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## Adverse childhood event experiences, fertility difficulties, and menstrual cycle characteristics

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### Abstract

**Introduction**—Increased childhood adversity may be affect adult fertility, however, the mechanism through which this occurs is unclear. Menstrual cycle abnormalities are predictive of fertility difficulties, and stress influences menstrual cycle characteristics. Here, we assesses whether adverse childhood experiences (ACEs) are associated with fertility difficulties and menstrual cycle dysregulation, offering a plausible mechanism for the link between lifetime stress and fertility.

**Methods**—From April 2012 – February 2014, 742 pregnant and non-pregnant women aged 18–45 years residing in southeastern Louisiana provided information on childhood adversity and reproductive history. Associations between ACEs and fertility difficulties and menstrual cycle patterns were evaluated.

**Results**—As the number of ACEs increased, risk of fertility difficulties and amenorrhea increased (RR = 1.09, 95% CI 1.05 – 1.13 and RR = 1.07, 95% CI 1.04 – 1.10, respectively), while fecundability decreased (FR = 0.97, 95% CI 0.95 – 1.00). Compared to women with no adversity, women in the high adversity group were more likely to experience both infertility and amenorrhea (RR = 2.75, 95% CI 1.45 – 5.21 and RR = 2.54, 95% CI 1.52 – 4.25, respectively), and reduced fecundability (FR = 0.75, 95% CI 0.56 – 1.00). Although similar patterns were seen for menstrual cycle irregularity, associations were diminished. Associations did not materially change following adjustment for age, BMI, race, education, smoking, and income. Results are

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constrained by the self-report nature of the study and the limited generalizability of the study population.

**Discussion**—To our knowledge, this is the first study to present evidence of a link between childhood stressors, menstrual cycle disruption, and fertility difficulties. The effect of childhood stress on fertility may be mediated through altered functioning of the HPA axis, acting to suppress fertility in response to less than optimal reproductive circumstances.

### Keywords

ACE; adverse childhood events; fertility; menstrual cycle; amenorrhea

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## INTRODUCTION

Infertility is a common, though poorly understood condition that affects, on average, 10% of child-bearing age couples. The contribution of stress to fertility difficulties is poorly specified, and is methodologically challenging to disentangle. Early research suggested that increased stress levels may reduce fertility during a particular menstrual cycle [1, 2], but more recent research indicates that chronic stress may also play an important role in fertility. An accumulating body of research supports the now common understanding that early life adversities may have an enduring effect on health outcomes over the life course [3] and are associated with chronic health conditions and illnesses through common pathways [4, 5]. Exposure to childhood stressors is associated with diminished ovarian reserve and function [6, 7], as well as reported infertility and reduced fecundability [8]. While the specific biological mechanism through which this association occurs is unclear, one possibility is menstrual cycle dysregulation.

Abnormalities in the menstrual cycle have been associated with various aspects of fertility. Atypical menstrual cycle length and high menstrual cycle variability may result in lower chances of conception [9–11] and longer time to pregnancy [12], while shorter mean cycle length has been associated with decreased ovarian reserve and lower chances of live-birth among women undergoing fertility treatment [13, 14]. Menstrual function is regulated by hypothalamic gonadotropin-releasing hormone, the function and secretion of which may be inhibited by hormones released by the hypothalamic-pituitary-adrenal (HPA) axis in response to stress [15, 16]. Stress during childhood has been shown to cause neuroendocrine disruption, especially altered functioning of the HPA axis [17], and chronic activation of the HPA axis around puberty may lead to menstrual cycle irregularities [15]. Although recent stressors have long been associated with menstrual cycle abnormalities [18–21], one study among a small group of newly incarcerated women also linked childhood stress to menstrual cycle irregularity [22].

Gestation and early childhood are thought to be especially critical periods for the development of the HPA axis. While the relationship between early social trauma and variation in HPA axis development in humans has not been as well documented, early childhood social experiences may have profound and permanent effects on later HPA axis regulation and stress responses [23]. Among children of all ages, traumatic family events (such as parental conflict and separation, death, or abuse) have been shown to be more

highly associated with elevated cortisol levels than any other factor studied, suggesting that family interactions are critical psychosocial stressors in most children's lives. The effects of cortisol on emotional memories and other socially salient information may be of special significance during child development; these stress responses may underlie short-term contingencies and guide long-term adjustments of behavioral strategies [23]. Thus, early life events may influence later reproductive strategies, as suggested by the life-history theory (LHT).

Classical LHT is based on optimization models, the fundamental assumption being that trade-offs exist between energy expended on growth, on the one hand, and reproduction on the other [24, 25]. More specifically, while reproduction has the benefit of producing offspring, it also has costs, such as increasing parental mortality, diverting energy from body repair and maintenance, decreasing the amount of energy invested in each offspring, and potentially decreasing future reproduction [24–27]. Life-history tactics aim to maintain a balance between preserving one's health and producing progeny that survive to reproduce themselves. Human behavioral ecology goes further to suggest that people have evolved to be able to respond flexibly to environmental conditions in ways that enhance their fitness [26]. Given the importance of maternal investment in child development, it has been hypothesized that when a woman's ability to invest in new offspring deteriorates, such as during times of stress, reproductive suppression may become advantageous, allowing existing offspring to thrive while avoiding new pregnancies with reduced prospects [23]. Variations in lifetime fertility reflect the costs of childrearing and availability of resources, and thus, it is very rarely optimal for women to achieve maximum fertility [24, 26–28]. Early stressful experiences are expected to result in different life-history strategies mediated by HPA axis activity, which may consequently lead to reproductive suppression when ecological and social conditions deteriorate [23]. By these arguments, early life stressors may predispose an individual to adaptively suppress fertility when situations are less than optimal, leading to periods of fertility difficulties even following previous births.

The present study investigated the relation between adverse experiences during childhood and menstrual cycle characteristics and fertility difficulties. Hypothetically, increased exposure to childhood adversities is associated with both fertility difficulties and menstrual cycle dysregulation, thus offering a plausible mechanism for the link between lifetime stress and fertility.

