Human Reproduction vol.12 no.10 pp.2324–2329, 1997

A prospective study of psychosocial stress and fertility in women

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The objective of this study was to compare average stress levels during the month of conception to those of previous infertile months. We postulated that stress level during the actual month of conception would be lower than that during previous non-conception cycles. Thirteen normal women from the general community, who were attempting pregnancy, kept daily records of coital activity and basal body temperature, and twice a month completed self-administered questionnaires and provided a 12 h overnight urine sample. On average, women reported significantly more favourable mood states on standard psychometric tests, during the month of conception than during the previous non-conception cycles. In addition, they felt significantly less 'hassled' during the month of conception. However, mean urinary hormone excretion of adrenaline, noradrenaline and cortisol did not significantly differ between conception and non-conception cycles and there was little relationship between the psychological measures of mood state and excretion of adrenaline and cortisol. There was no evidence of increased coital frequency during the month of conception when mood states were improved, suggesting that stress effects on libido were unlikely to account for the findings. The results support the conclusion that psychosocial stress influences fertility in females but as yet mechanisms remain unclear.

Key words: catecholamines/cortisol/female/fertility/psychosocial stress

Introduction

There is compelling evidence for an association between stress and infertility. Such evidence originated from the pioneering work of Selye (1950) who observed ovarian atrophy in rats exposed to a variety of noxious stimuli. More recently, laboratory studies in both experimental animals and humans have shown interactions between the physiological pathways activated during stress and the reproductive axes (Moberg, 1987). While it is generally accepted that some physical stressors such as undernutrition and exercise can affect human reproductive function, the role of psychosocial stress in this regard remains equivocal due, in part, to the difficulty in separating cause and effect (Edelmann and Connolly, 1986; Wright *et al*., 1989).

A line of argument often used in support of a psychosocial cause of infertility is the belief that relief from stress alone can promote fertility and lead to conception (Sandler, 1968; Nijs *et al*., 1984). Coupled with this is the notion that conception frequently follows adoption. Proponents of this line of argument emphasize that adoption resolves the conflicts, such as anxiety, insecurity or guilt regarding a woman's capacity as a mother, which inhibit conception (Mai, 1971). Although anecdotal reports of conception after adoption are numerous, the majority of investigations in this area do not support a causal association (Aronson and Glienke, 1963; Rock *et al*., 1965; Weir and Weir, 1966). There are, however, a number of methodological problems with these studies, for example, no authors have considered the possibility that for some couples adoption may have a detrimental effect on conception.

Tied also to the idea of relief from stress is the observation that a proportion of infertile couples seeking fertility treatment achieve pregnancy prior to any active treatment (Harrison *et al*., 1981; Dunphy *et al*., 1990). While attendance at an infertility clinic may assist to relieve anxiety and promote psychological well-being for some couples, for others a definitive diagnosis of infertility can exacerbate levels of stress (Connolly *et al*., 1992). Again, however, no study has assessed whether changes in stress levels before and after clinic attendance are concomitant with conception.

As part of a larger study, prospectively investigating the relationship between lifestyle, psychosocial stress and fertility in women, we had the unique opportunity to examine the level of stress experienced during consecutive non-conception and conception cycles of 13 normal women, actively attempting pregnancy. In accordance with the 'relief from stress' notion, we postulated that if psychosocial stress inhibits conception, the level of stress during the actual month of conception should be lower than that during previous unsuccessful cycles. The level of stress experienced was assessed in a number of ways including standardized psychometric questionnaires and measurement of urinary catecholamine and cortisol excretion. In addition to providing an objective measure of stress, the assessment of urinary stress hormone concentrations was expected to give some insight into the potential biological mechanisms through which stress and fertility might interact.

