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Effects of Perinatal Testosterone on Infant Health, Mother-Infant Interactions, and Infant Development

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Keywords

Perinatal Testosterone; Cortisol; Gender Differences; Infant Health; Mother-Infant Interactions; Infant Development

The infant mortality rate is higher in the US than in Europe because of a very high rate of preterm births (MacDorman & Mathews, 2009). Very-low-birth-weight (VLBW; birthweights less than 1,500 g) preterm infants have more health and developmental problems than full-term infants (Rose, Feldman, & Jankowski, 2002). In addition, VLBW preterm male infants experience these problems more frequently than female VLBW preterm infants do (Hintz et al., 2006). Male VLBW preterm infants also have less positive interactions with their mothers than female preterm infants (Cho, Holditch-Davis, & Belyea, 2007). This is problematic because positive mother-infant interactions serve as an important protective mechanism against the negative health and developmental outcomes associated with prematurity (Landry, Smith, Swank, Assel, & Vellet, 2001). Such associations raise important questions about the factors beyond gender socialization explaining the vulnerability of male VLBW preterm infants to health problems, suboptimal mother-infant interactions, and poor infant development and whether these factors are biological in origin. Answers to these questions could ultimately provide a basis for intervening with mothers and their VLBW preterm infants, especially males.

The purpose of this article is to review the literature on the subject and to introduce a conceptual framework focused on the associations of perinatal testosterone and cortisol with (1) infant health, (2) mother-infant interactions, and (3) infant cognitive/motor/language development. The framework is based on the associations among biological (perinatal testosterone), stress-related (perinatal and maternal cortisol), and developmental (infant cognitive/motor/language skills) factors. If these associations are established in mother-VLBW preterm dyads, the results may highlight the importance of nursing research addressing gender differences and lead to nursing interventions designed to reduce stress among mothers of VLBW preterm infants, particularly males.

Literature Review

The information contained in this paper was gathered through a review of the primary literature, utilizing the PsyInfo, ERIC, Medline, CHINAL, and PubMed databases. The terms used for the first search were gender differences in infant health, gender differences in mother-infant interactions, gender differences in infant cognitive/motor/language development, gender differences in infant temperament, and gender differences in maternal depressive symptoms. The terms used for the second round of the search were gender-difference theories, testosterone and infant health outcomes, and cortisol and infant health outcomes. The third and last search included the terms, relationship between testosterone and cortisol, relationship between maternal testosterone and infant health outcomes, and relationship between maternal cortisol and infant health outcomes. Information thus obtained is primarily from peer-reviewed studies or meta-analysis articles, with most publications dating from 1980 to 2012.

According to numerous gender-difference theories, prenatal exposure to high levels of testosterone influences infant health and mother-infant interactions by negatively affecting infant cognitive/motor/language development. These theories include a general theory (Geschwind, 1987; Grimshaw, Bryden, & Finegan, 1995; Witelson, 1985; Witelson & Nowakowski, 1991), the extreme male brain theory of autism (Baron-Cohen, 2002), and the empathizing-systemizing theory of sex differences (Baron-Cohen, 2003). The rationale for focusing on testosterone is that gender differences are commonly found in newborn behaviors and testosterone plays a crucial role in fetal brain development (Connellan, 2000).

Environmental stimuli such as maternal stress likely amplify the effects of perinatal testosterone on infant health and development. Maternal stress, manifested by high levels of cortisol, is known to induce elevated perinatal cortisol levels in fetuses/neonates at pre- and postnatal periods (Talge, Neal, & Glover, 2007). Perinatal cortisol level is inversely related to infant health and development (Diego et al., 2009). Both cortisol and testosterone are the end products of two hormonal axes, the hypothalamus-pituitary-adrenal (HPA) axis and the hypothalamus-pituitary-gonad (HPG) axis (Terburg, Morgan, & van Honk, 2009). More importantly, the two steroid hormones are correlated positively in fetuses and infants (Sarkar, Bergman, O'Connor, & Glover, 2008). A high level of maternal cortisol is often found in mothers with socio-demographic and psychological problems such as low-income and depressive symptoms (Field, Diego, & Hernandez-Reif, 2010). These problems could affect mother-infant interactions as well as infant development.

