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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 scare. As a result, the true scope of sex differences in vulnerability is unknown.

Keywords

sex differences; male vulnerability; fetal development; prenatal exposures; perinatal risk; pregnancy

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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 thirty 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 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 ounces, 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 caesarian 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 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 age 5, the rates of both minor disabilities and more significant developmental handicaps are roughly three times greater in boys born less that 32 weeks gestation than girls (Verloove-Vanhorick et al., 1994). Of infants born less than 1000 g, 65% of those without subsequent developmental impairment were female (Gargus et al., 2009). Differential impact in specific streams of development over time have also been noted; for example, preterm girls show specific advantages in terms of language and social skills at age two over boys (Brothwood et al., 1986).

Closer examination of data can reveal nuances based on perinatal risk factors. At times, male vulnerability is expressed only at certain thresholds of perinatal risk, although results across studies are not always consistent. For example, in one study excess male neurodevelopmental disabilities at ages 2 to 3 is present only for those born prior to 27 weeks gestation (Kent et al., 2012). In another, the male differential in cerebral palsy was expressed only in the heavier birth weight infants studied (i.e., 1000–1499 g) but not in children born lighter (Platt et al., 2007). The possibility that female sex lacks its protective effect at the highest level of biological vulnerability is also suggested by a finding of higher rates of cerebral palsy in boys relative to girls with less evidence of perinatal brain injury, but no sex differential when perinatal brain injury was present (Hintz et al., 2006). Although most of the literature notes a disadvantage for boys relative to girls, a report based on placenta pathology to infer evidence of chronic hypoxia during gestation found the reverse effect. Girls with placentas graded as evidencing signs of probable chronic hypoxia showed

lower verbal IQ scores at age 7 than boys along with greater behavioral inhibition (Anastario et al., 2012).

Fetal sex as a moderator of prenatal exposures

So far, we have illustrated instances of perinatal risk in which there is both heightened male exposure as well as potentiated consequences. However, when male infants exhibit poorer developmental outcomes following perinatal risks, such as preterm birth, it is not possible to disambiguate cause from effect. That is, it is unclear whether the greater incidence of shortened gestation should be viewed simply as a main effect or as a differential response to undetected intrauterine adversity which itself might be differentially distributed by sex. Preterm birth and other perinatal morbidities may be the result of undetected prenatal male vulnerabilities, such as susceptibility to infection, which may independently compromise the developing nervous system. In contrast, prenatal exposures to substances with developmental toxicity can be expected to be randomly distributed by fetal sex. Here we summarize current knowledge regarding human sex differentials in outcomes of exposures that have developmental toxicity.

Prenatal exposure to environmental toxins

Lead—Lead exposure has well known deleterious neurocognitive effects on child development. Prenatal maternal lead levels generated far more significant consequences for the developmental progress of male infants by six months than for girls (Dietrich et al., 1987). This disparity persisted when children were three years old. Specifically, higher cord blood lead levels were strongly and inversely correlated with lower MDI scores for boys but there was no association for girls (Jedrychowski et al., 2009). Given the very low level of lead discerned in this population born in the early 2000's, this pattern of findings suggests that males may be susceptible to lead exposure at a lower threshold than girls. Similarly, by early school age, lead is inversely related to performance for boys but not for girls on executive function tasks (Froehlich et al., 2007) and neuropsychological assessments associated with attention and visual matching (Ris et al., 2004). Findings from a longitudinal study into early adulthood reveal that exposure to moderate levels of lead is associated with volume loss of gray matter, particularly clustered in the prefrontal cortex, in men but not in women (Cecil et al., 2008). Lead levels were aggregated over early childhood but since data collection was initiated at birth it can have relevance for prenatal exposures as there is stability in individual variation in lead levels over time.

Methylmercury—*In utero* exposure to this toxicant has been associated with a number of developmental consequences, although findings are not strong and tend to be fairly specific. Effects, when detected, are more frequent in male offspring. At age 8, higher prenatal methylmercury was more strongly associated for boys than girls with interference in continuous attention performance and processing speed in a U.S. based sample (Sagiv et al., 2012b). Methylmercury-linked performance effects on neuropsychological testing, when detected, were also stronger exposure for boys than girls in French Guinea (Cordier et al., 2002), the Faroe Islands (Grandjean et al., 1998), and the Seychelles (Myers et al., 2003).

Pesticides, herbicides and other chemical exposures—There is growing interest in the developmental teratogenic properties of a number of commonly used agricultural and industrial substances. Many of these have been classified as endocrine disruptors, and perhaps as a result, investigators appear to be more sensitized to testing for sex-specific effects than for other exposures; we highlight some of these findings here. In an agricultural community, maternal levels of organophosphates were positively related to attention deficit hyperactivity disorder (ADHD) symptoms and attention problems in boys but not girls by school age (Marks et al., 2010). Exposure to prenatal PCBs, predominantly via maternal consumption of contaminated fish, had a deleterious effect on information processing in 8 year old boys; testing in girls was either unrelated to exposures or showed an opposite effect (Sagiv et al., 2012a). Chlorpyrifos (CPF), a ubiquitous insecticide, has been linked to deficits in working memory for boys only in one report (Horton et al., 2012). Occupational exposure to pesticides among women working in greenhouses has been associated with slower brainstem auditory transmission rates in boys only, although the interaction only reached a trend level of significanceb (Andersen et al., 2015). However, the same study found stronger effects of exposure on girls' intellectual abilities, particularly as related to language (Andersen et al., 2015).

Concerns regarding the safety of early exposure to bisphenol A (BPA) have resulted in a number of studies; reports of sex differences are contradictory. Maternal BPA concentrations as early as 16 weeks gestation were significantly associated with parentally reported externalizing behaviors in 2 year old girls, but not boys (Braun et al., 2009). In a subsequent follow-up, girls with greater exposure to BPA concentrations were rated as exhibiting higher levels of depression and anxiety as well as externalizing behaviors (Braun et al., 2011). In contrast, three studies indicated that by preschool or primary school age, higher maternal BPA during pregnancy is associated with increased anxiety, depression and/or externalizing behaviors in boys and is either unrelated or inversely related in girls (Perera et al., 2012, Harley et al., 2013, Evans et al., 2014). Phalates, a related compound, has also been linked to greater behavioral problems in boys, although there are also some inverse associations for girls (Kobrosly et al., 2014). Discrepancies in findings may be the result of true differential effects by sex due to their disruptive effects on the sex steroid milieu of the intrauterine environment. Imaging findings suggest that prenatal exposure to CPF, for example, exerts long term alternations to sexually dimorphic brain regions (Rauh et al., 2012). However, these studies are limited by near-exclusive reliance on maternal reports of child behavior. Although women are not aware of their exposures, women may systematically rate boys and girls differently which can exert unknown and systematic biases on results. There is significant investment in animal models to evaluate potential mechanisms that may mediate effects (Rosenfeld and Trainor, 2014, De Felice et al., 2015).

Prenatal maternal substance use

Investigation of the manner in which exposure to maternal substance use may affect the developing fetal nervous system has a long history in developmental sciences. Somewhat surprisingly, although sex is frequently used as a covariate or variable for matching purposes, report of sex by exposure interactions is the exception rather than the rule. Even when sex differentials are noted, they are often included only in a table or text in the results

section without mention in the abstract or elsewhere in the article. We are also unable to ascertain the degree to which lack of reporting reflects a null finding.

Opioids—Fetuses exposed to prenatal opioids, including methadone, are at risk for Neonatal Abstinence Syndrome (NAS), a constellation of neurological and physiological vulnerabilities during the first few postpartum days. In general, boys are more vulnerable to NAS than are girls. In particular, boys of methadone-maintained women display significantly more intense symptoms over the first 4 days of life, and when treated, require longer treatment durations and hospital stays (Jansson et al., 2007, 2010). Buprenorphine, a relatively new pharmacologic agent used to treat opioid dependency, also generates more intense symptoms and treatment in male offspring than in females (O'Connor et al., 2013). Although not all sample-based studies have found greater susceptibility in boys (Unger et al., 2011), population studies often report a sex differential of approximately ten percentage points (e.g., 45% girls, 55% boys) although do not always present significance testing (Patrick et al., 2012, Patrick et al., 2014). Prenatal rodent models suggest sex differences in opioid receptors in mesolimbic structures that are consistent with greater male sensitivity to exposures (Hou et al., 2004).

In addition to acute effects secondary to withdrawal, prenatal opioid exposure may generate more persistent teratogenic effects on development. Although this is a less frequently explored topic, two early studies reported that methadone exposure is associated with poorer performance on developmental assessments in the first two years of life in exposed boys as compared to exposed girls, although it is unclear from the analyses whether these reflect main effects for sex or differential vulnerability (Johnson et al., 1984, Suffet and Brotman, 1984).

Cigarette smoking—The most prominent effects of antenatal cigarette smoking are restrictions to fetal growth. These effects are stronger for male offspring, including higher rates of fetal growth restriction (Wertelecki et al., 1987, Spinillo et al., 1994). Males born to women who smoked more than ½ pack per day showed greater reductions in birth weight and less fat deposition; head circumference was unaffected in girls but significantly smaller in boys (Zaren et al., 2000). With respect to behavioral outcomes, prenatal smoking has been most often associated with behavioral disorders in offspring. A review of the literature conducted in 2002 suggests that conduct disorders and antisocial behavior are more frequent in boys exposed to smoking *in utero*, but smoking and does not increase risks for these diagnoses in girls (Wakschlag et al., 2002). Others have also shown a disproportionate effect of maternal smoking on behavioral disorders in boys (Hutchinson et al., 2010), although precursors do not appear to be evident in toddlers (Wakschlag et al., 2006). However, in a large study that included observer-ratings of 6 to 8 month old infant behaviors, prenatal exposure to ½ pack/day of cigarettes or more was associated with a number of significant interactions by infant sex. Specifically, male infants exposed to prenatal smoking exhibited reduced social approach, lower reactivity, less attention and lower gross motor behavior (Willoughby et al., 2007); there is another report of an association between exposure and less positive mood for boys in the same age range (Pickett et al., 2008).

Maternal smoking during pregnancy may simply be a marker for socialization, genetic or epigenetic transmission of effects related to maternal impulse control and unrelated to specific biochemical teratogenicity of agents found in cigarettes or secondary effects related to altered blood flow. In particular, associations between prenatal smoking exposure and subsequent behavioral or conduct disorders tend to disappear when subject to appropriate familial or statistical controls (D'Onofrio et al., 2008, Thapar et al., 2009). Studies that rely on physiologic responsivity as dependent measures may be less susceptible to threats to interpretation. At least two studies suggest differential activation of the hypothalamic-pituitary-adrenal axis in male and female infants in the first year of life following prenatal exposure. Prenatal cigarette exposure was associated with lower levels of salivary cortisol in male but not female infants (Eiden et al., 2015) and boys reacted to novelty challenge with exaggerated cortisol reactivity relative to exposed female and non-exposed male infants (Schuetze et al., 2008). Thus, regardless of the etiology of the link between maternal prenatal smoking and child outcomes, there appears to be differential susceptibility by fetal sex.

Alcohol—Fetal alcohol spectrum disorder (FASD) is characterized by gradients of growth deficiency, characteristic facial dysmorphology, and central nervous system disruptions manifest by intellectual and motor impairment in response to high and chronic levels of maternal alcohol use. One of the original epidemiological surveys of Native Americans in the Southwest noted a male to female ratio of 117:100 for Fetal Alcohol Syndrome (i.e., the most severe form diagnosis) and a 200:100 ratio for fetal alcohol effects, a less severe outcome (May et al., 1983). More recently, of all new FASD cases identified in a Canadian province annually for 10 years (~15,000), 57.2% were male; the incidence rate per live birth 1.4 times higher for boys than girls (Thanh et al., 2014). In a comprehensive report based on a statewide database of 1400 cases of individuals exposed to prenatal alcoholism, 60% of those determined to be unaffected by the exposure were girls. Boys predominated among those diagnosed within two categories corresponding to mild and severe alcohol related cognitive/behavioral dysfunction (58% and 64%, respectively) but there was no sex difference for the most affected category - those exhibiting both the facial dysmorphology of FAS in addition to cognitive impairment (Astley, 2010).