Materials and methods

Subjects

Thirteen women participated in the study. The women, who were all actively attempting to conceive, were recruited from the general community of Perth, Western Australia as part of a larger study

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investigating psychosocial stress, lifestyle and fertility. All women were Caucasian and their mean ± SD age was 31.0 ± 3.2 years. Six women (46.2%) were in the highest quartile for socio-economic status, three in the upper middle quartile, two in the lower middle quartile and two in the lowest quartile. Eight women (61.5%) had previously conceived in their current relationship and five women (38.5%) were nulligravid. The mean ± SD number of cycles required to achieve pregnancy [positive β-human chorionic gonadotrophin (βHCG) test as confirmed by the women's general practitioners], from the time of entering the study, was 4.0 ± 1.4.

Study design

From the time of entry into the study, each participant was requested to complete a questionnaire, twice during each menstrual cycle. In addition 10 women collected a 12 h overnight urine sample for the determination of urinary catecholamine and cortisol excretion. These activities were timed to coincide approximately with the mid-follicular and mid-luteal phase of the cycle (day 7 and day 21 of a 28 day cycle).

The questionnaire was designed to gain an understanding of the women's feelings and attitudes during the course of the menstrual cycle. The questionnaire incorporated two standard psychometric tests as indices of the level of psychosocial stress experienced. These were: the A-State form of the State-Trait Anxiety Inventory (Spielberger *et al*., 1970); and the Bi-polar Profile of Mood States (POMS; McNair and Lorr, 1982). The questionnaire also sought details of other aspects of general feelings including quality and quantity of sleep, level of work satisfaction, feelings of mental and physical tiredness associated with work, feelings of time pressure, and satisfaction with leisure time. These questions were derived from the lifestyle study of Palmer *et al*. (1980), and the women were asked to respond with reference to how they felt during the last week on a scale of 1–5 representing good to poor aspects respectively. In addition, a question was asked on the frequency of feeling 'hassled' over the time period. Hassles were defined as irritants that range from minor annoyances to fairly major pressures, problems or difficulties. Again, this was scored on a 5-point scale.

Overnight urine samples were collected for a period of ~12 h, into clean 2 l plastic bottles containing ~80 ml of 6.5% acetic acid to prevent degradation of catecholamine content. On return to the laboratory, the urine sample volume was noted and an aliquot of urine stored at –20°C until assayed for urinary free cortisol, adrenaline and noradrenaline.

To determine ovulation and the likelihood of conception, the women recorded daily basal body temperature changes, coital activity and periods of menstrual bleeding on a graph. Basal body temperature was recorded with a digital oral thermometer accurate to 0.1°C (Terumo ET-CIIS, Mordialloc Victoria, Australia or Becton Dickinson E4030, Knoxfield Victoria, Australia).

Hormone assays

Urinary free cortisol was assayed, without prior extraction, using the Amerlex cortisol radioimmunoassay (Amersham International, Little Chalfont, Buckinghamshire, UK). All samples from the same woman were assessed in the same assay. The within-assay precision, expressed as the coefficient of variation, was 9.2% (mean 8.88 μg/dl).

Urinary free adrenaline and noradrenaline were measured by high pressure liquid chromatography (HPLC) with electrochemical detection as described by Bioanalytical Systems (1988). In brief, adrenaline and noradrenaline were separated from impurities by cation exchange chromatography followed by suspension with alumina. The components were then separated by HPLC using a reverse phase column and electrochemical detection. Adrenaline, noradenaline and the internal standard 3,4-dihydroxybenzylamine (DHBA) were measured by oxidation at the electrochemical detector. All samples from the same woman were assayed in the same batch. The within-assay precision for adrenaline and noradrenaline was 12.7% (mean 1.69 ng/ml) and 7.2% (mean 20.2 ng/ml) respectively.

Catecholamine and cortisol concentrations were adjusted for dilution with the acid preservative, and to account for differences in urine volume, concentrations for all three hormones were converted to an excretion rate and expressed as ng/min.

