HHS Public Access

Author manuscript

Matern Child Health J. Author manuscript; available in PMC 2018 January 01.

Published in final edited form as:

Matern Child Health J. 2017 January ; 21(1): 147–155. doi:10.1007/s10995-016-2103-0.

Cumulative Physiologic Dysfunction and Pregnancy: Characterization and Association with Birth Outcomes

Kimberly Schmitt McKee, PhD, MPH,
Department of Public Health Sciences, University of Rochester Medical Center

Christopher Seplaki, PhD,
Department of Public Health Sciences, University of Rochester Medical Center

Susan Fisher, PhD, MS,
Department of Clinical Sciences, Temple University School of Medicine, Temple Clinical Research Institute, and Population Research, Fox Chase Cancer Center

Susan Groth, PhD, RN, WHNP-BC, FAANP, and
School of Nursing, University of Rochester Medical Center

I. Diana Fernandez, MD, PhD, MPH
Department of Public Health Sciences, University of Rochester Medical Center

Abstract

Objective—To characterize cumulative physiologic dysfunction (CPD) in pregnancy as a measure of the biological effects of chronic stress and to examine its associations with gestational age and birth weight.

Methods—Women ≤28 weeks gestation were enrolled from obstetric clinics in Rochester, NY and followed through their delivery. CPD parameters included total cholesterol, Interleukin 6 (IL-6), high sensitivity-C-reactive protein (hs-CRP), systolic and diastolic blood pressure, body mass index (BMI) at <14 weeks gestation, glucose tolerance, and urinary albumin collected in the third trimester. Linear regression was used to estimate the association between physiologic dysfunction and birth weight and gestational age, respectively (N=111).

Results—CPD scores ranged from 0-6, out of a total of 8 parameters (Mean 2.09; SD=1.42). Three-fourths of the participants had a CPD score of 3.0 or lower. The mean birth weight was 3,397 grams (SD=522.89), and the mean gestational age was 39.64 weeks (SD=1.08). CPD was not significantly associated with either birth weight or gestational age (p=0.42 and p=0.44, respectively).

Conclusion—CPD measured at >28 weeks was not associated with birth weight or gestational age. Refinement of a CPD score for pregnancy is needed, taking into consideration both the component parameters and clinical and pre-clinical cut-points for risk scoring.

Corresponding author: Kimberly McKee PhD, MPH, Department of Family Medicine, University of Michigan, 1018 Fuller Street, Ann Arbor Michigan 48104, kimckee@med.umich.edu, (P): 734-998-7120, (F): 734-998-7335.

Conflict of Interest

None of the authors have a conflict of interest to declare.

Keywords

cumulative physiologic dysfunction; birth weight; gestational age; allostatic load; pregnancy

Background

Understanding the etiologies of preterm birth (PTB) and low birth weight are among the most pressing public health issues (Institute of Medicine Committee on Understanding Premature Birth and Assuring Healthy Outcomes 2007), not only for their immediate costs to society but also for their latent effects on offspring risk of cardiovascular disease and type 2 diabetes (Barker 1995, Barker et al. 1989). Previous studies have demonstrated an inconsistent association between chronic maternal stress and adverse birth outcomes, in part due to heterogeneity in the scales and constructs that have been employed in the literature (Hobel et al. 2008). Prior research has shown the strongest associations with PTB using perceived stress, pregnancy-related anxiety, and life events scales early in pregnancy (Witt, 2014, Hobel and Barrett, 2008, Shapiro, 2013).

Population-based and animal studies suggest maternal stress is associated with adverse birth outcomes through neuroendocrine, inflammatory, and behavioral pathways. Stress has a cascading impact on an individual's appraisal and perception, biology, and subsequent level of adaptation, which incorporates multiple domains of stress (e.g. environmental, psychological, and biological) and time periods in a woman's life (e.g. preconception, the inter-conception period, and pregnancy) that might affect the health of her offspring although the underlying biological mechanisms remain poorly understood (Muglia and Katz 2010).

Allostatic load, which is hypothesized to reflect cumulative physiological dysfunction (CPD), is a conceptual framework for describing the toll imposed on the body from the ongoing activation of the stress response that often manifests in sub-clinical variations in neuroendocrine, cardiovascular, metabolic, inflammatory, and renal domains (McEwen 1998). It is cumulative in the sense of capturing the latent biological effects of chronic stress across multiple physiological systems (i.e. the sum of a range of parameters) and has been theoretically posited to be causally related to both PTB and low birth weight (Gupta et al. 2015, Lu and Halfon 2003, Shannon et al. 2007). It may also be one possible mechanism driving health disparities; black women and individuals of lower socioeconomic status, both of whom are more likely to have adverse birth outcomes (Martin et al. 2010), have been shown to have higher physiologic dysfunction burdens (Geronimus et al. 2006). Although biologically plausible in explaining birth disparities, how CPD may be manifested and measured in pregnancy is largely unknown.

