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Original article

The impact of periconceptional maternal stress on fecundability

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ABSTRACT

Purpose: To examine the association between periconceptional self-reported stress levels and fecundability in women.

Methods: Daily stress was reported on a scale from 1 to 4 (lowest to highest) among 400 women who completed daily diaries including data on lifestyle and behavioral factors, menstrual characteristics, contraceptive use, and intercourse for up to 20 cycles or until pregnancy. Discrete survival analysis was used to estimate the associations between self-reported stress during specific windows of the menstrual cycle and fecundability (cycles at risk until pregnancy), adjusting for potential confounders.

Results: One hundred thirty-nine women became pregnant. During the follicular phase, there was a 46% reduction in fecundability for a 1-unit increase in self-reported stress during the estimated ovulatory window (fecundability odds ratio [FOR] = 0.54; 95% confidence interval [CI] 0.35–0.84) and an attenuated trend for the preovulatory window (FOR = 0.73; 95% CI 0.48–1.10). During the luteal phase, higher stress was associated with increased probability of conception (FOR = 1.63, 95% CI 1.07–2.50), possibly due to reverse causality.

Conclusions: Higher stress during the ovulatory window may reduce probability of conception; however, once conception occurs, changes in the hormonal milieu and/or knowledge of the pregnancy may result in increased stress. These findings reinforce the need for encouraging stress management techniques in the aspiring and expecting mother.

Introduction

Perceived stress has long been hypothesized to reduce the probability of conception. The belief that stress decreases fertility can be partially attributed to studies reporting natural conception by infertile couples soon after the adoption of a child [1,2] and, more recently, increased probability of pregnancy among *in vitro* fertilization patients undergoing stress reduction interventions [3–5].

An effect of stress on conception may be the consequence of overactivation of the hypothalamic-pituitary-adrenal (HPA) axis. Stress may affect ovulation by causing a rise in plasma glucocorticoid levels, which consequently suppress gonadotrophin releasing hormone (GnRH) [6]. Increased HPA axis function and high concentrations of glucocorticoids can be detrimental to the developing endometrium [7]. The process of implantation is a form of uterine inflammation, and intracellular cytokines such as uterine NFkappaB are critical during implantation [8]. However, if glucocorticoids suppress NFkappaB and the local inflammation, then they are indirectly compromising the process of implantation [9].

Only a few prospective epidemiologic studies have rigorously investigated the hypothesis behind stress and fecundability, with varied results [10–13]. None of the studies compared the effects of stress across different windows of the menstrual cycle. If stress affects the process of ovulation or fertilization, then stress in the follicular phase (especially during the ovulatory window) may affect fecundability; rather, if stress interferes with implantation, then stress during the luteal phase would affect fecundability.

More research is clearly needed to quantify the effects of perceived stress on fecundability. The objective of this study is to examine the association between self-reported stress and fecundability and identify the window(s) of highest susceptibility during the menstrual cycle, using a large daily data set from a prospective pregnancy study of women office workers.

There are no conflicts of interest to declare.

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Materials and methods

Study population and eligibility

The Mount Sinai Study of Women Office Workers was a prospective study originally designed to evaluate the reproductive health of women office workers 40 years of age and younger. Through 1990–1994, women were enrolled from 14 companies and government agencies in New England [14,15]. Women who were sexually active while using inconsistent or no contraceptives in the month before the baseline questionnaire were eligible. Women using intrauterine devices, having a hysterectomy, or diagnosed with polycystic ovaries or current infertility (attempting to conceive for more than 12 months) were excluded. The Institutional Review Board at Mount Sinai School of Medicine, New York, NY, and Emory University, Atlanta, GA, approved the protocols, and all participants provided informed consent. Additionally, the Institutional Review Board at the University of Louisville approved this analysis.

Data collection

Participants were interviewed for demographic, behavioral, and anthropometric characteristics and reproductive history at baseline. Data collected included age, body mass index (BMI), ethnicity, race, marital status, education, pregnancy history, medical history, and desire to become pregnant (yes/no; henceforth called "trying to conceive"). Women were asked to complete daily diaries and return them by mail at the end of each month. Daily diaries contained information regarding menstruation, intercourse, contraceptive use, alcohol (number of alcoholic beverages), caffeine (number of caffeinated beverages), smoking (number of cigarettes), and stress levels (Supplementary Fig. 1). First-morning urine was collected during the first 2 days of each cycle, where day 1 was defined as the first day of menstruation. If pregnancy occurred during a cycle, women collected urine samples on the expected day of menses. Women were followed until pregnant or until the study end, for an average of eight menstrual cycles (maximum 20 cycles).

