Infertility-related stress in men and women predicts treatment outcome 1 year later

Jacky Boivin, Ph.D.,[a] *and Lone Schmidt, Ph.D.*[b]

[a] School of Psychology, Cardiff University, Cardiff, Wales, United Kingdom; and [b] Institute of Public Health, University of Copenhagen, Copenhagen, Denmark

Objective: To examine the separate and joint effects of male and female fertility problem (FP) stress and the source of stress (e.g., personal, social, marital) on treatment outcome.

Design: Prospective, epidemiological cohort design.

Setting: Fertility clinics in Denmark.

Patient(s): Eight hundred eighteen couples who were about to begin a new course of treatment.

Intervention(s): An FP stress inventory was administered at the start of treatment, and the treatment outcome was evaluated 12 months later.

Main Outcome Measure(s): Number of treatment cycles in 12-month study period and treatment outcome (i.e., success, no success).

Result(s): Fertility problem stress was associated with a poorer treatment outcome in women (pooled within-groups [WGr] correlation, WGr = .517) and men (WGr = .392) with the effect significantly more pronounced for women (z = 3.19, $P<.001$). Fertility problem stress arising in the personal and marital domain showed greater associations with treatment outcome than did FP stress from the social domain. Logistic regression indicated that women who reported more marital distress required more treatment cycles to conceive (median 3) than women reporting less marital distress (median 2) (odds ratio [OR] = 1.20: Model $\chi^2(3) = 77.21$, $P<.001$).

Conclusion(s): The findings provide evidence that infertility-related stress has direct and indirect effects on treatment outcome. (Fertil Steril® 2005;83:1745–52. ©2005 by American Society for Reproductive Medicine.)

Key Words: Stress, psychology, psychosocial, reproduction, marital, gender, counselling, infertility, in vitro fertilization, fertility

There is now converging evidence that negative psychological traits and mood states are associated with reduced conception rates in women. These effects have been found in women who are trying to conceive naturally (1) and in women undergoing fertility treatment—mainly IVF (2) but also donor insemination (3, 4). The association has been shown with diverse psychological measures: anxiety (5), depression (6), infertility-specific distress (7), and overly intense desire for a child (8) as well as diverse biological indicators of stress, for example, reactivity (9), hormonal (10), and immunological (5) parameters. In natural cycles, higher stress level and/or more negative psychological states and traits are associated with longer cycles (11) and lower pregnancy rates (12), whereas in treatment cycles, these are associated with a poorer biological response to treatment (13), and a lower pregnancy (14) and live birth rate (15). Finally, this psychobiological association remains if the investigator controls for procedural stress effects (i.e., negative feedback from staff during treatment [16]) and/or negative lifestyle factors associated with stress that also compromise success rates (such as smoking or poor diet) (15, 17).

Although the link between stress and fertility appears to be more and more convincing, especially in IVF, the phenomenon is not well delineated, especially with regard to the male contribution. Pregnancy depends on both male and female gametes, but the association between stress and conception is not examined in this context. Thus, it is not known to what extent findings reported for women are due uniquely to female distress compromising pregnancy and/or additionally or partly due to male distress indirectly compromising pregnancy. This confound appears particularly relevant given that partner stress scores are highly correlated during treatment (18), and that high psychological distress is associated with poor semen quality (e.g., volume, concentration, motility) (19). Thus, the association noted for women could partly be explained by the negative effect his stress may have on his sperm and the fertilization process. Even if male stress does not have direct effects on biological parameters, it may be that male stress contributes indirectly to the psychobiological association by adding to her stress level.

Another gap in the research is lack of specificity concerning the type of negative affect likely to impact on pregnancy rates during treatment. Infertility affects many different life domains and stress may therefore arise from many sources,

including from the marital, social, and personal sphere (20). Although much literature documents the link between personal distress (e.g., anxiety, depression) and treatment outcome, scant evidence exists for the effects of marital distress and social stress. Strauss et al. (21) found that marital strife had indirect effects on treatment outcome in that it was associated with premature treatment termination. These findings are in line with recent work showing that a proportion of couples drop out of treatment because of marital conflict (22) or avoid undertaking further treatment because treatment threatens marital stability (23). Social distress has not been studied in the context of treatment outcome, despite the fact that infertile couples report that social expectations, isolation, and lack of support from people in their social network is a significant source of distress (20).

