

# Building Resilience for Generations: The Tip of the Chromosome

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When all the children sleep  
She turns as long away  
As will suffice to light her lamps;  
Then, bending from the sky,

With infinite affection  
And infiniter care,  
Her golden finger on her lip,  
Wills silence everywhere.

—Emily Dickinson

There is little doubt that 2020 was not the year anyone had planned. The impact of the global SARS CoV-2 pandemic on all aspects of life has been unprecedented, particularly for pregnant women. COVID-driven alterations in prenatal care; uncertainty and anxiety about the effect of COVID on the developing fetus and newborn infants; social isolation before, during, and after the birth of the child; and heightened economic and employment stressors have all added to the “typical” stressors faced by pregnant women (1). Pregnancy represents one of the most biologically, psychologically, and physically demanding experiences for women. It also represents one of the most critical developmental windows for the next generation. Decades of research, beginning with the Barker hypothesis in 1992, has established direct ties between fetal exposures and later health and disease. The majority of this research has focused on negative maternal exposures—from nutrition and environmental factors to maternal mental illness and perceived stress—and the consequences to the child’s later health and development, including data tying maternal adversity and stressors before and during pregnancy to a tiny molecular marker of stress and aging, the telomere (2, 3). In this issue of the *Journal*, Verner et al. (4) present data suggesting that although maternal stress and exposures during pregnancy have negative consequences for the child, maternal resilience, a complex and difficult-to-define construct, may protect the child down to the very tips of his or her chromosomes.

Telomeres, the tiny DNA, RNA, and protein cap found at the end of every eukaryotic chromosome, play a complex role in cellular processes, including not only cellular senescence and apoptosis but also chromosomal transcriptional regulation, chromosome stability, mitochondrial function, meiotic regulation, and cellular differentiation. Meta-analytic studies have associated telomere length (TL)—measured in a variety

of different tissues, including peripheral blood, saliva, and buccal swabs—with more than 50 different conditions, including psychosocial stress and early-life adversity (5, 6). Despite these numerous associations with TL, much remains to be understood about the relation between TL and the role of telomerase in different tissues, particularly for the earliest TL, or baseline TL, which has unique relevance to health outcomes (7). Verner et al. test an innovative question: If maternal stress and negative exposures can lead to shorter TL in the newborn, can maternal resilience be protective? In this well-designed, comprehensive prospective study—the Prediction and Prevention of Preeclampsia and Intrauterine Growth Restriction (PREDO) study—Verner et al., in a subset of 656 mother/infant dyads from the larger cohort of more than 4,700 mothers, provide the first data suggesting a biological effect of maternal resilience on newborns. Consistent with multiple previous studies, a composite maternal prenatal stress score, obtained from repeated measures throughout pregnancy, predicted shorter TL measured in cord blood. Uniquely, maternal positivity, defined using factor analyses of multiple measures of maternal affect and perceived social support, also significantly predicted newborn TL, but in a positive manner. Lastly, a novel resilience construct that isolated individual differences in positivity after accounting for maternal stress was also associated with longer TL, and post hoc sensitivity analyses revealed a stronger effect with the highest reported stress. As child outcome data, including on psychopathology, are already available for this cohort, the authors are poised to test the intriguing hypothesis that TL moderates the relation between maternal resilience and later positive childhood psychological development, providing complementary data to previous studies in which accelerated TL shortening moderated the association between maternal adversity and child externalizing behaviors (3). The implications of this research are clear. If we are not able to decrease prenatal maternal stress, enhancing maternal coping and

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resilience may do far more than lower maternal stress—it may actually begin to build the first biological blocks of resilience in the next generation.

