Sex-Related Health Disparities among Preterm Babies

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Abstract: Infants born preterm are vulnerable to many complications. Our objective was to identify gender differences in morbidity and adverse outcomes among premature and low birth weight babies. A retrospective chart review of a general pediatric clinic records was conducted for children and adolescents who were born preterm. Demographic, maternal, family, neonatal, and postnatal data were abstracted. The data were analyzed using t-tests.

Out of a total of 160 charts reviewed, 59% were males and 41% were females. Most female babies were born small for gestational age, while most of the male babies, although preterm, were born as appropriate for gestational age. A greater incidence of complications associated with prematurity occurred among male babies including jaundice (63.1% *vs.* 36.8%; $p = 0.02$), metabolic issues (64.2% *vs.* 35.7%; $p = 0.03$), and respiratory distress syndrome (60.5% vs. 39.4%; $p = 0.02$). Differences in sepsis (54.0% *vs.* 45.8%; $p = 0.69$), intracranial hemorrhage (75% *vs.* 25%; $p = 0.33$), and hypertension (62% *vs*. 37%; $p = 0.11$) were not different between genders.

The reason for gender-related health disparities between preterm boys and girls is not sufficiently explained. Males had a higher incidence of prematurity and the sequelae that required intensive healthcare support compared with females.

Keywords: prematurity, health disparity, gender difference, preterm, male disadvantage.

INTRODUCTION

According to the Centers for Disease Control and Prevention, the preterm birth rate declined to 11.55% in 2012, down 2% from 2011, and 10% from 2006 [1]. The rate is still quite high, and more than 500,000 babies are born prematurely in the United States each year. Infants born preterm are vulnerable to many complications, including respiratory distress syndrome (RDS), cardiovascular disorders, chronic lung disease, compromised immune function, obesity, injury to the intestines, hearing and vision problems, and neurological insult [2, 3]. A "male disadvantage" with respect to neonatal mortality has been recognized for more than two decades [4]. In 1986, Brothwood *et al.* confirmed the "relative vulnerability of boys to perinatal mortality and morbidity" described in earlier reports [5]. They observed a higher mortality and more postnatal complications in very low birth weight (VLBW, less than 1,500 g) boys than in girls. More boys were depressed at birth as evidenced by their Apgar scores, had respiratory distress syndrome or lung-related injuries and disabilities, and were generally less stable than girls after birth [4].

In recent decades, neonatal care has improved dramatically. Babies born at 25 weeks have a 50% chance of survival and most babies born after 32 weeks are able to survive with the help of medical technology [6]. Unfortunately, 1 in 10 premature babies will develop a permanent disability such as lung disease, cerebral palsy, blindness, or deafness [7]. Fifty percent of premature babies born before the 26th week of gestation are disabled, a quarter severely so [8]. Cognitive and neurological impairments are common among school-age children born extremely preterm (fewer than 25 weeks of pregnancy) [9].

With recent advances in medical technology, the question remained whether gender differences still exist in morbidity among children born prematurely who survived the neonatal period.

METHODS

A retrospective chart review of general pediatric clinic records (1 university clinic, Texas Tech Health Sciences Center, Amarillo, TX, and 2 private pediatric offices, Amarillo, TX) was con-

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ducted for children and adolescents (between 10- and 21-years-old). Children and adolescents who were born at 37 or fewer weeks gestational age and visited the clinics between 2010-2011 and were between 10- and 21-years-old were reviewed. Charts were identified using the ICD-9 code for prematurity.

Demographic, maternal, family, neonatal, and postnatal data were abstracted. Maternal and family history data included previous premature births, race, marital status, presence or absence of prenatal care, health insurance, maternal age, maternal substance abuse, maternal illnesses (such as genital and urinary tract infections, preeclampsia, hypertension, and diabetes mellitus), family history of hypertension and kidney disease, and previous multiple gestations. History during the neonatal period included information about severe illnesses, respiratory distress syndrome, umbilical vein or artery catheter use, oxygen therapy, intracerebral and intraventricular hemorrhage, bacterial infections, and metabolic diseases, such as hypoglycemia and jaundice.

For analytical purposes, cases were classified as low birth weight (LBW) if birth weight was less than 2500 g, but greater than or equal to 1500 g. VLBW babies had a birth weight between 1500 g and 1000 g, and extremely low birth weight (ELBW) babies weighed less than 1000 g at birth. Babies who weighed more than 2500 g were considered of normal birth weight (NBW). Babies between 10-90% on the growth chart were termed appropriate for gestational age (AGA). Babies were small for gestational age (SGA) if birth weight was less than the 10th percentile for the baby's gestational age group, and large for gestational age (LGA) was defined as a birth weight greater than the 90% percentile for the infant's gestational age group. Delivery records from the neonatal hospital discharge summary were a part of the pediatric chart. The data were analyzed using a sample t-test between percentages. The null hypothesis stated that there was no gender difference in babies with respect to complications of prematurity. Comparisons with p values of < 0.05 were considered statistically significant. The study protocol was approved by the Amarillo Texas Tech University Health Sciences Center Institutional Review Board.

