Psychoneuroendocrinology 95 (2018) 74–85

Contents lists available at ScienceDirect

Psychoneuroendocrinology

journal homepage: www.elsevier.com/locate/psyneuen

Sex differences in effects of maternal risk and protective factors in childhood and pregnancy on newborn telomere length

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ARTICLE INFO

Keywords:
Newborn
Telomere length
Sex differences
Cord blood
Maternal exposures

ABSTRACT

Little research has examined determinants of newborn telomere length, a potential biomarker of lifetime disease risk impacted by prenatal exposures. No study has examined whether maternal exposures in childhood influence newborn telomere length or whether there are sex differences in the maternal factors that influence newborn telomere length. We tested whether a range of maternal risk and protective factors in childhood and pregnancy were associated with newborn telomere length among 151 sociodemographically diverse mother-infant dyads. We further examined whether the pattern of associations differed by infant sex. Newborn telomere length was assessed from cord blood collected at birth. Risk/protective factors included maternal health (smoking, body mass index), socioeconomic status (education, income), stress exposures, and mental health (depressive and posttraumatic stress disorder symptoms) in pregnancy as well as maternal experiences of abuse (physical, emotional, sexual) and familial emotional support in childhood. When examined within the whole sample, only maternal smoking in pregnancy and familial emotional support in childhood emerged as significant predictors of newborn telomere length. Male and female newborns differed in their pattern of associations between the predictors and telomere length. Among males, maternal smoking, higher body mass index, and elevated depressive symptoms in pregnancy and maternal sexual abuse in childhood were associated with shorter newborn telomere length; higher maternal educational attainment and household income in pregnancy and greater maternal familial emotional support in childhood were associated with longer newborn telomere length. Together, these factors accounted for 34% of the variance in male newborn telomere length. None of the risk/protective factors were associated with female newborn telomere length. The results suggest that male fetuses are particularly susceptible to maternal exposure effects on newborn telomere length. These findings have implications for elucidating mechanisms contributing to sex disparities in health.

1. Introduction

According to the Developmental Origins of Health and Disease theory, many human disease processes begin as early as the fetal period, even if symptoms do not emerge until late in life (Gluckman et al., 2008). Various maternal exposures have been identified as robust influencers on fetal development and, ultimately, offspring physical and mental health and neurodevelopment (Entringer et al., 2015; Van den Bergh et al., 2017). Importantly, evidence suggests that these exposures may not uniformly affect male and female offspring (Van den Bergh et al., 2017). The mechanisms underlying sex differences in outcomes related to maternal exposures in pregnancy are yet to be elucidated. Ascertaining biomarkers that capture disease vulnerability attributable to such exposures beginning in early life would inform our understanding of the earliest origins of sex differences in lifetime health and disease processes.

Newborn telomere length has emerged as a possible biomarker of the effects of maternal-fetal processes on offspring long-term health

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https://doi.org/10.1016/j.psyneuen.2018.05.025
Received 13 December 2017; Received in revised form 28 April 2018; Accepted 16 May 2018

(Entringer et al., 2015). Telomeres are repeating nucleotide sequences of variable number that protect against chromosome deterioration and regulate cellular and tissue function (Blackburn and Gall, 1978). Shorter telomere length has been associated with chromosomal instability and is predictive of decreased immunocompetence, the development of chronic disease throughout life (e.g., cardiovascular disease, diabetes, obesity, inflammatory diseases, depression), abnormalities in brain structure and functioning, and earlier mortality (Baragetti et al., 2015; Factor-Litvak et al., 2016; Geronimus et al., 2015; Hochstrasser et al., 2012; Mundstock et al., 2015; Qi Nan et al., 2015; Rode et al., 2015). Telomere length at birth provides an individual's initial telomere length setting, such that telomere length at any given time point is determined by newborn telomere length and subsequent attrition (Factor-Litvak et al., 2016; Martens et al., 2016). Therefore, processes that shorten newborn telomere length may be critical determinants of lifetime health, and newborn telomere length may be a powerful biomarker of lifetime disease risk. Notably, biomarkers of lifetime health that can be assessed in childhood are rare (Entringer et al., 2011; Entringer et al., 2013).

Limited research has explored determinants of newborn telomere length. Research among adults suggests high heritability, with a large meta-analysis estimating telomere length heritability as 0.70 (Broer et al., 2013). However, many biological variables show increased heritability with advancing age (Sillanpaa et al., 2017), such that heritability of telomere length is likely lower among newborns than adults. Moreover, data suggest that telomere dynamics during early development are largely determinative of relative telomere length for life and that environmental factors have major impact on telomere length at birth (Hjelmborg et al., 2015). To date, a number of environmental influences have been implicated (Broer et al., 2013; Entringer et al., 2015). The extant literature suggests that shorter telomere length at birth may be associated with a variety of maternal factors during pregnancy, including maternal health, socioeconomic status (SES), and stress. For example, studies have linked maternal smoking and increased maternal body mass index (BMI) during pregnancy with shorter newborn telomere length (Drury et al., 2015; Factor-Litvak et al., 2016; Martens et al., 2016). Two studies documented shorter telomere length among newborns of mothers with lower educational attainment (Martens et al., 2016; Wojcicki et al., 2016), although two others failed to find such effects (Drury et al., 2015; Factor-Litvak et al., 2016). Studies have also linked higher maternal self-reported stress during pregnancy to shorter newborn telomere length (Entringer et al., 2013; Marchetto et al., 2016; Salihu et al., 2016; Send et al., 2017). Although not yet directly tested, data suggest that maternal psychological functioning in pregnancy may also predict newborn telomere length. Internalizing symptoms/disorders (depression, anxiety, posttraumatic stress disorder) have been correlated with shorter telomere length and predict more rapid telomere length erosion across time in adults (Revesz et al., 2016; Shalev et al., 2014). Additionally, maternal depression has been associated with shortened telomere length in children, including among psychologically healthy children (Coimbra et al., 2017; Gotlib et al., 2015). Research is needed to determine if maternal mental health during pregnancy predicts newborn telomere length.