Epidemiologic studies that attempt to identify prevalence of FASD in a population at times fail to detect significance between sexes despite a sizable differential. For example, of identified children in a South African primary school population with FAS or the less severe diagnosis of FAE (Fetal Alcohol Effects), 58% and 61%, respectively, were boys (May et al., 2007). Significance testing may have been obscured by the categories including both affected groups of children in the chi-square. A similar value for FAS is reported elsewhere in the same age group (Streissguth et al., 2004). In contrast, other prevalence studies fail to find differences by sex (May et al., 2014, Fox et al., 2015). Examination of specific functional deficits among children with FASD reveals subtle processing differences of visual stimuli, including reduced accuracy in males (Paolozza et al., 2015), as well as elevated rates of ADHD (Herman et al., 2008). Animal models have shown profound detrimental effects of alcohol exposure on male but not female rodents (Tunc-Ozcan et al., 2013).

In general, deleterious effects of prenatal alcohol exposure of approximately 2–3 drinks per day or less have not been found on neurocognitive or behavioral outcomes, although linear negative relationships above this threshold are often detected (Streissguth et al., 1989, Kelly et al., 2012, Kesmodel et al., 2014). Despite the volume of research in this area dating back to the 1970s, when reports mention child sex it is generally only as a control or matching variable and not as a potential moderator of effects. We were unable to find reports of differential effects of moderate exposure on male and female offspring that included measurement of developmental outcomes. The single exception found that boys born to women who consumed 1–2 alcoholic drinks per week performed better on vocabulary and school readiness assessment scale than offspring of abstainers; there was no effect for girls (Kelly et al., 2009). As with all studies of developmental toxicology, it is difficult to know whether maternal substance use is a proxy for other features of child-rearing that contribute to child outcomes independent of putative effects of substances on prenatal brain development. This is particularly germane when findings lack compelling biological plausibility.

There have also been some findings of differential alterations to stress reactivity following modest levels of prenatal alcohol exposure. In infants, relatively low levels of exposure (i.e., maternal drinking more than twice a week) were associated with greater cortisol reactivity in response to a social stressor in boys but unrelated in girls (Haley et al., 2006). Consistent with this is a finding of a relation between lower baseline levels of cortisol coupled with increased cortisol reactivity to unfamiliar situations and prenatal exposure for toddler boys but not for girls (Ouellet-Morin et al., 2011). A fairly substantial, but at times conflicting, literature based on rodent studies supports differential effects of prenatal ethanol exposure on offspring behavioral and hypothalamic-pituitary-adrenal axis (HPA) responses to stressor (Weinberg et al., 2008).

Prenatal maternal stress

Prenatal stress is an umbrella term which encapsulates a variety of constructs ranging from self-reported maternal distress to activity of the HPA axis and encompasses a range of subjective states, including anxiety and depression. Human research on the former is fraught with interpretative challenges (Dipietro, 2012). The use of maternal report as both a dependent and independent measure is particularly problematic as there are well-known confounds between maternal assessment of child behavior and maternal psychological factors. The inclusion of child sex as a moderating factor further compounds this problem. Several studies report differential effects on maternally-reported child outcomes by sex (O'Connor et al., 2002, O'Connor et al., 2003, de Bruijn et al., 2009a). However, we confine our discussion to those studies that measure child outcome. In a large Dutch sample, male children of women who scored very highly on prenatal anxiety early in gestation (> 90^{th} percentile, $n = 100$) had longer response times on reaction time tasks; girls were unaffected (Loomans et al., 2012). This finding is consistent with earlier reports of poorer reaction time of 15 year old boys of highly anxious (> 75^{th} percentile) women, along with decreased performance on two IQ subtests (van den Bergh et al., 2005, van den Bergh et al., 2006). In contrast, analysis of school-age children revealed that higher maternal pregnancy specific anxiety interfered with inhibitory control in girls but not boys (Buss et al., 2011).

Maternal depressive symptoms are often measured within the constellation of maternal stress and anxiety. There is one unreplicated report that prenatal depression is linked to disruptions in neonatal motor behavior and state regulation for boys but not girls (Gerardin et al., 2011). Studies of maternal depression are complicated by potential medication confounds; developmental effects, when observed, are most often related to disruptions of motor development. In one report, antenatal antidepressant use was more strongly associated with later attainment of early motor milestones for male infants than for female infants (Pedersen et al., 2010). There is a report based on a population-based study in Denmark that male offspring of women who experienced bereavement as the result of death of close family member during pregnancy were more likely to be diagnosed with ADHD than female offspring (Li et al., 2010). Of course, maternal psychological distress during pregnancy generally continues into the postpartum, so it is difficult to untangle biological effects related to alterations in the intrauterine milieu as a result of maternal distress from the well-known socialization effects that maternal psychological factors confer on parenting and child rearing.

Maternal salivary cortisol levels are unrelated to maternal reports of subject states of distress (Voegtline et al., 2013b) and so can provide independent insight into physiological functioning of the HPA axis during pregnancy. Higher levels of maternal cortisol early in pregnancy were associated with decreased physical and neuromuscular maturation at birth for male neonates only (Ellman et al., 2008). A number of additional differential associations with sex effects have been recently uncovered by reanalysis of data collected in several longitudinal studies from this research group (Sandman et al., 2013). Findings include a stronger negative association between maternal cortisol and 12 month MDI scores for boys than girls. In addition, mid-gestation levels of maternal CRH and cortisol, respectively, were more strongly predictive of more fearful temperament marked by heightened negative reactivity in early infancy and anxiety in older children in girls than boys (Sandman et al., 2013). Variation in the cortisol response in childhood has been reported as linked to prenatal maternal psychological distress for girls, but not boys, expressed as higher levels of cortisol (de Bruijn et al., 2009b). Although these findings do not support greater male susceptibility, it should be noted that maternal cortisol levels are inherently different from the exposures discussed in prior sections. Cortisol is an endogenous substance, critical to fetal organ development, and embedded within a broader network of both HPA and hypothalamic–pituitary- gonadal axes. At physiologic levels, cortisol it is not a developmental teratogen. Thus, understanding the expression of differential effects by offspring sex may require a more complex model that goes beyond the notion of vulnerability to exogenous exposures. Animal models of sex differentials in response to stress provide insight into this complexity (Goel and Bale, 2009, Glover and Hill, 2012).

Sex differences before birth

The antepartum constitutes the most rapid developmental period, a time where structural development occurs in tandem with functional gains (DiPietro et al., 2010). In this section, we describe current knowledge regarding the development of sex differences in indicators of nervous system maturation prior to birth.

Prenatal neurobehavioral development

Behavior does not commence with birth—The prenatal period is marked by emergence of a neurobehavioral repertoire that becomes progressively consolidated over gestation such that the late term fetus exhibits behaviors consistent with that of a newborn, accounting for locale. Convergent evidence has supported the utility of fetal measures as markers for normative neurological development (Hepper, 1995, Sandman et al., 1997, Krasnegor et al., 1998, Nijhuis and tenHof, 1999, DiPietro et al., 2001, Amiel-Tison et al., 2006) along with documentation of their disruption in conditions that are expected to adversely affect development, including congenital anomalies related to the nervous system, intrauterine growth restriction, and exposure to potentially neurotoxic substances (Hepper and Shahidullah, 1992, Mulder et al., 1998, Nijhuis et al., 2000, Jansson et al., 2005, Visser et al., 2010, Morokuma et al., 2013).

Figure 1 illustrates our conceptualization of fetal neuromaturation as one of mutual and spiraling engagement between the pregnant woman and fetus, coupled with scaffolding between emerging regulatory dimensions of autonomic, motor, state and higher order processes within the fetus (DiPietro et al., 2015). This hierarchy presupposes that a certain degree of maturation in each earlier function is required before progression to the next (Als, 1982). Thus, identification of sex differences in fetal development along these dimensions would suggest early differences in neurological development. Research on fetal neurobehavior is a difficult endeavor and the more technically intensive the study, the smaller the sample. Many studies fail to report analyses for fetal sex; those that do often have generated conflicting results due perhaps to both insufficient power to detect real differences coupled with the vagaries of small samples. As a result, availability of empirical data in this area is sparse and is summarized below.

Fetal heart rate and patterns—Heart rate patterns are the most conspicuous indicator of fetal well being. Prior findings on antenatal sex differences in fetal heart rate and variability have yielded inconsistent results (DiPietro et al., 1998, Nijhuis et al., 1998, Lange et al., 2005). We have recently aggregated data collected over nearly 20 years generated from eight longitudinal cohorts, collectively known as the Johns Hopkins Fetal Neurobehavioral Project, and conducted a series of analyses on 740 maternal-fetal pairs. Data were collected near 24 weeks gestation, between 30 and 32 weeks, and again at or near 36 weeks. Sex difference findings were the focus of one chapter in a Monograph of the Society for Research in Child Development (DiPietro et al., 2015). Figure 2, newly presented here, depicts heart rate data for each fetus stratified by sex. Hierarchical linear modeling was employed to characterize developmental trends via the Mixed procedure in SAS (Version 9.2) to account for dependency in repeated measures data and evaluation of the full gestational span sampled (i.e., 23 to 38 weeks). Fetal sex was entered as a predictor of fetal heart rate trajectory and contrast estimates were specified to estimate moderating effects of sex on level and slope. As shown, findings revealed significantly faster heart rate in female fetuses at the second and third periods, but not earlier, along with a more decelerating trajectory for male fetuses. The small sex difference in size at birth was unrelated to this sex difference in heart rate. Figure 3 presents similar data generated from a like modeling

approach to heart rate for fetal heart rate variability, which was significantly elevated in male fetuses at the second two gestational periods, resulting from a steeper developmental trajectory between the first and second periods (DiPietro et al., 2015). Despite these differences in the mean, the overlap in distribution between sexes is apparent in both figures, and the magnitude of the differences are small (e.g., ~2 bpm in heart rate).

Motor behavior—Spontaneous fetal motor behavior can be measured qualitatively and quantitatively. There are two unreplicated reports suggesting differential expression and development of oral motor behaviors. Female fetuses have been observed to display more mouthing movements than male fetuses as early as 18 weeks gestation (Hepper et al., 1998), and exhibit more frequent and complex lingual, laryngeal and pharyngeal movements (Miller et al., 2006). There is one report that male fetuses make more leg movements (Almli et al., 2001). With respect to motor activity level, as with fetal heart rate, evidence for sex differences in motor activity has been inconsistent when examined in small samples. Male fetuses were more active than female fetuses in one of our small cohorts (DiPietro et al., 1996) but not in several later ones. Ultrasound observations of motor activity have also not yielded observation of sex differences (deVries et al., 1988, Hepper, 2012). Fetal motor activity was defined along several parameters in our aggregated cohort analysis, but findings were unremarkable (DiPietro et al., 2015). No sex differences were detected in either mean values or developmental trajectories for motor vigor or the total amount fetuses spent moving. The single finding was that male fetuses made more individual bouts of movement relative to female fetus only near term, consistent with another report (Robles de Medina et al., 2003).

Higher order processes—As gestation progresses, centrally mediated coactivation of cardiac and somatomotor processes mature to the extent that changes in motor activity increasingly correspond to changes in heart rate. This is manifest by the emergence of periods of quiescence and activity that ultimately correspond with segments of REM and non-REM sleep and wakefulness near term. There have been no reports of sex differences in fetal behavioral states per se, although there is the somewhat circular explanation of increased activity level being indicative of more wakefulness in male fetuses at or near term (DiPietro et al., 1998, Robles de Medina et al., 2003, Bernardes et al., 2008). There are, however, several unreplicated reports of differential responsiveness by sex to external stimuli, including greater orientation to speech sounds by female fetuses (Groome et al., 1999), more reactivity to a startling stimulus (Buss et al., 2009) and excess rebound in motor activity to the termination of a maternal stress manipulation in male fetuses (DiPietro et al., 2003). Two carefully conducted, separate reports using relatively large samples have found that female fetuses require fewer trials to habituate to vibroacoustic stimuli at three different gestational ages between 30 and 35 weeks gestation (McCorry and Hepper, 2007, Hepper, 2012). Potential confounding influences of sex differences in either response bias or sensory thresholds have been ruled out, thereby supporting interpretation of superior information processing in female fetuses (Hepper, 2012). Additionally, as compared to male fetuses, female fetuses showed steeper levels of continuing improvement in habituation performance over the time period studied (McCorry and Hepper, 2007).