Statistical analysis

Differences between day 7 and day 21 measures and differences between the conception and non-conception cycles were compared within women by paired *t*-tests. For the comparisons between conception and non-conception cycles the psychological and hormonal values were derived from the average of the measures taken on day 7 and 21 of the cycle; those for the non-conception cycle were an average of all non-conception cycles. As the hormonal values were positively skewed, log transformation was applied prior to all analyses. Hence, for hormone excretion rates, geometric means and the 95% confidence intervals are displayed in the Tables. Pearson correlation coefficients were calculated to measure the association between hormonal and psychological measures. The incidence of intercourse between conception and non-conception cycles was compared by paired *t*-test.

Responses to questions regarding sleep and work characteristics and feelings of time pressure and hassles were collapsed into three categories with scores of 1–2 , 3, and 4–5 representing 'good', 'moderate' and 'poor' aspects respectively. The frequency distribution of responses was compared between conception and non-conception cycles by χ^2-test, treating day 7 and day 21 questionnaires as separate observations.

Results

The 13 women exhibited significantly improved mood states on all six POMS scales during the conception cycle and thus reported themselves to be more composed, agreeable, elated, confident, energetic and clear-headed at this time. The lower level of anxiety during the conception cycle was also confirmed by the State anxiety test ($P < 0.01$) (see Table I). There was no significant difference between women's psychological test scores from questionnaires completed on day 7 and day 21 of the non-conception cycles, with the exception of the POMS confident–unsure scale in which more favourable scores were reported during the luteal phase (paired *t*-test, $P < 0.05$). Furthermore, there was no significant difference between women's test scores from questionnaires completed on day 7 and day 21 of the conception cycle. No difference was detected in overnight catecholamine or cortisol excretion rates within women between the conception and non-conception cycles (Table II).

Correlation coefficients were calculated between the psychological measures and hormonal concentrations separately for the conception and non-conception cycles. There was little correlation between hormonal concentrations and scores on the psychological tests during the non-conception cycles, with the exception of a negative association between noradrenaline excretion and scores on the composed–anxious ($r = -0.3362$, $n = 45$, $P < 0.05$) and clear-headed–confused ($r = -0.3670$, $n = 45$, $P < 0.05$) scales of the POMS. During the conception cycle there was a significant inverse relationship between

Table I. Comparison of emotional state during conception and non-conception cycles

Psychological measure	Non-conception cycle	Conception cycle	Difference (paired data)[a]	*P* (*t*-test)
POMS scales[b]				
Composed–anxious	21.5 ± 1.75	26.6 ± 1.66	5.08 ± 1.05	0.0004
Agreeable–hostile	22.5 ± 1.14	27.3 ± 1.12	4.81 ± 0.62	<0.0001
Elated–depressed	21.3 ± 1.28	26.9 ± 1.21	5.59 ± 0.93	<0.0001
Confident–unsure	21.1 ± 1.28	24.9 ± 1.45	3.75 ± 1.00	0.0029
Energetic–tired	15.4 ± 1.17	20.4 ± 1.80	5.05 ± 1.98	0.0258
Clear-headed–confused	24.5 ± 1.84	27.3 ± 1.58	2.75 ± 0.95	0.0135
State anxiety[c]	40.3 ± 2.71	32.2 ± 1.79	8.09 ± 2.44	0.0091

[a]Values are means ± SEM.
[b]A higher score indicates a more favourable mood state with POMS (Bi-polar Profile of Mood States).
[c]A higher score indicates greater anxiety with State anxiety.