## METHODS

Data for the present study was drawn from “The Deepwater Horizon Disaster, Lifetime Adversity, and Reproductive Aged Women Study” conducted as part of the Gulf Resilience on Women's Health Consortium (GROWH) at Tulane University. The ongoing sub-study aims to determine how social and environmental adversity affect the mental and physical health of reproductive-aged women. Pregnant and non-pregnant reproductive aged women (ages 18–45 years) residing in southeastern Louisiana were eligible to participate. Women were recruited both in-person and via study flyers at public events, obstetrician/gynecologists (OB/GYN) offices, and neighborhood facilities, such as Women, Infants & Children (WIC) clinics and community centers. The study consisted of an in-person

interview, a take-home questionnaire, and a brief follow-up call, all of which assessed various aspects of adversity and reproductive health. The current investigation utilized data collected from April 2012 – February 2014, at which point 774 women (195 pregnant, 579 non-pregnant) had enrolled.

The study received approval from the Tulane University Human Research Protection Program. All participants provided written informed consent.

### Outcome Measures

Fertility difficulties were measured by self-report on three questions: “Did you ever try to get pregnant but were not able to?” and “Did you or your partner ever go to a doctor or other medical care provider to talk about ways to help you have a baby together?”, which were both included on the take-home questionnaire, and “Did you take any fertility drugs or receive any medical procedures from a doctor, nurse, or other health care worker to help you get pregnant?”, which was asked during the in-person interview. Women who answered “yes” to any of these questions were considered to have fertility difficulties. Participants who reported their partner was diagnosed with male infertility were excluded. Of the 774 participants, 22 were missing information on fertility difficulties and 10 reported a male infertility diagnosis, resulting in a final sample size of 742 women for fertility analyses.

A secondary assessment of fertility used self-reported time-to-pregnancy (TTP) to estimate fecundability. Participants were asked to report the number of months not using birth control prior to each pregnancy, and the longest TTP was considered the measure of potential fertility difficulties. TTP was reported by 495 women. Validation studies suggest that retrospective reporting of TTP measures give an accurate representation of true time-to-pregnancy estimates [29]. Women with TTP measures were more likely to be in a committed partnership ( $p < 0.05$ ) than participants who did not provide a TTP or those who said they didn’t know; no differences were seen with regard to age, race, education, income, or BMI (data not shown).

Menstrual cycle irregularities were measured in two different ways on the take-home questionnaire. First, participants were asked about the pattern of their menstrual cycles from ages 18–22. Women who reported their cycles were usually or always irregular, or that they typically had no periods were coded as having irregular menstrual cycles. Second, participants were asked whether they had experienced a time interval of 3 or more months without a menstrual period since age 18. Women who reported absence of a menstrual period for one or more times when not pregnant or breastfeeding were considered to have a history of amenorrhea. The take-home questionnaire had not yet been received for 100 participants, and an additional 63 participants did not provide information on characteristics of their menstrual cycle. A sensitivity analysis was conducted to explore any demographic differences between participants who completed the take-home survey and provided information on their menstrual cycles and those who did not; no differences were seen between the groups with respect to age, race, education, income, partnership status, or BMI (data not shown). Thus, 611 women were available for inclusion in analyses of menstrual cycle characteristics.

## Exposure Measures

Adverse childhood experiences were assessed using the Adverse Childhood Experiences Survey (ACE) and the Brief Trauma Questionnaire (BTQ), both of which were included during the in-person interview. The ACE was adapted from the Family Health History Questionnaire developed by Kaiser Permanente, in conjunction with the Centers for Disease Control and Prevention (CDC), as part of the Adverse Childhood Experiences Study [5, 30]. The present survey assessed a variety of childhood hardships including abuse (physical, sexual, emotional), neglect (emotional and physical), and household dysfunction (exposure to domestic violence, household substance abuse, household mental illness, parental separation/divorce, and incarceration of family members), experienced prior to age 12, in order to capture experiences that likely preceded menarche. A modified version of the Child Trauma Questionnaire (CTQ) [31], which measures emotional abuse and neglect, was constructed from a subset of the questions included in the ACE [30]. Affirmative answers were summed across items, both overall and within factors. The maximum score possible for the full survey was 24; subscales included: childhood experiences excluding CTQ (max = 16), CTQ (8), childhood household dysfunction (10), childhood abuse (6), sexual abuse (3), physical abuse (4), emotional abuse (7), household substance use (3), and childhood neglect (4). Prior studies have suggested an increase in poor health outcomes following report of adverse childhood events in four or more of the 10 ACE domains: physical abuse, verbal abuse, sexual abuse, physical neglect, emotional neglect, parental substance use, parental domestic violence, household criminal activity, household mental illness, and familial separation [5, 30, 32]. Thus, ACE scores were also used to classify level of childhood adversity: high (endorsement of four or more ACE domains), low (endorsement of one to three ACE domains), and none (no domains endorsed).

The BTQ [33] was derived from the Brief Trauma Interview [34], a clinician administered 10-item interview based on the Trauma Assessment for Adults [35]. The measure evaluates a number of potentially traumatic life events including: motor vehicle accidents, death of a close friend or family member, and life-threatening illnesses, and the age at which they occurred. Affirmative responses prior to age 12 were summed across the survey. As three of the items referred to experiences at ages 18 or older only, the maximum possible score during childhood was seven. Therefore, a higher score on all scales indicated a greater number of adverse experiences during childhood. A description of all items and subscale details are presented in Table 1.

## Covariates

Known predictors of infertility or factors previously associated with increased childhood hardships were examined as covariates. These included age at the time of the survey and body mass index (BMI), calculated from reported height and weight (current for non-pregnant women and pre-pregnancy for pregnant women). Self-reported race/ethnicity was considered as white non-Hispanic, black non-Hispanic, Hispanic, or Asian. Education was the highest level completed, and was classified as high school or less, some college or associates degree, and college or more. Estimated household income in the last year was divided into seven categories, ranging from < \$10,000 to \$50,000. Current relationship status was categorized as married or living with a steady partner, or not in a partnership.

