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Are increased levels of self-reported psychosocial stress, anxiety, and depression associated with fecundity?

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Abstract

Objective—To assess the association between self-reported measures of stress, anxiety, depression, and related constructs and fecundity.

Design—Prospective cohort study of women trying to conceive.

Setting—United Kingdom.

Patient(s)—Three hundred thirty-nine women aged 18–40 years who were attempting to conceive.

Intervention(s)—Completed daily diaries for up to six cycles or until pregnancy was detected. For each cycle, stress biomarkers were measured and psychosocial questionnaires were completed.

Main Outcome Measures(s)—Fecundability odds ratios (FORs) and 95% confidence intervals were calculated using discrete time survival methods, and the day-specific probabilities of pregnancy were calculated using Bayesian statistical techniques.

Result(s)—Among the 339 women, 207 (61%) became pregnant during the study, 69 (20%) did not become pregnant, and 63 (19%) withdrew. After controlling for maternal age, parity, months trying to conceive before enrollment, smoking, caffeine use, and frequency of intercourse, we found no association between most psychosocial measures and FORs or the day-specific probabilities of pregnancy save for an increased FOR for women reporting higher versus lower levels of social support.

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Conclusion(s)—Self-reported psychosocial stress, anxiety, and depression were not associated with fecundity. Any adverse effect of stress or psychological disturbance on fecundity does not appear to be detectable via the questionnaires administered.

Keywords

Fertility; stress; anxiety; depression; social support

The question of whether stress contributes to conception delay is a controversial issue that has received much attention in recent years (1–3), in part owing to the fact that despite advances in medicine some cases of infertility remain unexplained. Conception delay is a form of fecundity impairment, with fecundity defined as the biologic capacity for reproduction irrespective of pregnancy intentions. An association between stress and subfertility was first suggested by Selye, who noted ovarian atrophy in rats exposed to stressful stimuli (4). Since then, experimental research has elucidated physiological compensatory linkages between the hypothalamic pituitary adrenal (HPA) axis and the hypothalamic pituitary gonadal axis (5). It is now generally accepted that physical stressors such as undernutrition and/or excessive exercise may lead to functional anovulation and amenorrhea (6–8). What remains unclear, however, is the role that stress, defined as a physiological or psychological response to a positive or negative external stimulus, may play in reproductive function, in part due to an inability to separate cause and effect.

Stress may influence time to pregnancy via several pathways. The first and most obvious pathway is that increased stress levels may contribute to a decrease in sexual libido and/or coital frequency. Another possibility is that increased cortisol production as a result of HPA axis activation may lead to a delay in or inhibition of the requisite preovulatory GnRH and LH surge (9). Increased levels of stress may result in altered blood flow through the fallopian tubes, thereby potentially impacting gamete movement (10). Lastly, psychological disturbances have been shown to be associated with hyposecretion of corticotrophin-releasing hormone, which may contribute to the development of a uterine autoimmune state that is unfavorable for implantation (11).

One indirect observation that is consistent with the idea that stress levels may impact fecundity is that stress reduction and/or psychological counseling is associated with spontaneous pregnancy among some infertile couples. For instance, there are many reports in the literature of infertile couples who spontaneously conceive after adopting a child (12–14). In addition, Domar and colleagues have demonstrated higher pregnancy rates among women randomized to structured cognitive-behavioral therapy groups or standard support groups compared with infertile women who did not participate in such programs (15). They have also shown increased pregnancy rates in couples randomized to a mind-body intervention program (16). Still other investigators reported increased pregnancy rates in depressed patients presenting to an infertility clinic who were randomized to treatment with an antidepressant and psychotherapy (17).

To address some of these important issues prospectively in an attempt to separate stress as a potential causal factor versus infertility effect, we undertook a prospective study of women attempting to conceive. We have previously reported in this cohort that increased levels of

the stress biomarker alpha-amylase, which suggests activation of the sympathetic medullary pathway, were associated with decreased probabilities of pregnancy across the fertile window (18). The purpose of this paper is to describe the correlation among various self-reported measures of stress, anxiety, depression, related constructs, and the stress biomarkers as well as to assess the independent effects of scores on the various psychosocial instruments in relation to fecundability and the day-specific probabilities of pregnancy.