Table II. Comparison of hormone excretion rates for conception and non-conception cycles

Hormonal excretion rate (ng/min)	Non-conception cycle[a]	Conception cycle[a]	*P* (*t*-test)[b]
Catecholamines			
Noradrenaline	12.4 (10.4, 14.7)	12.8 (10.1, 16.2)	0.7777
Adrenaline	1.20 (0.91, 1.58)	1.11 (0.74, 1.66)	0.5150
Cortisol	54.2 (40.9, 71.7)	49.2 (35.2, 68.7)	0.6499

[a]Values are geometric means (95% confidence intervals).
[b]*t*-test on paired data.

noradrenaline excretion and the composed–anxious scale ($r = -0.5164$, $n = 19$, $P < 0.05$), the agreeable–hostile scale ($r = -0.5794$, $n = 19$, $P < 0.01$) and the energetic-tired scale ($r = -0.5088$, $n = 19$, $P < 0.05$).

Figures 1 and 2 show the frequency distribution of responses to the questions on sleep habits, work characteristics and feelings of time pressure and hassles. The question on hassles exhibited a significant difference between the non-conception and conception cycles. Women reported feeling significantly less hassled during the conception cycles compared to the previous unsuccessful cycles ($P = 0.0116$, χ^2-test). There was also a trend for women to have more adequate sleep and find their work less mentally tiring during the conception cycle although this was not significant.

The mean ± SEM incidence of sexual intercourse during non-conception cycles was 7.63 ± 0.61 acts. This compared to 7.22 ± 0.81 acts during the conception cycle (not significant, paired *t*-test). To reflect better the chance of conception per cycle, the incidence of intercourse was calculated for the 6 day period encompassing the time of expected ovulation, based on basal body temperature observations. Here too there was no difference in the incidence of intercourse (2.49 ± 0.36 and 2.78 ± 0.40 non-conception cycle and conception cycle respectively).

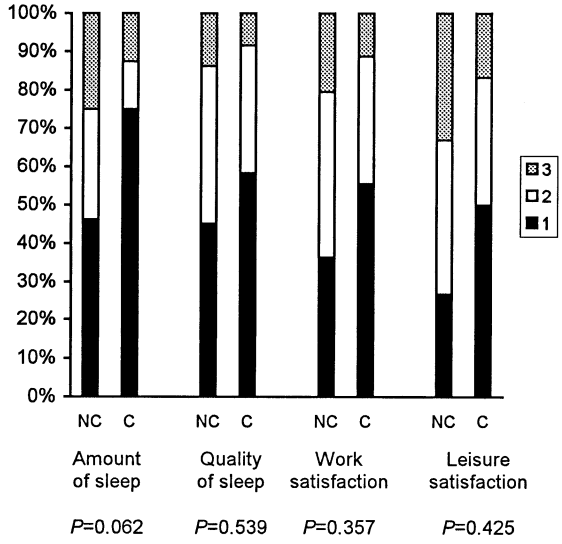

Figure 1. Subjective estimates of amount of sleep, quality of sleep, satisfaction with work and satisfaction with the leisure time for women during non-conception cycles (NC) and conception cycles (C). The height of each bar segment represents the proportion of questionnaires with each response. 1 = favourable, 2 = moderate, 3 = unfavourable responses. There were no significant differences (χ^2-test).

Discussion

The objective of this study was to compare average stress levels during the month of conception to those of previous infertile months in a group of normal women. If stress inhibits conception, it was postulated that during the actual month of conception, stress levels should be reduced. The comparison of mood state during conception and prior non-conception cycles of 13 women revealed a powerful effect. The women exhibited significantly improved mood states on all six POMS scales and lower state anxiety. Indeed for the first three POMS scales, all of the 13 women reported more positive emotions during the conception cycle. Put into perspective, the difference in level of state anxiety between conception and non-conception cycles approximated that observed in a college population under normal and exam conditions (Spielberger *et al.*, 1970). It is also interesting to note that the women reported feeling significantly less hassled, and tended to have more adequate sleep (not significant) during the conception cycle.

