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THE GESTATIONAL FOUNDATION OF SEX DIFFERENCES IN DEVELOPMENT AND VULNERABILITY

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Abstract—Despite long-standing interest in the role of sex on human development, the functional consequences of fetal sex on early development are not well understood. Here we explore the gestational origins of sex as a moderator of development. In accordance with the focus of this special issue, we examine evidence for a sex differential in vulnerability to prenatal and perinatal risks. Exposures evaluated include those present in the external environment (e.g., lead, pesticides), those introduced by maternal behaviors (e.g., alcohol, opioid use), and those resulting from an adverse intrauterine environment (e.g., preterm birth). We also provide current knowledge on the degree to which sex differences in fetal neurobehavioral development (i.e., cardiac and motor patterns) are present prior to birth. Also considered are contemporaneous and persistent sex of fetus effects on the pregnant woman. Converging evidence confirms that infant and early childhood developmental outcomes of male fetuses exposed to prenatal and perinatal adversities are more highly impaired than those of female fetuses. In certain circumstances, male fetuses are both more frequently exposed to early adversities and more affected by them when exposed than are female fetuses. The mechanisms through which biological sex imparts vulnerability or protection on the developing nervous system are largely unknown. We consider models that implicate variation in maturation, placental functioning, and the neuroendocrine milieu as potential contributors. Many studies use sex as a control variable, some analyze and report main effects for sex, but those that report interaction terms for sex are scarce. As a result, the true scope of sex differences in vulnerability is unknown.

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Key words: sex differences, male vulnerability, fetal development, prenatal exposures, perinatal risk, pregnancy.

INTRODUCTION

The morphological differentiation of sex commences early in embryogenesis and unfolds in a well-known sequence. Less well-understood are the functional consequences of sex on physiological, metabolic, and hormonal systems and, in turn, their influence on the developing nervous system before birth and ramifications for postnatal life. Here we explore the gestational origins of sex as a moderator of development. In keeping with the focus of this special issue on early adversity, we will also examine how sex modulates vulnerability to prenatal exposures and consider models that have been developed to account for these observations. Scientific interest in the role of sex in human development has waxed and waned over time in tandem with societal forces that emphasized either biological or social influences on observed differences. Currently, the role of sex as a biological variable is of rising academic significance, illustrated by a call from leaders of the National Institutes of Health for investigators to both identify and include animals and cell lines of both sexes (Clayton and Collins, 2014). This is the result of converging evidence for sexual dimorphisms that include findings as diverse as differential immunological responsiveness to vaccine challenges and variation in sensitivity of neurons to stimulation depending on sex of cell origin.

The construct of differential sex-based vulnerability to adversity has been well-identified. In 1985, a section of *The Behavioral and Brain Sciences* (Gualtieri and Hicks, 1985) was devoted to consideration of an immunoreactive theory to explain greater vulnerability of male offspring to obstetric, pediatric, psychiatric and developmental disorders. This theory posited that maternal immunological response to an antigenic factor found on the Y chromosome conferred long-lasting deleterious influence on multiple developing systems within the fetus, including the nervous system. In doing so, it summarized the existing empirical data supportive of greater male vulnerability, termed ''selective male affliction'', available at the time. These findings have been largely confirmed and expanded in the 30 years since, along with new theories afforded by new assays and methodologies available to research.

The current literature on sex-related variation with relevance to neuroscience is too large and diverse for a single article. Instead we focus on the foundational role of the period before birth and examine the origins of sex differences in function and on prenatal exposures that differentially affect development in boys and girls. From a statistical standpoint, the former observation can be

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Abbreviations: ADHA, attention deficit hyperactivity disorder; BPA, bisphenol A; CPF, chlorpyrifos; FASD, fetal alcohol spectrum disorder; MDI, mental development index; NAS, Neonatal Abstinence Syndrome.

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viewed as a main effect, while the latter is more traditionally detected as an interaction.

MALE VULNERABILITY AND THE CONTINUUM OF REPRODUCTIVE CASUALTY

That adversities experienced during the prenatal and perinatal period have consequences that persist through life, independent of fetal sex, was promulgated in the 1960's as the "continuum of reproductive casualty" (Pasamanick and Knobloch, 1964). Until very recently, it has been scientific dogma that there is an excess of male conceptions but greater loss in male pregnancies throughout gestation. However, based on a comprehensive study of multiple sources of data, it appears that the ratio of male-to-female conceptuses is equivalent and that this ratio waxes and wanes during gestation. Specifically, in the first few weeks there are more male losses, primarily due to a higher rate of abnormalities in male embryos, followed by an increased loss of female fetuses later in the first trimester, and concluding with increased mortality of male fetuses from mid-gestation onward (Orzack et al., 2015).