The purpose of this study was to characterize CPD in pregnancy as a measure of the biological effects of chronic stress and to examine its associations with gestational age and birth weight. We hypothesized that higher maternal physiologic dysfunction scores would be associated with shorter gestational lengths and lower infant birth weights.

Methods

Study Population

The study population was drawn from two sources: 1) women enrolled in the e-Moms of Rochester Study, and 2) pregnant patients from one of two obstetric (OB) clinic settings. e-Moms is a randomized clinical trial designed to prevent excessive weight gain and postpartum weight retention using electronically based behavioral interventions in pregnant women from Monroe County, New York (Fernandez et al. 2015). Pregnant women from the e-Moms study who had agreed to be re-contacted about additional research studies and had not yet delivered by October 2012 were contacted via email and phone and invited to participate in the current study. If interested, a member of the study staff met participants at their next OB visit or home to consent, enroll, and complete data collection. Similarly, between March 2013 and August 2013, women at the OB offices meeting study criteria were presented information about the study from clinic staff, and if interested, were instructed to see study staff, where they were screened, consented, and enrolled. Per participants' preference, follow-up was conducted at a clinic visit or at home.

To be eligible for the study, women had to be 18 – 35 years of age and <28 weeks gestation at the time of enrollment, plan to deliver in one of the four hospitals in Monroe County, have a singleton pregnancy, and read English. Women who had a body mass index (BMI) > 35.0 kg/m^2, had blood pressure treated with medication at enrollment, and other chronic diseases were excluded; further details on the cohort have been published elsewhere (Fernandez et al, 2015). Miscarriages and stillbirths (i.e. neonatal death within 24 hours of birth) were excluded. The University of Rochester Institutional Review Board approved the study.

Data Collection

Data collection occurred at three time points: 1) prenatal survey at enrollment, 2) at a second visit ≥28 weeks we collected dried blood spots, and 3) after delivery the birth record and prenatal chart were abstracted for the remaining physiologic dysfunction parameters and outcome variables.

The methods of obtaining, analyzing, and applying dried blood spot (DBS) biomarkers for population research have been published by McDade et al. (McDade et al. 2007). Blood spots were collected by finger prick onto Whatman 903 protein saver cards and dried for 4 hours overnight before being packaged with dessicant and stored in a -20 degree freezer. Sample degradation is minimal at room temperature for at least two weeks (McDade et al. 2007). Interleukin-6 (IL-6), cholesterol, and high sensitivity C-reactive protein (hs-CRP) content in the DBS were measured using previously published methods (Lakshmi 2012, McDade et al. 2004, Ramakrishnan et al. 2001). The methods were validated by comparing DBS measurements with venipuncture samples, the gold-standard for validation in a separate cohort (McDade et al. 2004). Samples were run in batches using biological duplicates (when the size of the blood spots allowed). Inter-assay coefficients of variation ranged from 6.7-12%, and intra-assay coefficients of variation ranged from 7.1-17% (with the exception of IL-6 because there was not enough sample for biological duplicates) with

the following detection limits: IL-6 (0.37 pg/mL), hs-CRP (30ng/mL), and total cholesterol (43 ng/mL), respectively.

Measures

There were two primary outcomes: birth weight and gestational age. Birth weight, the primary dependent variable, was abstracted from the infant medical chart and treated continuously in grams. Gestational age was measured in weeks using the best estimate of gestational length abstracted from the delivery record; this method of ascertainment in the clinical record integrates information of maternal last menstrual period, ultrasound dating, and clinical exam data. All of the women had a first trimester ultrasound that was used to confirm gestational dating.

The CPD score was constructed from systolic and diastolic blood pressure, early pregnancy BMI (i.e. <14 weeks gestation), urinary albumin, and one-hour glucose tolerance test. These parameters were abstracted from the prenatal medical record at the visit closest to biomarker collection (often the same day). These data were combined with IL-6, high sensitivity CRP, and total cholesterol biomarkers from DBS. All parameters were based on candidate measures from allostatic load domains previously published (Seeman et al. 1997). The range of parameter measurement was 28-40 weeks, and the mean was 31.84 weeks. In a separate analysis we adjusted for gestational age at biomarker collection, but it did not qualitatively change the results of the study.