This is the first study in which the level of stress experienced during the actual month of conception has been compared with the level during previous unsuccessful months within a group of conceiving women. It should be pointed out that the values of the POMS and state scores during the conception cycle were based on two measures only (days 7 and 21), and therefore may not have been as accurately determined as the

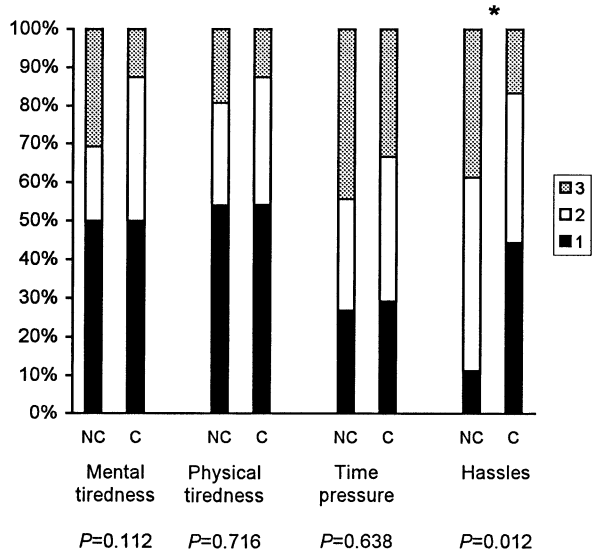

Figure 2. Subjective feelings of mental and physical tiredness associated with work, feelings of time pressure and feelings of being hassled, during non-conception cycles (NC) and conception cycles (C). The height of each bar segment represents the proportion of questionnaires with each response. 1 = favourable, 2 = moderate, 3 = unfavourable feelings. *Frequency distribution for conception cycles is significantly different from non-conception cycles ($P = 0.012$, χ^2-test).

non-conception cycle values, which were the mean of all non-conception cycles scores. This, however, would be expected to reduce the ability to detect significant differences between conception and non-conception cycles rather than to enhance it. It is important to note that only 13 women were included in the analyses, which limits the degree to which these results can be generalized to the wider community; however, the statistical strength of these findings ($P < 0.03$ to $P < 0.0001$) all but rules out chance effects and thus further studies of this type are warranted.

The question arises whether conception, itself, could have influenced the women's emotional state. The conceptus, within hours of fertilization, is reported to affect its mother's physiology through secretion of a platelet activating factor (O'Neill, 1985; O'Neill *et al*., 1985) and so an effect on emotion is not unrealistic. If such an effect did occur, the post-conception psychological test on approximately day 21 may have biased the mean test scores for the conception cycle. This possibility was tested by comparing scores from day 21 tests to the scores obtained on day 7, before conception could have occurred. There was no significant difference between the days on any scale of the POMS or the State anxiety test and so it is unlikely that the more favourable emotions experienced during the conception cycle were a result of unconscious knowledge of pregnancy. There was also no significant difference, on the majority of scales, between day 7 and day 21 measures during the non-conception cycles. Thus it is also unlikely that the observed differences in mood state between conception and non-conception cycles were caused by onset of a premenstrual syndrome in non-conception cycles, negatively biasing responses on the day 21 measures.

For psychosocial stress to affect fertility it must do so either by altering behaviour relating to fertility or by biological mechanisms directly affecting the reproductive organs or gametes produced. Although our study was not specifically designed to elucidate mechanisms, some speculation as to possible pathways can be made. Feelings of stress may be accompanied by suppressed libido and a reduction in the frequency of intercourse. It is well established that the probability of conception is influenced by the frequency and/or timing of intercourse in relation to the fertile phase of the cycle (Pepperell *et al*., 1977; Bongaarts and Potter, 1983; World Health Organization, 1983). In a recent prospective study, Stoleru *et al*. (1993) found that the effect of psychological disturbances on the time to pregnancy in a group of fertile couples was related to the frequency of intercourse. However, in the present study, frequency of intercourse was not a contributing factor since there was no apparent difference in the incidence of intercourse between conception and non-conception cycles. Thus, mechanisms can be narrowed down to biological effects of stress on the production or quality of gametes, or subsequent fertilization, implantation and pregnancy maintenance.