Insurance coverage was classified as none, Medicaid, or non-Medicaid. Smoking was considered as a bivariate yes/no variable if any cigarette use in the past two years was reported. Average alcohol use (when not pregnant) was categorized as no alcohol, < 4 drinks per week, or 4 drinks per week; 4 drinks per week is often suggested as the cut-point for alcohol consumption among women trying to conceive [36], although we were unable to account for variation in drink strength.

### Statistical Analysis

Demographic and behavioral characteristics between the reported fertility and menstrual cycle groups were compared using t-test for continuous variables and chi-square for categorical variables. The relationship between menstrual cycle characteristics and fertility difficulties was also confirmed using chi-square analysis.

Log-Poisson regression was used to assess whether there was an association between the childhood hardship scales (ACE, CTQ, and BTQ) and ACE subscales and reported fertility difficulties, irregular menstrual cycles, and periods of amenorrhea. Crude odds ratios for all subscales were compared to the full ACE scale by calculating a z-score for the betas that examined whether there was a statistical difference between any of the subscales and the full scale. Demographic covariates previously associated with adverse childhood experiences and reproductive factors, identified a priori, were controlled for: age, BMI, race, education, smoking, and income, to better facilitate comparison with existing literature [8]. No other covariates examined were associated with fertility difficulties in this data. A sensitivity analysis was conducted to examine whether more recent traumatic events may be accounting for associations between childhood stressors and fertility difficulties and menstrual cycle characteristics by including the number of BTQ items endorsed at ages 18 or older in final models.

Secondary TTP analyses were conducted using discrete proportional hazards models to estimate the fecundability ratio (FR), a measure of fertility representing the ratio of the cycle-specific probabilities of conception among the exposed compared to the unexposed [29]. Thus, a  $FR < 1$  indicates reduced fecundability (or increased TTP). TTP was truncated at 60 months, and a sensitivity analysis was conducted excluding women who reported a 0 month TTP [37]. Age at maximum TTP was controlled for, in addition to the covariates previously identified. Previous studies have noted “digit preference” with regard to retrospective TTP, and in the present study, preferential reporting of “years” (i.e. 12 months, 24 months) was noted beyond the first six months. However, these are generally thought to be non-differential reporting errors, and stable estimates of TTP distributions are thought to be obtained with at least 200 respondents [29]. Finally, a mediation analysis was conducted to evaluate any indirect effects of cumulative adverse childhood events overall on fertility, as potentially mediated through menstrual cycle disruption, using the bootstrapping techniques and PROCESS macro developed by Hayes [38]. Amenorrhea and menstrual cycle irregularity were considered as ordinal variables in order to run these analyses [never (0), one time only (1), more than once (2), and regular (0), usually irregular (1), always irregular (2), and no periods (3), respectively]. Using this method, evidence of mediation exists when

the estimate of the indirect effect differs from 0. All analyses were completed using SAS 9.3. A  $p$ -value  $< 0.05$  was considered significant for all analyses.

## RESULTS

The mean age of the women in our sample was  $29.0 \pm 6.8$  years (75% were under the age of 35), with an average BMI of  $30.2 \pm 8.0$ . Overall, 66.9% of the participants identified as black, non-Hispanic, 20.7% white, non-Hispanic, 9.5% Hispanic, and 2.9% Asian. About half of the women (52.7%) reported a high school education or less. Difficulty conceiving was reported by 88 (11.9%) of the women, while 253 (41.4%) reported irregular menstrual cycles and 126 (20.7%) reported periods of amenorrhea. Overall, 29.3% of the participants endorsed four or more ACE domains (see Table 1).

Characteristics of the study sample by fertility group are presented in Table 2. Women who reported a history of fertility difficulties had a higher BMI than those with no fertility reported difficulties (33.1 vs. 29.1,  $p < 0.01$ ). No other significant differences were seen between the groups. Patterns were consistent among the regular and irregular menstrual pattern groups and those with and without a history of amenorrhea (data not shown). Women who had experienced fertility difficulties were significantly more likely to report irregular menstrual cycles than those who reported no difficulties (66.7% vs. 36.7%,  $p < 0.01$ ), and were more likely to have experienced periods of amenorrhea lasting three months or more (41.5% vs. 17.2%,  $p < 0.01$ ). Thus, initial analyses supported the association between menstrual cycle irregularities and reported fertility difficulties. In addition, maximum TTP was slightly longer among women who reported fertility difficulties compared to those who did not (11.1 months vs. 8.9,  $p = 0.16$ ).

Associations between adverse event scales and fertility difficulties are shown in Table 3. All ACE measures, including the CTQ, were associated with fertility difficulties, and suggested that as the number of adverse events experienced increased, risk of experiencing fertility difficulties increased as well. Overall, for each additional adverse event experienced, the risk of fertility difficulties increased by 9% (RR = 1.09, 95% CI 1.05 – 1.13). The child abuse subscale, sexual abuse and physical abuse more specifically, and experiencing parental substance use or neglect during childhood, showed stronger associations with fertility issues than the full ACE scale. As compared to the no adversity group, women in the high adversity group were 2.75 times more likely to have experienced fertility difficulties (95% CI 1.45 – 5.21). Estimates were slightly attenuated after controlling for age, BMI, race, education, smoking, and income, but remained significant. No difference in reported fertility difficulties was seen between the low adversity and no adversity groups (RR = 1.56, 95% CI 0.81 – 3.00).

Associations between all adverse event scales and menstrual cycle patterns are presented in Table 4. Associations for a history of amenorrhea were nearly identical to those observed for fertility difficulties, with the exception of a stronger effect seen for the sexual abuse subscale. Additionally, increasing scores on the BTQ were associated with reported periods of amenorrhea only (RR = 1.32, 95% CI 1.08 – 1.62). As compared to women who did not endorse any adversity, women in the high adversity group were 2.54 times more likely to

have experienced amenorrhea (95% CI 1.52 – 4.25), while risk was 1.65 times higher in the low adversity group (95% CI 0.98 – 2.76), which reached significance following adjustment for age, BMI, race, education, smoking, and income (RR = 1.82, 95% CI 1.05 – 3.17). Although similar patterns of association were noted for menstrual cycle irregularity, associations were diminished. Patterns of association remained the same following adjustment for age, BMI, race, education, and income.

