Sex-specific and lasting effects of a single course of antenatal betamethasone treatment on human placental 11β-HSD2. Placenta 2018;69:9–19. [PubMed: 30213491]

[61]. Stark MJ, Hodyl NA, Wright IMR, Clifton V, Stark M. The Journal of Maternal-Fetal & Neonatal Medicine The influence of sex and antenatal betamethasone exposure on vasoconstrictors and the preterm microvasculature The influence of sex and antenatal betamethasone exposure on vasoconstrictors and the preterm microvasculature 2011;24:1215–20.

[62]. Roberge S, Lacasse Y, Tapp S, Tremblay Y, Kari A, Liu J, et al. Role of fetal sex in the outcome of antenatal glucocorticoid treatment to prevent respiratory distress syndrome: systematic review and meta-analysis. J Obstet Gynaecol Can 2011;33:216–26. [PubMed: 21453561]

[63]. Ramos-Navarro C, Sánchez-Luna M, Zeballos-Sarrato S, Pescador-Chamorro I. Antenatal corticosteroids and the influence of sex on morbidity and mortality of preterm infants. J Matern Fetal Neonatal Med 2020.

[64]. Van Marter LJ, Leviton A, Kuban KCK, Pagano M, Allred EN. Maternal Glucocorticoid Therapy and Reduced Risk of Bronchopulmonary Dysplasia 1990;86:149.

[65]. Kari MA, Heinonen K, Ikonen RS, Koivisto M, Raivio KO. Dexamethasone treatment in preterm infants at risk for bronchopulmonary dysplasia. Arch Dis Child 1993;68:566–9. [PubMed: 8323356]

[66]. Shaffer ML, Baud O, Lacaze-Masmonteil T, Peltoniemi OM, Bonsante F, Watterberg KL. Effect of Prophylaxis for Early Adrenal Insufficiency Using Low-Dose Hydrocortisone in Very Preterm Infants: An Individual Patient Data Meta-Analysis. J Pediatr 2018;207:136–142.e5. [PubMed: 30416014]

[67]. Baud O, Maury L, Lebail F, Ramful D, Moussawi F el, Nicaise C, et al. Eff ect of early low-dose hydrocortisone on survival without bronchopulmonary dysplasia in extremely preterm infants (PREMILOC): a double-blind, placebo-controlled, multicentre, randomised trial. WwwThelancetCom 2016;387.

[68]. Ment LR, Vohr BR, Makuch RW, Westerveld M, Katz KH, Schneider KC, et al. Prevention of intraventricular hemorrhage by indomethacin in male preterm infants. Journal of Pediatrics 2004;145:832–4. [PubMed: 15580211]

[69]. Ohlsson A, Roberts RS, Schmidt B, Davis P, Moddeman D, Saigal S, et al. Male/female differences in indomethacin effects in preterm infants. J Pediatr 2005;147:860–2. [PubMed: 16356449]

[70]. Ahamed MF, Verma P, Lee S, Vega M, Wang D, Kim M, et al. Predictors of successful closure of patent ductus arteriosus with indomethacin. J Perinatol 2015;35:729–34. [PubMed: 25856764]

[71]. Tarnow-Mordi W, Morris J, Kirby A, Robledo K, Askie L, Brown R, et al. Delayed versus Immediate Cord Clamping in Preterm Infants. New England Journal of Medicine 2017;377:2445–55. [PubMed: 29081267]

[72]. Mercer JS, Vohr BR, McGrath MM, Padbury JF, Wallach M, Oh W. Delayed cord clamping in very preterm infants reduces the incidence of intraventricular hemorrhage and late-onset sepsis: a randomized, controlled trial. Pediatrics 2006;117:1235–42. [PubMed: 16585320]

[73]. Mercer JS, Vohr BR, Erickson-Owens DA, Padbury JF, Oh W. Seven-month developmental outcomes of very low birth weight infants enrolled in a randomized controlled trial of delayed versus immediate cord clamping. J Perinatol 2010;30:11–6. [PubMed: 19847185]

[74]. Deulofeut R, Golde D, Augusto S. Treatment-by-gender effect when aiming to avoid hyperoxia in preterm infants in the NICU. Acta Paediatr 2007;96:990–4. [PubMed: 17577339]

[75]. Askie LM, Darlow BA, Finer N, Schmidt B, Stenson B, Tarnow-Mordi W, et al. Association Between Oxygen Saturation Targeting and Death or Disability in Extremely Preterm Infants in the Neonatal Oxygenation Prospective Meta-analysis Collaboration. JAMA 2018;319:2190. [PubMed: 29872859]

[76]. Vento M, Cubells E, Escobar JJ, Escrig R, Aguar M, Brugada M, et al. Oxygen saturation after birth in preterm infants treated with continuous positive airway pressure and air: assessment of gender differences and comparison with a published nomogram. Arch Dis Child Fetal Neonatal Ed 2013;98:F228–32. [PubMed: 23123635]

[77]. Nopoulos PC, Conrad AL, Bell EF, Strauss RG, Widness JA, Magnotta VA, et al. Long-term outcome of brain structure in premature infants: effects of liberal vs restricted red blood cell transfusions. Arch Pediatr Adolesc Med 2011;165:443–50. [PubMed: 21199970]

[78]. Benavides A, Bell EF, Georgieff MK, Josephson CD, Stowell SR, Feldman HA, et al. Sex-specific cytokine responses and neurocognitive outcome after blood transfusions in preterm infants. Pediatr Res 2022;91:947–54. [PubMed: 33911194]

[79]. Benavides A, Bell EF, Conrad AL, Feldman HA, Georgieff MK, Josephson CD, et al. Sex Differences in the Association of Pretransfusion Hemoglobin Levels with Brain Structure and Function in the Preterm Infant. J Pediatr 2022;243:78–84.e5. [PubMed: 34968498]

[80]. Alur P, Kalikkot Thekkeveedu R, Meeks M, Hart KC, Desai J, Johnson M, et al. Calorie intake is associated with weight gain during transition phase of nutrition in female extremely low birth weight infants. Biol Sex Differ 2020;11.

[81]. Tottman AC, Oliver CJ, Alsweiler JM, Cormack BE. Do preterm girls need different nutrition to preterm boys? Sex-specific nutrition for the preterm infant n.d.

[82]. Sex-Specific Reporting of Scientific Research: A Workshop Summary. Sex-Specific Reporting of Scientific Research 2012.

[83]. Avery E, Clark J. Sex-related reporting in randomised controlled trials in medical journals. Lancet 2016;388:2839–40. [PubMed: 27979393]

[84]. Clayton JA, Tannenbaum C. Reporting Sex, Gender, or Both in Clinical Research? JAMA 2016;316:1863–4. [PubMed: 27802482]