

Preconception stress and the secondary sex ratio in a population-based preconception cohort

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Objective: To examine the association between preconception parental stress and the secondary sex ratio, defined as the ratio of males to females at birth.

Design: A population-based preconception cohort.

Setting: Not applicable.

Patient(s): A total of 235 couples who were enrolled before conception in Michigan and Texas between 2005 and 2009 and who had a singleton birth during the follow-up period. Couples were interviewed separately at baseline to obtain information on perceived stress (Cohen's Perceived Stress Scale) and lifetime history of physician-diagnosed anxiety and/or mood disorders. Female partners were also trained to collect basal saliva samples for the measurement of salivary stress markers, alpha-amylase and cortisol.

Intervention(s): None.

Main Outcome Measure(s): Birth outcome data including infant sex were collected upon delivery. Modified Poisson regression models were used to estimate the relative risks (RRs) of a male birth for each stress marker.

Result(s): After adjusting for potential confounders, we observed a 76% increase in the risk of fathering a male infant (RR 1.76; 95% confidence interval 1.17–2.65) in men diagnosed with anxiety disorders compared with those who were not diagnosed. When lifetime history of physician-diagnosed anxiety disorders was modeled jointly for the couple, the association was slightly strengthened (RR 2.03; 95% confidence interval 1.46–2.84).

Conclusion(s): This prospective cohort study suggests that paternal lifetime history of physician-diagnosed anxiety disorders may be associated with an increase in the secondary sex ratio, resulting in an excess of male births. (Fertil Steril® 2016; ■:■–■. ©2016 by American Society for Reproductive Medicine.)

Key Words: Alpha-amylases, anxiety disorders, hydrocortisone, sex ratio, stress

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Human sex ratios from birth through the lifespan have shown their modulation at the population level depending upon a variety of factors (1). The primary sex ratio (PSR), or the ratio of males to

females at conception, is relatively unknown owing to the difficulty in measuring conceptions (2). Although it is conventionally recognized that the PSR is male-biased (1), a recent comprehensive study reported that the PSR is unbiased (3). On the other hand the secondary sex ratio (SSR), or the ratio of males to females at birth, is expected to range from 1.05 to 1.07 in the United States and worldwide, indicative of a slight excess of male births (4, 5). The SSR has been suggested as a possible indicator of population health and fertility despite the

Received June 28, 2016; revised November 23, 2016; accepted December 12, 2016.

J.B. has nothing to disclose. C.D.L. has nothing to disclose. S.K. has nothing to disclose. R.S. has nothing to disclose. K.J.S. has nothing to disclose. G.M.B.L. has nothing to disclose.

Supported by the Intramural Research Program of the Eunice Kennedy Shriver National Institute of Child Health and Human Development (contracts nos. N01-HD-3-3355, N01-HD-3-3356, and N01-HD-3-3358). J.B. was supported by the Korea-US Visiting Scientist Training Award of the Eunice Kennedy Shriver National Institute of Child Health and Human Development (award no. VFTB057303).

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Fertility and Sterility® Vol. ■, No. ■, ■ 2017 0015-0282/\$36.00

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<http://dx.doi.org/10.1016/j.fertnstert.2016.12.011>

controversy over its utility, given that it is easy to measure, frequently recorded, and hardly subject to recall bias (6–9). Recent declines in the SSR observed in several developed countries have raised concerns about biological, psychological, and social factors disturbing sex selection and sex-selective survival in humans (7, 9).

Stress, which comprises multiple domains (e.g., biologic and psychological stress) that induce physiologic and behavioral responses, has been extensively evaluated in relation to human reproduction and development (10, 11). For instance, given the complex neuro-hormonal response elicited by stress, maternal stress is hypothesized to be responsible for various adverse reproductive outcomes, including preterm birth, low birth weight, and small for gestational age (12). It has also been suggested that the SSR, as a fertility endpoint, may be associated with maternal stress from various sources, such as economic contraction (13), stressful life events (14, 15), weather extremes (16), natural disasters (17–19), human-made disasters including wars (20), political upheaval (21), and terrorist attacks (22, 23), and psychiatric disorders including anxiety and depression (24, 25).