Childhood adversity remained associated with fertility difficulties and amenorrhea after conducting sensitivity analyses controlling for traumatic events that occurred as an adult, in addition to all other covariates. Overall, the risk of fertility difficulties increased by 6% for each additional adverse childhood event experienced (RR = 1.06, 95% CI = 1.01 – 1.12), while the risk of amenorrhea increased by 7% (RR = 1.07, 95% CI = 1.03 – 1.10). Compared to women who endorsed no adversity, women in the high adversity group were 2.12 times more likely to report experiencing fertility difficulties (95% CI = 1.02 – 4.37), and 2.42 times more likely to have a history of amenorrhea (95% CI = 1.36 – 4.31). Women in the low adversity group remained 1.80 times more likely to have experienced amenorrhea (95% CI = 1.02 – 3.17) compared to those who reported no childhood adversity.

Results of the TTP analyses are presented in Table 5. In general, increasing childhood hardships were associated with reduced fecundability, primarily when all types of hardship were taken into account. For example, women reporting high levels of childhood adversity had a 30% decrease in fecundability compared to those reporting no adversity, even after adjustment for previously identified covariates (FR = 0.70, 95% CI 0.52 – 0.96). Results were similar, albeit slightly attenuated, after excluding participants who reported a TTP = 0 (data not shown).

Results of the mediation analyses indicated that amenorrhea may be partially mediating the effect of childhood adversities on fertility. A borderline indirect effect was seen when total ACE score was considered ( $\beta = 0.009$ , 95% CI 0.000 – 0.022), and when number of ACE domains was considered as a three-level categorical variable, evidence of indirect effects between adverse childhood events and infertility were seen ( $\beta = 0.049$ , 95% CI 0.004 – 0.136). No indirect effects through menstrual pattern were noted. Results did not change when women who reported no periods were excluded or combined with those who said their periods were always irregular. Direct effects remained significant in all analyses.

## DISCUSSION

Results from the present study support recent findings suggesting that adversities experienced during childhood are associated with fertility later in life. Women who reported experiencing abuse, neglect, household dysfunction or parental substance abuse prior to age 12 were more likely to have experienced fertility difficulties and periods of amenorrhea lasting three months or more, and had an increased time to pregnancy. Associations between adverse event experiences and amenorrhea were nearly identical to those seen between ACEs and fertility difficulties, and mediation analyses suggested that a history of amenorrhea may partially mediate the association between adverse childhood events and adult fertility, although direct effects remained significant. While statistically significant



associations were not observed for menstrual cycle irregularity, the pattern of association was the same.

It is possible that amenorrhea may reflect greater disruption of ovarian function than irregular periods, and therefore may be more predictive of fertility issues. Returning to life-history theory, periods of amenorrhea may represent suppression of fertility at various time-points in a woman's life, as opposed to consistent menstrual cycle irregularity, which may be more indicative of other medical issues. In this view, early life stressors may lead to differential patterns of reproductive receptivity in response to environmental changes across the lifespan [23, 26]. This may help explain why women who are able to conceive at one time point may have difficulties at another, in the absence of age-related fertility decline. Additionally, it may be more difficult for women to accurately recollect and report menstrual cycle irregularity as compared to amenorrhea. Whereas periods of amenorrhea was specifically defined as three months or more without a period, typical menstrual pattern was left up to interpretation, and women may not know the characteristics of a typical menstrual cycle or be able to accurately assess their own cycle regularity [39–41]. Thus, periods of amenorrhea may be a more accurate representation of menstrual cycle dysfunction than cycle pattern in this self-report population.

Findings from the current investigation also suggest that certain types of adverse events may have a greater impact on fertility than others, potentially reflecting more stressful childhood experiences. In particular, sexual abuse, physical abuse, including witnessing domestic violence, parental substance use, and childhood neglect may be more stressful for children than other types of hardship. In support of this, the CDC has recognized child abuse, neglect, and exposure to intimate partner violence, as being particularly important childhood stressors affecting health across the lifespan [42]. Evolutionary studies also suggest that severe hardships, especially with regard to parental attachment and relationships, may cause earlier maturation and program HPA axis regulation, at the expense of future reproduction and child-rearing investment [43–46]. Additionally, cumulative exposure to 4 or more childhood adversities was more strongly associated with fertility difficulties and amenorrhea, suggesting that in addition to the type of hardship experienced the level of exposure to adverse experiences during childhood may also affect health.

One limitation of the present study is that all outcome measures are based on self-report. This may have resulted in over-reporting of outcomes, particularly menstrual cycle abnormalities, which had a higher prevalence in the present sample than what would be expected in the general population. In addition, we did not assess oral contraceptive use from ages 18 – 22, so it is unknown how this may have affected reporting of cycle regularity. Likewise, caution needs to be taken when considering our fertility difficulties groups, as many of these women self-defined as having fertility difficulties without a formal diagnosis. It is likely that the fertility questions referring to medical care are more relevant to women whose fertility problems were deemed to be significant enough for them to seek out medical attention, while the question that asks whether the participant tried unsuccessfully to get pregnant may be a more general personal assessment that likely gets at lesser fertility difficulties. However, it may also be likely that fertility difficulties were recognized by the participant, but she was unable to seek out professional help. This is particularly relevant in

the present population as studies suggest that non-white women and women of low socioeconomic status are less likely to seek treatment for infertility [47], although they may be more likely to experience fertility difficulties [48]. Therefore, it is thought that inclusion of all three questions better evaluates the totality of fertility problems in this population.

A sensitivity analysis was conducted to determine whether women reporting fertility difficulties would have met criteria for infertility assessment based on reported TTP for any pregnancy (>12 months for women <35, and >6 months for women 35+). Overall, 18% met criteria based on reported TTP, and women reporting fertility difficulties were more likely to meet this criteria (28% vs. 17%,  $p = 0.05$ ), although many women were unable to recall TTP. Additionally, women in the fertility difficulties group reported fewer live-births (1.7 vs. 2.1,  $p = 0.02$ ), although the number of pregnancies was similar (2.6 vs. 2.7,  $p = 0.79$ ). Despite these limitations, the level of self-reported fertility difficulties observed in our population (11.9%) is consistent with published infertility prevalence (9% – 15%) among the childbearing population [49].