The influence of fetal sex on the pregnant woman

The model presented in Figure 1 portrays the dynamic and bidirectional relationship between the contemporaneous development of the pregnant woman and the fetus. Developmental psychobiology has long-recognized the importance of fetal behavior to the ontogeny of the individual and adaptation to pregnancy in animal models and established that fetal behaviors were not simply epiphenomena secondary to neural maturation (Smotherman and Robinson, 1987, Hofer, 1988). There is little doubt, although limited substantiation, that the fetus plays an active role in instigating parturition. More recently, the role of the fetus in affecting the broader maternal context is becoming better understood although there remains little information regarding differential inputs based on fetal sex. Idiosyncratic findings include a well-established heightened incidence of hyperemesis of pregnancy in women carrying female fetuses (Naumann et al., 2012) and some evidence that women carrying male fetuses consume more calories (Tamimi et al., 2003). One report notes a higher level of anxiety in the first half of pregnancy in women carrying male fetuses (VandenBergh and Marcoen, 2004). There is a report that women carrying boys performed better on three of eight neurocognitive tasks as compared to women carrying girls, which happened to represent the most challenging tasks of the battery used and related to verbal, spatial and arithmetic working memory (Vanston and Watson, 2005).

Soranus, the 2nd century A.D. physician whose work formed the basis for modern obstetrics, observed that women carrying female fetuses were more pallid that those carrying males as a result of the more vigorous stimulating nature of male fetuses (Temkin, 1991). More recent information suggests that there may indeed be physiological adaptations for women based on fetal sex. Maternal systolic and diastolic blood pressure has been observed to be lower in women carrying girls as compared to boys, but the reverse is true in at risk pregnancies; pulsatility of the uterine artery was lower in women carrying girls regardless of complications (Brown et al., 2015). We have also reported sex-based variation in maternal heart rate such that women carrying female fetuses had faster heart rates at and beyond 30 to 32 weeks gestation, and that this was a response to, and not a cause of, the elevated heart rate of female fetuses (DiPietro et al., 2015). At 36 weeks, women carrying male fetuses were more likely to express the highest levels of electrodermal activity, a reflection of greater innervation of the sympathetic nervous system. In contrast, women carrying female fetuses have been reported to have higher daily levels of salivary alpha-amylase, an indicator autonomic arousal (Giesbrecht et al., 2015). There are three reports that trajectories and/or levels of maternal salivary cortisol during the second half of pregnancy differ by fetal sex such that by the third trimester women carrying females have higher cortisol levels and flattened diurnal patterns (DiPietro et al., 2009, DiPietro et al., 2011, Giesbrecht et al., 2015).

Perhaps the most firmly established effect of having carried a male fetus are the persistent vestiges of male DNA material in the maternal circulation, tissues, and brain long after gestation has ended (Bianchi et al., 1996, Chan et al., 2012). Microchimerism of fetal origin is generated by both male and female pregnancies, but male DNA is most easily detected due to the Y chromosome. Most attention to date has been on the role of male microchimerism in increasing the risk of maternal autoimmune diseases but in lowering risk

from cancer; a recent report found higher survival rates in women with past male pregnancies (Miech, 2010, Nelson, 2012, Kamper-Jorgensen et al., 2014). On-going research is directed at identifying both potentially deleterious and beneficial aspects of fetal microchimerism on women's health.

Summary—Figure 4 consolidates the most well-supported and documented sex differences in women, fetuses and neonates. Although some differences may not be expressed until later in development, such as heightened vulnerability of the male central nervous system to environmental exposures or preterm birth, their origins are in the prenatal or perinatal period. Placement within columns is somewhat arbitrary as a number of these observations affect both the mother and fetus, or the prenatal and perinatal domains, depending on when either the exposure or delivery occurs. Nonetheless, fetal sex confers broad effects on early development and the intrauterine milieu.

On the origins of male vulnerability

So far we have presented evidence the there is both greater exposure and greater vulnerability to many prenatal and perinatal adversities for male fetuses than for female fetuses. In contrast, there are relatively few well-documented sex differences expressive of neurological development before birth. When significant differences are detected, as illustrated in Figures 2 and 3, they are accompanied by highly overlapping distributions. This finding echoes the long-standing conclusion of others with respect to sex differences in early child development (Jacklin, 1981, Maccoby and Jacklin, 1984). The small number of observed sex differences in infancy and toddlerhood, along with the tenuous nature of much of the evidence, has been more recently reviewed in a thoughtful pair of articles (Fausto-Sterling et al., 2012a, b). The authors propose a dynamic systems-based model for understanding the evolving sex-typed landscape. It is likely a similarly complex effort is required to understand emergent differentials in vulnerability. Such an approach may explain why the same prenatal measure of function may differentially predict outcomes for boys and girls. For example, male fetuses that move more frequently become toddlers who are more active; but female fetuses who are more active become less active toddlers (DiPietro et al., 2002). A systems approach allows consideration of the manner in which motor activity may have different "meaning" for male and female fetuses and recognition that the postnatal environment can amplify or constrain such associations.

The etiology of the well-known vulnerabilities, such as poorer outcomes of boys exposed to lead or delivered preterm, remains largely unknown. We now briefly review some of the mechanisms that have been proposed to account for some of the findings presented here. Although presented separately there is obvious overlap among mechanisms.

1. Male fetuses mature slower than female fetuses, and thus have prolonged vulnerability. It is widely believed that prenatal development proceeds more slowly for male fetuses than for female fetuses. The evidence for this is not overwhelming and generally extrapolated from the observation of higher rates and intensity of respiratory disease in male infants to other organ systems. An oft-cited report suggests that girls have more mature

skeletal systems at birth (Tanner, 1978). Data provided herein on the sex difference in fetal heart rate variability suggests that male fetuses express more mature patterns of parasympathetic control from mid-gestation to term. In contrast, functional support for accelerated neuromaturation in female fetuses includes earlier behavioral responsiveness to a vibratory stimulus placed on the maternal abdomen of approximately 2 weeks (Leader et al., 1982) and attainment of maximal responsiveness earlier than observed in male fetuses (Buss et al., 2009). Perhaps more convincingly, two replicated and well-controlled studies have shown that female fetuses take fewer stimulus presentations to habituate to vibratory stimuli at the same gestational ages as males, and also show steeper rates of improvement (McCorry and Hepper, 2007, Hepper, 2012). In the neonatal period, girls display evidence of more mature cortical EEG activity during sleep and wakefulness (Thordstein et al., 2006) and there are reports of faster neural conduction within evoked auditory (DiPietro et al., 2010) and visual response pathways (Malcolm et al., 2002). Corresponding anatomical differences in the fetal brain have not been found, with the exception of a report of slightly earlier (~1 week) formation of the corpus callosum in female fetuses (Achiron et al., 2001). While there is a suggestion that male and female fetuses may mature differently based on the timing of maternal HPA activation (Ellman et al., 2008), confirmatory evidence that male vulnerability is mediated by delayed maturation is fairly limited and maturational differences, when detected, are small.

2. The uterus is less hospitable to male fetuses than it is to female fetuses. A number of intersecting models support this theme. The notion that the presence of a foreign Y chromosome elicits an immunoreactive response in women carrying boys is not new (Gualtieri and Hicks, 1985), and the manner in which maternal antibodies might target the central nervous system remains unspecified. Offspring born after male pregnancies experience shorter gestations and are 10% more likely to be born preterm as compared to those born after female pregnancies, suggesting potentially persistent effects on the intrauterine environment (Mortensen et al., 2011). The observation that male fetuses are significantly more vulnerable to maternal alloimmunization due to RH incompatibility can be interpreted as indicative of more generalized maternal immunoreactivity (Ulm et al., 1999). The placenta is the prime candidate for transduction of this response as it has become clear that placental function differs by sex of fetus. For example, placentae of male fetuses born preterm are more likely to show evidence of chronic inflammation (Ghidini and Salafia, 2005) and infection (Goldenberg et al., 2006) suggesting a diminished protective mechanism. Additional supportive findings, along with excellent reviews of this literature, have generated a view of the intrauterine environment of male fetuses as pro-inflammatory (Clifton, 2010, Challis et al., 2013). As a result, the downstream effects on perinatal outcomes become clearer,

although the manner in which a less hospitable intrauterine environment translates to effects on the developing central nervous system remains relatively obscure. Nonetheless, there is intense interest in applying emergent knowledge of the altered metabolic milieu of male and female fetuses to understanding its effects on neural circuitry with behavioral and affective consequences that are expressed after birth. In particular, efforts to understand developmental outcomes with well-known sex differentials, such as autism spectrum disorder, through the lens of the prenatal environment may yield important clues to etiology and pathogenesis (Davis and Pfaff, 2014).

3. Prenatal sex steroids differentially affect the intrauterine environment and developing fetal brain. Sex steroids play well known roles in masculinization and feminization of the genitalia and sex organs; broader consequences on prenatal neurological development resulting in sex differences in behavior are less well-established (Fausto-Sterling et al., 2012a, Hines et al., 2015). Variation in prenatal androgenic exposure has been implicated as a mediating influence on developmental disorders by, in part, impeding developmental progress and expanding the window of vulnerability (Martel, 2013). There is some evidence to support that testosterone, assessed by proxy using digit ratios, interacts with environmental exposures, including maternal cigarette and alcohol use, and at times can generate 3-way interactions (Martel and Roberts, 2014) that make it difficult to isolate its contributions. There are other reports of differential effects of testosterone exposure in male and female fetuses, including a significant relationship with fetal and infant growth for male but not female fetuses (Voegtline et al., 2013a). Sex steroids may exert independent effects or interact with other neuroendocrine outputs, such as glucocorticoids in modifying the intrauterine milieu (Clifton, 2010, Challis et al., 2013). With respect to fetal neurobehavior, for example, maternal cortisol levels are associated with fetal motor activity in mid-third trimester primarily for male but not female fetuses (DiPietro et al., 2009); for fetal responsivity to vibroacoustic stimulation, this association is reversed (Glynn and Sandman, 2012).

4. From an evolutionary biology standpoint, male and female fetuses may rely on different adaptation strategies to maximize survival early in life. This approach can be summed up by the dramatic title of “Boys live dangerously in the womb” (Eriksson et al., 2010). That report, which linked placental measurements to hypertension in late adulthood, found that lower weight at birth was associated with subsequent hypertension in both sexes but that only the placentae from male pregnancies evidenced signs of compensatory growth suggesting lessened reserve capacity. Lessened reserve capacity in males at birth translates to greater risk in the neonatal period, as indicated by sex differentials in morbidity and mortality rates, and adverse outcomes in the long term (Clifton, 2010).

Maternal asthma has also been used as a model to evaluate sex specific fetal adaptation, generating reduced growth and glucocorticoid activity in female but not male pregnancies (Clifton, 2005). Although on the surface this might appear to indicate male resiliency to disrupted oxygenation, continuing normal growth trajectories under conditions of stress in tandem with altered glucocorticoid production and disrupted biochemical regulation may spare growth at the expense of other organ processes. There are essentially two components to this evolutionary framework for sex differences: a) male and female fetuses use different coping strategies in the face of adversity, and b) as a result, developmental trade-offs are sex specific; for example, the compensatory growth strategy used by male fetuses garner short term gain but longer term disadvantage. Thus, male investment in physical growth makes them less adaptable to fluctuating conditions within the intrauterine environment than females, with negative downstream effects on development of function (Clifton, 2010). This perspective is bolstered by correspondence to a long-standing natural selection theory focused on reproductive success (Trivers and Willard, 1973) that is described elsewhere (Aiken and Ozanne, 2013, Sandman et al., 2013). Support for this theory is primarily based on observations of sex differentials in size at birth and/or placental histology or assay in relation to maternal factors or to subsequent disease in offspring. Its utility and explanatory power in fostering understanding of more complicated behavioral outcomes has been challenged (Hankin, 2013). We concur that its application to understanding sex differences in the development of the central nervous system in the face of adversity is untested and, while we agree that it is an interesting theory, are unconvinced of its ultimate usefulness in understanding the complexities of human development beyond the central construct of survival and the subtleties of sex differentials.

