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At the forefront of psychoneuroimmunology in pregnancy: Implications for racial disparities in birth outcomes:

PART 2: Biological mechanisms

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Abstract

As reviewed in Part 1 of this two part review, birth prior to full term is a substantial public health issue. In the US, ~400, 000 babies per year are born preterm (< 37 weeks), while > 1 million are early term (37–$38^{6/7}$ weeks) and remarkable racial disparities in shortened gestation are observed among African Americans as compared to Whites. Biomechanisms linking stressor exposures with birth outcomes are increasingly being explicated. The current paper reviews the mechanistic role of maternal biological functioning in the link between behavioral exposures and birth outcomes. These include the inter-related roles of neuroendocrine function, inflammatory regulation, biological aging, and the microbiome. An integrative approach which addresses both behavioral and biological factors within the same study, carefully considers the role of race/ethnicity, and rigorously defines birth outcomes (e.g., spontaneous versus medically-indicated and inclusive of early term birth) is needed to move research in this field toward better mechanistic understanding and clinical application.

Keywords

Inflammation; Neuroendocrine; Social genomics; Transcriptomics; Microbiome; Psychoneuroimmunology; Stress; Pregnancy; Birth outcomes; Racial disparities

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1. Introduction

As reviewed in Part 1, there are considerable data linking depression and anxiety, and to a lesser extent sleep, with shortened gestation. However, as detailed in this companion paper, biological mechanisms require greater attention. Neuroendocrine and inflammatory mechanisms are implicated; however, there are significant gaps in these data. Moreover, enhanced inflammatory activity is commonly indicative of underlying biological aging. Although chronological age is a known risk factor for shortened gestation (Heffner, 2004; Laopaiboon et al., 2014), limited data are available regarding the role of individual differences in biological aging. In addition, increasing data demonstrates the value of social genomics for examining stress and perinatal health. Finally, data on the role of the microbiome is growing at a remarkable pace; however, studies are predominately in animal models, limiting ability to address issues relevant to exposure to stressors such as racial discrimination. Key focal points of this review are highlighted in Fig. 1.

2. Neuroendocrine regulation

During pregnancy, the functioning of the hypothalamic-pituitary-adrenal (HPA) axis is substantially altered and neuroendocrine mediators including corticotrophin releasing hormone (CRH), cortisol, and brain derived neurotrophic factor (BDNF) are implicated in fetal growth and delivery timing. Critical to these relationships, the placenta becomes an active organ within the HPA axis during gestation. During pregnancy, the placenta synthesizes the vast majority of CRH found in the maternal bloodstream, resulting in CRH concentrations 1,000–10,000 times higher than those seen in non-pregnant women (Thomson, 2013). A primary function of placental CRH is to regulate and stimulate the development of the fetal HPA axis (Mastorakos and Ilias, 2003). With predictive value for birth timing, CRH has been dubbed a “placental clock” (Mclean et al., 1995; Sandman et al., 2006). CRH has repeatedly been linked with perinatal stress, particularly pregnancy-specific anxiety. For example, in a prospective study of 337 pregnant Latina and non-Latina White women, pregnancy anxiety was predictive of CRH in late pregnancy as well as increases in CRH over time. Notably, in predicting length of gestation, moderating mediation effects were observed whereby pregnancy anxiety contributed to shorter gestation via CRH only among Latina women (Ramos et al., 2018). The importance of considering race/ethnicity is highlighted by other research showing that the association between CRH and length of gestation is race-specific when examining African American versus White women, because, overall African American women tend to exhibit lower CRH than Whites (Chen et al., 2010; Holzman et al., 2001).

Driven by placental production of CRH, which stimulates both the pituitary and adrenal glands, maternal cortisol increases by 2 to 3-fold by late gestation (Duthie and Reynolds, 2013; Mastorakos and Ilias, 2000). Increasing maternal cortisol further stimulates CRH production, in a feed forward loop. Although considerable heterogeneity has been observed across studies, attributable to differences in sampling time-point, maternal characteristics, and other factors, a meta-analysis of nine studies including a total of 1606 maternal-fetal dyads concluded that elevated maternal cortisol during pregnancy is consistently negatively correlated with birth weight (Cherak et al., 2018).