Additionally, our study population may represent a more fertile population than the average population, as participants were mainly recruited from sites likely to attract pregnant women or women with children, such as OB/GYN and WIC clinics. Overall, 92.8% of the participants reported at least one pregnancy (range 0 – 14, median 2), and 85.1% were parous (range 0 – 12, median 2). No differences in number of pregnancies were noted between pregnant and non-pregnant participants, although non-pregnant participants were found to have had more live births (2.3 vs. 1.4,  $p < 0.01$ ). Furthermore, given the relatively young age of the study population, lifetime fertility difficulties may be underestimated since most participants are not through their reproductive years. As a result, findings from the present study may be more relevant to fertility issues among a younger population rather than age-related fertility decline. In addition, generalizability of the present study may be limited as the population is primarily African American, which, although in line with the population of New Orleans (60%), differs from the general population (13%) [50].

Finally, there are inherent limitations in retrospective measures of adverse childhood experiences. Adverse event reporting is likely to be influenced by the age at which the event occurred, as well as how traumatic the experience was perceived to be. In spite of this, reviews of the research surrounding retrospective reporting of childhood hardships suggest that, although not without bias, structured retrospective reporting of ACEs can be valuable research tools, and, if anything, adverse events are likely to be underreported [32, 51]. Thus, if inconsistencies exist, it is likely our results would be biased towards the null. Along these lines, an alternative explanation for the associations seen in the present study is that women who recall stressful childhood experiences may be more likely to perceive other aspects of their life, such as trying to conceive, as difficult as well. However, it is thought that assessment of FRs using TTP, a more concrete outcome than reported fertility difficulties, provides support for an association between hardships and fertility that is not the result of reporting bias alone.

Likewise, women who experience traumatic experiences during childhood are at increased risk for re-victimization during adulthood [52], and therefore it may be that more recent

stressors not assessed here are influencing fertility in this population. However, other studies have shown childhood hardships to be associated with adult fertility independent of more recent hardships [6]; thus it is plausible that childhood stressors may be associated with reported fertility difficulties irrespective of more recent stressors. While we were not able to comprehensively study more recent hardships, additional analyses adjusting for traumatic events that occurred at ages 18 or older, in addition to covariates already controlled for, suggested that adverse childhood events independently influence adult fertility. Although associations were slightly attenuated following adjustment for more recent events, main effects remained significant and the pattern of association overall persisted. As the field moves forward, additional studies may want to consider additional intermediary effects that may be associated with adverse childhood experiences and fertility that we did not assess, such as risky sexual behavior, chronic illnesses, and medication and drug use.

In summary, the present study supports an association between adverse experiences during childhood and self-report of fertility difficulties in adulthood. Additionally, the equally strong relation between adverse experiences and periods of amenorrhea suggests the effect of childhood stress on fertility may be mediated by altered functioning of the HPA axis, manifesting as menstrual cycle disruption. This association may represent suppression of fertility when situations are deemed as less than optimal for conception via learned stress responses in childhood. These associations persisted controlling for likely confounders, including age, race, BMI, education, tobacco use, or income level. Future research is warranted to investigate this association prospectively, and further explore the biological mechanism through which adverse childhood experiences may influence fertility.

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## Appendix 1

### Adverse Childhood Experiences Scale (Adapted from the ACE Family Health History Questionnaire)

For the following questions, we are going to ask about your childhood experiences that occurred when you were a child (<12 years) and an adolescent (12–17 years).

<i>During your first 18 years of life,</i>		
	As a child (<12 years)	As an adolescent (12–17 years)
1. Did you live with anyone who was a problem drinker or alcoholic?	Yes (1) No (2) Don't know (8) Refused (9)	Yes (1) No (2) Don't know (8) Refused (9)
<i>1a. If "yes" check all who were:</i>	Father (1)	Father (1)
	Mother (2)	Mother (2)
	Other relative (3)	Other relative (3)
	Other non-relative (4)	Other non-relative (4)
2. Did you live with anyone who used street drugs?	Yes (1) No (2) Don't know (8) Refused (9)	Yes (1) No (2) Don't know (8) Refused (9)
3. Were your parents ever separated or divorced?	Yes (1) No (2) Don't know (8) Refused (9)	Yes (1) No (2) Don't know (8) Refused (9)
4. Were you a foster child?	Yes (1) No (2) Don't know (8) Refused (9)	Yes (1) No (2) Don't know (8) Refused (9)
5. Was anyone in your household depressed or mentally ill?	Yes (1) No (2) Don't know (8) Refused (9)	Yes (1) No (2) Don't know (8) Refused (9)
6. Did anyone in your household attempt to commit suicide?	Yes (1)	Yes (1)

<i>During your first 18 years of life,</i>		
	<b>As a child (&lt;12 years)</b>	<b>As an adolescent (12–17 years)</b>
	No (2) Don't know (8) Refused (9)	No (2) Don't know (8) Refused (9)
7. Did anyone in your household go to prison?	Yes (1) No (2) Don't know (8) Refused (9)	Yes (1) No (2) Don't know (8) Refused (9)
8. Did anyone in your household ever commit a serious crime?	Yes (1) No (2) Don't know (8) Refused (9)	Yes (1) No (2) Don't know (8) Refused (9)
<i>Sometimes physical blows occur between parents. While you were growing up, how often did your father (or stepfather) or mother's boyfriend do any to these things to your mother (or stepmother)?</i>		
9. Push, grab, slap or throw something at her?	Never (1) Once, twice (2) Sometimes (3) Often (4) Very often (5) Don't know (8) Refused (9)	Never (1) Once, twice (2) Sometimes (3) Often (4) Very often (5) Don't know (8) Refused (9)
10. Threaten her with a knife or gun, or use a knife or gun to hurt her?	Never (1) Once, twice (2) Sometimes (3) Often (4) Very often (5) Don't know (8) Refused (9)	Never (1) Once, twice (2) Sometimes (3) Often (4) Very often (5) Don't know (8) Refused (9)
<i>While you were growing up during your first 18 years of life, how often was it true that:</i>		
11. You didn't have enough to eat?	Never true (1) Rarely true (2) Sometimes true (3) Often true (4) Very often true (5) Don't know (8) Refused (9)	Never true (1) Rarely true (2) Sometimes true (3) Often true (4) Very often true (5) Don't know (8) Refused (9)
12. People in your family called you things like "lazy" or "ugly"?	Never true (1)	Never true (1)