This synthesis of potential mechanisms that may mediate prenatal sex as a moderating factor for outcomes is not meant to be exhaustive. Not covered, for example, are potential beneficial effect introduced by the duplicate copy of the X chromosome, potential direct and non-gonadal effects of genes found on the X and Y chromosomes, or the burgeoning interest in sex differences in epigenetic transmission which may ultimately be highly relevant to understanding differentials in environmental exposures (Gabory et al., 2009, Ngun et al., 2011). Genetic sex also appears to play an important role on cell function and death in neonatal neurons derived from male and female animal models, providing further impetus for study (Johnston and Hagberg, 2007).

Conclusion

The review consolidated empirical information regarding prenatal sex differentials in vulnerability from a variety of diverse sources and literatures. We found converging evidence that developmental outcomes of male fetuses and infants exposed to prenatal and perinatal adversities are more highly impaired than those of female fetuses and infants.

Although sex differences in vulnerability are most often found for male offspring, there are reports of female vulnerability, particularly with respect to affective outcomes (Sandman et al., 2013). Sex differentials appear to be affected by timing of exposures over gestation and are perhaps coupled with different developmental trajectories in male and female fetuses, although empirical evidence is limited and often based on ad hoc interpretations of unexpected results. We propose that part of this may be the result of differential susceptibility based on the intensity as well as the timing of the exposure. For example, in children, higher socioeconomic status is protective of prenatal lead exposure effects on developmental progress, but only up to a certain dosage; above this threshold both poorer and more advantaged children are affected equally (Bellinger et al., 1988). Thus, we suspect that female sex might also be protective only to a threshold of biological risk, which likely varies by exposure.

The mechanisms through which biological sex imparts vulnerability or protection are largely unknown, as is the true scope of the role of early sex given the relative scarcity of studies that report analysis of sex differences in general, and interaction terms in particular. We urge investigators to routinely include and examine both in studies ranging from cells to animals or persons. This is particularly essential for neuroscience which exhibits a particularly pronounced male bias in animal studies when compared to other disciplines (Zucker and Beery, 2010). We also hope that attention is invigorated in pursuing the generally unrecognized, and often surprising, role that fetal sex imparts on pregnant women with both short-term and potential long term effects on their well-being.

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References

Achiron R, Lipitz S, Achiron A. Sex-related differences in the development of the human fetal corpus callosum: in utero ultrasonographic study. Prenat Diagn. 2001; 21:116–120. [PubMed: 11241538]

Aibar L, Puertas A, Valverde M, Carrillo MP, Montoya F. Fetal sex and perinatal outcomes. J Perinat Med. 2012; 40:271–276. [PubMed: 22505506]

Aiken CE, Ozanne SE. Sex differences in developmental programming models. Reproduction (Cambridge, England). 2013; 145:R1–13.

Aliyu MH, Salihu HM, Lynch O, Alio AP, Marty PJ. Fetal sex and differential survival in preeclampsia and eclampsia. Arch Gynecol Obstet. 2012; 285:361–365. [PubMed: 21773785]

Almli CR, Ball RH, Wheeler ME. Human fetal and neonatal movement patterns: Gender differences and fetal-to-neonatal continuity. Dev Psychobiol. 2001; 38:252–273. [PubMed: 11319731]

Als H. Toward a synactive theory of development: Promise for the assessment and support of infant individuality. Infant Ment Health J. 1982; 3:229–243.

Amiel-Tison C, Gosselin J, Kurjak A. Neurosonography in the second half of fetal life: a neonatologist's point of view. J Perinat Med. 2006; 34:437–446. [PubMed: 17140292]

Anastario M, Salafia CM, Fitzmaurice G, Goldstein JM. Impact of fetal versus perinatal hypoxia on sex differences in childhood outcomes: developmental timing matters. Soc Psychiatry Psychiatr Epidemiol. 2012; 47:455–464. [PubMed: 21327969]

Andersen HR, Debes F, Wohlfahrt-Veje C, Murata K, Grandjean P. Occupational pesticide exposure in early pregnancy associated with sex-specific neurobehavioral deficits in the children at school age. Neurotoxicol Teratol. 2015; 47:1–9. [PubMed: 25450661]

Astley SJ. Profile of the first 1,400 patients receiving diagnostic evaluations for fetal alcohol spectrum disorder at the Washington State Fetal Alcohol Syndrome Diagnostic & Prevention Network. Can J Clin Pharmacol. 2010; 17:e132–164. [PubMed: 20335648]

Bekedam DJ, Engelsbel S, Mol BW, Buitendijk SE, van der Pal-de Bruin KM. Male predominance in fetal distress during labor. Am J Obstet Gynecol. 2002; 187:1605–1607. [PubMed: 12501071]

Bellinger D, Leviton A, Waternaux C, Needleman H, Rabinowitz M. Low-level lead exposure, social class, and infant development. Neurotoxicol Teratol. 1988; 10:497–503. [PubMed: 3244341]

Bernardes J, Goncalves H, Ayres-de-Campos D, Rocha AP. Linear and complex heart rate dynamics vary with sex in relation to fetal behavioural states. Early Hum Dev. 2008; 84:433–439. [PubMed: 18248921]

Bernardes J, Goncalves H, Ayres-de-Campos D, Rocha AP. Sex differences in linear and complex fetal heart rate dynamics of normal and acidemic fetuses in the minutes preceding delivery. J Perinat Med. 2009; 37:168–176. [PubMed: 19021459]

Bianchi DW, Zickwolf GK, Weil GJ, Sylvester S, DeMaria MA. Male fetal progenitor cells persist in maternal blood for as long as 27 years postpartum. Proc Natl Acad Sci U S A. 1996; 93:705–708. [PubMed: 8570620]

Blencowe H, Lee AC, Cousens S, Bahalim A, Narwal R, Zhong N, Chou D, Say L, Modi N, Katz J, Vos T, Marlow N, Lawn JE. Preterm birth-associated neurodevelopmental impairment estimates at regional and global levels for 2010. Pediatr Res. 2013; 74(Suppl 1):17–34. [PubMed: 24366461]

Braun JM, Kalkbrenner AE, Calafat AM, Yolton K, Ye X, Dietrich KN, Lanphear BP. Impact of early-life bisphenol A exposure on behavior and executive function in children. Pediatrics. 2011; 128:873–882. [PubMed: 22025598]

Braun JM, Yolton K, Dietrich KN, Hornung R, Ye X, Calafat AM, Lanphear BP. Prenatal bisphenol A exposure and early childhood behavior. Environ Health Perspect. 2009; 117:1945–1952. [PubMed: 20049216]

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; 61:559–564. [PubMed: 2425752]

Brown ZA, Schalekamp-Timmermans S, Hofman A, Jaddoe V, Steegers E. [60-OR]: Fetal sex specific differences in maternal vascular adaptation to pregnancy. Pregnancy Hypertens. 2015; 5:31–32.

Buss C, Davis E, Class Q, Gierczak M, Pattillo C, Glynn L, Sandman C. Maturation of the human fetal startle response: evidence for sex-specific maturation of the human fetus. Early Hum Dev. 2009; 85:633–638. [PubMed: 19726143]

Buss C, Davis E, Hobel C, Sandman C. Maternal pregnancy-specific anxiety is associated with child executive functioning at 6–9 years age. Stress. 2011; 14:665–676. [PubMed: 21995526]

Cecil KM, Brubaker CJ, Adler CM, Dietrich KN, Altaye M, Egelhoff JC, Wessel S, Elangovan I, Hornung R, Jarvis K, Lanphear BP. Decreased brain volume in adults with childhood lead exposure. PLoS medicine. 2008; 5:e112. [PubMed: 18507499]

Challis J, Newnham J, Petraglia F, Yeganegi M, Bocking A. Fetal sex and preterm birth. Placenta. 2013; 34:95–99. [PubMed: 23261268]

Chan WF, Gurnot C, Montine TJ, Sonnen JA, Guthrie KA, Nelson JL. Male microchimerism in the human female brain. PLoS One. 2012; 7:e45592. [PubMed: 23049819]

Clayton JA, Collins FS. Policy: NIH to balance sex in cell and animal studies. Nature. 2014; 509:282–283. [PubMed: 24834516]

Clifton V. Sex and the human placenta: mediating differential strategies of fetal growth and survival. Placenta. 2010; 24:S33–S39. [PubMed: 20004469]

Clifton VL. Sexually dimorphic effects of maternal asthma during pregnancy on placental glucocorticoid metabolism and fetal growth. Cell Tissue Res. 2005; 322:63–71. [PubMed: 16052336]

Cooperstock M, Campbell J. Excess males in preterm birth: Interactions with gestational age, race, and multiple birth. Obstet Gynecol. 1996; 88:189–193. [PubMed: 8692499]

Cordier S, Garel M, Mandereau L, Morcel H, Doineau P, Gosme-Seguret S, Josse D, White R, Amiel-Tison C. Neurodevelopmental investigations among methylmercury-exposed children in French Guiana. Environ Res. 2002; 89:1–11. [PubMed: 12051779]

D'Onofrio B, vanHulle C, Waldman I, Rodgers J, Harden K, Rathouz P, Lahey B. Smoking during pregnancy and offspring externalizing problems: an exploration of genetic and environmental confounds. Dev Psychopathol. 2008; 20:139–164. [PubMed: 18211732]

Davis EP, Pfaff D. Sexually dimorphic responses to early adversity: implications for affective problems and autism spectrum disorder. Psychoneuroendocrinology. 2014; 49:11–25. [PubMed: 25038479]

Dawes N, Dawes G, Moulden M, Redman C. Fetal heart rate patterns in labor vary with sex, gestational age, epidural analgesia, and fetal weight. Am J Obstet Gynecol. 1999; 180:181–187. [PubMed: 9914601]

de Bruijn AT, van Bakel HJ, van Baar AL. Sex differences in the relation between prenatal maternal emotional complaints and child outcome. Early Hum Dev. 2009a; 85:319–324. [PubMed: 19162414]

de Bruijn AT, van Bakel HJ, Wijnen H, Pop VJ, van Baar AL. Prenatal maternal emotional complaints are associated with cortisol responses in toddler and preschool aged girls. Dev Psychobiol. 2009b; 51:553–563. [PubMed: 19688770]

De Felice A, Scattoni ML, Ricceri L, Calamandrei G. Prenatal exposure to a common organophosphate insecticide delays motor development in a mouse model of idiopathic autism. PLoS One. 2015; 10:e0121663. [PubMed: 25803479]

deVries JIP, Visser GHA, Prechtl HFR. The emergence of fetal behaviour. III. Individual differences and consistencies. Early Hum Dev. 1988; 16:85–103. [PubMed: 3278881]

Di Renzo GC, Rosati A, Sarti RD, Cruciani L, Cutuli AM. Does fetal sex affect pregnancy outcome? Gend Med. 2007; 4:19–30. [PubMed: 17584623]

Dietrich K, Krafft K, Bornschein R, Hammond P, Berger O, Succop P, Bier M. Low-level fetal lead exposure effect on neurobehavioral development in early infancy. Pediatrics. 1987; 80:721–730. [PubMed: 2444921]

DiPietro JA, Costigan K, Gurewitsch E. Fetal response to induced maternal stress. Early Hum Dev. 2003; 74:125–138. [PubMed: 14580752]

DiPietro JA, Costigan K, Kivlighan K, Chen P, Laudenslager M. Maternal salivary cortisol differs by fetal sex during the second half of gestation. Psychoneuroendocrinology. 2011; 36:588–591. [PubMed: 20940089]

DiPietro JA, Costigan K, Voegtline K. Studies in fetal behavior: Revisited, renewed, and reimagined. Monogr Soc Res Child Dev. 2015; 80(3):1–151.