The stress response in humans is mainly regulated by the sympathetic–adrenal–medullary (SAM) system and the hypothalamic–pituitary–adrenal (HPA) axis (26). The SAM system is the primary mechanism in control of the fight-or-flight response and the secretion of catecholamines, such as norepinephrine and epinephrine, by the adrenal medulla. Meanwhile, the HPA axis is responsible for the release of glucocorticoids, such as cortisol, which is modulated by the secretion of corticotropin-releasing hormone and adrenocorticotropic hormone in hypothalamus and pituitary gland, respectively. These pathways are believed to interact with the reproductive system, wherein the hypothalamic–pituitary–gonadal axis plays an important role in the regulation of normal reproductive function (27). The physiologic role of these neuroendocrine systems in stress response is evident by several readily measurable biomarkers, such as salivary α -amylase and cortisol (28, 29), which have been investigated in the search for possible predictors of adverse reproductive endpoints in population-based studies (30, 31). To our knowledge, only one study evaluated maternal salivary stress markers, such as α -amylase and cortisol, in relation to the SSR. In a population-based preconception cohort study of 130 singleton births, the adjusted odds ratio (OR) for a male birth was decreased for women in the highest quartile of preconception salivary cortisol levels in comparison with women in the lowest quartile (adjusted OR 0.26; 95% confidence interval [CI] 0.09–0.74) (32).

Of note, less attention has been paid to the impact of paternal stress in comparison with that of maternal stress on human reproduction and development, despite the couple-dependent nature of human conception. Although prior research on paternal stress and the SSR is lacking, several hypotheses have been proposed to explain the role of both maternal and paternal stress in offspring sex determination (8, 33–39). As theorized previously, maternal and paternal stress may affect the SSR in diverse ways, eliciting opposite effects on human sex selection. Namely, maternal stress is related to increased T secretion from the adrenal

glands, whereas paternal stress is related to decreased T production by the testes (40, 41). According to one of the prevailing hypotheses on the SSR focusing on parental hormone levels around the time of conception (8, 37–39), stressed women tend to produce sons, whereas stressed men tend to produce daughters. Furthermore, maternal stress results in high circulating glucose levels, which may be related to the development of male blastocysts relative to female blastocysts, possibly owing to sex differences in the rate of glucose uptake (33, 34). However, as pregnancy continues, persistent maternal stress, especially during early pregnancy, may reduce or reverse an excess of male births, because it may be related to selective male losses relative to female losses (35, 36).

On the basis of the existing hypotheses on the SSR, the present study aimed to evaluate the impact of both maternal and paternal stress on the SSR in a population-based preconception cohort. Specifically, multiple domains of stress, which comprised both biologic (i.e., salivary stress markers) and psychological (i.e., perceived stress) stress markers, were investigated in the present study in light of possible divergent human reactivity to various stressors.

MATERIALS AND METHODS

Study Population

The Longitudinal Investigation of Fertility and the Environment (LIFE) Study is a prospective cohort study in which 501 couples discontinuing contraception and attempting pregnancy were recruited from 16 counties in Michigan and Texas between 2005 and 2009, as described previously in detail (42). Couples were followed until pregnant or up to 12 months of trying to conceive and through delivery for those becoming pregnant. The eligibility criteria for participation included the following: [1] couples in a committed relationship; [2] women aged 18–40 years and men aged ≥ 18 years; [3] female partner's self-reported menstrual cycle length of 21–42 days; [4] no use of injectable contraceptives during the past year; [5] no sterilization procedures or physician-diagnosed infertility; and [6] couples able to communicate in English or Spanish. Of the 501 couples, 237 couples (47.3%) had a live birth during the follow-up period, two of whom had twins. Our study cohort comprised 235 couples with a singleton birth.

Data Collection

Baseline and follow-up data collection. Research assistants visited the couple's home and interviewed each partner of the couple separately using standardized baseline questionnaires, allowing for ascertaining baseline characteristics of the couple, such as socio-demographic (i.e., age, sex, race/ethnicity, annual income, education level, and research site) and lifestyle factors (i.e., perceived stress) and medical (i.e., self-reported physician-diagnosed anxiety and/or mood disorders) and reproductive histories (i.e., maternal parity and number of pregnancies fathered). Upon the baseline visit, the female partner underwent a urine pregnancy test to ensure the absence of a pre-existing pregnancy. Blood was collected

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