Since this was one of the first studies of CPD in pregnancy, we used CPD parameters used in non-pregnant populations, but we adapted three for pregnancy for pragmatic and scientific reasons. For example, waist-hip ratio is a superior measure for central adiposity in the general population (Gelber et al. 2008), but it is not a valid measure of metabolic risk in pregnancy. Similarly, rather than hemoglobin A1C, we used values from the glucose tolerance test, which is the standard of care for screening for insulin sensitivity in pregnancy (i.e. diagnosis of gestational diabetes is based on serial testing of the one-hour and three-hour challenge) (Gupta et al. 2015). The inflammatory markers we chose, IL-6 and hs-CRP, have been used in previous allostatic load studies to capture sub-clinical pro-inflammatory states (Seeman, 2009, Singer, 2004), as well as in studies examining the biological effects of stress during pregnancy and their effect on gestation (Azar, 2013, Blackmore, 2014, Heibisch et al 2004). While cholesterol, blood pressure, and other cardio-metabolic parameters may shift during pregnancy to meet the demands of the growing fetus, recent evidence suggests that maternal metabolic profiles (including early-pregnancy BMI) are associated with offspring adiposity likely due to altered fetal programming (Daraki, et al, 2015). Urinary albumin was selected because it is routinely collected in pregnancy, and while proteinuria may be common in pregnancy, it may also signal infections as well as more serious conditions such as kidney obstructions or pre-eclampsia. Furthermore, although there may be differences in the values of different parameters between pregnant and non-pregnant women, our study only included pregnant women and was designed to detect sub-clinical, relative differences between pregnant women.

In deriving the CPD score, we considered both clinical as well as sub-clinical cut-points previously published in studies among the general population (Singer et al. 2004, Seplaki et

al. 2006). To construct the elevated risk zone score of physiologic dysfunction, individuals were classified according to quartile of each of the discrete physiologic measures, and cut-offs were established at the 75th percentile of the population distribution according to convention in the literature. A point was assigned to each individual's score for each component that exceeded the threshold cut-point. Covariates included: maternal age at enrollment, marital status, maternal educational attainment, household income, race, and ethnicity based on factors thought to be associated with birth outcomes or CPD. We also included smoking status during pregnancy (i.e. smoking status assessed <28 weeks gestation by self-reported survey). Only covariates that improved the model fit were retained in the adjusted models. Model selection was determined by improvements in the adjusted R-squared as well as inspection of changes in the F-test for the overall model compared to a model with only an intercept.

Statistical Analysis

Descriptive statistics were calculated to characterize physiologic dysfunction in this sample of pregnant women. Bivariate analyses examining the association between CPD and each categorical covariate were first conducted using ANOVA tests to assess the mean differences in CPD across all categories of covariates. Multivariable ordinary least square models were used to estimate the association of physiologic dysfunction with birth weight and gestational age, respectively, while controlling for potential confounders. A sensitivity analysis was conducted to examine the effect of omitting large for gestational age (LGA) infants and women diagnosed with gestational diabetes (i.e. observations in the far right tail of the birth weight distribution) who were more likely to have macrosomic infants. We utilized multivariable ordinary least square models to estimate the association between CPD and birth weight once these observations were removed.

Results

A total of 181 women were recruited for the study, of whom 168 were retained until delivery. Two of the women delivered prior to 28 weeks gestation, two moved prior to delivery, and there was one stillbirth at 28 weeks. Seven women were lost to follow-up or withdrew their consent. Of the 168 women on whom delivery data were available, N=111 had complete data for analysis based on availability of the DBS since the amount of sample that was needed was greater than initially planned and collected.

Demographic and other characteristics are shown in Table 1. A third of the women were Black, and 17% were Hispanic. Most were in a relationship (42%) or married (39%), but only a third had an income of >$50,000 per year. Approximately 13.5% of the sample reported smoking during their pregnancy, and the majority of the sample had an early pregnancy BMI within the normal range (i.e. 18.5-<25kg/m^2).

The birth weight of the sample was approximately normally distributed with a mean of 3397 grams (SD=522.89), of which 3.6% were low birth weight infants (<2,500 grams) (Table 2). The distribution of gestational age was also approximately normal with a mean of 39.67 weeks (SD=1.08). The proportion of PTBs among women retained through delivery was 1.8%, which was lower than expected (Martin et al. 2010) although births <28 weeks

gestation were excluded due to the design of the study. Approximately 8.11% of the infants were small for gestational age (SGA), and 4.5% were considered LGA based on clinical diagnosis abstracted from the medical chart. The mean gestational age at blood spot collection was 31 weeks.

Among the pregnant women sampled, CPD scores ranged from 0-6, out of a total of 8 parameters. The mean was 2.09 (SD=1.42). The distribution was slightly right-skewed, with 75% of women having a score of 3 or less. The interquartile range was 2.0. The 75th percentile for each parameter of the CPD score is listed in Table 3. Several of the specific components' cut-points using this methodology were similar to established clinical parameters although the cut-points for systolic and diastolic blood pressure were lower in our pregnant sample.