<i>During your first 18 years of life,</i>		
	<b>As a child (&lt;12 years)</b>	<b>As an adolescent (12–17 years)</b>
	Rarely true (2)	Rarely true (2)
	Sometimes true (3)	Sometimes true (3)
	Often true (4)	Often true (4)
	Very often true (5)	Very often true (5)
	Don't know (8)	Don't know (8)
	Refused (9)	Refused (9)
13. Your parents were too drunk or high to take care of the family?	Never true (1)	Never true (1)
	Rarely true (2)	Rarely true (2)
	Sometimes true (3)	Sometimes true (3)
	Often true (4)	Often true (4)
	Very often true (5)	Very often true (5)
	Don't know (8)	Don't know (8)
	Refused (9)	Refused (9)
14. You had to wear dirty clothes?	Never true (1)	Never true (1)
	Rarely true (2)	Rarely true (2)
	Sometimes true (3)	Sometimes true (3)
	Often true (4)	Often true (4)
	Very often true (5)	Very often true (5)
	Don't know (8)	Don't know (8)
	Refused (9)	Refused (9)
15. There was someone who made you feel special?	Never true (1)	Never true (1)
	Rarely true (2)	Rarely true (2)
	Sometimes true (3)	Sometimes true (3)
	Often true (4)	Often true (4)
	Very often true (5)	Very often true (5)
	Don't know (8)	Don't know (8)
	Refused (9)	Refused (9)
16. You thought your parents wished you had never been born?	Never true (1)	Never true (1)
	Rarely true (2)	Rarely true (2)
	Sometimes true (3)	Sometimes true (3)
	Often true (4)	Often true (4)
	Very often true (5)	Very often true (5)
	Don't know (8)	Don't know (8)
	Refused (9)	Refused (9)
17. You felt that someone in your family hated you?	Never true (1)	Never true (1)
	Rarely true (2)	Rarely true (2)
	Sometimes true (3)	Sometimes true (3)



<i>During your first 18 years of life,</i>		
	<b>As a child (&lt;12 years)</b>	<b>As an adolescent (12–17 years)</b>
	Often true (4) Very often true (5) Don't know (8) Refused (9)	Often true (4) Very often true (5) Don't know (8) Refused (9)
18. People in your family said hurtful or insulting things to you?	Never true (1) Rarely true (2) Sometimes true (3) Often true (4) Very often true (5) Don't know (8) Refused (9)	Never true (1) Rarely true (2) Sometimes true (3) Often true (4) Very often true (5) Don't know (8) Refused (9)
19. You believed that you were emotionally abused?	Never true (1) Rarely true (2) Sometimes true (3) Often true (4) Very often true (5) Don't know (8) Refused (9)	Never true (1) Rarely true (2) Sometimes true (3) Often true (4) Very often true (5) Don't know (8) Refused (9)
<i>Sometimes parents or other adults hurt children. While you were growing up, that is, during your first 18 years of life, how often did a parent, step-parent, or adult living in your home:</i>		
20. Swear at you, insult you, or put you down?	Never (1) Once, twice (2) Sometimes (3) Often (4) Very often (5) Don't know (8) Refused (9)	Never (1) Once, twice (2) Sometimes (3) Often (4) Very often (5) Don't know (8) Refused (9)
21. Threaten to hit you or throw something at you, but didn't do it?	Never (1) Once, twice (2) Sometimes (3) Often (4) Very often (5) Don't know (8) Refused (9)	Never (1) Once, twice (2) Sometimes (3) Often (4) Very often (5) Don't know (8) Refused (9)
22. Actually push, grab, shove, slap you, or throw something at you?	Never (1) Once, twice (2) Sometimes (3)	Never (1) Once, twice (2) Sometimes (3)

<i>During your first 18 years of life,</i>		
	<b>As a child (&lt;12 years)</b>	<b>As an adolescent (12–17 years)</b>
	Often (4) Very often (5) Don't know (8) Refused (9)	Often (4) Very often (5) Don't know (8) Refused (9)
23. Do you think that you were sexually abused as a child?	Yes (1) No (2) Don't know (8) Refused (9)	Yes (1) No (2) Don't know (8) Refused (9)
24. Did a boy or group of boys about your own age, ever force or threaten you with harm in order have sexual contact?	Yes (1) No (2) Don't know (8) Refused (9)	Yes (1) No (2) Don't know (8) Refused (9)
24a. Did the contact involve a person actually having intercourse with you (vaginal, oral or anal)?	Yes (1) No (2) Don't know (8) Refused (9)	Yes (1) No (2) Don't know (8) Refused (9)

**Current knowledge on the subject**

- Exposure to chronic stressors may be associated with fertility difficulties, however, the mechanism through which this association occurs is unclear
- Abnormalities in the menstrual cycle have been associated with various aspects of fertility, and stress has been shown to disrupt menstrual function
- Disruption of the hypothalamic-pituitary-adrenal (HPA) axis during childhood might influence adult fertility via dysregulation of the menstrual cycles, although this has not been directly assessed

**What this study adds**

- The present study evaluated whether hardships experienced during childhood are associated with fertility difficulties and menstrual cycle abnormalities
- Increased adverse childhood events were associated with fertility difficulties and periods of amenorrhea
- The similarity of the associations suggest that the effect of childhood stress on fertility may be mediated through altered functioning of the HPA axis, manifesting as menstrual cycle disruption