Dipietro JA. Maternal stress in pregnancy: considerations for fetal development. J Adolesc Health. 2012; 51:S3–8. [PubMed: 22794531]

DiPietro JA, Bornstein MH, Costigan KA, Pressman EK, Hahn CS, Painter K, Smith BA, Yi LJ. What does fetal movement predict about behavior during the first two years of life? Dev Psychobiol. 2002; 40:358–371. [PubMed: 12115294]

DiPietro JA, Costigan KA, Shupe AK, Pressman EK, Johnson TRB. Fetal neurobehavioral development: Associations with socioeconomic class and fetal sex. Dev Psychobiol. 1998; 33:79–91. [PubMed: 9664173]

DiPietro JA, Hodgson DM, Costigan KA, Hilton SC, Johnson TRB. Fetal neurobehavioral development. Child Dev. 1996; 67:2553–2567. [PubMed: 9022256]

DiPietro JA, Irizarry RA, Hawkins M, Costigan KA, Pressman EK. Cross-correlation of fetal cardiac and somatic activity as an indicator of antenatal neural development. Am J Obstet Gynecol. 2001; 185:1421–1428. [PubMed: 11744919]

DiPietro JA, Kivlighan KT, Costigan KA, Laudenslager ML. Fetal motor activity and maternal cortisol. Dev Psychobiol. 2009; 51:505–512. [PubMed: 19630038]

DiPietro JA, Kivlighan KT, Costigan KA, Rubin SE, Shiffler DE, Henderson J, Pillion JP. Prenatal antecedents of newborn neurological maturation. Child Dev. 2010; 81:115–130. [PubMed: 20331657]

Eiden RD, Molnar DS, Granger DA, Colder CR, Schuetze P, Huestis MA. Prenatal tobacco exposure and infant stress reactivity: Role of child sex and maternal behavior. Dev Psychobiol. 2015; 57:212–225. [PubMed: 25650169]

Ellman LM, Schetter CD, Hobel CJ, Chicz-DeMet A, Glynn LM, Sandman CA. Timing of fetal exposure to stress hormones: Effects on newborn physical and neuromuscular maturation. Dev Psychobiol. 2008; 50:232–241. [PubMed: 18335490]

Eogan MA, Geary MP, O'Connell MP, Keane DP. Effect of fetal sex on labour and delivery: retrospective review. BMJ. 2003; 326:137. [PubMed: 12531846]

Eriksson JG, Kajantie E, Osmond C, Thornburg K, Barker DJ. Boys live dangerously in the womb. Am J Hum Biol. 2010; 22:330–335. [PubMed: 19844898]

Evans SF, Kobrosly RW, Barrett ES, Thurston SW, Calafat AM, Weiss B, Stahlhut R, Yolton K, Swan SH. Prenatal bisphenol A exposure and maternally reported behavior in boys and girls. Neurotoxicology. 2014; 45:91–99. [PubMed: 25307304]

Fausto-Sterling A, Coll CG, Lamarre M. Sexing the baby: Part 1--What do we really know about sex differentiation in the first three years of life? Soc Sci Med. 2012a; 74:1684–1692. [PubMed: 21802808]

Fausto-Sterling A, Coll CG, Lamarre M. Sexing the baby: Part 2--Applying dynamic systems theory to the emergences of sex-related differences in infants and toddlers. Soc Sci Med. 2012b; 74:1693–1702. [PubMed: 21862195]

Fox DJ, Pettygrove S, Cunniff C, O'Leary LA, Gilboa SM, Bertrand J, Druschel CM, Breen A, Robinson L, Ortiz L, Frias JL, Ruttenber M, Klumb D, Meaney FJ. Fetal alcohol syndrome among children aged 7–9 years - Arizona, Colorado, and New York, 2010. MMWR Morb Mortal Wkly Rep. 2015; 64:54–57. [PubMed: 25632951]

Froehlich TE, Lanphear BP, Dietrich KN, Cory-Slechta DA, Wang N, Kahn RS. Interactive effects of a DRD4 polymorphism, lead, and sex on executive functions in children. Biol Psychiatry. 2007; 62:243–249. [PubMed: 17239353]

Gabory A, Attig L, Junien C. Sexual dimorphism in environmental epigenetic programming. Mol Cell Endocrinol. 2009; 304:8–18. [PubMed: 19433243]

Gargus RA, Vohr BR, Tyson JE, High P, Higgins RD, Wrage LA, Poole K. Unimpaired outcomes for extremely low birth weight infants at 18 to 22 months. Pediatrics. 2009; 124:112–121. [PubMed: 19564290]

Gerardin P, Wendland J, Bodeau N, Galin A, Bialobos S, Tordjman S, Mazet P, Darbois Y, Nizard J, Dommergues M, Cohen D. Depression during pregnancy: is the developmental impact earlier in boys? A prospective case-control study. J Clin Psychiatry. 2011; 72:378–387. [PubMed: 21208585]

Ghidini A, Salafia CM. Gender differences of placental dysfunction in severe prematurity. BJOG. 2005; 112:140–144. [PubMed: 15663576]

Giesbrecht GF, Campbell T, Letourneau N. Sexually dimorphic adaptations in basal maternal stress physiology during pregnancy and implications for fetal development. Psychoneuroendocrinology. 2015; 56:168–178. [PubMed: 25827961]

Glover V, Hill J. Sex differences in the programming effects of prenatal stress on psychopathology and stress responses: an evolutionary perspective. Physiol Behav. 2012; 106:736–740. [PubMed: 22353310]

Glynn LM, Sandman CA. Sex moderates associations between prenatal glucocorticoid exposure and human fetal neurological development. Dev Sci. 2012; 15:601–610. [PubMed: 22925508]

Goel N, Bale T. Examining the intersection of sex and stress in modelling neuropsychiatric disorders. J Neuroendocrinol. 2009; 21:415–420. [PubMed: 19187468]

Goldenberg RL, Andrews WW, Faye-Petersen OM, Goepfert AR, Cliver SP, Hauth JC. The Alabama Preterm Birth Study: intrauterine infection and placental histologic findings in preterm births of males and females less than 32 weeks. Am J Obstet Gynecol. 2006; 195:1533–1537. [PubMed: 16796981]

Grandjean P, Weihe P, White RF, Debes F. Cognitive performance of children prenatally exposed to "safe" levels of methylmercury. Environ Res. 1998; 77:165–172. [PubMed: 9600810]

Greenough A, Lagercrantz H, Pool J, Dahlin I. Plasma catecholamine levels in preterm infants. Effect of birth asphyxia and Apgar score. Acta Paediatr Scand. 1987; 76:54–59. [PubMed: 3565002]

Groome L, Mooney D, Holland S, Smith L, Atterbury J, Dykman R. Behavioral state affects heart rate response to low-intensity sound in human fetuses. Early Hum Dev. 1999; 54:39–54. [PubMed: 10195714]

Gualtieri T, Hicks R. An immunoreactive theory of selective male affliction. Behav Brain Sci. 1985; 8:427–441.

Haley DW, Handmaker NS, Lowe J. Infant stress reactivity and prenatal alcohol exposure. Alcohol Clin Exp Res. 2006; 30:2055–2064. [PubMed: 17117971]

Hankin BL. Critical reflections on evolutionary psychology and sexual selection theory as explanatory account of emergence of sex differences in psychopathology: comment on Martel (2013). Psychol Bull. 2013; 139:1260–1264. [PubMed: 24188421]

Harley KG, Gunier RB, Kogut K, Johnson C, Bradman A, Calafat AM, Eskenazi B. Prenatal and early childhood bisphenol A concentrations and behavior in school-aged children. Environ Res. 2013; 126:43–50. [PubMed: 23870093]

Hepper P. Sex differences in fetal habituation. Dev Sci. 2012; 15:373–383. [PubMed: 22490177]

Hepper P, Shannon E, Dorman J. Sex differences in fetal mouth movements. Lancet. 1998; 350:1820. [PubMed: 9428256]

Hepper, PG. The behavior of the fetus as an indicator of neural functioning. In: Lecanuet, JP., et al., editors. Fetal development: A psychobiological perspective. Hillsdale, NJ: Lawrence Erlbaum Associates; 1995. p. 405-417.

Hepper PG, Shahidullah S. Habituation in normal and Down's syndrome fetuses. Q J Exp Psychol. 1992; 44:305–317.

Herman LE, Acosta MC, Chang PN. Gender and attention deficits in children diagnosed with a Fetal Alcohol Spectrum Disorder. Can J Clin Pharmacol. 2008; 15:e411–419. [PubMed: 18953085]

Hines M, Constantinescu M, Spencer D. Early androgen exposure and human gender development. Biol Sex Differ. 2015; 6:3. [PubMed: 25745554]

Hintz SR, Kendrick DE, Vohr BR, Kenneth Poole W, Higgins RD. Gender differences in neurodevelopmental outcomes among extremely preterm, extremely-low-birthweight infants. Acta Paediatr. 2006; 95:1239–1248. [PubMed: 16982497]

Hofer, MA. On the nature and function of prenatal behavior. In: Smotherman, W.; Robinson, S., editors. Behavior of the Fetus. Caldwell, NJ: Telford Press; 1988. p. 3-18.

Horton MK, Kahn LG, Perera F, Barr DB, Rauh V. Does the home environment and the sex of the child modify the adverse effects of prenatal exposure to chlorpyrifos on child working memory? Neurotoxicol Teratol. 2012; 34:534–541. [PubMed: 22824009]

Hou Y, Tan Y, Belcheva MM, Clark AL, Zahm DS, Coscia CJ. Differential effects of gestational buprenorphine, naloxone, and methadone on mesolimbic mu opioid and ORL1 receptor G protein coupling. Brain Res Dev Brain Res. 2004; 151:149–157. [PubMed: 15246701]

Hutchinson J, Pickett KE, Green J, Wakschlag LS. Smoking in pregnancy and disruptive behaviour in 3-year-old boys and girls: an analysis of the UK Millennium Cohort Study. J Epidemiol Community Health. 2010; 64:82–88. [PubMed: 19887578]

Ingemarsson I. Gender aspects of preterm birth. BJOG. 2003; 110(Suppl 20):34–38. [PubMed: 12763109]

Jacklin C. Methodological issues in the study of sex-related differences. Dev Rev. 1981; 1:266–273.

Jansson L, DiPietro J, Elko A, Velez M. Maternal vagal tone change in response to methadone predicts neonatal abstinence syndrome severity in exposed neonates. J Matern Fetal Med. 2007; 20:677–685.

Jansson L, DiPietro J, Elko A, Velez M. Infant autonomic functioning and neonatal abstinence syndrome. Drug Alcohol Depend. 2010; 109:198–204. [PubMed: 20189732]

Jansson LM, DiPietro JA, Elko A. Fetal response to maternal methadone administration. Am J Obstet Gynecol. 2005; 193:611–617. [PubMed: 16150250]

Jedrychowski W, Perera F, Jankowski J, Mrozek-Budzyn D, Mroz E, Flak E, Edwards S, Skarupa A, Lisowska-Miszczyk I. Gender specific differences in neurodevelopmental effects of prenatal exposure to very low-lead levels: the prospective cohort study in three-year olds. Early Hum Dev. 2009; 85:503–510. [PubMed: 19450938]

Johnson H, Diano A, Rosen T. 24-month neurobehavioral follow-up of children of methadone-maintaned mothers. Infant Behav Dev. 1984; 7:115–123.