We did not find statistically significant associations between CPD score and birth weight in the unadjusted (p=0.59) or in the adjusted model (p=0.42) when accounting for race, income, and smoking status. In the adjusted analysis, there was a reduction in birth weight of 276.77 grams for women with household incomes <$20,000 per year (p=0.04) and a 298.98 gram reduction for women with household incomes $20,000-$50,000 per year compared to women with household incomes >$50,000 per year (p=0.035) (Table 4).

A sensitivity analysis was also conducted to examine the effect of omitting LGA infants and women diagnosed with gestational diabetes. When these observations were removed from the dataset, the beta-coefficient for CPD was negative as hypothesized although it was not significant (p=0.68). There was a significant reduction in birth weight of 350.69 grams for women with household incomes <$20,000 per year and a 280.08 gram reduction for women with household incomes $20,000-$50,000 per year compared to women with household incomes >$50,000 per year (data not shown). Black race was also significantly inversely associated with birth weight in this subset (β=-223.74; p=0.02). Although birth weight and gestational age are related, they are distinct outcomes that may differ in their underlying pathophysiology. Therefore, a multivariable model adjusted for gestational age was also estimated. We found that for each week of gestation at birth, there was an increase of 170.34 grams in birth weight (< .001) although it did not qualitatively change the results.

We also examined gestational age, treated continuously, as an outcome. In the bivariate analysis and the unadjusted model, gestational age was not associated with CPD score (p=0.56). After adjustment for race, income, education, relationship status, and smoking, CPD remained insignificant, but the coefficient was negative as hypothesized (β= -0.06 weeks; p= 0.44) (Table 5).

Discussion

Our analysis is one of the first studies to examine CPD in pregnancy and the first to incorporate inflammatory biomarkers into a measure of CPD in pregnancy. As such, it required adapting a measure of CPD using methods for characterizing allostatic load in the general population in relation to health outcomes more common in older adults (Seplaki et al. 2004, Logan and Barksdale 2008) for one in pregnancy.

Only a few studies have examined physiologic dysfunction in relation to pregnancy, most of which measured allostatic load prior to or after pregnancy (Wallace and Harville 2013, Wallace et al. 2013, Morrison et al. 2013). In one study, CPD parameter components were collected an average of 6.8 years prior to conception (Wallace et al. 2013) with a mean age of 13 years, which likely did not adequately capture the divergence in allostatic load trajectories as women age that Geronimus et al. have reported (Geronimus et al. 2006). Although blood was collected via venipuncture preconceptionally rather than from DBS in the third trimester of gestation, the upper quartile of allostatic load overall was 3 in both studies, and the means and standard deviations were similar. Our results were also consistent with Morrison et al. in terms of their description and distribution of physiologic dysfunction in pregnancy although they did not examine birth outcomes (Morrison et al. 2013).

Using NHANES data, Hux et al. found that women with a history of SGA or PTBs had higher physiologic dysfunction burdens postpartum than did those with normal birth weight outcomes when adjusted for BMI (Hux et al. 2014). Temporality was not established in their study, which given the potential bi-directional association between adverse birth outcomes and physiologic dysfunction, is an important consideration for future research.

In the one other study to date that has attempted to measure allostatic load in pregnancy, blood samples from 42 women at 26-28 weeks gestation were assayed for cholesterol, glycosylated hemoglobin, dehydroepiandrosterone-sulfate, and serum cortisol (not a bioavailable form of cortisol) and were added together with systolic blood pressure (Wallace and Harville 2013). In contrast to our results, black women unexpectedly had a significantly lower allostatic load index than white women, and gestational age at birth was the only outcome significantly associated with allostatic load although the magnitude of the effect was small (adjusted β=-0.18, 95 % CI -0.35, 0.00). The extent to which their results may have been impacted by a lack of inflammatory markers in their measure is unknown.

While there was some variation in the pregnancy-specific components of our measure of CPD from those used previously in the literature (Dowd et al. 2009, Seeman et al. 2010, Seeman et al. 2001), our measure expanded upon the few studies of allostatic load in women of reproductive age by including cardiovascular, metabolic, inflammatory, and kidney function parameters. We replaced waist-to-hip ratio by early pregnancy BMI abstracted from the medical chart, and glycosylated hemoglobin was replaced by the one-hour glucose tolerance challenge test (i.e. 50 grams of administered glucose)(Gupta et al. 2015, Committee on Practice Bulletins--Obstetrics 2013).