In terms of psychological factors, numerous studies have linked cortisol with stress, anxiety, and mood in pregnancy (e.g., Evans et al., 2008; Kane et al., 2014; Pluess et al., 2010). In particular, higher pregnancy anxiety has been associated with steeper increases in cortisol trajectories across pregnancy (Kane et al., 2014). Building upon these findings, we found that higher cortisol observed in women pregnant for the first time (primiparous) versus those who have previously given birth (multiparous) during pregnancy is partially mediated by higher pregnancy-specific anxiety among the primiparous women (Gillespie et al., 2018). In addition, among African American women, exposure to childhood stress predicted shorter gestation, an effect partially mediated by elevations in maternal cortisol (Gillespie et al., 2017). Overall, the literature on psychosocial factors and maternal cortisol regulation is characterized by wide variability in measurement approaches, including a range of psychological assessment instruments and approaches to cortisol assessment including via serum, saliva, and hair levels and with focus on a single assessment versus diurnal slopes or cortisol awakening responses. However, despite inconsistencies (including reports of blunting versus heightened effects) and null findings, evidence suggests that maternal psychological functioning is associated with neuroendocrine adaptation in pregnancy (Entringer et al., 2015; Glover et al., 2010). Moreover, data indicate that psychological factors alter the regulation of 11 beta-hydroxysteroid dehydrogenase 2 (11b-HSD2), the enzyme that metabolizes cortisol and largely determines the degree to which maternal cortisol is transferred to the fetus (Glover et al., 2009). Therefore, there exists more than one pathway via which neuroendocrine disruption may ultimately impact birth outcomes and fetal development.

Of methodological and clinical importance, our data demonstrate that race is associated with differential cortisol adaptation in pregnancy. We found that, compared to demographically similar White women, African American women exhibited less robust increases in serum cortisol in the 2nd and 3rd trimesters of pregnancy (Christian et al., 2016). These findings correspond with those of Glynn et al. (2007), who reported lower cortisol among African American women in late pregnancy as compared to Whites, as well as higher levels of adrenocorticotrophic hormone (ACTH) and lower CRH.

Differential cortisol adaptation by race may directly affect fetal development and birth outcomes, and also exert indirect effects, via related processes including production of brain derived neurotrophic factor (BDNF) - a neurotrophin involved not only in fetal brain development, but also in placental function. In correspondence with racial differences in cortisol adaptation across pregnancy, we observed associations between higher cortisol levels and lower serum levels of BDNF (Christian et al., 2016). Further, lower serum BDNF in late pregnancy predicted risk for delivering a low birth weight baby. While this effect was observed in both African Americans and Whites, a moderating effect of race was observed, whereby the prediction line among African Americans was shifted upward due to paradoxically higher BDNF in this group. These data speak to the complex interplay amongst neuroendocrine mediators – the functioning of a given biomarker is dependent on the overall milieu in which it exerts its effects. Altogether, data on CRH, cortisol, and BNDF highlight the importance of considering moderating effects of race and ethnicity.

3. Inflammation

Intricately linked with HPA functioning, the maternal immune system changes substantially in parallel to support fetal development. Localized inflammatory responses at the site of implantation appear essential to successful pregnancy (Mor et al., 2011). Moreover, systemically, elevations in some serum inflammatory markers (e.g., IL-6, TNF-α) are observed across the course of pregnancy (e.g., Christian and Porter, 2014). However, excessive inflammation is incompatible with healthy pregnancy; preterm compared to term delivery has repeatedly been linked with elevations in proinflammatory cytokines in maternal serum and amniotic fluid in the context of infection as well as idiopathic cases (Cappelletti et al., 2016; Muglia and Katz, 2010). Inflammation can promote early delivery by triggering contractions, cervical ripening, and rupture of the membranes.