RESULTS

A total of 160 charts were reviewed. There were 95 (59%) males and 65 (41%) females in the study group. The main characteristics of the study group are presented in Table **1**. Female babies were more likely to be of LBW compared to the male babies (63.0% vs. 47.3%; $p < 0.05$). Both groups' birth weights were comparable for gestational age. More female babies were born as SGA compared to the male babies (21% *vs*. 9%; $p<0.05$), while most of the male babies, although preterm, were born as AGA (Table **1**).

During the babies' NICU stays, higher incidences of complications associated with prematurity were observed among the male babies than among the female babies (Figure **1**). Jaundice that required treatment was observed in 63% of preterm boys compare to 37% of the girls ($p = 0.02$). Hypoglycemia occurred in 64% of baby boys *vs.* 36% of baby girls ($p = 0.03$). The same gender-related disparity was noticed in RDS (60% *vs.* 39%; $p = 0.02$). The other major complications were found in similar percentages among babies of both genders.

Long-term morbidity results (data from 10-18-year-old children) are represented in Table **2**. Although the majority of recorded cases of chronic morbidity were equal among both groups, male children demonstrated a significantly higher frequency of behavioral problems (mostly Attention Deficit Hyperactivity Disorder) (6% *vs*. 2%; $p < 0.01$).

DISCUSSION

Male sex is a well-known risk factor for unfavorable perinatal outcomes [10]. Comparisons of the characteristics between infants who survived without major morbidities (such as severe neurological injury, severe retinopathy of prematurity, necrotizing enterocolitis, bronchopulmonary dysplasia, and ≥ stage 3 intraventricular hemorrhage or parenchymal injury [including periventricular leukomalacia]) and those who developed major morbidities found sex as one of the leading factors for poor outcomes [11]. Among pre-term infants, a

Table 1: Demographic Data by Gender. *($p < 0.05$), Comparisons were Made between Males and Females

Maternal Demographic Data		
Race	Hispanic (38.0%) White (39.2%) African American (14.2%) Asian (8.6%)	
Marital status	Single Parent (33.8%)	Married (66.2%)
Presence or absence of prenatal care	Yes (64.4%)	No (35.6%)
Health insurance	Yes (98.1%)	No (1.9%)
Maternal age	≤17 (10.0%) 18-34 (61.2%) ≥ 35 (28.8%)	
Maternal substance abuse	Yes (23.1%)	No (76.9%)
Previous premature births	Yes (11.2%)	No (88.8%)
Maternal illnesses	Yes (28.7%)	No (71.3%)
Neonatal Demographic Data		
Baby Gender (n=160)	Male (59%)	Female (41%)
Gestational Age		
Gestational age 32-37 weeks	42%	30%
Gestational age < 32 weeks	17%	11%
Birth Weigh		
Extremely low birth weight (ELBW)	12%	11%
Very low birth weight (VLBW)	15%	9%
Low birth weight (LBW)	47%	63%*
Normal birth weight (NBW)	26%	17%
Gestational Age	Male	Female
Appropriate for Gestational Age (AGA)	80%	65%*
Small for Gestational Age (SGA)	10%	22%*
Large for Gestational Age (LGA)	10%	13%

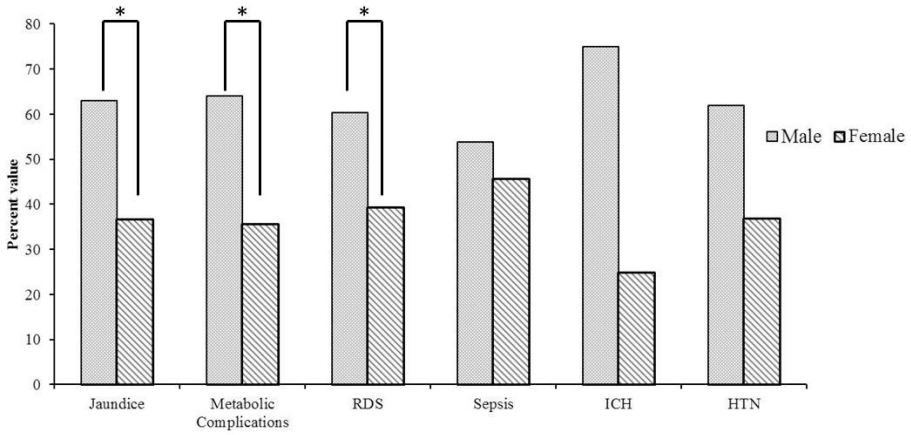

Figure 1. Incidence of complications associated with prematurity at NICU. RDS: respiratory distress syndrome; ICH: intracranial hemorrhage; HTN: hypertension. *two tailed $p < 0.05$.