Other factors that may influence gender differences in mother-infant interactions and infant development are infant temperament and maternal depressive symptoms. Males and preterm infants tend to show more difficult temperaments than both females and full-term infants (Crockenberg & Smith, 2002). Compared with mothers without depressive symptoms, mothers with depressive symptoms interact more negatively when their infants have difficult temperaments, are male, and are preterm (Righetti-Veltema, Bousquet, & Manzano, 2003).

Gender Differences in Infant Health

The research literature has identified gender differences in infant health. These gender differences occur quite early because males are more likely to be born prematurely and tend to have more neonatal complications than females (Hintz et al., 2006; James, 2000). The higher rate of male preterm births occurs in both singleton and multiple births (Cooperstock, Bakewell, Herman, & Schramm, 1998) and in both Whites and Blacks (Cooperstock & Campbell, 1996). Compared with females, males are more likely to be intubated, receive more resuscitation medications, and have a 20% higher risk for low 1- and 5-min Apgar scores (Stevenson et al., 2000). Males have higher rates of respiratory distress syndrome (RDS) and chronic lung disease (CLD; Bartels, Kreienbrock, Dammann, Wenzlaff, & Poets, 2005); as well as, severe sepsis and septic shock (Bindl et al., 2003). Consequently, prematurely born males are more likely to be exposed to a greater number of medications, including surfactants and antibiotics, receive mechanical ventilation (Warrier, Du, Natarajan, Salari, & Aranda, 2006), and be diagnosed with grades III and IV intraventricular hemorrhage (IVH) and periventricular leucomalacia (PVL; Bartels et al., 2005; Nunez & McCarthy, 2003; Tioseco, Aly, Essers, Patel, & El-Mohandes, 2006). As a result of these neonatal health problems, males have a 20% higher perinatal and neonatal mortality rate (Gissler, Jarvelin, Louhiala, & Hemminki, 1999).

Testosterone appears to play a role in these gender differences in health. Compared with normative levels of perinatal testosterone, elevated levels delay pulmonary maturation and inhibit synthesis of lung surfactant during the last 20% of gestation (Bartels et al., 2005). Thus, preterm infants with high levels of testosterone may have more health problems related to respiratory function than other preterm infants. Testosterone increases susceptibility to neurological insults and limits recovery from brain damage because it exacerbates hippocampal neuronal loss in preterm infants (Nunez & McCarthy, 2003; Tioseco et al., 2006). This may account for the significantly higher rates of grades III and IV IVH and of death in males, especially in extremely low birth weight (ELBW, birthweights less than 1,000 g) and VLBW infants (Nunez & McCarthy, 2003). Compared to a normative level of perinatal testosterone, an increased level is associated with a smaller thymus gland, and thus, infants with high levels of testosterone may have more immune disorders such as allergies and asthma (Gissler et al., 1999). Perinatal exposure to high levels of testosterone is also associated with intrauterine growth retardation (Carlsen, Jacobsen, & Romundstad, 2006; Steckler, Wang, Bartol, Roy, & Padmanabhan, 2005) and postnatal catch-up growth (Manikkam et al., 2004).

Gender Differences in Mother-Infant Interactions

Another factor examined in the research literature is the relationship between gender and the quality of mother-infant interactions. Mothers tend to be more protective and less restrictive of their male VLBW preterm infants than females before 6 months and to talk to and look at female VLBW preterm infants more than males (Cho et al., 2007). Because high quality mother-infant interactions significantly reduce the negative health and developmental outcomes related to prematurity (Landry et al., 2001), male infants are at a greater risk for negative outcomes than female infants.