In terms of cut-points for the CPD components in our study, the pregnancy risk zones were very similar to those observed in non-pregnant populations (Seeman et al. 2010, Peek et al.). Following the literature (Singer et al. 2004), risk zones were dichotomized at >75% percentile in our study, and these were quite consistent with clinical cut-points for non-pregnant individuals, with the exception of the glucose tolerance test results, in five out of the eight CPD components.

A limitation to our measure of CPD for pregnancy is that it did not contain any of the “primary neuroendocrine mediators” components, such as cortisol, used in the literature

(McEwen 1998, Seeman et al. 2001). Valid measurement of cortisol is difficult; due to its diurnal pattern, salivary cortisol (i.e. its active unbound form) must be collected at multiple times throughout the day, beginning with early morning and should be collected on more than one day, given its wide variability within individuals (Dowd et al. 2009, Smyth et al. 1997). It is also not known how cortisol patterns may vary during pregnancy. For this reason, our CPD measure for pregnancy is more a reflection of the construct of physiologic dysfunction than allostatic load per se.

In our sensitivity analysis—in which women with LGA infants and gestational diabetes were removed from the sample (n=11)—the significance of our results did not change, but the coefficient for CPD became negative in the model for birth weight, as we initially hypothesized. This may suggest that rather than being an issue of power, some of the CPD parameters and the theoretical model underlying their constructs, should continue to be improved as to better reflect processes of dysregulation among pregnant women, which may differ from that in the general population. Higher values from the glucose tolerance test, for example, were associated with an increase in birth weight (data not shown), which was not entirely surprising given the known association between gestational diabetes and macrosomia and may underscore the need to modify the parameters of CPD for pregnancy and to refine the theoretical model for allostatic load in pregnancy.

Other limitations to our study exist. The power of the study was impacted by the small sample size and the fewer than anticipated low birth weight and preterm infants. The enrollment criteria for our study was based on the parent clinical trial, which may have limited the generalizability of our study by excluding severely obese women, women with multiples, and women with certain health conditions which may have lowered the PTB rate in our study. The lower than expected PTB rate in our study could have shifted our results towards the null. Furthermore, we used DBS for collection of the inflammatory biomarkers and cholesterol, and while the IL-6 and CRP results obtained appear consistent with other studies that have examined inflammatory markers in pregnancy that were collected via venipuncture (Hebisch et al. 2004, Coussons-Read et al. 2007), how our cholesterol values may have compared to those from venipuncture is unknown (Crimmins et al. 2014).

In this study, biomarker collection occurred any time in the third trimester. However, CPD may change over the course of pregnancy due to normal physiologic changes associated with pregnancy (e.g. blood volume increases up to 50%), and thus may need to be assessed multiple times in pregnancy and ideally before conception (Wallace et al. 2013, Morrison et al. 2013). It is also unknown if the source of IL-6 collection could have made a difference given that it can be obtained from amniotic fluid, cervico-vaginally, or from peripheral blood. A more nuanced understanding of the stress response specifically in pregnancy may improve the timing of biomarker collection to more accurately reflect the relevant window of exposures and the biological pathways that result in birth disparities.

Acknowledgments

The first author was supported by a T32 National Institutes of Health Training Grant at the time of the study. The e-Moms of Rochester study was supported by a grant from the EARLY Trials, National Heart, Lung, and Blood Institute and the Eunice Kennedy Shriver National Institute of Child Health and Human Development, Grant No.

HL096760. The second author was supported by a Mentored Research Scientist Development Award number K01AG031332 from the National Institute on Aging. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute on Aging or the National Institutes of Health. We would also like to acknowledge the Obstetrics and Gynecology and Ultrasound practices who contributed their time and personnel resources to this study.