Johnston MV, Hagberg H. Sex and the pathogenesis of cerebral palsy. Dev Med Child Neurol. 2007; 49:74–78. [PubMed: 17209983]

Kamper-Jorgensen M, Hjalgrim H, Andersen AM, Gadi VK, Tjonneland A. Male microchimerism and survival among women. Int J Epidemiol. 2014; 43:168–173. [PubMed: 24345850]

Kelly Y, Sacker A, Gray R, Kelly J, Wolke D, Quigley MA. Light drinking in pregnancy, a risk for behavioural problems and cognitive deficits at 3 years of age? Int J Epidemiol. 2009; 38:129–140. [PubMed: 18974425]

Kelly YJ, Sacker A, Gray R, Kelly J, Wolke D, Head J, Quigley MA. Light drinking during pregnancy: still no increased risk for socioemotional difficulties or cognitive deficits at 5 years of age? J Epidemiol Community Health. 2012; 66:41–48. [PubMed: 20924051]

Kent AL, Wright IM, Abdel-Latif ME. Mortality and adverse neurologic outcomes are greater in preterm male infants. Pediatrics. 2012; 129:124–131. [PubMed: 22184652]

Kesmodel U, Kjaersgaard M, Denny C, Bertrand J, Skogerbo A, Eriksen HL, Bay B, Underbjerg M, Mortensen E. The association of pre-pregnancy alcohol drinking with child neuropsychological functioning. BJOG. 2014

Khoury MJ, Marks JS, McCarthy BJ, Zaro SM. Factors affecting the sex differential in neonatal mortality: the role of respiratory distress syndrome. Am J Obstet Gynecol. 1985; 151:777–782. [PubMed: 3976790]

Kobrosly RW, Evans S, Miodovnik A, Barrett ES, Thurston SW, Calafat AM, Swan SH. Prenatal phthalate exposures and neurobehavioral development scores in boys and girls at 6–10 years of age. Environ Health Perspect. 2014; 122:521–528. [PubMed: 24577876]

Krasnegor N, Fifer W, Maulik D, McNellis D, Romero R, Smotherman W. Fetal behavioral development: a transdisciplinary perspective for assessing fetal well-being and predicting outcome. Prenat Neonatal Med. 1998; 3:185–190.

Lange S, Van Leeuwen P, Geue D, Hatzmann W, Gronemeyer D. Influence of gestational age, heart rate, gender and time of day on fetal heart rate variability. Med Biol Eng Comput. 2005; 43:481–486. [PubMed: 16255430]

Leader LR, Baillie P, Martin B, Vermeulen E. The assessment and significance of habituation to a repeated stimulus by the human fetus. Early Hum Dev. 1982; 7:211–219. [PubMed: 7160332]

Li J, Olsen J, Vestergaard M, Obel C. Attention-deficit/hyperactivity disorder in the offspring following prenatal maternal bereavement: a nationwide follow-up study in Denmark. Eur Child Adolesc Psychiatry. 2010; 19:747–753. [PubMed: 20495989]

Lieberman E, Lang JM, Cohen AP, Frigoletto FD Jr, Acker D, Rao R. The association of fetal sex with the rate of cesarean section. Am J Obstet Gynecol. 1997; 176:667–671. [PubMed: 9077626]

Loomans EM, van der Stelt O, van Eijsden M, Gemke RJ, Vrijkotte TG, Van den Bergh BR. High levels of antenatal maternal anxiety are associated with altered cognitive control in five-year-old children. Dev Psychobiol. 2012; 54:441–450. [PubMed: 21953508]

Maccoby, E.; Jacklin, C. The psychology of sex differences. Palo Alto: Stanford University Press; 1984.

Mage DT, Donner EM. Is excess male infant mortality from sudden infant death syndrome and other respiratory diseases X-linked? Acta Paediatr. 2014; 103:188–193. [PubMed: 24164639]

Malcolm C, McCulloch D, Shepherd A. Pattern-reversal visual evoked potentials in infants: gender differences during early visual maturation. Dev Med Child Neurol. 2002; 44:345–351. [PubMed: 12033721]

Marks AR, Harley K, Bradman A, Kogut K, Barr DB, Johnson C, Calderon N, Eskenazi B. Organophosphate pesticide exposure and attention in young Mexican-American children: the CHAMACOS study. Environ Health Perspect. 2010; 118:1768–1774. [PubMed: 21126939]

Martel MM. Sexual selection and sex differences in the prevalence of childhood externalizing and adolescent internalizing disorders. Psychol Bull. 2013; 139:1221–1259. [PubMed: 23627633]

Martel MM, Roberts BA. Prenatal testosterone increases sensitivity to prenatal stressors in males with disruptive behavior disorders. Neurotoxicol Teratol. 2014; 44:11–17. [PubMed: 24819590]

May PA, Baete A, Russo J, Elliott AJ, Blankenship J, Kalberg WO, Buckley D, Brooks M, Hasken J, Abdul-Rahman O, Adam MP, Robinson LK, Manning M, Hoyme HE. Prevalence and characteristics of fetal alcohol spectrum disorders. Pediatrics. 2014; 134:855–866. [PubMed: 25349310]

May PA, Gossage JP, Marais AS, Adnams CM, Hoyme HE, Jones KL, Robinson LK, Khaole NC, Snell C, Kalberg WO, Hendricks L, Brooke L, Stellavato C, Viljoen DL. The epidemiology of fetal alcohol syndrome and partial FAS in a South African community. Drug Alcohol Depend. 2007; 88:259–271. [PubMed: 17127017]

May PA, Hymbaugh KJ, Aase JM, Samet JM. Epidemiology of fetal alcohol syndrome among American Indians of the Southwest. Soc Biol. 1983; 30:374–387. [PubMed: 6336013]

McCorry N, Hepper P. Fetal habituation performance: gestational age and sex effects. Br J Dev Psychol. 2007; 25:272–292.

Miech RP. The role of fetal microchimerism in autoimmune disease. Int J Clin Exp Med. 2010; 3:164–168. [PubMed: 20607042]

Miller JL, Macedonia C, Sonies BC. Sex differences in prenatal oral-motor function and development. Dev Med Child Neurol. 2006; 48:465–470. [PubMed: 16700938]

Morokuma S, Fukushima K, Otera Y, Yumoto Y, Tsukimori K, Ochiai M, Hara T, Wake N. Ultrasound evaluation of fetal brain dysfunction based on behavioral patterns. Brain Dev. 2013; 35:61–67. [PubMed: 22321861]

Mortensen LH, Nielsen HS, Cnattingius S, Andersen AM. Sex of the first-born and risk of preterm birth in the subsequent pregnancy. Epidemiology. 2011; 22:328–332. [PubMed: 21283010]

Mulder EJ, Morssink LP, van-der-Schee T, Visser GH. Acute maternal alcohol consumption disrupts behavioral state organization in the near term fetus. Pediatr Res. 1998; 44:774–779. [PubMed: 9803461]

Myers GJ, Davidson PW, Cox C, Shamlaye CF, Palumbo D, Cernichiari E, Sloane-Reeves J, Wilding GE, Kost J, Huang LS, Clarkson TW. Prenatal methylmercury exposure from ocean fish consumption in the Seychelles child development study. Lancet. 2003; 361:1686–1692. [PubMed: 12767734]

Naeye RL, Burt LS, Wright DL, Blanc WA, Tatter D. Neonatal mortality, the male disadvantage. Pediatrics. 1971; 48:902–906. [PubMed: 5129451]

Naumann CR, Zelig C, Napolitano PG, Ko CW. Nausea, vomiting, and heartburn in pregnancy: a prospective look at risk, treatment, and outcome. J Matern Fetal Neonatal Med. 2012; 25:1488–1493. [PubMed: 22122296]

Nelson JL. The otherness of self: microchimerism in health and disease. Trends Immunol. 2012; 33:421–427. [PubMed: 22609148]

Ngun TC, Ghahramani N, Sanchez FJ, Bocklandt S, Vilain E. The genetics of sex differences in brain and behavior. Front Neuroendocrinol. 2011; 32:227–246. [PubMed: 20951723]

Nijhuis I, tenHof J, Mulder E, Nijhuis J, Narayan H, Taylor D, Westers P, Visser G. Numerical fetal heart rate analysis: nomograms, minimal duration of recording, and intrafetal consistency. Prenat Neonatal Med. 1998; 3:314–322.

Nijhuis IJM, tenHof J. Development of fetal heart rate and behavior: indirect measures to assess the fetal nervous system. Eur J Obstet Gynecol Reprod Biol. 1999; 87:1–2. [PubMed: 10579609]

Nijhuis IJM, tenHof J, Mulder EJ, Nijhuis JG, Narayan H, Taylor D, Visser GHA. Fetal heart rate in relation to its variation in normal and growth retarded fetuses. Eur J Obstet Gynecol Reprod Biol. 2000; 89:27–33. [PubMed: 10733020]

O'Connor AB, O'Brien L, Alto WA. Are there gender related differences in neonatal abstinence syndrome following exposure to buprenorphine during pregnancy? J Perinat Med. 2013; 41:621–623. [PubMed: 23612625]

O'Connor T, Heron J, Golding J, Beveridge M, Glover V. Maternal antenatal anxiety and children's behavioural/emotional problems at 4 years. Br J Psychiatry. 2002; 180:502–508. [PubMed: 12042228]

O'Connor TG, Heron J, Golding J, Glover V. Maternal antenatal anxiety and behavioural/emotional problems in children: a test of a programming hypothesis. J Child Psychol Psychiatry. 2003; 44:1025–1036. [PubMed: 14531585]

Orzack S, Stubblefield J, Akmaev V, Coll P, Munne S, Scholl T, Steinsaltz D, Zuckerman J. The human sex ratio from conception to birth. Proc Natl Acad Sci U S A. 2015; doi: 10.1073/pnas.1416546112

Ouellet-Morin I, Dionne G, Lupien SJ, Muckle G, Cote S, Perusse D, Tremblay RE, Boivin M. Prenatal alcohol exposure and cortisol activity in 19-month-old toddlers: an investigation of the moderating effects of sex and testosterone. Psychopharmacology. 2011; 214:297–307. [PubMed: 20717651]

Paolozza A, Munn R, Munoz DP, Reynolds JN. Eye movements reveal sexually dimorphic deficits in children with fetal alcohol spectrum disorder. Fronti Neurosci. 2015; 9:76.

Parker S, Greer S, Zuckerman B. Double jeopardy: The impact of poverty on early child development. Pediatr Clin North Am. 1988; 35:1227–1240. [PubMed: 3059296]

Pasamanick, B.; Knobloch, H. The epidemiology of reproductive casualty. In: VanKrevalen, DA., editor. Child Psychiatry and Prevention. Berne: Huber; 1964.

Patrick SW, Kaplan HC, Passarella M, Davis MM, Lorch SA. Variation in treatment of neonatal abstinence syndrome in US Children's Hospitals, 2004–2011. J Perinatol. 2014; 34:867–872. [PubMed: 24921412]

Patrick SW, Schumacher RE, Benneyworth BD, Krans EE, McAllister JM, Davis MM. Neonatal abstinence syndrome and associated health care expenditures: United States, 2000–2009. JAMA. 2012; 307:1934–1940. [PubMed: 22546608]

Pedersen LH, Henriksen TB, Olsen J. Fetal exposure to antidepressants and normal milestone development at 6 and 19 months of age. Pediatrics. 2010; 125:e600–608. [PubMed: 20176667]

Perera F, Vishnevetsky J, Herbstman JB, Calafat AM, Xiong W, Rauh V, Wang S. Prenatal bisphenol a exposure and child behavior in an inner-city cohort. Environ Health Perspect. 2012; 120:1190–1194. [PubMed: 22543054]

Persson M, Fadl H. Perinatal outcome in relation to fetal sex in offspring to mothers with pre-gestational and gestational diabetes-a population-based study. Diabet Med. 2014; 31:1047–1054. [PubMed: 24773081]

Pickett K, Wood C, Adamson J, DeSouza L, Wakschlag L. Meaningful differences in maternal smoking behaviour during pregnancy: implications for infant behavioural vulnerability. J Epidemiol Community Health. 2008; 62:318–324. [PubMed: 18339824]

Platt MJ, Cans C, Johnson A, Surman G, Topp M, Torrioli MG, Krageloh-Mann I. Trends in cerebral palsy among infants of very low birthweight (<1500 g) or born prematurely (<32 weeks) in 16 European centres: a database study. Lancet. 2007; 369:43–50. [PubMed: 17208641]

Prior T, Wild M, Mullins E, Bennett P, Kumar S. Sex specific differences in fetal middle cerebral artery and umbilical venous Doppler. PLoS One. 2013; 8:e56933. [PubMed: 23437275]

Rauh VA, Perera FP, Horton MK, Whyatt RM, Bansal R, Hao X, Liu J, Barr DB, Slotkin TA, Peterson BS. Brain anomalies in children exposed prenatally to a common organophosphate pesticide. Proc Natl Acad Sci U S A. 2012; 109:7871–7876. [PubMed: 22547821]

Ris MD, Dietrich KN, Succop PA, Berger OG, Bornschein RL. Early exposure to lead and neuropsychological outcome in adolescence. J Int Neuropsychol Soc. 2004; 10:261–270. [PubMed: 15012846]

Robles de Medina P, Visser G, Huizink A, Buitelaar J, Mulder E. Fetal behaviour does not differ between boys and girls. Early Hum Dev. 2003; 73:17–26. [PubMed: 12932890]

Rosenfeld CS, Trainor BC. Environmental Health Factors and Sexually Dimorphic Differences in Behavioral Disruptions. Curr Environ Health Rep. 2014; 1:287–301. [PubMed: 25705580]

Sagiv S, Thurston S, Bellinger D, Altshul L, Korrick S. Neuropsychological measures of attention and impulse control among 8-year-old children exposed prenatally to organochlorines. Environ Health Perspect. 2012a epub ahead of print.