Testosterone appears to be associated with the gender differences in mother-infant interactions. Elevated levels of testosterone in amniotic fluid are negatively related to sociality such as eye contact, interest in others, and empathy (Knickmeyer, Baron-Cohen, Raggatt, & Taylor, 2005; Knickmeyer, Baron-Cohen, Raggatt, Taylor, & Hackett, 2006; Lutchmaya, Baron-Cohen, & Raggatt, 2002). At birth, males looked longer at a mobile object, whereas females looked longer at a human face (Connellan, 2000). Similarly, at 12 months, males looked longer at a video of cars moving, and females looked longer at a video of a moving face (Lutchmaya & Baron-Cohen, 2002). At 12 and 24 months, males made less and shorter eye contact with their mothers than females, and the amount of eye contact was inversely correlated with the level of testosterone in amniotic fluid (Lutchmaya et al., 2002). Testosterone in amniotic fluid is negatively correlated with quality of social relationships and empathy at 4 years in males but positively correlated with lack of interest in others (Knickmeyer et al., 2005; 2006). On the basis of the extreme male brain theory of autism and the empathizing-systemizing theory of sex differences (Baron-Cohen, 2002; 2003), the male preference for mechanical rather than social stimuli originates in the effects of perinatal testosterone on brain development.

Gender Differences in Infant Cognitive/Motor/Language Development

The research literature has also examined the relationship between gender and infant development. At 2 years of age, male VLBW preterm infants are more likely to be delayed in cognitive development, especially language and social skills, than females (Brothwood, Wolke, Gamsu, Benson, & Cooper, 1986). This finding is possibly due to the higher incidences of RDS, pulmonary interstitial emphysema, and neurodevelopmental disorders such as autism and dyslexia in males (Taylor, Klein, Schatschneider, & Hack, 1998).

Despite the male disadvantage on health outcomes, males on average develop several motor skills earlier than females do, including the ability to lift their head while lying on their stomach, standing with support, and crawling independently (Reinisch & Sanders, 1992). Males are more active than females, and these differences increase with age (Campbell & Eaton, 1999). Differences also occur in motor development patterns: males spend longer transitioning from crawling independently to walking with support, whereas females require more time between sitting without support and standing with support (Reinisch & Sanders, 1992). The male superiority in motor development may not occur in VLBW preterm infants because of motor delays caused by respiratory problems and neurological insults associated with prematurity (Taylor et al., 1998). Slower motor and cognitive development at 3 years has been predicted by the presence of respiratory problems and neurological insults (Singer, Yamashita, Lilien, Collin, & Baley, 1997), both of which occur more commonly in male than female VLBW infants.

Testosterone levels have been found to be related to the gender-related differences in development. A high level of testosterone in cord blood was negatively related to language development in males, but not in females (Whitehouse et al., 2012). In comparison to the lowest testosterone concentration quartile, males in the highest quartile were at increased risk for a language delay with an odds ratio 2.47, while females in same quartile were at decreased risk for a language delay with an odds ratio 0.46 (Whitehouse et al., 2012). On the

other hand, no association between fetal testosterone and vocabulary size or verbal IQ was found when data were examined within genders at 2 years or at 6-10 years (Auyeung et al., 2009; Lutchmaya, Baron-Cohen, & Raggatt, 2001). The findings may be explained based on gender-difference theories that male brain is more sensitive to testosterone than female brain. In fact, prenatal exposure to a high level of testosterone is associated with neurodevelopmental disorders more common in males such as reading disability, autism spectrum disorder, and attention-deficit-hyperactivity disorder (Baron-Cohen, Knickmeyer, & Belmonte, 2005; James, 2008).

Relationships between Maternal Hormones and Infant Health and Development

The literature also indicated that testosterone and cortisol are related to infant health and development. As testosterone and cortisol are very similar in physical structure and correlated positively in fetuses and infants, the two steroid hormones need to be considered together in assessing infant health and development. Fetal and maternal testosterone levels are independent; no association has been found between testosterone levels in amniotic fluid and those in maternal blood (Troisi, Potischman, Roberts, Harger et al., 2003). On the other hand, the levels of fetal and maternal cortisol are positively related each other (Sarkar, Bergman, Fisk, O'Connor, & Glover, 2007). Furthermore, fetal testosterone concentrations differ by fetal gender and by gestational age (Troisi, Potischman, Roberts, Siiteri et al., 2003). Testosterone level decreases gradually after the second trimester until the end of gestation. However, the concentration increases again in males immediately after birth through 3 months and then decreases by 6 months and stays low until puberty (Bouvattier et al., 2002). In contrast, a low concentration occurs in females across age (Anderson et al., 1998).