References

1. Institute of Medicine Committee on Understanding Premature Birth and Assuring Healthy Outcomes. Preterm Birth: Causes, Consequences, and Prevention. Washington (DC): National Academies Press (US); 2007.
2. Barker D. Fetal origins of coronary heart disease. BMJ. 1995; 311(6998):171–174. [PubMed: 7613432]
3. Barker D, Osmond C, Winter P, Margetts B, Simmonds S. Weight in infancy and death from ischaemic heart disease. Lancet. 1989; 2(8663):577–580. [PubMed: 2570282]
4. Hobel C, Goldstein A, Barrett E. Psychosocial stress and pregnancy outcome. Clinical Obstetrics and Gynecology. 2008; 51(2):333–348. [PubMed: 18463464]
5. Muglia L, Katz M. The enigma of spontaneous preterm birth. New England Journal of Medicine. 2010; 362(6):529–535. [PubMed: 20147718]
6. McEwen BS. Stress, adaptation, and disease: allostasis and allostatic load. Annals of the New York Academy of Sciences. 1998; 840(1):33–44. [PubMed: 9629234]
7. Gupta Y, Kalra B, Baruah MP, Singla R, Kalra S. Updated guidelines on screening for gestational diabetes. International Journal of Women's Health. 2015; 7:539–550.
8. Lu M, Halfon N. Racial and ethnic disparities in birth outcomes: a life-course perspective. Maternal and Child Health Journal. 2003; 7(1):13–30. [PubMed: 12710797]
9. Shannon M, King TL, Kennedy HP. Allostasis: a theoretical framework for understanding and evaluating perinatal health outcomes. Journal of Obstetric, Gynecologic, and Neonatal Nursing. 2007; 36(2):125–134.
10. Martin, J., Hamilton, B., Sutton, P., Ventura, S., Mathews, T., Osterman, M. National Vital Statistics Report. Washington (DC): Department Health and Human Services, Centers for Disease Control and Prevention, Division of Vital Statistics; 2010.
11. Geronimus A, Hicken M, Keene D, Bound J. Weathering and age patterns of allostatic load scores among blacks and whites in the United States. American Journal of Public Health. 2006; 96(5): 826–832. [PubMed: 16380565]
12. Fernandez ID, Groth SW, Reschke JE, Graham ML, Strawderman M, Olson CM. eMoms: electronically-mediated weight interventions for pregnant and postpartum women. Study design and baseline characteristics. Contemporary Clinical Trials. 2015; 43:63–74. [PubMed: 25957183]
13. McDade T, Williams S, Snodgrass J. What a drop can do: dried blood spots as a minimally invasive method for integrating biomarkers into population-based research. Demography. 2007; 44(4):899–925. [PubMed: 18232218]
14. Lakshmi R, et al. Measurement of cholesterol and triglycerides from a dried blood spot in an Indian Council of Medical Research-World Health Organization multicentric survey on risk factors for noncommunicable diseases in India. Journal of Clinical Lipidology. 2012; 6(1):33–41. [PubMed: 22264572]
15. McDade TW, Burhop J, Dohnal J. High-sensitivity enzyme immunoassay for C-reactive protein in dried blood spots. Clinical Chemistry. 2004; 50(3):652–654. [PubMed: 14981035]
16. Ramakrishnan L, Reddy KS, Jailkhani BL. Measurement of cholesterol and triglycerides in dried serum and the effect of storage. Clinical Chemistry. 2001; 47(6):1113–1115. [PubMed: 11375303]
17. Seeman T, Singer B, Rowe J, Horwitz R, McEwen B. Price of adaptation--allostatic load and its health consequences. MacArthur studies of successful aging. Archives of Internal Medicine. 1997; 157(19):2259–2268. [PubMed: 9343003]
18. Gelber RP, Gaziano JM, Orav EJ, Manson JE, Buring JE, Kurth T. Measures of obesity and cardiovascular risk among men and women. Journal of the American College of Cardiology. 2008; 52(8):605–615. [PubMed: 18702962]