Relationships between psychological functioning (i.e., depression, anxiety), and inflammation are seen in adults across the life span (Kiecolt-Glaser et al., 2015; Segerstrom and Miller, 2004; Toker et al., 2005). Accumulating evidence from our group and others show that, despite substantial immune changes, effects of anxiety and depression on inflammation are observed in pregnancy, with elevations in serum proinflammatory cytokines and exaggerated proinflammatory cytokine production among women reporting higher perceived stress, depressive symptoms, or history of trauma (for review see Christian, 2014; Osborne and Monk, 2013). For example, our data link higher depressive symptoms during pregnancy to elevations in serum IL-6 and TNF-α (Christian et al., 2009), as well as exaggerated inflammatory responses to the in vivo immune challenge of seasonal influenza virus vaccination (Christian et al., 2010). Together, studies in this area indicate that pregnant women with particular psychological risk factors may experience higher daily exposure to inflammatory mediators, as well as exaggerated responses to biological challenges.

Closely tied with mood and anxiety, effects of sleep on inflammatory processes also warrant attention. Poor sleep – as operationalized by short sleep duration (objectively and subjectively assessed) and poor subjective sleep quality – has been linked with inflammation in numerous studies throughout the lifespan (Irwin et al., 2016). Notably, the deleterious inflammatory effects of poor sleep appear to be stronger among women than men (Irwin et al., 2016). The effects of sleep on inflammation in pregnancy are only beginning to be explored (e.g., Blair et al., 2015; Okun and Coussons-Read, 2007, 2006). In a racially diverse sample of 138 pregnant women, we found that, among African American women only, poor subjective sleep quality predicted elevations in serum IL-8, which corresponded to risk for shortened gestation (Blair et al., 2015). Importantly, in this cohort, no significant differences in sleep quality were observed by race. These data suggest that, in the context of similar exposure to poor sleep, African American women have heightened vulnerability to experience adverse physiological sequelae. Subsequent data from our lab confirmed a similar effect in a different cohort assessed at early postpartum. In this study of 69 women (32 African American, 37 White), poorer subjective sleep quality predicted greater ex vivo LPS-stimulated production of both IL-6 and IL-8 by PBMCs among African American women, but not Whites (Christian et al., 2018). Coupled with greater overall exposure to sleep disturbances and short sleep, racial differences in susceptibility to sleep-induced

immune dysregulation may contribute to marked racial disparities in perinatal health outcomes in the US.

Of relevance in the context of inflammation, infections including bacterial vaginosis and chorioamniotitis contribute considerably to risk for spontaneous preterm birth (Cappelletti et al., 2016; Goldenberg et al., 2008, 2000). While infection is rarely a causal factor in births occurring at > = 34 weeks, it does contribute to most cases of birth at < 30 weeks (Goldenberg et al., 2000). These types of infections are more common among African Americans than Whites. Psychosocial stress has been associated with increased risk for bacterial vaginosis during pregnancy (Nansel et al., 2006). As described earlier, stress is also associated with exaggerated inflammatory responses to biological challenges (Christian et al., 2010; Coussons-Read et al., 2007). Thus, racial differences in stressor exposure may contribute to both occurrence and response to infection during pregnancy.

Across studies of psychological factors, contrasting results are seen with regard to which specific constructs (e.g., perceived stress, depression, trauma) are related to inflammation. Differing results may be attributable, in part, to differences in study samples including race and socioeconomic background. In addition, other exposures, such as obesity (Cassidy-Bushrow et al., 2012) and sleep disturbance (Okun et al., 2013) may serve as moderators which can obscure or heighten observed effects. Thus, while literature in this area is growing, understanding is far from complete. As in the literature linking psychological factors to birth outcomes, literature in relation to inflammatory regulation lacks a focus on clinical diagnoses (e.g., clinical depression, insomnia) and objective assessment of sleep per actigraphy. In addition, given the potential for confounding as well as moderating effects, simultaneous assessment of psychological functioning and sleep health would greatly forward understanding.

Finally, in terms of clinical applicability, the ultimate physical health implications of stress and sleep-related inflammatory dysregulation in pregnancy remain largely unknown. One study has linked maternal anxiety with shortened gestation via inflammatory mechanisms; among 173 women (67% Hispanic, 14% White, 11% African American), the association between anxiety and gestational age at birth was mediated by serum IL-6 & TNF-α (Coussons-Read et al., 2012). As described earlier, our data from 132 pregnant women (79 African American) demonstrated that elevations in serum IL-8 mediated the relationship between poor subjective sleep quality and shortened gestation in African American women (Blair et al., 2015). Altogether, data on inflammation as a mediator linking psychological health or sleep with perinatal health outcomes is very limited.