Sagiv SK, Thurston SW, Bellinger DC, Amarasiriwardena C, Korrick SA. Prenatal exposure to mercury and fish consumption during pregnancy and attention-deficit/hyperactivity disorder-related behavior in children. Arch Pediatr Adolesc Med. 2012b; 166:1123–1131. [PubMed: 23044994]

Sandman CA, Glynn LM, Davis EP. Is there a viability-vulnerability tradeoff? Sex differences in fetal programming. J Psychosom Res. 2013; 75:327–335. [PubMed: 24119938]

Sandman CA, Wadhwa P, Hetrick W, Porto M, Peeke H. Human fetal heart rate dishabituation between thirty and thirty-two weeks gestation. Child Dev. 1997; 68:1031–1040. [PubMed: 9418223]

Schuetze P, Lopez FA, Granger DA, Eiden RD. The association between prenatal exposure to cigarettes and cortisol reactivity and regulation in 7-month-old infants. Dev Psychobiol. 2008; 50:819–834. [PubMed: 18690653]

Sheiner E, Levy A, Katz M, Hershkovitz R, Leron E, Mazor M. Gender does matter in perinatal medicine. Fetal Diagn Ther. 2004; 19:366–369. [PubMed: 15192298]

Smotherman WP, Robinson SR. Prenatal influences on development: Behavior is not a trivial aspect of fetal life. J Dev Behav Pediatr. 1987; 8:171–175. [PubMed: 3597784]

Spinillo A, Capuzzo E, Nicola S, Colonna L, Iasci A, Zara C. Interaction between fetal gender and risk factors for fetal growth retardation. Am J Obstet Gynecol. 1994; 171:1273–1277. [PubMed: 7977533]

Spinillo A, Montanari L, Gardella B, Roccio M, Stronati M, Fazzi E. Infant sex, obstetric risk factors, and 2-year neurodevelopmental outcome among preterm infants. Dev Med Child Neurol. 2009; 51:518–525. [PubMed: 19416336]

Stevenson DK, Verter J, Fanaroff AA, Oh W, Ehrenkranz RA, Shankaran S, Donovan EF, Wright LL, Lemons JA, Tyson JE, Korones SB, Bauer CR, Stoll BJ, Papile LA. Sex differences in outcomes of very low birthweight infants: the newborn male disadvantage. Arch Dis Child Fetal Neonatal Ed. 2000; 83:F182–185. [PubMed: 11040165]

Streissguth A, Sampson P, Barr H, Darby B, Martin D. IQ at age 4 in relation to maternal alcohol use and smoking during pregnancy. Dev Psychol. 1989; 25:3–11.

Streissguth AP, Bookstein FL, Barr HM, Sampson PD, O'Malley K, Young JK. Risk factors for adverse life outcomes in fetal alcohol syndrome and fetal alcohol effects. J Dev Behav Pediatr. 2004; 25:228–238. [PubMed: 15308923]

Suffet F, Brotman R. A comprehensive care program for pregnant addicts: obstetrical, neonatal, and child development outcomes. Int J Addict. 1984; 19:199–219. [PubMed: 6724763]

Tamimi RM, Lagiou P, Mucci LA, Hsieh CC, Adami HO, Trichopoulos D. Average energy intake among pregnant women carrying a boy compared with a girl. BMJ. 2003; 326:1245–1246. [PubMed: 12791740]

Tanner, JM. Foetus into man: Physical growth from conception to maturity. Cambridge, MA: Harvard University Press; 1978.

Temkin, O. Soranus' Gynecology. Baltimore: Johns Hopkins University Press; 1991.

Thanh NX, Jonsson E, Salmon A, Sebastianski M. Incidence and prevalence of fetal alcohol spectrum disorder by sex and age group in Alberta, Canada. J Popul Ther Clin Pharmacol. 2014; 21:e395–404. [PubMed: 25381628]

Thapar A, Rice F, Hay D, Boivin J, Langley K, vandenBree M, Rutter M, Harold G. Prenatal smoking might not cause attention-deficit/hyperactivity disorder: evidence from a novel design. Biol Psychiatry. 2009; 66:722–727. [PubMed: 19596120]

Thordstein M, Lofgren N, Flisberg A, Lindecrantz K, Kjellmer I. Sex differences in electrocortical activity in human neonates. Neuroreport. 2006; 17:1165–1168. [PubMed: 16837847]

Trivers RL, Willard DE. Natural selection of parental ability to vary the sex ratio of offspring. Science. 1973; 179:90–92. [PubMed: 4682135]

Tunc-Ozcan E, Ullmann TM, Shukla PK, Redei EE. Low-dose thyroxine attenuates autism-associated adverse effects of fetal alcohol in male offspring's social behavior and hippocampal gene expression. Alcohol Clin Exp Res. 2013; 37:1986–1995. [PubMed: 23763370]

Ulm B, Svolba G, Ulm MR, Bernaschek G, Panzer S. Male fetuses are particularly affected by maternal alloimmunization to D antigen. Transfusion (Paris). 1999; 39:169–173.

Unger A, Jagsch R, Bawert A, Winklbaur B, Rohrmeister K, Martin PR, Coyle M, Fischer G. Are male neonates more vulnerable to neonatal abstinence syndrome than female neonates? Gend Med. 2011; 8:355–364. [PubMed: 22088886]

Van den Bergh BR, Mennes M, Stevens V, van der Meere J, Borger N, Stiers P, Marcoen A, Lagae L. ADHD deficit as measured in adolescent boys with a continuous performance task is related to antenatal maternal anxiety. Pediatr Res. 2006; 59:78–82. [PubMed: 16327007]

Van den Bergh B, Marcoen A. High antenatal maternal anxiety is related to ADHD symptoms, externalizing problems, and anxiety in 8- and 9-year-olds. Child Dev. 2004; 75:1085–1097. [PubMed: 15260866]

Van den Bergh B, Mennes M, Oosterlaan J, Stevens V, Stiers P, Marcoen A, Lagae L. High antenatal maternal anxiety is related to impulsivity during performance on cognitive tasks in 14- and 15-year-olds. Neurosci Biobehav Rev. 2005; 29:259–269. [PubMed: 15811497]

Vanston CM, Watson NV. Selective and persistent effect of foetal sex on cognition in pregnant women. Neuroreport. 2005; 16:779–782. [PubMed: 15858424]

Verloove-Vanhorick SP, Veen S, Ens-Dokkum MH, Schreuder AM, Brand R, Ruys JH. Sex difference in disability and handicap at five years of age in children born at very short gestation. Pediatrics. 1994; 93:576–579. [PubMed: 8134212]

Visser G, Mulder E, Ververs FT. Fetal behavioral teratology. J Mater Fetal Neonatal Med. 2010; 23:14–16.

Voegtline KM, Kivlighan KCK, Henderson J, DiPietro J. Sex-specific associations of maternal prenatal testosterone levels with birth weight and weight gain in infancy. J Dev Orig Health Dis. 2013a; 4:280–284. [PubMed: 24993000]

Voegtline KM, Costigan KA, Kivlighan KT, Laudenslager ML, Henderson JL, DiPietro JA. Concurrent levels of maternal salivary cortisol are unrelated to self-reported psychological measures in low-risk pregnant women. Arch Womens Ment Health. 2013b; 16:101–108. [PubMed: 23269500]

Wakschlag LS, Leventhal BL, Pine DS, Pickett KE, Carter AS. Elucidating early mechanisms of developmental psychopathology: the case of prenatal smoking and disruptive behavior. Child Dev. 2006; 77:893–906. [PubMed: 16942496]

Wakschlag LS, Pickett KE, Cook E Jr, Benowitz NL, Leventhal BL. Maternal smoking during pregnancy and severe antisocial behavior in offspring: a review. Am J Public Health. 2002; 92:966–974. [PubMed: 12036791]

Weinberg J, Sliwowska JH, Lan N, Hellemans KG. Prenatal alcohol exposure: foetal programming, the hypothalamic-pituitary-adrenal axis and sex differences in outcome. J Neuroendocrinol. 2008; 20:470–488. [PubMed: 18266938]

Wertelecki W, Hoff C, Zansky S. Maternal smoking: greater effect on males, fetal tobacco syndrome? Teratology. 1987; 35:317–320. [PubMed: 3629511]

Willoughby M, Greenberg M, Blair C, Stifter C. Neurobehavioral consequences of prenatal exposure to smoking at 6 to 8 months of age. Infancy. 2007; 12:273–301.

Zaren B, Lindmark G, Bakketeig L. Maternal smoking affects fetal growth more in the male fetus. Paediatr Perinat Epidemiol. 2000; 14:118–126. [PubMed: 10791654]

Zeitlin J, Ancel PY, Larroque B, Kaminski M. Fetal sex and indicated very preterm birth: results of the EPIPAGE study. Am J Obstet Gynecol. 2004; 190:1322–1325. [PubMed: 15167836]

Zucker I, Beery AK. Males still dominate animal studies. Nature. 2010; 465:690. [PubMed: 20535186]

Highlights

- Fetal sex confers effects on pregnancy, the intrauterine milieu and early development
- Prenatal and perinatal adversity affects male fetuses and neonates more negatively
- Fetal sex has been under-recognized as physiologically consequential for pregnant women
- Mechanisms by which biological sex imparts vulnerability or protection are largely unknown

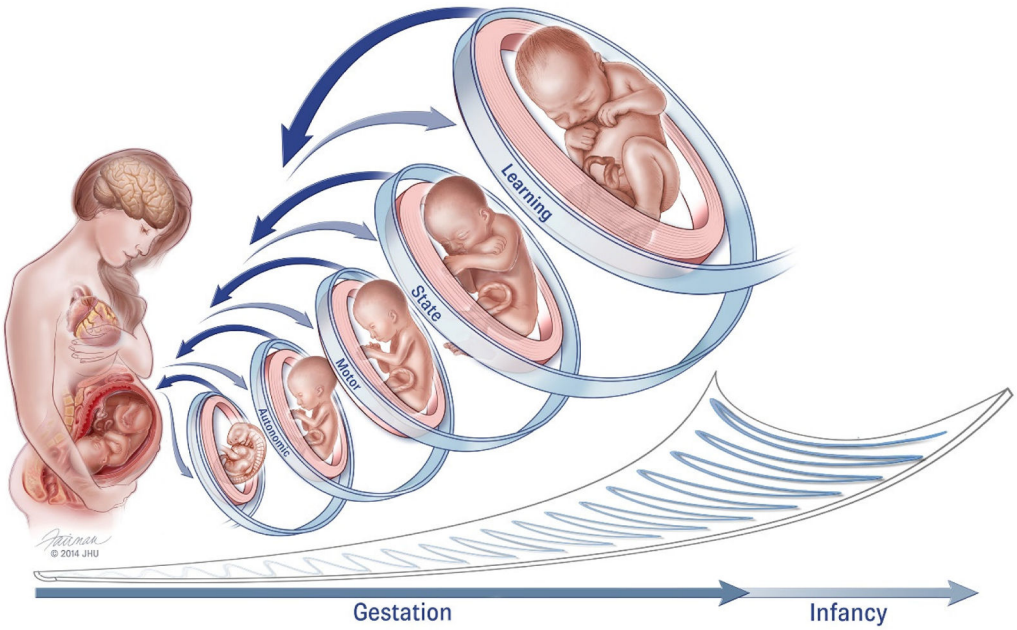

Figure 1.
Conceptual model of fetal neurobehavioral development within the maternal context (DiPietro et al, 2015.