The aims of the present prospective study were to investigate [1] joint and unique effects of male and female infertility-related stress at the start of IVF treatment on pregnancy rates 12 months later, [2] cumulative (total) and individual effects of infertility-related stress in the personal, marital and social domain on treatment outcome, and [3] moderating effects of stress on the relationship between treatment cycles to pregnancy and treatment success. The sample for this study included couples participating in the Copenhagen Multi-Centre Psychosocial Infertility (COMPI) research program, which is a longitudinal psychosocial investigation of infertile couples in Denmark (see Schmidt et al. [24]). Based on the research reviewed, it was hypothesized that both male and female personal stress would have direct effects on pregnancy, with female stress having a stronger contribution, in line with the more intense emotional experiences they report (18). Marital distress was expected to have additive effects, with the link between personal distress and treatment outcome stronger when couples were additionally experiencing marital distress. No specific hypotheses were made with respect to social distress. Finally, we expected that stress (e.g., personal, marital) would be associated with the need for more treatment cycles before pregnancy was achieved.

MATERIALS AND METHODS
Sample
The sample consisted of 818 couples who were undergoing treatment at 1 of 5 clinics in Denmark and participating in the first (Time 1 [T1]) and 12-month follow-up assessment (Time 2 [T2]) of the COMPI project.

In total, 2,812 questionnaires were distributed to men and women at clinics during the data collection at the first assessment (see Schmidt et al. [24] for a detailed analysis of distribution and response rates for T1 and T2 assessment). Of these, 2,250 (80.0%) were returned. Among this group were 1,070 couples. All these Time 1 couples were mailed the follow-up questionnaire 12 months later, and 888 (82.9%) returned questionnaires for both spouses, 79 (7.4%) for only one spouse, and 103 (9.6%) did not respond.

Of those returning for both partners, only 818 were retained for final analyses in the present study. To make the sample as homogeneous as possible, couples who had had a child with fertility treatment at study entry were excluded (1.8%, n = 16, including 5 couples who did not answer this question). Similarly, couples who adopted a child in the 12-month study period were excluded (2.0%, n = 18, including 7 who did not answer this question) to keep the outcome variable biological (i.e., pregnancy). An additional 14 couples (1.6%) were excluded because they did not have treatment during the study period, and another couple was excluded because the number of treatments reported (i.e., 17) was an outlier relative to the group median (i.e., 2). Finally, 25 couples (2.8%) were excluded because the spouses completed the Time 2 questionnaire at different times, either before or after a significant event like pregnancy or delivery. We excluded these couples because ratings on emotional and marital variables would be affected by the occurrence of these events. Thus, the final sample (n = 818) consisted of 92.1% of the original set of couples (n = 888) having returned questionnaires at Time 2 and 76.4% of couples participating at Time 1 (n = 1,070).

Couples were in their mid 30s with men being older (mean = 33.8 years old, SD = 5.1 years) than their partners (mean = 31.5 years old, SD = 3.5 years). Couples had been living together almost 8 years (mean = 7.6 years, SD = 3.6 years), and most men (92.4%, n = 756) and women (86.9%, n = 711) were employed. The majority of couples had no children either together or from previous relationships (75.1%, n = 614). The average duration of infertility was 4.09 (2.12) years, with a range of <1 year to 16 years. In total, 58.1% (n = 475) of couples had had previous infertility treatments, mainly intrauterine insemination (78.5% of the treated sample, n = 373) but also in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI) (24.6% of treated sample, n = 117) or both.

Materials
The COMPI questionnaire booklet contains numerous questions about stress and coping with infertility (see Schmidt et al. [24] for a more detailed description of materials). Only those questions relevant to the present study are described.

Time 1 Assessment. *Demographic and medical information.* These questions were used to obtain demographic (e.g., age, years married) and medical (e.g., years infertile, children) information.

Infertility-related stress. Infertility-related stress was assessed using the Fertility Problem (FP) Stress Inventory (25, 26), which was designed to assess the amount of disruption and stress that the fertility problem had produced overall and in relation to specific domains. The "Personal stress" subscale contained six items that reflected FP stress for the person (e.g., "It is very stressful for me to deal with this fertility problem," "My life has been disrupted because of

this fertility problem"). The "Social stress" subscale contained four items that reflected FP stress in relationships with immediate family, in-laws, friends, and colleagues. Finally, the "Marital stress" factor contained four items that reflected the stress of infertility on the marital and sexual relationship (e.g., "caused thoughts about divorce," "stress on our partnership"). Items were rated on different response keys (i.e., either "strongly disagree (1) to strongly agree (5)" or "'none at all (1) to a great deal (4)").