4. Cellular aging

Enhanced inflammatory activity often corresponds with underlying cellular aging. The risk for adverse perinatal health outcomes increases with maternal chronological age. Importantly from a prediction and clinical intervention standpoint, the role of biological indicators of aging is not fully delineated, even though women of the same chronological age exhibit variability in cellular indicators of aging (Müezzinler et al., 2013). Psychological

stress and sleep disturbance may increase risk for adverse perinatal health outcomes in part by promoting biological aging.

The length of telomeres, DNA-protein complexes located at the end of chromosomes, is a critical indicator of biological aging. Likened to the aglets – plastic protective tips – on shoelaces that prevent unraveling, telomeres play a crucial role in the protection of genetic stability (Blackburn, 2005). Telomeres shorten every time that a cell replicates. When shortened to a critical length, genomic instability occurs, along with cessation of cellular replication and cell senescence - the end state of the cell when it no longer divides (Campisi and di Fagagna, 2007). Senescent cells promote further cellular aging via the release of inflammatory mediators and stimulating inflammatory processes (Freund et al., 2010; O'Donovan et al., 2011).

As a sensitive indicator of cellular aging, shorter telomere length has predictive value in relation to numerous age-related health outcomes, including myocardial infarction, stroke, cancer, and all-cause mortality (D'Mello et al., 2015; Marioni et al., 2016; Rode et al., 2015). Importantly, there is a considerable literature indicating that the placenta has a finite lifespan. In pregnant women, placental senescence as indicated by shorter telomere length and other indicators of biological aging in placental cells has been linked with preeclampsia, intrauterine growth restriction, and obstetric complications including increased risk for fetal death at late term (Biron-Shental et al., 2016; Cox and Redman, 2017; Davy et al., 2009; Maiti et al., 2017; Sultana et al., 2018; Toutain et al., 2013). Moreover, racial differences in placental aging have been implicated in racial disparities in birth outcomes (Jones et al., 2017). From a clinical application standpoint, placental measures of biological aging such as telomere length can only be obtained invasively, with considerable risk, or after delivery.

Data on telomere length in maternal cells (e.g., circulating leukocytes) in relation to perinatal health outcomes is relatively limited. However, available data suggest that shorter maternal leukocyte telomere length is observed in gestational diabetes, recurrent miscarriages, and idiopathic pregnancy loss (Hanna et al., 2009; Harville et al., 2010) suggesting accelerated reproductive aging may drive pregnancy complications. For example, in a case-control study, women with history of recurrent miscarriage (n = 95) had shorter age-adjusted telomeres than women from the general population or those with healthy pregnancy after 37 years of age (Hanna et al., 2009). Overall, this is an untapped area which presents a clear potential path to clinical application.

In relation to psychological health, peripheral blood telomere length has been examined in relation to depression, anxiety, and other types of exposure to subjective and objective stress in numerous studies (Adler et al., 2013; Carroll et al., 2013a; Carroll et al., 2013b; Entringer et al., 2011; Epel et al., 2004; Hanssen et al., 2017; Kiecolt-Glaser et al., 2011; Mitchell et al., 2018; Needham et al., 2015; Puterman et al., 2015; Ridout et al., 2015a, b; Schutte and Malouff, 2015; Shalev et al., 2013; Vance et al., 2018). Altogether, these data suggest the presence of effects, which are moderated by specific risk factors (e.g., age, sex, symptom severity). For example, in a population-based study of 1290 adults, shorter telomere length was observed among women with generalized anxiety disorder or panic disorder, an effect not observed in men (Needham et al., 2015). Further, shorter telomeres were observed

among those with major depressive disorder, but only among those who were treated pharmacologically, suggesting effects only in the context of more severe symptomatology (Needham et al., 2015).