MATERIALS AND METHODS

Study Design and Population

This study of the association between stress and fertility was designed as an embedded study within the ongoing Oxford Conception Study (OCS). The aim of the stress study was to investigate the impact of psychosocial and physiological stress on time to pregnancy and the day-specific probabilities of pregnancy. Three hundred seventy-four women participated in the protocol. Women were recruited and enrolled via media campaigns in the United Kingdom in 2005 and 2006. Eligibility criteria for the OCS included women aged 18–40 years trying to conceive for <3 months, menstrual cycle length 21–39 days, no history of infertility, not undergoing fertility treatment, not currently breastfeeding, no use of oral hormonal contraception in the last three cycles, no emergency hormonal contraception use in the last two cycles, and no history of injectable contraceptive use within the past year (19).

Data Collection

The protocol was Institutional Review Board approved, and all women provided written informed consent for participation. Participating women completed a baseline questionnaire and then a daily diary in which they recorded bleeding, sexual intercourse (in 12-hour intervals), smoking, and alcohol consumption for up to six cycles as they attempted to conceive. From day 6 to 26 of each cycle, women tested their urine using a modified Clearblue Easy Fertility Monitor (SPD Development Company Ltd., formerly Unipath). The monitor uses changes in estrone-3-glucoronide (E_3G) and LH to identify the likely day of ovulation. It has been shown to be highly accurate in relation to E_2, serum LH, and follicular ultrasound (20). On day 6 of each cycle, women collected a saliva specimen for the measurement of physiologic markers of stress (i.e., cortisol and α-amylase) as well as completed a series of self-administered psychosocial questionnaires. Saliva collection procedures and laboratory methods for analysis of the physiologic markers of stress have been published elsewhere (18). Table 1 presents the psychosocial instruments completed, the domains measured by each instrument, frequency of data collection, psychometric properties, ranges, and interpretation of each scale.

Operational Definitions

Menstrual cycles were delineated according to the first day of bleeding reported on the daily diary. The likely date of ovulation was then determined by matching the calendar days from the diary to the first day of the LH surge as detected by the fertility monitor under the assumption that the ovulation was expected to have occurred within 24 hours of the surge. Pregnancies were identified via a positive home pregnancy test and then were confirmed by

a nurse. All lifestyle consumption variables were standardized to a 28-day cycle to adjust for varying menstrual cycle lengths and varying lengths of time required for pregnancy.

Statistical Analysis

Exploratory data analyses were conducted to evaluate data completeness and quality. Demographic characteristics and scores on the psychosocial instruments completed during cycle 1 were compared by study outcome (i.e., pregnant in the first or second cycle, pregnant in the third cycle or later, not pregnant, and withdrew). For statistical significance testing, χ^2-tests were used for categorical variables, and *t*-tests or analysis of variance for continuous data. To examine the correlation between various measures, we used the Pearson product-moment correlation coefficient.

For each psychosocial scale, we created quartiles based on the distribution of scores in the study population. We then used Cox proportional hazards models for discrete survival time, which is a proportional odds model in SAS software (SAS version 9.2, SAS Institute, Inc.), to estimate the effect of a given self-reported psychosocial construct on time to pregnancy (in cycles). The model takes into account all observed cycles, while taking into account the dependence of cycles within women, and allows for probabilities to vary from cycle to cycle. We estimated a fecundability odds ratio (FOR) and 95% confidence interval (CI) for each separate psychosocial scale while adjusting for relevant covariates. FORs above 1.0 denote increased fecundability (shorter time to pregnancy), while FORs below 1.0 suggest decreased fecundability (longer time to pregnancy). We also used Bayesian statistical techniques to assess the associations of the psychosocial stress markers and the day-specific probabilities of pregnancy taking into account intercourse during the fertile window and other relevant covariates using the Dunson and Stanford adaptation of the Barrett and Marshall model (21, 22).