Table 2: Long-Term Morbidities and Gender Differences

Morbidities	Male (%)	Female (%)
Asthma	33.7	23.0
Allergic rhinitis	24.2	18.5
Cardiac defects	16.8	20.0
Behavioral issues	20.0	6.1; ($p < 0.01$)
Developmental delays	9.5	13.8
Growth delay	5.3	9.2
Kidney anomaly and diseases	7.3	7.7

gender-specific difference favoring more positive results among females regarding morbidity is evident [12]. Male sex is an important risk factor for poor neonatal outcome and poor neurological and respiratory outcomes at follow-up [13]. Our data show that despite the recent advances in the technology used by neonatologists and decline in the incidence of preterm births, the gender-related neonatal and long-term morbidity still exists.

Previous study demonstrated that very preterm SGA infants have significantly more mortality and morbidity in comparison to AGA preterm babies [14]. Another study showed that there were no sex-related differences in outcomes in groups with intrauterine growth restriction [15]. Among surviving preterm babies in our group, the majority of males, although born AGA, had a higher incidence of sequelae during the neonatal period that required intensive healthcare support compared with females. Females had a greater probability of being born SGA with a low birth weight, but had fewer complications.

Polglase *et al.* showed that the cardiopulmonary transition at birth is not influenced by sex and cannot explain the neonatal 'male disadvantage' [16]. Another study demonstrated that preterm male infants need more initial respiratory and circulatory support than female infants [17]. In our cohort, the premature males had an increased incidence of RDS. A previous study showed sex-specific differences in microvascular blood flow and vasodilatory capacity in the immediate newborn period [18]. Male gender is also a predictor of elevated diastolic blood pressure [19].

In our study, more males than females had metabolic problem such as hypoglycemia. These data are in agreement with the study of Tundidor *et al.* who showed male sex as an independent predictor of neonatal hypoglycemia [10]. Males also had poorer outcomes than females when they were born to mothers with diabetes, despite similar maternal characteristics [20].

Males also have a tendency to develop more grade III-IV intra-ventricular hemorrhage and increased levels of bilirubin compared to their female counterparts. It seems that in the modern era of neonatal management, male infants still have poorer long-term neurologic outcomes and longer lasting sequelae from damage to the central nervous system [21,22]. Gender is now recognized as a significant predictor of low cognitive functioning among prematurely born singletons [23].

Carrying a male fetus is an independent risk factor for spontaneous preterm labor [24]. Interestingly, previous exposure to a male fetus increases a woman's risk of preterm delivery in the next pregnancy [25].

Several theories have been promulgated to explain the higher risk of preterm births in pregnancies carrying male fetuses. Biochemical processes causing estrogen conversion from androgen, heavier body weight, increased risk of infections, preeclampsia, and early conception of male fetuses during the beginning of fertile periods have been cited as possible causes [26]. Current evidence suggests sex-specific adaptations of the placenta may be central to the differences in fetal growth and survival [27]. The developmental biology of this disadvantage is not well understood. It is a known fact that even some pregnancy-related complications, such as hyperemesis gravidarum,

might depend on the fetal gender, but the mechanisms of these phenomena are not known [28].

Not all neonatal complications are sex dependent. We did not see any difference in the frequency of sepsis or necrotizing enterocolitis between the genders, which confirms previous findings of other investigators [29]. This might be explained by the fact that only children, who survived and were discharged from the NICU, were included in the study.

The recent study of Neubauer *et al.* demonstrated that the parents of preterm boys should be prepared for a potentially higher frequency of readmission after initial discharge [30]. Although it has been shown before that behavioral and emotional problems are more prominent in girls born moderately preterm [31], in our study behavior problems were recorded more often in boys, which is also true for the general population [32,33].

In spite of established high morbidity rates among preterm males, the long-term outcome might be optimistic. More research in this area is warranted, as this will shed some light on recognizing factors responsible for premature births and gender-related health disparities.

CONCLUSION

A gender-related health disparity exists among preterm infants during the neonatal period, but the etiology still remains unknown. With age the health disparity leveled out and is no different from the general population, except for behavioral problems.

CONFLICTS OF INTEREST

There are no conflicts of interest to declare.

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Received On: 23-April-2014 Accepted On: 04-January-2015 Published On: 01-April-2015

DOI: 10.6000/ijipem/2015/1