In addition, poor sleep quality and shorter sleep duration have been linked with shortened leukocyte telomeres in numerous studies (Carroll et al., 2016b; Cribbet et al., 2014; Jackowska et al., 2012; Prather et al., 2015, 2011). Data from our group demonstrated that early life exposure to socioeconomic adversity as well as current social support predicted differences in PBMC telomere length in women assessed during pregnancy and postpartum (Mitchell et al., 2018). However, the extent to which maternal anxiety, mood, and sleep health may affect risk for adverse birth outcomes through cellular aging remains to be determined.

Also of note, in our study of perinatal women, we observed a trend for African Americans to exhibit longer telomeres than Whites, after accounting for chronological age ($p = 0.10$) (Mitchell et al., 2018). This effect of race is consistent with prior research suggesting that longer telomeres are observed in African Americans (Hunt et al., 2008). This difference may be accounted for by racial differences in biological factors, particularly differential rates of replication of hematopoietic stem cells (Hunt et al., 2008). Regardless of the cause, the predictive value of telomere length for health outcomes may be moderated by race. Data from samples of sufficient size and racial diversity are needed to permit statistical power to empirically determine if race-specific associations are present. In addition, as described earlier, shortened gestation shows intergenerational transmission of risk; women who were born preterm or low birth weight have increased risk for having preterm and low birth weight babies themselves – particularly African American women (Smid et al., 2017). The potential role of prenatal programming through biological aging pathways remains to be explicated.

5. Social genomics

As evidenced by expanding data in this area, transcriptomics approaches hold promise for evaluating both inflammation and cellular aging. As compared to circulating indicators of inflammation, whole genome transcriptional analysis provides a comprehensive and unbiased assessment of the inflammatory pathways with unique advantages in mechanistic understanding at the cellular level as well as greater precision and statistical power. There is growing interest in applying transcriptomics approaches to understanding risk for mood and anxiety disorders (Redei and Mehta, 2015). Relatedly, social genomics approaches in a small but growing literature have demonstrated that psychosocial stress is linked with a specific pattern of gene expression characterized by 1) up-regulation of genes indicative of inflammation, and 2) down-regulation of genes involved in glucocorticoid activity (Cole, 2009; Cole et al., 2011). This pattern has been coined the “conserved transcriptional response to adversity” (CTRA) (Cole, 2009). Similarly, in transcriptomics studies, sleep disturbance has been linked with inflammatory and cell-stress pathways implicated in biological aging (e.g., Carroll et al., 2016a).

In relation to transcriptomics and birth timing, a reasonably large literature has developed. However, it is characterized by notable gaps. First, although spontaneous early births are both much more common and difficult to predict, a systematic review of transcriptomics in preterm birth studies found that 76% focused on medically-indicated cases, predominately preeclampsia (Eidem et al., 2015). Second, despite the remarkable racial disparity observed in early birth in the US, data on African American women are lacking. Third, data inclusive of births occurring between 37–38 weeks gestation (early term births) are limited due to the relatively recent recognition of adverse outcomes associated with this timing. Finally, the vast majority of existing transcriptomics data focus on the placenta, myometrium, or fetal membranes (Eidem et al., 2015). While such data hold great promise for identifying and addressing mechanistic pathways to early birth, they do not provide clinical utility for prediction because they cannot be examined non-invasively during pregnancy. Two published studies (lacking African Americans or behavioral measures) have examined peripheral gene expression and shortened gestation (Enquobahrie et al., 2009; Heng et al., 2016). These data suggest that pregnancies that result in preterm birth are characterized by greater proinflammatory gene expression and differences in cell cycle activity and metabolism indicative of cell stress. Moreover, emerging data link exposure to life stress with inflammatory gene expression in pregnant women (Ross et al., 2018). Further research in this area using racially diverse samples, with a focus on peripheral markers, and representation of spontaneous occurrence of shortened gestation (inclusive of early term birth) is needed to advance this line of inquiry.