RESULTS

Of the 374 women who participated in the stress protocol of the OCS, 339 had complete psychosocial questionnaire data and fecundability data available for analysis. Of the 35 women who were excluded, 28 were missing psychosocial questionnaires and seven had missing monitor or daily diary data. Table 2 presents the demographic characteristics and mean scores from the battery of self-administered questionnaires completed during cycle 1 by study outcome. Women who did not become pregnant while under observation were systematically older than those who became pregnant or withdrew. They also were less likely to report a previous pregnancy. There were, however, no other differences by study outcome. Most notably, there were no differences in the scores on any of the baseline psychosocial instruments.

One of the issues in which we were particularly interested is how the scores on the psychosocial instruments compared with the cortisol and alpha-amylase levels reported in our previous publication (18). As described in the Methods section, the salivary sample that was analyzed for the stress bio-markers was collected on the same day that the questionnaires were completed, day 6 of the women's menstrual cycle. As shown in Table 3, we found no correlation between the cycle 1 salivary cortisol and alpha-amylase levels and

scores on the baseline psychosocial instruments, with the exception of the Hospital Anxiety and Depression (HAD) depression scale, in which a correlation with the alpha-amylase (r = 0.14) was noted. We then examined the correlations between the salivary biomarkers and psychosocial instruments that were repeated in cycles 2–6 and again found little to no correlation. We again noted a correlation between alpha-amylase and the HAD depression scale in cycle 4 (r = 0.24) and a correlation between salivary cortisol and the Perceived Stress Scale (PSS) in cycle 6 (r = 0.32), but the correlations were neither strong nor consistent.

We then examined separately for each psychosocial instrument the effect of the score on that questionnaire in cycle 1 on the FOR after adjustment for relevant covariates. The results of these regression analyses are presented in Table 4. In summary, even after adjustment for relevant confounders, we found no association between the scores on almost any of the baseline psychosocial measures and the odds of becoming pregnant while in the study. The one exception to this was that we noted a suggestion of an increase in fecundability (decrease in time to pregnancy) for those individuals with higher self-reported levels of social support compared with those with lower levels; however, this finding was only statistically significant for women in the second highest quartile.

To test the robustness of our findings, we then used Bayesian statistical techniques to examine the association between scores on the baseline psychosocial instruments and the day-specific probabilities of pregnancy after adjustment for relevant confounders. Performing a separate regression analysis for each psychosocial measure, we again found no association between scores on the psychosocial instruments and the adjusted day-specific probabilities of pregnancy (data not shown).

DISCUSSION

To our knowledge, this is the first study to prospectively examine the effect of self-reported psychosocial stress and related constructs on fecundity and their correlation with concurrently obtained biomarkers of stress. In summary, we found little to no correlation between the stress biomarkers and any of the scores on the psychosocial questionnaires completed at the same time the saliva sample was taken. Further, we found no association between scores on any of the psychosocial instruments and fecundability or the day-specific probabilities of pregnancy, with the exception of a suggestion of a possible association between increased levels of social support and increased fecundability.

While the lack of correlation between the stress biomarkers and scores on the psychosocial questionnaires remains somewhat perplexing, it was not entirely unexpected. In a population of roughly 1,500 pregnant women, Harville and colleagues examined salivary cortisol and corticotrophin-releasing hormone measurements in relation to scores on a variety of questionnaires (23). Our findings mirror theirs in that they observed no correlations greater than 0.15. Similarly, van Eck and colleagues found no association between scores on the PSS and cortisol levels in a sample of male white collar workers; however, they found that self-reported chronic stressors were associated with increased cortisol levels (24). One possible explanation is that individuals who are accustomed to high levels of daily stress

may be less likely to perceive stress due to everyday hassles as a result of habituation. Another explanation is that chronic stress is the important factor in leading to a physiological response, and chronic stress, such as that caused by racism or poverty, is extremely difficult to capture via questionnaire (23).