Notably, each of these factors (i.e., maternal smoking and BMI in pregnancy; maternal SES; maternal stress and internalizing symptoms/disorders in pregnancy) has been associated with mechanisms hypothesized to contribute to telomere length erosion, including elevated oxidative stress, inflammation, and hypothalamic-pituitary-adrenal axis [HPAA] activity (Choi et al., 2008; Gotlib et al., 2015; Price et al., 2013; Revesz et al., 2016; Shalev, 2012; Shiels et al., 2011; Tomiyama et al., 2012; Van den Bergh et al., 2017; von Zglinicki, 2002; Wikgren et al., 2012; Wolkowitz et al., 2011). Disrupted functioning of these key physiological systems in pregnancy may negatively impact the initial setting and on-going regulation of newborn telomere length via epigenetic and other gene-regulating processes across cells (Entringer et al., 2011; Entringer et al., 2013; Lupien et al., 2009; Shiels et al., 2011; Steptoe et al., 2011; Van den Bergh et al., 2017).

Studies have not examined whether maternal experiences prior to pregnancy predict newborn telomere length. However, several lines of research suggest that adverse maternal exposures during her childhood, specifically maltreatment, may increase risk for shortened newborn telomere length. A number of studies have correlated retrospective reports of childhood maltreatment to shorter leukocyte telomere length in adults (Boeck et al., 2017; Kananen et al., 2010; Kiecolt-Glaser et al., 2011; Price et al., 2013; Shalev et al., 2013; Tyrka et al., 2010; Vincent et al., 2017). In fact, severe stressors in childhood, including maltreatment, have greater impact on telomere length shortening than more recent stress in adults (Tyrka et al., 2010). One study in children prospectively linked exposure to violence, including physical abuse and witnessing domestic violence, to telomere attrition (Shalev et al., 2013). Moreover, childhood maltreatment predicts persistent disruptions to the key physiological systems described above, potentially influencing maternal-fetal processes in pregnancy (Lupien et al., 2009). Furthermore, maternal exposures may influence maternal oocyte telomere length beginning in childhood, thereby impacting offspring telomere length (Ozturk et al., 2014). Thus, a maternal history of maltreatment in childhood may increase risk for shortened newborn telomere length through effects on maternal oocyte telomere biology and maternal physiological stress reactivity in pregnancy. Although studies suggest that different types of maltreatment may have differential effects on telomere biology (Ridout et al., 2017; Tyrka et al., 2010; Vincent et al., 2017), the specific forms of maltreatment likely to have greatest impact on offspring newborn telomere length are unknown.

Examination of protective factors that confer resilience against telomere attrition is lacking (Ridout et al., 2017), and no study has explored whether positive maternal experiences predict longer newborn telomere length. Emotionally supportive parental caregiving in childhood has been shown to promote more optimal development and long-term functioning of stress reactivity systems (Bosquet Enlow et al., 2014). Interestingly, preliminary data suggest that increased oxytocin, a possible result of sensitive caregiving, may protect again telomere attrition (Boeck et al., 2017). Therefore, receiving supportive caregiving in a mother's childhood may confer a protective influence on her newborn's telomere biology through programming of key maternal physiological systems that influence maternal oocyte telomere length and maternal-fetal physiological processes. Notably, in adults, including pregnant women, greater current family social support is associated with longer telomere length, providing evidence that family support may provide a buffering effect against telomere attrition (Mitchell et al., 2017).

Although a few studies have tested for sex differences in mean newborn telomere length, with some finding no differences and others finding longer telomere length among females (Factor-Litvak et al., 2016; Martens et al., 2016; Okuda et al., 2002; Wojcicki et al., 2016), there has yet to be an examination of whether maternal factors differentially impact telomere length among male versus female infants. A body of research suggests that males and females may differ in the patterns of associations between prenatal exposures and telomere length at birth. An extensive review of studies examining the developmental effects of prenatal stress exposures found that, although both male and female fetuses are susceptible to prenatal stress effects, there are sex differences in the response to specific types of stress at different periods of gestation for different developmental outcomes (Van den Bergh et al., 2017). Also, male and female fetuses experience different patterns of cortisol exposure during gestation (DiPietro, Costigan et al., 2011), which has implications for telomere biology. Further, changes in epigenetic regulation of factors affecting fetal cortisol exposure show sex-specific effects (Gabory et al., 2009; Ostlund et al., 2016). In children and adults, sex differences in the effects of various risk factors (e.g., internalizing disorders, parental caregiving quality, family violence exposure) on telomere attrition have been documented, with