A key pathway by which behavioral exposures alter gene expression is via epigenetic modifications. Of particular relevance in the context of perinatal health, such modifications are documented to underlie intergenerational transmission of adversity (Lester et al., 2018; Meaney, 2001). One of several epigenetic mechanisms controlling gene expression, DNA methylation is affected by differential environmental exposures. In mice, chronic and unpredictable maternal separation at 1–14 days increases depressive-like behaviors in adults with accompanying alterations in DNA methylation, affecting gene expression (Franklin et al., 2010). Moreover, these differences in behavior and DNA methylation are, in part, transmitted to subsequent generations (Franklin et al., 2010). Another epigenetic mechanism is altered microRNA (miRNA) expression. Animal models show that stress-induced differences in length of gestation correspond with changes in miRNA expression and these effects are transmitted to subsequent generations (Yao et al., 2014). Thus, complementary data, particularly in animal models, which provide the ability to carefully control environments and study multiple generations, is necessary to explicate the mechanisms underlying differential gene expression.

6. Microbiome

A rapidly expanding literature links the microbiome – particularly the gut microbiome – with mood and behavior. To-date, these studies have overwhelming been conducted in rodent models, and data specific to the perinatal period is limited. For example, a recent systematic review of the literature on microbiota-brain axis in perinatal mood and anxiety disorders identified only 17 peer-reviewed publications for inclusion, ten of which were conducted in mice (Rackers et al., 2018). In contrast to data on mental health, there is a more

sizable literature linking the maternal microbiome, including the vaginal, gut, oral, cervical and even possibly the placental microbiome to birth outcomes and fetal development (Christian et al., 2015; Galley et al., 2014; Hyman et al., 2014b; Lamont et al., 2011; Paropkari et al., 2016; Vinturache et al., 2016). In particular, literature on the vaginal microbiome and birth outcomes is substantial and growing (Hyman et al., 2014a; Prince et al., 2014; Ravel et al., 2011; Stout et al., 2017). Racial differences in the maternal microbiome and relevance to health outcomes are also increasingly being explicated (Human Microbiome Project, C, 2012), however, these data lack integration with the larger literature on mood/anxiety as well as racial disparities in stressor exposure.

Beyond birth outcomes, our own data link temperament in toddlers (18–27 months of age) with differences in gut microbiome composition; in particular greater phylogenetic diversity is observed in association with higher maternal ratings of Surgency\Extraversion (Christian et al., 2015). Our data also link maternal obesity with differences in the gut microbiome in toddlers (Galley et al., 2014), supporting intergenerational transmission of risk. Rodent models support similar intergenerational transmission of risk in relation to behavioral factors; prenatally stressed dams exhibit differences in the gut microbiome which correspond with differences in the gut microbiome and behavior in offspring (Rackers et al., 2018). In addition, the mode of delivery (vaginal versus C-section), considerably impacts the composition of the infant microbiome across multiple body locations (Dominguez-Bello et al., 2010), with potential long-term implication for physical (e.g., obesity) and mental health. Of note, maternal depression and insomnia have been associated with increased risk for delivery by C-section.

In sum, offspring physical, cognitive, and physiological development may be affected via 1) direct effects of the maternal microbiome on the establishment of the offspring microbiome, 2) effects of the maternal microbiome on birth outcomes (birth weight, length of gestation), thereby affecting long-term child health, and 3) effects of maternal psychosocial stress, sleep, and other behavioral factors on mode of delivery – ultimately affecting the composition of the infant microbiome with corresponding health effects. The microbiome is intimately and bi-directionally linked with HPA axis functioning, autonomic nervous system, and immune system, providing compelling avenues of investigation in relation to well-developed lines of research described above. It also provides a compelling target for intervention. Thus, research in this line of inquiry will continue to expand rapidly.

7. Advancing understanding and moving toward clinical translation

Although efforts to integrate findings across the medical and psychology literatures are increasing, to-date these literatures remain largely distinct. Anxiety, depression, and sleep have received limited consideration in studies of biological pathways, and vice versa. Integration of these literatures is needed to fully inform data interpretation and clinical application, as well as provide for appropriate measurement/control of confounds and moderators, clarifying understanding. In addition, the existing literature focuses disproportionately on medically-indicated cases; spontaneous occurrence of shortened gestation is both more prevalent and unpredictable. Finally, given the remarkable racial disparities in perinatal health, and evidence for moderating effects of race in relation to

stress physiology, better representation of African American women as well as addressing the unique considerations of women of Hispanic ethnicity (e.g., the role of acculturation) is needed in studies linking behavior, biology, and birth outcomes moving forward. With a rigorous transdisciplinary approach addressing these gaps, the next decade of investigation holds great promise for clinical impact in addressing racial disparities as well as ameliorating effects of stress on perinatal health more broadly across women of all races/ethnicities.