Although the levels of testosterone of fetuses and mothers are independent, neonates tend to have more health problems when their mothers have elevated levels of prenatal testosterone (Furui, Imai, & Ohno, 2007). Recently, theoretical literature shows that maternal testosterone levels above the mean are more likely to be associated with high rates of male mortality and morbidity (Grant & Irwin, 2009). In comparison to normative levels, elevated maternal testosterone or androstenedione levels during pregnancy are associated with increased levels of antimüllerian hormone in the fetus (Hart et al., 2010), increased risk of polycystic ovary syndrome in female offspring in adolescence (Abbott, Barnett, Bruns, & Dumesic, 2005), and increased risk of testicular and prostate cancer in male offspring in adolescence (Holl et al., 2009; Rohrmann et al., 2009). However, other studies found no association between prenatal androgen exposure and polycystic ovary syndrome in female offspring (Hickey et al., 2009).

Elevated levels of maternal testosterone during pregnancy have been found to be associated with intrauterine growth retardation in animal (Manikkam et al., 2004) and human studies (Carlsen et al., 2006). Elevated levels of maternal testosterone during the second trimester at week 17 and the third trimester at week 33 are associated decreases in body weight and length at birth (Carlsen et al., 2006). On the other hand, no associations were found between elevated maternal testosterone levels (>90 percentile) and preterm delivery and low birth weight (Gustin et al., 2012). Elevated levels of maternal testosterone have also been

associated with postnatal catch-up growth in mammals, a risk factor for future adult disease along with intrauterine growth retardation (Manikkam et al., 2004).

A high level of maternal cortisol during pregnancy is associated with poor neonatal outcomes such as preterm birth and growth delays including low birth weight, short length and small head circumference (Bolten et al., 2011; Diego et al., 2009). Elevated cortisol level, a biological factor, was a better predictor of birth weight and length than psychological factors such as perceived stress (Bolten et al., 2011). Similar to testosterone, cortisol has a critical role in the immune system (Johannsen, Rylander, Soder, & Asberg, 2006), regulation of placenta enzymes (Benediktsson, Calder, Edwards, & Seckl, 1997) and production of passive immunity (Merlot, Couret, & Otten, 2008). Thus, infants exposed to high levels of prenatal cortisol are more susceptible to illness than other infants (Beijers, Jansen, Riksen-Walraven, & de Weerth, 2010).

Effects of Gender and Maternal Depressive Symptoms on Mother-Infant Interactions

Another potential factor affecting the quality of mother-infant interactions is the combined effects of infant gender and maternal depressive symptoms. Male infants of mothers with elevated depressive symptoms were vulnerable to insecure attachment and delayed cognitive development (Righetti-Veltema et al., 2003). Mothers with elevated depressive symptoms tend to show significantly negative attitudes toward male infants than towards females (Grace, Evindar, & Stewart, 2003), whereas no differences are observed with mothers without depressive symptoms between male and female infants (Murray & Fiori-Cowley, 1996). Mothers with elevated depressive symptoms and with male infants show poorer maternal self-esteem and adaptation to maternal role than mothers of female infants (Weinberg et al., 2001). Mothers of male infants have a higher risk for developing major depression than mothers of female infants (Beeghly et al., 2002). When their mothers have more depressive symptoms, male infants score lower on the Bayley Motor and Mental Scales than female infants (Righetti-Veltema et al., 2003). Mothers with elevated symptoms on the Beck Depression Inventory are also more intrusive and experience greater difficulties during interactions with male infants than with female infants (Hart, Field, del Valle, & Pelaez-Nogueras, 1998), possibly because male infants tend to be more demanding, cry and fuss more, and exhibit more anger (Weinberg et al., 2001).