Despite this innovative addition to the literature, critical questions remain. The authors note the limitation of an ethnically homogeneous and socioeconomically well-off maternal sample. Given the persistence of health disparities in maternal-child outcomes, particularly in the United States, concerted efforts are needed to increase the racial, ethnic, and socio-demographic diversity in studies examining the cross-generational effects of maternal stress. Beyond the obvious need to enhance diversity in ethnic representation and to employ analytic methodologies capable of integrating multi-ethnic data into all genetic and epigenetic studies, the characterization of stress and resilience likely differs across cultures. The use of culturally responsive and validated measures will enhance and strengthen future findings. The Verner et al. study, like most previous such studies, relies on maternal report of stress (and resilience), but studies that capture both self-report and objective cross-system measurements of stress, while complex and expensive, are necessary. Interestingly, a recent proteomics study found that three inflammatory proteins in maternal blood tied to apoptosis and cellular replication, including CASP8, an upstream protease that induces apoptosis, were significantly predictive of newborn TL (8). While that study did not assess maternal stress, the integration of maternal proteomics with maternal stress (self-report and physiologic measures) and newborn TL and other outcomes is a promising next research direction.

Correlation is not causation. As the underlying biological pathways remain obscure, advancing the field of maternal stress requires partnerships with basic and preclinical researchers. While predominant models of biological embedding across generations posit a role for cortisol and other stress response systems as mediators between maternal stress and newborn biology, it is unlikely to be that direct. For example, there is not a clear relation between maternal report of stress and maternal or fetal cortisol levels. Further, while in vitro studies find that cortisol decreases telomerase activity, and potentially TL, preclinical animal models did not find an effect of chronic corticosteroids on TL in the brain (9). Whether maternal stress would drive high enough and persistent enough levels of cortisol to cross the placenta and down-regulate telomerase in the fetus, resulting in detectable differences in newborn TL, is doubtful, particularly given the physiologic down-regulation of telomerase in the fetus during development (10). In the maternal-fetal-placental unit, telomeres not only have cell-specific effects but also exhibit paracrine and autocrine effects. More recent studies have demonstrated that exposure to dexamethasone, a corticosteroid often used in pregnancies at risk of preterm delivery, accelerates telomere loss in a replication-independent manner and triggers p21-mediated cellular senescence in fetal tissues (11). These are just a few examples of the increasingly complex role of telomeres and telomerase in fetal development that have not yet been explored in relation to maternal stress.

Beyond the gaps in our understanding of *how* maternal stress and resilience are transmitted to the tiny shoelace caps at the end of every chromosome, one might also ponder the next question: “So what?” The unclear implications of shorter TL at birth, in light of the substantial interindividual differences in TL, highlights the need for longitudinal studies with mechanistically driven hypotheses to fully understand the role of TL in predicting future child health. Perhaps shorter TL at birth, while indicative of advanced development across physiologic systems, comes at the cost of decreased plasticity and leads to earlier onset of negative health outcomes related to poorer regulation of physiologic systems, for example, cardiovascular disease and diabetes. This model aligns well with the adaptive calibration model that suggests that early adversity drives accelerated development of different processes in an effort to advance reproductive potential but also results in less openness to experiences and environments that would have permitted enhanced adaptation and learning (12). Recent data suggest that damaged telomeres, regardless of length, send signals to other cells and that telomere dynamics are important in terminal differentiation, meiosis, and chromosome stability. The telomere complex is also an epigenetic regulator of genes such as TERT, the catalytic subunit of telomerase located in the peri-telomeric region, as well as genes located farther away on the chromosome, through dynamic changes to the three-dimensional structure of the chromosome and folding over of the telomeres, referred to as telomere position effects. Thus, it is clear that the telomere story will continue to unfold and, for early development, may be more related to changing cellular gene expression than the traditional role of telomeres in senescence and cellular apoptosis.

As researchers and clinicians, we recognize the value of the integration of multiple perspectives when seeking to understand complex problems. The mitigation of the lasting biological effects of prenatal maternal stress is one such complex issue. Verner and colleagues’ elegant study provides a new, and positive, perspective on this model while identifying multiple avenues of future research. Most important, the study illuminates a missed component of previous work. While it is clear that maternal adversity and stress exert effects on the developing fetus, the authors’ far more important finding alludes to the potential that facilitating maternal resilience across the life course may be a potent antidote to the ever-increasing challenges facing a mother and the vulnerable fetus developing in her womb.

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