Our finding that scores on the various psychosocial questionnaires were not overall associated with decreased fecundability or decreased day-specific probabilities of pregnancy was contrary to what we had hypothesized. In fact, at a conceptual level our findings are in contrast to that reported by the handful of studies to have examined this issue previously. Stoleru and colleagues followed a cohort of 63 recently married couples with undetermined fertility status for 13 months as they tried to conceive (25). The purpose of the study was to identify and measure the psychological correlates of fertility. Among the 63 couples, 17 (27%) had not conceived by the end of 12 months. Two psychological factors, namely, the women's attitude toward motherhood and the quality of the men's integration between the wish for a child and sexual relationships, were found to be significantly higher among the fertile couples as compared with the infertile couples. Time to pregnancy was also shown to be related to psychological disturbances.

In a similar study, Sanders and Bruce prospectively followed a cohort of 13 women in Australia to evaluate whether or not average stress levels during the cycle in which pregnancy occurred differed from stress levels during nonpregnancy cycles (26). Stress levels were assessed with the State-Trait Anxiety Inventory (STAI) and the Bi-polar Profile of Moods Scale. Ten (77%) women provided 24-hour urine samples for the measurement of catecholamine and cortisol excretion. Although they found no difference in urinary cortisol, adrenaline, or noradrenaline, women were found to have reported more favorable mood states during the month of pregnancy. There was no evidence to suggest that the association was due to an increase in coital frequency during those months.

Hjollund and colleagues reported an association between increased levels of distress and reduced fertility among a cohort of 430 couples who were planning their first pregnancy (27). However, the effect was seen only among those women with long menstrual cycles, not among those with normal length cycles. Distress was measured using the General Health Questionnaire, which measures aspects of fatigue, anxiety, and depression. Women completed the questionnaire on day 21 of their cycle before learning whether or not their pregnancy attempt that cycle had been successful. As a result of their unanticipated finding, the authors suggested that alterations in fertility due to psychosocial stress could be mediated by alterations in the length of the menstrual cycle (27).

One reason that our results differ from those reported by Hjollund and colleagues could be that they measured stress during the luteal rather than during the follicular phase of the menstrual cycle. Levels of perceived stress have been shown to vary across the cycle, and perhaps stress during the luteal phase during which implantation occurs is the most important (28). In this study, we chose to administer the psychosocial instruments on day 6 of the cycle because that was the day on which the monitor first requested that participants test their urine and, as such, it was easy to remember. Further, it was far enough away from the start of menses that we felt that any stress related to the participant not having become

pregnant in the last cycle would have decreased somewhat by that point. Future studies examining the role of stress on fecundity should consider collecting biomarker and questionnaire data at various points throughout the cycle to evaluate whether the timing of stress plays an important role.

To further put our findings into context, one possible explanation for the fact that our findings differ somewhat from those reported by others is that the women in our sample did not report particularly high levels of perceived stress, anxiety, or depression. For instance, the mean score for a normative sample of females completing the PSS is 13.7 ± 6.6, which is similar to what we found in this population (29). Further, the STAI scores in our population were in the 51st percentile compared with a normative sample of 19- to 39-year-old females (30). The HAD anxiety and depression scores in our population were all within the normal range (i.e., most women were not depressed or anxious). As a result, this limited our ability to examine the role that high levels of psychological disturbance may play in relation to fecundity.

Finally, we did identify the suggestion of an increase in fecundability among those reporting high levels of social support. This seems reasonable in that having a network of friends and colleagues with whom an individual feels she can share her problems may mitigate the effects of some stressful life events. In fact, a recent study reported that social support was directly related to infertility-related stress among a sample of 252 women seeking infertility treatment (31).