Testosterone and cortisol levels have been found to affect these relationships. The level of cortisol are higher in mothers with more stressors and depressive symptoms ($r = .37$) (Diego et al., 2009). An elevated level of maternal cortisol induces an increase in fetal cortisol level, and this increase functions as a trigger for increasing fetal testosterone level (Sarkar et al., 2008). A large number of prenatal stressors increases the level of fetal cortisol as fetuses respond to the stressful stimuli by increasing their cortisol secretion (Diego et al., 2009). A positive association between cortisol and testosterone concentrations has been reported in amniotic fluid, fetal blood, and cord blood (Gitau, Adams, Fisk, & Glover, 2005; Sarkar et al., 2008). Interestingly, these findings are opposite to those in adults who exhibit a negative association between cortisol and testosterone (Granger et al., 2003). Compared to normative levels of prenatal cortisol and testosterone, high levels of the hormones are associated with

more negativism and less sensitivity of infants during the interactions with their mothers (de Weerth, van Hees, & Buitelaar, 2003; Lundy et al., 1999; Lutchmaya et al., 2002).

Gender Differences in Infant Temperament

Finally, the literature indicated that there are gender-related differences in infant temperament. The biological bases of infant temperament, including genetic inheritance and prenatal environmental factors, is believed to be stronger than environmental effects on temperament (Saudino, 2005). Difficult infant temperament such as frequent negative mood and difficulty in adapting to changes in surroundings is associated with infant biological factors and with maternal maladaptive responses to infants (Larroque, N'Guyen The Tich, Guedeney, Marchand, & Burguet, 2005; Muller-Nix et al., 2004). Fussing and crying are more frequently observed in neonates of less responsive mothers than those of responsive mothers (Crockenberg & Smith, 2002). However, some unresponsive mothers of infants with difficult temperament respond more when infants are more alert and achieve eye contact for longer periods, and this response is more likely to occur with female infants or full-term infants than with male infants or VLBW infants (Crockenberg & Smith, 2002).

Female infants have lower levels of testosterone in amniotic fluid and show significantly longer periods of eye contact with their mothers than male infants do (Lutchmaya et al., 2002). The level of perinatal testosterone was also found to be positively related to postnatal behaviors including aggression, tumbling and rough play, and attention deficient hyperactivity disorder (Azurmendi et al., 2006). Thus, one biological basis of difficult infant temperament might be elevated levels of testosterone and cortisol in the perinatal period.

Discussion

Based on the above literature review, we developed the following conceptual framework to guide future research and practice (Figure). It shows the relationships among a biological basis of gender differences (perinatal testosterone), a physiological indicator of stress (perinatal and maternal cortisol), and infant development outcomes (cognitive/motor/ language skills). Based on gender-difference theories as well as research findings, perinatal testosterone and its positive relationship with perinatal cortisol is assumed to influence infant health and mother-infant interactions by negatively affecting infant development after adjusting for maternal depressive symptoms and infant temperament. Testosterone has a crucial role in brain development, especially during the second trimester, by increasing cerebral lateralization (Geschwind, 1987; Grimshaw et al., 1995), decreasing interhemispheric connectivity (Witelson & Nowakowski, 1991), and decreasing the size of the corpora callosa (Witelson, 1985).

Utilizing this conceptual framework may help researchers focus their questions and hypotheses from the biophysiological and socioenvironmental perspectives. There is a large body of knowledge on the role of testosterone in various cognitive and behavioral outcomes (Auyeung et al., 2009; Booth, Johnson, Granger, Crouter, & McHale, 2003; Knickmeyer et al., 2005). Nonetheless, this conceptual framework may serve as guide researchers to a new area of study: the association between perinatal testosterone and early infant health and cognitive/motor/ language development. Future research can also focus on the basis of each

possible association, for example, perinatal testosterone and infant health and growth, perinatal testosterone and mother-infant interactions, or perinatal testosterone and infant development.