Subscale and total scores were computed by summing the relevant items. For all variables, higher scores indicated greater FP stress, with a range of 14–60 for the overall FP stress, 6–26 for the personal subscale, 4–16 for the social subscale, and 4–18 for the marital subscale. The Chronbach alpha coefficient for the total scores was .87 and .85 for women and men, respectively; it ranged between .74–.81 for FP stress subscales for women and between .71–.84 for subscales in men.

Time 2 Assessment (12-Month Follow-Up). *Treatment cycles and outcome.* At the 12-month follow-up, participants were asked to detail their treatment experiences since completing the first questionnaire. First, participants were asked to indicate the types of treatments they had received and the number of treatment cycles they had undergone. Second, participants were asked to indicate whether they had achieved a pregnancy and if they had, whether they were currently pregnant or had delivered. These women comprised the "success" group. Women who had become pregnant but did not fall into either of the latter categories were considered to have had a pregnancy failure (e.g., miscarriage, ectopic pregnancy). These women comprised the "no success" group.

Procedure

Infertility clinics were contacted to enlist their participation in the COMPI project. Interested clinics were given a presentation that detailed what would be required of clinic staff and patients. All clinics (n = 5) agreed to distribute questionnaires. Clinics were provided with all necessary materials including questionnaire booklets for men and women as well as preaddressed, stamped envelopes for the return of completed questionnaires. Spouses were instructed to complete questionnaires separately within 10 days of receipt and to post the completed questionnaires in the envelopes provided. Participants who did not wish to participate returned an enclosed nonparticipating form. If the questionnaires or nonparticipating forms were not received, participants were sent a maximum of two reminders at 10-day intervals. Data for this study were collected between January 2000 and August 2001 (T1) and between January 2001 and August 2002 (T2).

The Scientific Ethical Committee of Copenhagen and Frederiksberg Municipalities assessed the study; the study complied with ethical standards according to the Helsinki II

declaration. The Danish Data Protection Agency also approved the study.

Data Analysis

Discriminant analysis was used to determine whether people who were successful with treatment could be differentiated from those who were not on the basis of their FP stress scores. Because age (male and female) and years infertile were related to both FP stress and outcome, these demographic variables were also entered into the discriminant analysis to control for their potential confounding influence. Pooled WGr correlations (i.e., loadings) between predictors and the discriminant function were presented. Loadings above .30 were considered significant (27). Fisher's r-to-z transformation was used to evaluate differences between correlations. This analysis was computed examining cumulative (i.e., total) FP stress scores and individual (i.e., personal, marital, and social) FP stress scores.

To examine the moderating effect of FP stress on the relationship between number of cycles and treatment outcome, interactions (i.e., product terms) were calculated between each of the FP stress scores (i.e., overall, personal, social, and marital) and number of treatment cycles. Separate logistic regressions were then computed for each FP score, predicting treatment outcome. In this analysis, the main effects of the FP stress score and the number of treatment

TABLE 1

Mean (±SD) and percentages for sample medical characteristics sample (n = 818 couples).

Treatment characteristic	Mean (±SD)	% (n)
Average treatment cycles	2.1 ± 1.2	
<3 cycles		71.0 (583)
3–5 cycles		26.4 (216)
>5 cycles		2.3 (19)
Type of treatment		
IVF (n = 563)		68.9 (563)
ICSI (n = 205)		25.1 (205)
IUI (n = 156)		19.1 (156)
Treatment outcome		
Success (n = 488)		
Currently pregnant		25.6 (209)
Live birth		34.1 (279)
No success (n = 330)		
Never pregnant		32.8 (268)
Pregnancy failure		7.6 (62)

Note: IVF = in vitro fertilization; ICSI = intracytoplasmic sperm injection; IUI = intrauterine insemination.

Boivin and Schmidt. Infertility-related stress and treatment outcome. Fertil Steril 2005.

TABLE 2

Means (±SD) for demographic, medical, and psychological variables according to gender and outcome group.