Despite this study's strengths, it has several limitations worth noting. First, due to the desire to minimize participant burden, the only instruments repeated in every cycle were the PSS and the HAD scale; as such, we were unable to evaluate the correlation between the biomarkers and the remaining psychosocial instruments as well as their association with time to pregnancy in a longitudinal manner. Moreover, our estimates of effect on the day-specific probabilities of pregnancy must be interpreted within the context of using the LH surge as a proxy for ovulation. Finally, it is possible that the effect of stress is only relevant for subfecund couples. Given that women were only followed for six cycles, we were unable to examine the effect of stress on the probability of pregnancy among women who have tried longer than 6 months to conceive.

Whether high levels of stress and psychological disturbance play a role in fecundity impairment remains an unanswered question. In this study, we have demonstrated that any role that stress may play does not appear to be detectable via self-administered questionnaires completed during the follicular phase of the menstrual cycle. Our findings highlight the need to study women reporting high levels of stress and psychological disturbance; as well, it is a call to collect information on stress and mood throughout the menstrual cycle to permit a more accurate picture of the relation between stress and fecundity.

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TABLE 1

Psychosocial questionnaires administered, domains measured, timing of data collection, and psychometric properties.

Scale	Domain	Cycle 1[a]	Cycles 2–6[a]	Cronbach's α[b]	Range of possible scores	Scoring
Cohen's PSS (32)	Perceived stress	X	X	0.78	0–40	Higher scores = more stress
HADS (33)	Anxiety and depression	X	X	0.78	0–21 for each scale	≥11 = anxious or depressed
STAI (30)	State and trait anxiety	X		0.91–0.93	20–80 for each scale	Higher scores = higher levels of anxiety
Medical Outcomes Study Social Support Survey (34)	Social support	X		0.77–0.91	0–100	Higher scores = more social support
Pearlin's Mastery Scale (Pearlin) (35)	Locus of control	X		0.71	7–28	Higher scores = increased belief that one can control her life

[a] Administered on day 6 of the cycle.

[b] Measure of internal consistency or reliability.

TABLE 2

Selected maternal characteristics upon enrollment or while attempting to become pregnant by study outcome.

	Pregnant in observed cycles 1–2 (n = 145)	Pregnant in observed cycles 3 + (n = 62)	Not pregnant (n = 69)	Withdrew (n = 63)
Maternal age[a]	29.25 (4.39)	30.24 (4.16)	31.54 (4.11)	28.56 (4.94)
Maternal race				
White	139 (95.9)	58 (93.6)	63 (91.3)	61 (96.8)
Other	6 (4.1)	4 (6.4)	6 (8.7)	2 (3.2)
Gravid[a]	113 (77.9)	46 (74.2)	41 (59.4)	40 (63.5)
Parous	77 (53.1)	31 (50)	28 (40.6)	22 (34.9)
Smoked (%)	30 (20.7)	19 (30.7)	12 (17.4)	13 (20.6)
Drank alcohol (%)	128 (88.3)	56 (90.3)	66 (95.7)	58 (92.1)
Average no. of acts of intercourse/ cycle	10.8 (7.0)	10.4 (5.8)	9.9 (4.4)	12.2 (8.5)
Cycle 1 measures				
STAI, state	37.2 (12.1)	36.8 (10.1)	37.2 (10.9)	39.0 (10.7)
STAI, trait	38.9 (10.2)	37.2 (8.8)	38.6 (10.2)	40.0 (9.3)
Medical Outcomes Study	82.7 (11.9)	82.0 (11.2)	81.3 (13.3)	80.4 (11.1)
Pearlin's Mastery	21.5 (4.0)	22.0 (3.30)	22.4 (3.5)	21.4 (3.7)
HADS, anxiety	6.9 (3.4)	6.2 (3.4)	6.3 (3.4)	6.8 (3.8)
HADS, depression	3.0 (2.7)	3.0 (2.7)	2.8 (2.8)	3.7 (3.0)
PSS	15.7 (7.1)	14.3 (7.0)	14.7 (6.4)	16.7 (7.0)
Cortisol (μg/dL)	0.4 (0.2)	0.5 (0.2)	0.4 (0.2)	0.4 (0.2)
Alpha-amylase (U/mL)	6.7 (6.7)	9.4 (8.8)	7.7 (6.8)	10.0 (20.2)

Note: Values in parentheses are percentages.