Implications for Research

This conceptual framework can be applied to an exploratory, comparative, and longitudinal research design that aims to relate perinatal testosterone levels to (1) infant health and growth, (2) mother-infant interactions, and (3) infant cognitive/motor/language development. Adjustment will be needed for characteristics of infant and mother, infant temperament, and maternal depressive symptoms. Infant characteristics may include gender and ethnicity. Characteristics of the mother might include age, race, body mass index, education, and marital status. Measures of infant health might include birth weight, gestational age, Apgar scores, presence of medical complications, and technology-dependence.

In addition, examining correlations between the levels of testosterone and cortisol in infants and in mothers will provide a meaningful basis for developing interventions for families and their VLBW preterm infants. If positive correlations between the levels of testosterone and cortisol are found in both infants and mothers, a stress-reducing nursing intervention may be desirable. This is particularly true if testosterone level can be lowered by reducing the cortisol level. This intervention may ultimately help families reduce health problems and developmental delays in their VLBW preterm infants, especially males. Measuring the effectiveness of a stress-reducing intervention in diverse populations and ages will be a challenging task. A feasibility study of testosterone measurement in infants and mothers is a necessary future step because the measurement is technically challenging as the concentrations of testosterone were low in these populations (Rosner, Auchus, Azziz, Sluss, & Raff, 2007).

Although health care providers have often noted male vulnerability in infant health, mother-infant interactions, and cognitive development, what factors beyond gender explain these observed gender differences has never been clear. With the present state of understanding, cause-and-effect relationships cannot be unambiguously established. However, the conceptual framework presented here may lead to some potential answers. One possible source of male vulnerability would be the level of perinatal testosterone as indicated by the gender-differences theories (Geschwind, 1987; Witelson & Nowakowski, 1991) and brain models (Baron-Cohen, 2002; 2003). This hypothesis is supported by our recent study that, in comparison with cortisol, elevated levels of postnatal salivary testosterone are associated with more health (e.g., shorter gestational age and higher rate of receiving CPR at birth) and growth (e.g., smaller birth weight and length) problems among VLBW preterm infants (Cho, Carlo, Su, & McCormick, in press).

Implications for Practice

The findings of our literature review also have implications for clinical practice. If elevated levels of perinatal testosterone are found to be negatively associated with infants' health and growth outcomes (e.g., delayed weight gain), VLBW preterm infants, especially males, need to receive more attention from health care providers and families. This clinical attention

could potentially alleviate negative health and growth outcomes at an early stage of infant development. As more studies are designed to measure both the levels of testosterone and cortisol in the neonatal period and the infancy, the information needed to justify the use of hormonal measurements as part of neonatal screening tests will be developed. For example, if a newborn has high or low level of testosterone or cortisol, it may be an endocrine abnormality. Therefore, a pediatric endocrine consult would be required.

Health care providers could support distressed pregnant women and mothers. Stress-reducing interventions should prevent negative outcomes including not only maternal depressive symptoms and poor mother-infant interactions but also unfavorable infant health (Diego et al., 2009) and cognitive/motor/language development (Phillips, 2007). Elevated level of cortisol in pregnant women and mothers thus can provide early indications of maternal depressive symptoms and fetal/neonatal stresses (Diego et al., 2009).

Conclusion

The level of perinatal testosterone may be the underlying cause of gender differences in infant health, mother-infant interactions, and infant cognitive/motor/language development. Our conceptual framework for establishing the associations among perinatal testosterone and infant health, mother-infant interactions, and infant development can provide guidance for future research and practice. Based on the psychobiosocial model (Halpern, 1997), examining the combined effects of biophysiological factors such as perinatal testosterone and cortisol, and socioenvironmental factors such as quality of mother-infant interactions and infant temperament would provide broader view of gender differences in infant health and development.

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Figure.

Conceptual framework on the relationships among perinatal testosterone and infant health, mother-infant interactions, and infant cognitive/motor/language development (in *italics*). It is based on the associations among biological (perinatal testosterone), stress-related (perinatal and maternal cortisol), and developmental (infant cognitive/motor) factors (in **bold**).

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