Table 1

## Childhood hardship scale items and subscales

Scale	Items	Prevalence	Sub-scale <sup>a</sup>
ACE	Lived with alcoholic	20.0%	1, 3, 8
	Lived with illegal drug user	13.7%	1, 3, 8
	Parents separated/divorced	45.3%	1, 3
	Ever a foster child	2.3%	1, 3, 9
	Member of household depressed/mentally ill	18.0%	1, 3
	Member of household attempted suicide	6.0%	1, 3
	Member of household incarcerated	17.1%	1, 3
	Member of household committed serious crime	6.3%	1, 3
	Father/stepfather pushed/slapped/threw something at mother	22.5%	1, 3, 6
	Father/stepfather threatened/hurt mother with knife/gun	7.5%	1, 3, 6
	Didn't have enough to eat	16.2%	2, 9
	Family called you names (i.e. "lazy", "ugly")	24.4%	2, 7
	Parents too drunk or high to care for family	7.0%	2, 8, 9
	Had to wear dirty clothes	4.3%	2, 9
	Someone made you feel special ( <i>*reverse coded</i> )	7.3%	2, 7
	Felt parents wished you had never been born	10.9%	2, 7
	Felt someone in family hated you	17.8%	2, 7
	Family said hurtful or insulting things	27.4%	2, 7
	Emotionally abused	18.5%	1, 4
	BTQ	Parent swore at you/insulted you/put you down	22.8%
Parent threatened to hit you or throw something at you		29.0%	1, 4, 6
Parent pushed/grabbed/shoved/slapped/threw something at you		22.9%	1, 4, 6
Sexually abused		10.5%	1, 4, 5
Someone same age forced sexual contact		2.1%	1, 4, 5 <sup>b</sup>
ACE domain endorsement:			
4+ ACE domains (high adversity)		29.3%	
1 – 3 ACE domains (low adversity)		47.6%	
0 ACE domains (none)		23.1%	
Been in a serious accident		3.0%	
Been in a major natural or human-made disaster	3.9%		
Had a serious/life-threatening illness	1.0%		
Separated from someone under stressful circumstances	3.5%		
Witnessed situation in which someone seriously injured/killed	4.1%		
Situation in which feared you might be seriously injured/killed	1.3%		
Had close family member/friend die suddenly and violently	3.5%		

<sup>a</sup>1. Childhood experiences, excluding CTQ; 2. CTQ; 3. Childhood household dysfunction; 4. Childhood abuse; 5. Sexual abuse; 6. Physical abuse; 7. Emotional abuse; 8. Household substance use; 9. Childhood neglect

<sup>b</sup>Additional point given if contact involved intercourse

ACE: Adverse Childhood Experiences Scale; CTQ: Child Trauma Questionnaire; BTQ: Brief Trauma Questionnaire

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**Table 2**

Demographic, behavioral, and menstrual cycle characteristics and reported fertility difficulties in 742 reproductive-aged southern Louisiana women

<b>Variable</b>	<b>No fertility difficulties (n = 654)</b>	<b>Fertility difficulties (n = 88)</b>	<b>p-value<sup>a</sup></b>
Current pregnancy status			0.20
Pregnant	24.3	30.7	
Non-pregnant	75.7	69.3	
Age (mean)	29.1	28.8	0.75
BMI (mean)	29.8	33.1	< <b>0.01</b>
Race			0.66
White, non-Hispanic	20.4	23.4	
Hispanic	9.3	11.7	
Black, non-Hispanic	67.3	63.6	
Asian	3.1	1.3	
Education			0.57
High school or less	52.9	51.3	
Some college/associate	39.3	43.7	
College or more	7.8	5.0	
Annual income <sup>b</sup>			0.23
< \$10,000	28.7	34.6	
\$10,000 – 19,999	28.6	17.9	
\$20,000 – 34,999	23.9	24.4	
\$35,000 or more	18.8	23.1	
Relationship status			0.17
Married/living with partner	32.7	40.2	
Not in a partnership	67.3	59.8	
Insurance coverage			0.86
No insurance	19.0	17.0	
Medicaid	61.8	64.8	
Non-Medicaid	19.3	18.2	
Smoking, past 2 years			0.12
No	75.4	67.5	
Yes	24.6	32.5	
Average alcohol use			0.60
None	45.1	46.8	
< 4 drinks/week	45.3	40.5	
4 or more drinks/week	9.6	12.7	
Typical menstrual pattern			< <b>0.01</b>
Regular	63.3	33.3	
Irregular/no periods	36.7	66.7	
Amenorrhea history (3+ months)			< <b>0.01</b>
No	82.8	58.5	

<b>Variable</b>	<b>No fertility difficulties (n = 654)</b>	<b>Fertility difficulties (n = 88)</b>	<b>p-value<sup>a</sup></b>
Yes	17.2	41.5	
Maximum time-to-pregnancy (mean)	8.9	11.1	0.16

<sup>a</sup> p-values based on chi-square for categorical variables and t-test for continuous variables

<sup>b</sup> Income treated as a 7-category ordinal variable for multi-variable analysis

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**Table 3**

Association between adverse childhood experiences and fertility difficulties: results of log Poisson regression

Scale	RR	95% CI	aRR <sup>b</sup>	95% CI
ACE (all)	<b>1.09</b>	<b>1.05 – 1.13</b>	<b>1.08</b>	<b>1.03 – 1.12</b>
ACE, no CTQ	<b>1.12</b>	<b>1.06 – 1.18</b>	<b>1.11</b>	<b>1.04 – 1.18</b>
CTQ	<b>1.21</b>	<b>1.09 – 1.34</b>	<b>1.16</b>	<b>1.03 – 1.31</b>
Household dysfunction	<b>1.16</b>	<b>1.07 – 1.26</b>	<b>1.14</b>	<b>1.04 – 1.26</b>
Abuse (any)	<b>1.27<sup>a</sup></b>	<b>1.14 – 1.42</b>	<b>1.22</b>	<b>1.08 – 1.38</b>
Sexual	<b>1.72<sup>a</sup></b>	<b>1.32 – 2.26</b>	<b>1.49</b>	<b>1.01 – 2.19</b>
Physical	<b>1.29<sup>a</sup></b>	<b>1.13 – 1.49</b>	<b>1.23</b>	<b>1.04 – 1.44</b>
Emotional	<b>1.17</b>	<b>1.07 – 1.28</b>	<b>1.14</b>	<b>1.02 – 1.27</b>
Parental substance use	<b>1.43<sup>a</sup></b>	<b>1.18 – 1.74</b>	<b>1.40</b>	<b>1.12 – 1.74</b>
Neglect	<b>1.46<sup>a</sup></b>	<b>1.15 – 1.84</b>	<b>1.34</b>	<b>1.00 – 1.80</b>
BTQ	1.16	0.88 – 1.54	1.02	0.73 – 1.42
ACE domains				
High (4+)	<b>2.75</b>	<b>1.45 – 5.21</b>	<b>2.49</b>	<b>1.23 – 5.05</b>
Low (1 – 3)	1.56	0.81 – 3.00	1.51	0.75 – 3.05
None (0)	Ref.	--	Ref.	--