It is possible that the stress factors identified in this study were operating on female fertility through a hormonal pathway. There is extensive evidence that acute psychosocial stressors can potentiate the secretion of cortisol and catecholamines (Mason, 1968; Frankenhauser, 1975; Biondi and Brunetti, 1990). In humans, pathological conditions accompanied by elevated concentrations of circulating corticosteroids, such as Cushing's disease, and long-term treatment with exogenous glucocorticoids are associated with ovulatory dysfunction (Sakakura *et al*., 1975; Aron *et al*., 1987). Women with functional hypothalamic amenorrhoea are reported to have increased day-time cortisol secretion compared to normal women (Suh *et al*., 1988). Furthermore, cortisol has immunosuppressant properties (Guyton, 1986), and thus, an effect on the immunological conditions needed for implantation to occur is also possible. Since the female reproductive tract contains catecholamine receptors (Moran, 1975), catecholamines may potentially affect fertility, for example, by interfering with the transport of gametes through the Fallopian tube or by altering uterine blood flow (Schenker *et al*., 1992).

In our study, urinary free cortisol and catecholamine excretion rates were determined as an objective measure of the level of stress experienced, and to give insight into potential biological mechanisms. However, despite clear changes in mood state among the 13 women, there was no difference in urinary excretion of cortisol or catecholamines between non-conception and conception cycles. Furthermore, there was little relationship between the psychological measures and output of cortisol or adrenaline during either infertile or conception cycles, although higher noradrenaline excretion was associated with less favourable moods on some scales of the POMS. The general failure of stress hormone excretion rates to be correlated with mood states may possibly be explained by the overnight collection regime since individual variability in hormone excretion rate appears to be reduced when the body is at rest (Jenner *et al*., 1980). However, an alternative explanation is that because the study women were from a 'normal' population,

participating in their routine daily activities, the levels of psychosocial stress experienced were insufficient to induce measurable changes in stress hormone excretion, yet were enough to affect fertility.

An important factor that was not specifically addressed in the present study is the role of the male. It is not unreasonable to assume that any condition that causes stress in a woman may also lead to stress in her partner. Stoleru *et al*. (1993) found male attitudes and feelings towards having a child significantly predicted the time to pregnancy. In the fertile group, this effect was related to the frequency of intercourse as previously mentioned. However, for the whole group, male psychological factors predicted the risk of infertility, even after adjusting for frequency of intercourse. Stoleru *et al*. (1996) suggested that in men, less favourable male attitudes and feelings towards having a child, and greater sexual problems, represent aetiological factors for infertility. Several studies suggest that stress may have a negative influence on semen quality (Hellhammer *et al*., 1985; Harrison *et al*., 1987). Notwithstanding controversy over what constitutes 'normal' semen, it is possible that any stress-related reduction in sperm quality could adversely affect the probability of pregnancy, especially if the female's fertility is also compromised. If this was a factor in the present work it would imply that stress levels in both male and females covaried. Males were not assessed in the present study due to possible lack of compliance, but given the strength of the present result such an examination is warranted.

Irrespective of mechanisms, the important finding from this study is that it supports the view that relief from stress promotes fertility and thereby the tenet that psychosocial stress contributes to infertility. It is particularly interesting that this can be perceived in a group of 'normal' women who did not report themselves to be infertile nor appear to have extreme levels of psychosocial stress. The question arises as to whether this effect is even more evident in an infertile group, and, if so, whether an active programme to relieve stress (e.g. Domar *et al*., 1990, 1992) should be an important component of infertility treatment.

Acknowledgements

We thank the late Dr A.Landauer for advice on the psychological questionnaires, Mrs J.Wellstead for assistance with the data collection and the volunteer women for their participation and co-operation. K.A.S. was supported by an Australian Postgraduate Research Award.

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Received on March 31, 1997; accepted on July 23, 1997