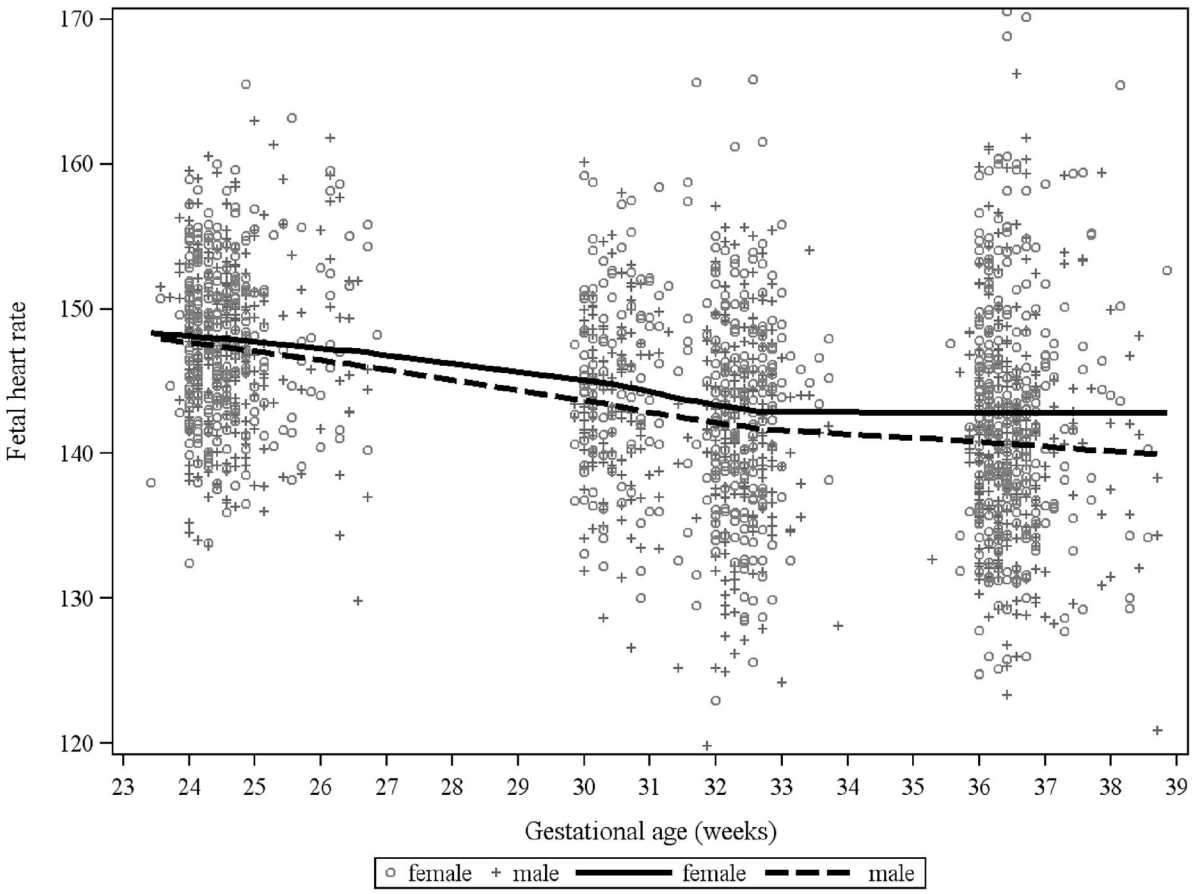

Figure 2.

Fetal heart rate by fetal sex. Female fetuses had significantly faster heart rates at the second and third gestational periods and Lowess curve estimates depict significantly greater decline in fetal heart rate from the second to third periods in male fetuses. Scatter points represent data from individual fetuses at each gestational age and illustrate inter-individual variation and distributional overlap between sexes.

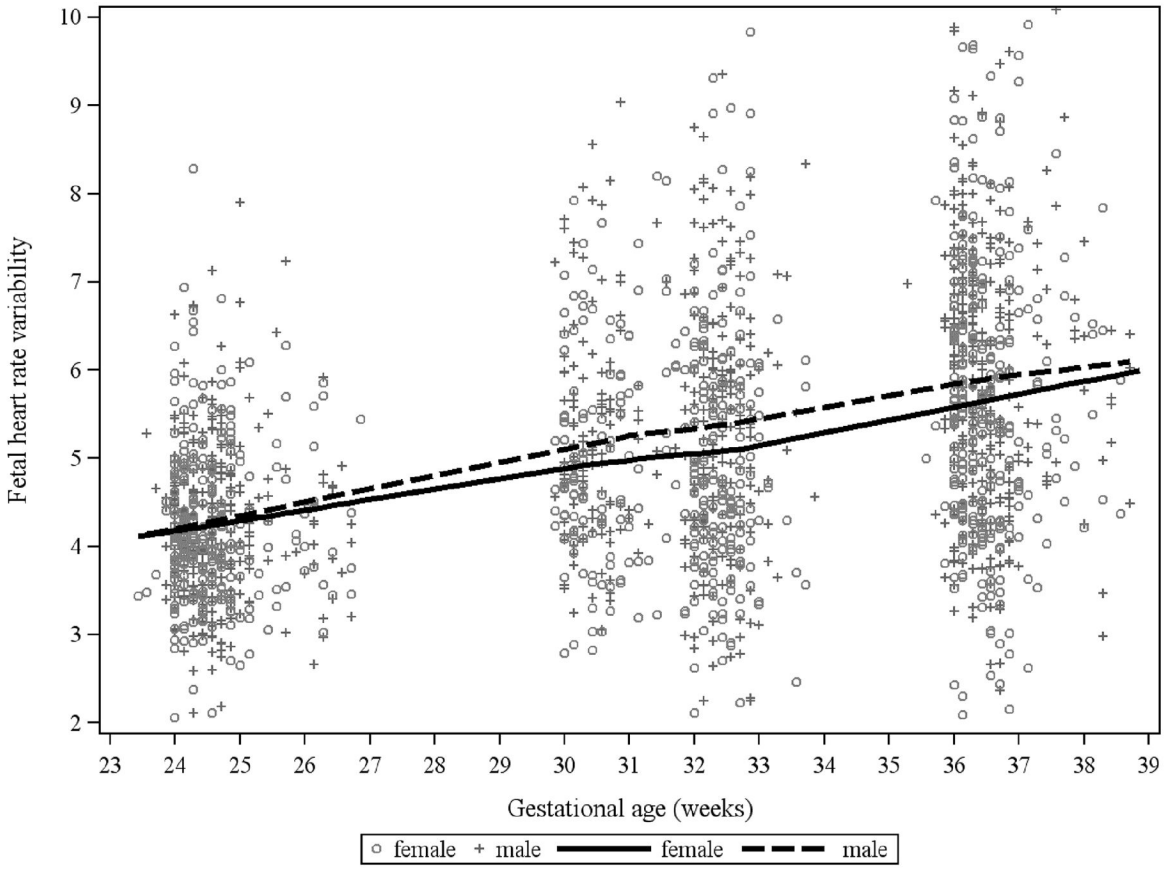

Figure 3.

Fetal heart rate variability by fetal sex. Male fetuses had significantly greater variability in fetal heart rate at the second and third gestational periods and Lowess curve estimates depict a steeper developmental trajectory between the first and second periods in male fetuses. Scatter points represent data from individual fetuses at each gestational age and illustrate inter-individual variation and distributional overlap between sexes.

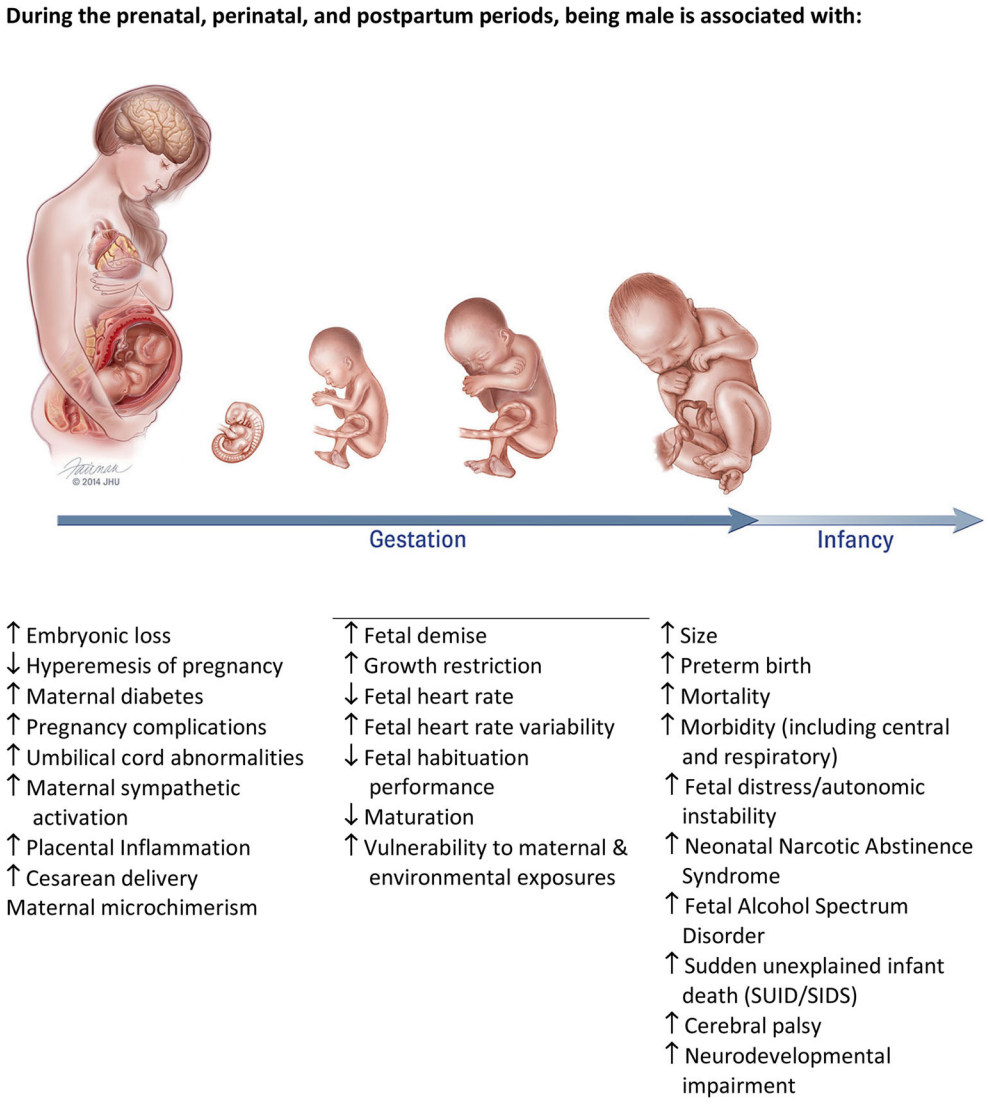

Figure 4.

Schematic representation of early sex differences, distributed over gestation. Depicted are the most well-supported and documented sex differences in pregnant women, fetuses and neonates. Although some differences may not be expressed until later in development, such as heightened vulnerability of the male central nervous system to environmental exposures or preterm birth, their origins are in the prenatal or perinatal period. Placement within columns is somewhat arbitrary as a number of these observations affect both the mother and fetus, or span the prenatal and perinatal domains, depending on when either the exposure or delivery occurs. Maternal microchimerism (first column) typically refers to that observed as the result of vestiges of the Y chromosome, its implications for long term maternal well-being remains uncertain. Variation in fetal neurobehavioral indicators (second column) has primarily been observed in the 3rd trimester. Morbidity and mortality (final column) spans the gestational age and birth weight continuum.