19. Singer, B., Ryff, C., Seeman, T. Operationalizing allostatic load. In: Schulkin, J., editor. Allostasis, homeostasis, and the costs of physiological adaptation. New York: Cambridge UP; 2004. p. 113-147.
20. Seplaki CL, Goldman N, Weinstein M, Lin YH. Measurement of cumulative physiological dysregulation in an older population. Demography. 2006; 43(1):165–183. [PubMed: 16579213]
21. Seplaki C, Goldman N, Weinstein M, Lin Y. How are biomarkers related to physical and mental well-being? The Journals of Gerontology Series A: Biological Sciences and Medical Sciences. 2004; 59(3):B201–B217.
22. Logan JG, Barksdale DJ. Allostasis and allostatic load: expanding the discourse on stress and cardiovascular disease. Journal of Clinical Nursing. 2008; 17(7b):201–208. [PubMed: 18578796]
23. Wallace M, Harville E. Allostatic load and birth outcomes among white and black women in New Orleans. Maternal and Child Health Journal. 2013; 17(6):1025–1029. [PubMed: 22833335]
24. Wallace M, Harville E, Theall K, Webber L, Chen W, Berenson G. Neighborhood poverty, allostatic load, and birth outcomes in African American and white women: findings from the Bogalusa Heart Study. Health and Place. 2013; 24(2013):260–266. [PubMed: 24184350]
25. Morrison S, Shenassa E, Mendola P, Wu T, Schoendorf K. Allostatic load may not be associated with chronic stress in pregnant women, NHANES 1999-2006. Annals of Epidemiology. 2013; 23(2013):294–297. [PubMed: 23621995]
26. Hux VJ, Catov JM, Roberts JM. Allostatic load in women with a history of low birth weight infants: the national health and nutrition examination survey. J Womens Health (Larchmt). 2014; 23(12):1039–1045. [PubMed: 25495368]
27. Dowd JB, Simanek AM, Aiello AE. Socio-economic status, cortisol and allostatic load: a review of the literature. International Journal of Epidemiology. 2009; 38(5):1297–1309. [PubMed: 19720725]
28. Seeman T, Gruenewald T, Karlamangla A, Sidney S, Liu K, McEwen B, et al. Modeling multisystem biological risk in young adults: The Coronary Artery Risk Development in Young Adults Study. American Journal of Human Biology. 2010; 22(4):463–472. [PubMed: 20039257]
29. Seeman T, McEwen B, Rowe J, Singer B. Allostatic load as a marker of cumulative biological risk: MacArthur studies of successful aging. Proceedings of the National Academy of Sciences of the United States of America. 2001; 98(8):470–475.
30. Committee on Practice Bulletins--Obstetrics. Practice Bulletin No. 137: Gestational diabetes mellitus. Obstetrics and Gynecology. 2013; 122(2 Pt 1):406–416. [PubMed: 23969827]
31. Peek MK, Cutchin MP, Salinas JJ, Sheffield KM, Eschbach K, Stowe RP, et al. Allostatic load among non-Hispanic Whites, non-Hispanic Blacks, and people of Mexican origin: effects of ethnicity, nativity, and acculturation. American Journal of Public Health. 100(5):940–946.
32. Smyth JM, Ockenfels MC, Gorin AA, Catley D, Porter LS, Kirschbaum C, et al. Individual differences in the diurnal cycle of cortisol. Psychoneuroendocrinology. 1997; 22(2):89–105. [PubMed: 9149331]
33. Hebisch G, Neumaier-Wagner P, Huch R, von Mandach U. Maternal serum interleukin-1 beta, -6 and -8 levels and potential determinants in pregnancy and peripartum. Journal of Perinatal Medicine. 2004; 32(6):475–480. [PubMed: 15576267]
34. Coussons-Read M, Okun M, Nettles C. Psychosocial stress increases inflammatory markers and alters cytokine production across pregnancy. Brain, Behavior, and Immunity. 2007; 21(2007):343–350.
35. Crimmins E, Kim J, McCreath H, Faul J, Weir D, Seeman T. Validation of blood-based assays using dried blood spots for use in large population studies. Biodemography and Social Biology. 2014; 60(1):38–48. [PubMed: 24784986]
36. Witt WP, Litzelman K, Cheng ER, Wakeel F, Barker ES. Measuring stress before and during pregnancy: A review of population-based studies of obstetric outcomes. Maternal and Child Health Journal. 2014; 18(1):52–63. [PubMed: 23447085]
37. Shapiro GD, Fraser WD, Frasch MG, Séguin JR. Psychosocial stress in pregnancy and preterm birth: Associations and mechanisms. Journal of Perinatal Medicine. 2013; 41(6):631–645. [PubMed: 24216160]

38. Daraki V, Georgiou V, Papavasiliou S, Chalkiadaki G, Karahaliou M, Koinaki S, Sarri K, Vassilaki M, Kogevinas M, Chatzi L. Metabolic profile in early pregnancy is associated with offspring adiposity at 4 years of age: The Rhea pregnancy cohort Crete, Greece. PLoS One. 2015; 10(5):e0126327. [PubMed: 25970502]

Significance

What is known? The association between psychosocial stress and adverse birth outcomes is well established but poorly understood. Allostatic load, a conceptual framework for physiological dysfunction arising from exposure to chronic stress, refers to the cumulative, physiological toll imposed on the body from the ongoing activation of the stress response.

What does this study add? Cumulative physiologic dysfunction has been theoretically applied to pregnant populations to explain adverse birth outcomes; our study was one of the first to characterize it during pregnancy. We found no evidence that physiologic dysfunction measured in pregnancy, as operationalized in this study, was associated with adverse birth outcomes.

Table 1

Demographic Characteristics of the Pregnant Sample (N=111)

Variable Name	N[a]	%
Ethnicity		
Non-Hispanic	94	84.68
Hispanic	17	15.32
Race		
Black	31	27.92
White	73	65.77
Other/Mixed race	7	6.30
Educational Attainment		
<High school	18	16.22
High school	15	13.51
Some college	45	40.54
College graduate	15	13.51
Graduate school degree	18	16.22
Maternal Marital Status		
Single	17	15.31
Committed relationship	46	41.82
Married	43	39.09
Separated, divorced, or widowed	5	3.64
Household Income		
<$20,000 per year	50	45.05
$20,000-$50,000 per year	23	20.72
>$50,000 per year	34	30.63
Unknown[b]	4	3.60
Smoking status		
Current use before 28 weeks gestation	15	13.51
None	96	86.49
Early Pregnancy (<14 weeks gestation) BMI		
Normal weight (18.5-<25 kg/m^2)	53	47.74
Overweight (25-<30 kg/m^2)	38	34.23
Obese (30-35 kg/m^2)	20	18.01
Maternal Age at enrollment in years (Mean, SD)	26.37	4.71

[a] Based on final retained sample N=111 with complete data for all time points.