Variable	Total sample (n = 818)	t(817)[a]	No success (n = 330)	Success (n = 488)	t(816)[b]
Woman's age	31.5 ± 3.5	15.89[c]	31.9 ± 3.7	31.2 ± 3.4	2.68[d]
Man's age	33.8 ± 5.1	—	34.3 ± 3.7	33.56 ± 4.8	2.26[e]
Years infertile	4.1 ± 2.1	NA	4.3 ± 2.3	3.9 ± 2.0	2.52[d]
No. of treatment cycles	2.1 ± 1.2	NA	2.5 ± 1.2	1.8 ± 1.1	8.56[c]
Overall FP stress					
Woman	28.66 ± 8.5	15.68[c]	29.41 (8.8)	28.15 (8.3)	2.08[e]
Man	24.70 ± 7.3	—	25.18 (7.5)	24.37 (7.2)	1.57
Personal					
Woman	14.34 ± 4.6	19.41[c]	14.71 (4.7)	14.10 (4.4)	1.89[f]
Man	11.42 ± 3.7	—	11.71 (3.8)	11.21 (3.7)	1.90[f]
Social					
Woman	6.34 ± 2.6	9.61[c]	6.49 (2.7)	6.30 (2.6)	1.01
Man	5.48 ± 2.2	—	5.45 (2.3)	5.50 (2.1)	0.29
Marital					
Woman	7.94 ± 3.2	1.58	8.21 (3.3)	7.76 (3.2)	2.00[e]
Man	7.80 ± 3.1	—	8.02 (3.1)	7.65 (3.1)	1.69[f]

Note: NA = not applicable; t = *t*-test and the number in parentheses is for degrees of freedom.
[a] Paired *t*-tests between spouses.
[b] Independent *t*-tests between outcome groups.
[c] $P<.001$.
[d] $P<.01$.
[e] $P<.05$.
[f] $P<.10$

Boivin and Schmidt. Infertility-related stress and treatment outcome. Fertil Steril 2005.

cycles were entered in the first step, followed by the product term on the second step of the analysis. Regression coefficients, Wald statistics, and probability values were presented for significant interaction terms. In these analyses, FP stress scores were residualized for age and years infertile to control for their potential confounding influence. Significant interactions were followed up with the Kaplan–Meier survival analysis to compare the median treatment cycles to pregnancy required in high and low FP stress groups. High and low stress levels were determined on the basis of a median split on the relevant FP stress variable.

RESULTS
Biological Characteristics at 12-Month Follow-Up

Table 1 lists treatment characteristics and outcomes for the sample. Couples had undergone an average of approximately 2 treatment cycles with a range of 1–9. More than two-thirds of the sample had had fewer than 3 treatments cycles in the 12-month period. The majority of couples had tried IVF or ICSI, and less than 20% of couples had tried insemination. Slightly more than half of the sample (59.6%) achieved success with treatment in that they had either delivered or

were currently pregnant. The remaining women had never achieved a pregnancy or were no longer pregnant at the time of completing the T2 questionnaire.

Psychological Characteristics at Study Entry

Table 2 lists means and standard deviations for study variables at T1 for the total sample and according to outcome group. As indicated by comparisons between spouses, women reported significantly more FP stress overall, as well as in the personal and social domain, compared to their partners. However, marital distress scores were not significantly different. In line with these results, the correlations between partner scores for overall FP stress (r(816) = .592, $P<.001$), as well as FP stress in the personal (r(816) = .471, $P<.001$) and social (r(816) = .393, $P<.001$) domain were lower than the correlation between partner scores in the marital domain (r(816) = .693, $P<.001$).

FP Stress and Treatment Outcome Groups

As indicated by comparisons between treatment outcome groups (see Table 2), the couples who did not achieve a

TABLE 3

Pooled WGr correlations between overall FP stress (and control variables) and the function discriminating between success and no success groups.

Predictors	Discriminant function (WGr)
Overall female FP stress	.517
Overall male FP stress	.392
Female age	.666
Male age	.562
Years infertile	.627

Note: Correlations (loadings) above .30 were considered significant. Each coefficient is computed after controlling for all other predictors in the analysis. WGr = within-groups; FP = fertility problem.

Boivin and Schmidt. Infertility-related stress and treatment outcome. Fertil Steril 2005.

pregnancy in the 12-month study period (no success group) were older, had been infertile for longer, and had had more treatment cycles in the study period than the couples in the success group. At a univariate level, the FP stress scores indicated that women in the no success group experienced significantly more overall and marital FP stress and marginally more FP stress in the personal domain than did women in the success group. Men in the no success group reported marginally more FP stress in the personal and marital domain than did their counterparts in the success group.