[a] $P<.05$.

TABLE 3

Correlation between psychosocial and physiologic measures at baseline (cycle 1).

	STAI-S	STAI-T	Medical Outcomes Study	Mastery	HADS, anxiety	HADS, depression	PSS
Cortisol, μg/dL	−0.01	−0.02	0.04	0.02	−0.02	0.05	−0.02
Alpha-amylase, U/mL	0.09	0.02	−0.05	0.02	0.08	0.14[a]	0.06

[a] $P<.05$.

TABLE 4

Unadjusted and adjusted FORs by baseline psychosocial stress measures.

	Unadjusted		Adjusted[b]	
Measure[a]	**FOR**	**95% CI**	**Adjusted FOR**	**95% CI**
PSS				
Quartile 1 (2–9)	1.00	–	1.00	–
Quartile 2 (10–14)	0.82	0.54, 1.25	0.81	0.52, 1.25
Quartile 3 (15–19)	0.92	0.59, 1.43	0.98	0.61, 1.56
Quartile 4 (20–33)	0.89	0.57, 1.39	0.94	0.59, 1.50
HADS, anxiety				
Quartile 1 (0–3)	1.00	–	1.00	–
Quartile 2 (4–5)	0.93	0.59, 1.45	0.98	0.62, 1.56
Quartile 3 (6–8)	1.22	0.81, 1.84	1.26	0.82, 1.94
Quartile 4 (9–17)	1.21	0.78, 1.89	1.26	0.79, 2.02
HADS, depression				
Quartile 1 (0)	1.00	–	1.00	–
Quartile 2 (1)	0.92	0.57, 1.47	0.88	0.55, 1.35
Quartile 3 (2–4)	1.04	0.69, 1.55	1.08	0.69, 1.57
Quartile 4 (5–14)	0.89	0.56, 1.40	0.78	0.47, 1.20
STAI, state				
Quartile 1 (20–28)	1.00	–	1.00	–
Quartile 2 (29–34)	1.38	0.90, 2.12	1.62	1.04, 2.54
Quartile 3 (35–43)	0.99	0.64, 1.52	1.06	0.67, 1.67
Quartile 4 (44–70)	0.93	0.60, 1.45	0.97	0.60, 1.54
STAI, trait				
Quartile 1 (23–31)	1.00	–	1.00	–
Quartile 2 (32–35)	1.27	0.84, 1.92	1.33	0.87, 2.04
Quartile 3 (36–44)	1.02	0.65, 1.60	1.07	0.66, 1.72
Quartile 4 (45–66)	0.99	0.64, 1.53	1.10	0.69, 1.73
Medical Outcomes Study Social Support				
Quartile 1 (36–75)	1.00	–	1.00	–
Quartile 2 (76–84)	1.14	0.74, 1.76	1.23	0.78, 1.94
Quartile 3 (85–91)	1.58	1.03, 2.42	1.79	1.14, 2.82
Quartile 4 (92–95)	1.22	0.78, 1.92	1.35	0.83, 2.20
Pearlin Mastery Scale				
Quartile 1 (12–18)	1.00	–	1.00	–
Quartile 2 (19–21)	0.74	0.48, 1.12	0.75	0.48, 1.19
Quartile 3 (22–24)	0.94	0.62, 1.43	1.07	0.67, 1.70
Quartile 4 (25–28)	0.74	0.46, 1.19	0.79	0.46, 1.36

[a] Range represents the range of scores in that quartile.

[b] Adjusted for woman's age, parity, number of months trying to conceive before study entry, woman's average smoking, woman's average caffeine consumption, and woman's average number of acts of intercourse during the fertile window.