The greater incidence of male fetuses born before term and of low birth weight has been well-documented, as has higher weight and gestational age-specific mortality and morbidity for male fetuses as compared to females. That is, when matched for gestational duration and/or weight at birth, male infants are less likely to survive and more frequently exhibit morbidities such as respiratory distress syndrome and intraventricular hemorrhage (Naeye et al., 1971; Khoury et al., 1985; Cooperstock and Campbell, 1996; Stevenson et al., 2000; Ingemarsson, 2003; Zeitlin et al., 2004; Di Renzo et al., 2007; Kent et al., 2012; Blencowe et al., 2013). The excess morbidity and mortality of boys persists through the first year of life and includes greater vulnerability to sudden infant death syndrome (Mage and Donner, 2014) which is commonly considered of neurologic origin. Despite these long-standing observations, potential mechanisms remain poorly understood. Thus, despite the male advantage in average birth weight of nearly 8 oz, size at birth is not isomorphic with maturation of organ systems, including those that govern respiration and the nervous system, both of which develop more slowly in male fetuses. Sex differences in maturation rates will be revisited in a later section.

In addition to the well-known disparity in preterm birth and related morbidities, male pregnancies are also associated with other less well-recognized consequences. Male fetuses more often develop and/or activate a range of obstetric complications, including those that affect the proximal intrauterine environment as well as those that affect maternal well-being. For example, male fetuses are more likely to develop umbilical cord abnormalities, including knots and nuchal cords (Sheiner et al., 2004; Aibar et al., 2012). There is also a report of reduced venous blood flow to male fetuses with normal umbilical cords (Prior et al., 2013). Male pregnancies are more often subject to obstetric complications, including gestational diabetes, placenta previa and preeclampsia (Sheiner et al., 2004; Di Renzo et al., 2007; Aibar et al., 2012; Aliyu et al., 2012). The etiology and pathophysiology of these associations is largely unknown.

Labor and delivery are unique stressors in that these are biologically anticipated endpoints of gestation but can also exceed the physiological coping abilities of some fetuses. Fetal distress during labor, evidenced by decelerative patterns in heart rate and/or alterations to blood gases, is more frequent in male infants. In accordance, the higher rate of cesarean delivery in male fetuses is frequently attributable to greater incidence of distress, even when controlling for the physical size differential (Lieberman et al., 1997; Bekedam et al., 2002; Eogan et al., 2003; Di Renzo et al., 2007; Aibar et al., 2012; DiPietro et al., 2015). This phenomenon suggests that the male autonomic system is less functionally capable of tolerating the physical challenge of labor. More subtle changes in autonomic responsiveness have also been reported, including a propensity for the heart rate to speed up in response to the stress of labor in female fetuses but to slow down in male fetuses (Dawes et al., 1999). A finding of higher levels of catecholamines in female neonates after preterm labor, with and without distress, has been proposed as a beneficial and protective adaptation to labor (Greenough et al., 1987). In addition, female fetuses, and particularly those showing signs of distress, react to imminent delivery with greater change in indicators of complexity within fetal heart rate than do male fetuses (Bernardes et al., 2009). This observation also supports the notion that female fetuses show more adaptive activation of the autonomic nervous system in response to acute stress.

Increased exposure to adversity coupled with increased vulnerability has been termed "double jeopardy" in application to the multiplicative effects of poverty on child development (Parker et al., 1988). This construct is also applicable to sex effects. As noted above, some obstetric complications are more likely to be present in women carrying male fetuses but male fetuses are also more likely to be adversely affected than female fetuses also exposed to the same condition. For example, male pregnancies are more likely to be complicated by maternal gestational diabetes, and boys born from such pregnancies have a higher risk of congenital anomalies and respiratory disorders than do girls born to women with gestational diabetes (Persson and Fadl, 2014). This phenomenon has been particularly well-documented with respect to preterm birth and neurocognitive and neuromotor outcomes. Not only are male fetuses more likely to be delivered preterm, but preterm male infants are more likely to show poorer developmental outcomes than female preterm infants as they develop, including cerebral palsy, developmental impairment, and lower scores on developmental assessments (Verloove-Vanhorick et al., 1994; Johnston and Hagberg, 2007; Platt et al., 2007; Spinillo et al., 2009). For example, in a follow-up study of children born less than 28 weeks of gestation during the second year of life boys had higher rates of neurodevelopmental impairment and low mental development index (MDI) scores, controlling for the higher incidence of perinatal morbidities (Hintz et al., 2006). By

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