[b] Unknown income was an option on the survey.

Table 2

Birth Outcomes (N=111)

	N[a]	%
Birth Weight		
Low birth weight (<2,500 grams)	4	3.60
≥2,500 grams	107	96.40
Gestational Age		
Preterm (<37 weeks gestation)	2	1.80
≥37 weeks gestation	109	98.20
Birth Weight by Gestational Age		
Small for Gestational Age	9	8.11
Large for Gestational Age	5	4.50
Appropriate for Gestational Age	97	87.39
	Mean	SD
Birth Weight (grams)	3397	522.89
Gestational Age (weeks)	39.64	1.08

[a]Based on final retained sample N=111 with complete data for all time points.

Table 3

Cumulative Physiologic Dysfunction Component Cut-Points in Pregnancy (N=111) [a]

Component	75th Percentile	Clinical Cut-Point
CRP[b] (Inflammatory)	≥2.07 mg/mL	variable
IL6 (Inflammatory)	≥0.63 pg/mL	variable
Total Cholesterol (Metabolic)	≥193.70 ng/mL	>200 ng/mL
Systolic Blood Pressure (Cardiovascular)	≥120 mmHg	≥140 mmHg
Diastolic Blood Pressure (Cardiovascular)	≥71 mmHg	≥90 mmHg
Early Pregnancy BMI[c] (Metabolic)	≥28.30 kg/m2	25-30 kg/m2 (overweight)
		≥30 kg/m2 (obese)
Glucose Tolerance[d] (Metabolic)	≥125.5 mg/dL	≥100 mg/dL with re-testing
Urinary protein (Kidney Function)	Presence of any	n/a

[a] Components were constructed from the prenatal visit closest to the dried blood spot collection in the third trimester (≥28 weeks gestation).

[b] High risk categorization constructed using cut-points for ≥ 75th percentile for each component.

[c] Based on a pre-pregnancy weight or pregnancy weight ≤14 weeks gestation.

[d] Based on the one-hour glucose challenge (50 gm) Clinical diagnosis involves serial testing for glucose tolerance.

CRP=C-reactive protein
IL6= Interleukin 6
BMI=Body Mass Index

Table 4

Adjusted Model for Birth Weight (in grams) and Cumulative Physiologic Dysfunction (N=111)

Parameter	β	SE (OLS)	p-value (OLS)
Intercept	3695.97	372.20	<.0001
Cumulative Physiologic Dysfunction	28.24	34.55	0.4157
Black Race[a]	-175.34	115.98	0.1336
Other Race[a]	-130.89	205.07	0.5247
Income <$20,000 per year[b]	-276.77	133.34	0.0404
Income $20,000-$50,000 per year[b]	-298.98	139.92	0.0350
Smoking (<28 weeks)[c]	-82.21	148.44	0.5809

[a]Reference: White

[b]Reference: > $50,000 per year

[c]Reference: None

Table 5

Adjusted Model for Gestational Age (in weeks) and Cumulative Physiologic Dysfunction (N=111)

Parameter	β	OLS SE	OLS p-value
Intercept	42.10	0.96	<.0001
Cumulative Physiologic Dysfunction	-0.06	0.07	0.4407
Black race[a]	-0.06	0.03	0.6112
Other race[a]	0.13	0.25	0.0308
Age	-0.03	0.46	0.9446
Income <$20,000 per year[b]	0.01	0.32	0.9879
Income $20,000-$50,000 per year[b]	0.52	0.34	0.1244
<High school education[c]	0.07	0.43	0.8653
High school education[c]	-0.36	0.48	0.4503
Some college[c]	-0.54	0.35	0.1344
College graduate[c]	-0.70	0.38	0.0688
Single[d]	-0.58	0.42	0.1683
Unmarried, committed relationship[d]	-0.58	0.30	0.0536
Separated, divorced, or widowed[d]	-0.32	0.62	0.6112
Smoking <28 weeks[e]	-0.49	0.32	0.1224

[a]Reference: White.

[b]Reference: Income > $50,000 per year

[c]Reference: graduate or professional degree

[d]Reference: Married

[e]Reference: None