Exposure assessment and definition of windows

In the daily diaries, women reported stress on an ordinal scale with 1 being the lowest and 4 the highest (Supplementary Fig. 1). The mean stress was calculated during different windows of susceptibility in a woman's menstrual cycle (Supplementary Fig. 2). The estimated day of ovulation was defined as day -14 using the Knaus-Ogino method [16,17]. During a cycle in which conception occurred, a woman's average cycle length was used to estimate the day of ovulation. The follicular phase was divided into preovulatory and ovulatory windows. The preovulatory window was defined as more than 19 days before the onset of the next menses (days < -19) and varied in length. The ovulatory window was defined as 19 days before the onset of the next menses until the estimated day of ovulation (days -19 to -14) [18]. The luteal phase was defined as beginning one day after the estimated day of ovulation and continuing until the day before the next menstrual period begins (days -13 to -1). Implantation occurs during the luteal phase, likely 6 to 12 days after conception [19]. Box plots were created using R statistical package (The R Foundation for Statistical Computing, Vienna, Austria) to examine the distribution of stress across the menstrual cycles [20].

Covariate assessment

A set of relevant covariates to consider as potential confounders was chosen through review of literature. A directed acyclic graph was constructed to evaluate the roles of potential covariates and assign them as either possible confounders or mediators (or potentially both) (Supplementary Fig. 3).

Outcome assessment

Pregnancies were defined by urinary human chorionic gonadotropin levels greater than 0.25 ng/mL for two consecutive days. Two laboratories assayed samples for human chorionic gonadotropin levels including the Core Laboratory at the Irving Center for Clinical Research at Columbia University and the Center for Clinical Research at Mount Sinai School of Medicine [21]. Split sample comparison between both laboratories allowed for similar results. All clinical pregnancies were confirmed by physician diagnosis.

Statistical analysis

Analyses other than box plots were performed using SAS version 9.4 (The SAS Institute, Cary, NC). Distributions of all variables were examined, and impossible and inconsistent values were set to missing before analysis. Pearson χ^2 tests were used to evaluate the association between the pregnancy outcomes and the distribution of demographic data and covariates. Time to pregnancy (fecundability) was assessed by counting the number of cycles up to and including the cycle of pregnancy. Discrete survival analysis was used to determine whether self-reported stress levels were associated with fecundability. This approach is statistically more powerful than dichotomizing reproductive success as fertile and/or infertile [22]. The discrete time hazard is defined as the probability that a woman became pregnant in a given menstrual cycle conditional on a pregnancy not occurring in prior cycles. It assumes the probability of conception is the same across cycles within individual women. The likelihood for a discrete time hazard rate is equivalent to that of binary regression models [23]. The discrete time hazard was included in the model through indicator variables for each cycle a woman was at risk for pregnancy.

Three models were constructed to evaluate the association between stress and fecundability. The directed acyclic graph informed variable selection. Model 1 was a minimal model that included maternal age and the mean stress for each of the three windows of the menstrual cycle; thus, the estimates for the preovulatory window, ovulatory window, and luteal phase (implantation window) were mutually adjusted for one another. Model 2 also included the following potential confounders: parity (0 vs. >0), intention to conceive (yes/no), education (less than high school, high school, college, or greater than college), and marital status (married, single, or divorced/separated/widowed), all assessed at baseline. Model 3 additionally included variables which may act as either confounders or mediators: BMI at baseline, and the following time-varying covariates: average weekly number of alcoholic beverages, average weekly number of cigarettes smoked, cycle length, and frequency of unprotected intercourse during the ovulatory window. Maternal age and BMI were left as categorical variables due to an absence of a linear trend. Cycle-level means for alcohol consumption, number of cigarettes, cycle length, and frequency of intercourse were calculated from the daily diaries and left as continuous variables because linear trends were observed for these variables. There was no evidence of collinearity among the variables used.

For each model, the fecundability odds ratios (FORs) for the effect of stress during each of the three windows on fecundability were estimated. The FOR represents the ratio of the odds of conception in one group to the odds in the referent group. An FOR $<$ 1.0 indicates a decrease in fecundability and $>$1.0 indicates an increase in fecundability (higher probability of pregnancy per cycle) for any 1-unit increase in mean stress (e.g., 1.0–2.0 or 2.4–3.4).