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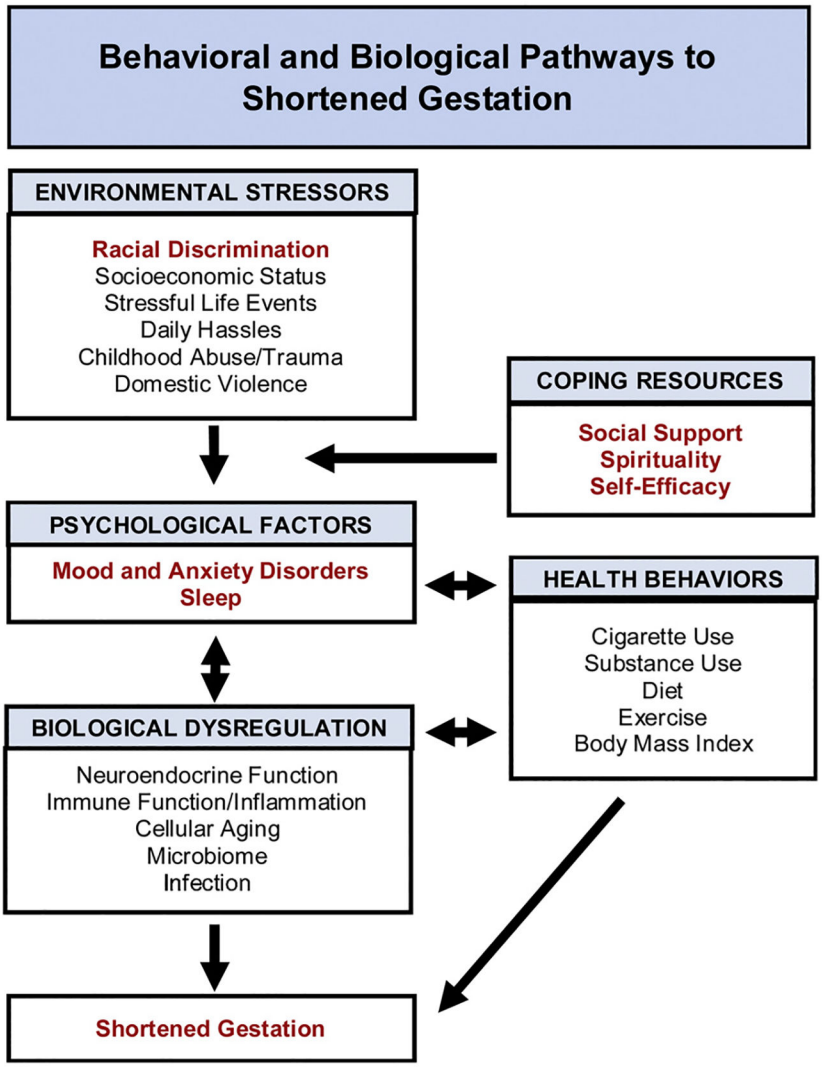

Fig. 1.

Behavioral and Biological Pathways to Shortened Gestation. Racial discrimination and other objective stressors are psychosocial exposures that increase the risk for shortened gestation. These are not necessarily clinically modifiable at the individual level. However, as reviewed herein, biological sequelae (neuroendocrine function, immune function, cellular aging, microbiome) present promising targets for identifying risk and targeting intervention. These may directly impact delivery length, contributing to spontaneous occurrence of shortened gestation. In addition, these pathways can contribute to medically-indicated shortened gestation by increasing risk for clinical conditions including pre-eclampsia and gestational diabetes. Pathways bolded in red print are emphasized in the current review.