<sup>a</sup>Subscale estimate significantly different from full ACE scale at  $p < 0.05$ <sup>b</sup>Relative risk (RR) adjusted for: age, BMI, race, education, smoking, and income

ACE: Adverse Childhood Experiences Scale; CTQ: Child Trauma Questionnaire; BTQ: Brief Trauma Questionnaire



**Table 4**  
Association between adverse childhood experiences and menstrual cycle patterns: results of log Poisson regression

Scale	Irregular periods			Amenorrhoea history		
	RR	95% CI	aRR <sup>b</sup>	95% CI	aRR <sup>b</sup>	95% CI
ACE (all)	<b>1.03</b>	<b>1.01 – 1.05</b>	<b>1.02</b>	<b>1.00 – 1.04</b>	<b>1.07</b>	<b>1.04 – 1.11</b>
ACE, no CTQ	<b>1.05</b>	<b>1.02 – 1.08</b>	<b>1.03</b>	<b>1.00 – 1.06</b>	<b>1.11</b>	<b>1.06 – 1.17</b>
CTQ	1.06	1.00 – 1.12	1.05	0.99 – 1.11	<b>1.13</b>	<b>1.03 – 1.24</b>
Household dysfunction	<b>1.09<sup>a</sup></b>	<b>1.04 – 1.13</b>	<b>1.06</b>	<b>1.01 – 1.11</b>	<b>1.16</b>	<b>1.07 – 1.25</b>
Abuse (any)	1.05	0.99 – 1.12	1.04	0.97 – 1.10	<b>1.21<sup>a</sup></b>	<b>1.10 – 1.34</b>
Sexual	1.15	0.96 – 1.39	1.16	0.97 – 1.38	<b>1.33</b>	<b>1.02 – 1.75</b>
Physical	<b>1.09</b>	<b>1.01 – 1.18</b>	1.05	0.97 – 1.15	<b>1.23<sup>a</sup></b>	<b>1.10 – 1.44</b>
Emotional	1.04	0.99 – 1.10	1.05	1.00 – 1.10	<b>1.12</b>	<b>1.04 – 1.22</b>
Parental substance use	<b>1.17<sup>a</sup></b>	<b>1.05 – 1.30</b>	1.06	0.94 – 1.20	<b>1.39<sup>a</sup></b>	<b>1.13 – 1.63</b>
Neglect	<b>1.14</b>	<b>1.01 – 1.29</b>	1.06	0.91 – 1.23	<b>1.39<sup>a</sup></b>	<b>1.02 – 1.58</b>
BTQ	1.13	0.98 – 1.30	1.11	0.94 – 1.29	<b>1.32</b>	<b>1.08 – 1.62</b>
ACE domains						
High (4+)	1.31	1.00 – 1.72	1.14	0.86 – 1.53	<b>2.54</b>	<b>1.47 – 4.60</b>
Low (1 – 3)	1.05	0.80 – 1.37	1.03	0.78 – 1.35	1.65	<b>1.08 – 3.33</b>
None (0)	Ref.	--	Ref.	--	Ref.	--

<sup>a</sup>Subscale estimate significantly different from full ACE scale at p < 0.05

<sup>b</sup>Relative risk (RR) adjusted for: age, BMI, race, education, smoking, and income

ACE: Adverse Childhood Experiences Scale; CTQ: Child Trauma Questionnaire; BTQ: Brief Trauma Questionnaire

**Table 5**

Adverse childhood experiences and fecundability: results of discrete proportional hazards modeling (n = 495)

Scale	FR	95% CI	aFR <sup>a</sup>	95% CI
ACE (all)	<b>0.97</b>	<b>0.95 – 1.00</b>	<b>0.97</b>	<b>0.94 – 0.99</b>
ACE, no CTQ	<b>0.96</b>	<b>0.93 – 1.00</b>	<b>0.96</b>	<b>0.93 – 1.00</b>
CTQ	0.94	0.88 – 1.01	<b>0.92</b>	<b>0.85 – 0.99</b>
Household dysfunction	0.95	0.90 – 1.00	0.95	0.90 – 1.01
Abuse (any)	0.94	0.87 – 1.00	0.93	0.86 – 1.00
Sexual	0.78	0.61 – 1.00	0.79	0.61 – 1.03
Physical	0.94	0.86 – 1.03	0.94	0.85 – 1.03
Emotional	<b>0.94</b>	<b>0.89 – 0.99</b>	<b>0.92</b>	<b>0.86 – 0.98</b>
Parental substance use	0.94	0.83 – 1.07	0.95	0.83 – 1.09
Neglect	0.91	0.78 – 1.07	0.86	0.72 – 1.03
BTQ	1.01	0.85 – 1.21	1.04	0.85 – 1.26
ACE domains				
High (4+)	<b>0.75</b>	<b>0.56 – 1.00</b>	<b>0.72</b>	<b>0.52 – 0.99</b>
Low (1 – 3)	0.84	0.64 – 1.09	0.81	0.60 – 1.08
None (0)	Ref.	--	Ref.	--

<sup>a</sup>Fecundability ratio (FR) adjusted for age, age at longest time to pregnancy, BMI, race, education, smoking, and income

ACE: Adverse Childhood Experiences Scale; CTQ: Child Trauma Questionnaire; BTQ: Brief Trauma Questionnaire