Cumulative FP Stress and Additive Effects Differentiating Treatment Outcome Groups

A discriminant analysis was computed to determine whether overall male and female FP stress scores could differentiate between the success and no success groups (while controlling for male and female age and years infertile). The discriminant function was significant (χ^2 (5) = 15.9, $P<.01$, canonical correlation .14). Table 3 lists the pooled WGr correlations between individual predictors and the function discriminating between the success and no success groups. As presented in Table 3, both male and female stress significantly contributed to the function, but the coefficient was larger for women (WGr = .517) than men (WGr = .392). Fisher's r-to-z transformation showed a significant difference between these coefficients (z = 3.19, $P<.001$), with overall female FP stress having a greater correlation to outcome than male FP stress, even after controlling for age and years of infertility. Group centroids on the discriminant function indicated that the no success group scored significantly higher on the function (centroid = .171) than did the success group (−.116). Older age, more years of infertility, and higher overall FP stress in men and women was associated with a poorer treatment outcome.

We examined whether the link between overall FP stress and treatment outcome was stronger if one's partner also reported high overall FP stress. The interaction term for joint male and female overall FP stress was not significant in predicting outcome groups (B = .019 ± .068; *Wald*(1) = .78, $P=NS$, OR = 1) in logistic regression.

Type of Stress and Treatment Outcome

To examine whether the type of FP stress was important in discriminating between the no success and success groups, individual FP stress domains were entered into the equation instead of the overall measure. The discriminant function was significant (χ^2 (9) = 21.4, $P<.01$, canonical correlation .16). Within-groups correlations (above .30) indicated that all predictors were important in differentiating outcome groups except FP stress in the social domain (men and women) (see Table 4). Higher personal and marital stress, older age, and more years of infertility were associated with a poorer treatment outcome. Loadings for FP stress were not significantly different between men and women in the personal (z = .097, $P=NS$) or marital domain (z = 1.58, $P=NS$). Although the coefficient for FP stress in the social domain was significantly greater for women (z = 3.14, $P<.01$), the loading (WGr = .215) was not significant in differentiating between outcome groups. Group centroids indicated that the no success group scored significantly higher on the function (centroid = .199) than did the success group (centroid = −.134).

TABLE 4

Pooled WGr correlations between personal, social, or marital FP stress (and control variables) and the function discriminating between success and no success groups.

Predictors	Discriminant function (WGr)
Female FP stress	
Personal	.403
Social	.215
Marital	.428
Male FP stress	
Personal	.407
Social	−.063
Marital	.362
Female age	.666
Male age	.562
Years infertile	.627

Note: Correlations (loadings) above .30 were considered significant. Each coefficient is computed after controlling for all other variables in the analysis. WGr = within-groups; FP = fertility problem.

Boivin and Schmidt. Infertility-related stress and treatment outcome. Fertil Steril 2005.

FP Stress, Number of Treatment Cycles, and Treatment Outcome

We examined whether FP stress effects were having their impact on treatment outcome via the number of treatment cycles couples had during the 12-month period. As noted, interaction terms between each of the FP stress scores and the number of treatment cycles were computed and entered into logistic regressions that predicted treatment outcome. Interactions were not significant for the total or any FP stress subscales for men. For women, the only significant interaction was for marital FP stress scores (B = .182 ± .08, $Wald(1) = 4.76$, $P<.05$, odds ratio (OR) = 1.20: Model $\chi^2(3) = 77.21$, $P<.001$). Analysis of the interaction term revealed that the number of cycles-to-pregnancy was higher in women reporting high marital distress than in women reporting low marital distress. Specifically, Kaplan–Meier survival analysis results showed that the median number of treatment cycles needed to become pregnant was lower (median = 2.0 ± .17) among women who reported low marital distress compared with those reporting high marital distress (median = 3.0 ± .20) (Breslow statistic, df = 1, 4.96, $P<.05$).

DISCUSSION

There is converging evidence that negative psychological states and traits are related to treatment success (3–10, 13–17, 21–23, 28). We extend these findings by demonstrating that such effects are more pronounced for women than men, and more likely when the source of stress is personal or marital than when it is social. Furthermore, the results indicate that marital distress in women increases the number of treatment cycles required for pregnancy. The findings are compelling given that they were based on an epidemiological cohort of more than 800 couples, a 12-month prospective design, and the use of a valid psychological measure of infertility-related stress with good psychometric properties.

Our results clearly demonstrate that male stress does play a role in treatment failure, albeit a weaker one than that observed for women. This difference may be attributed to two factors. First, men reported experiencing stress from fewer sources than did women and experienced stress at a less intense level than did their partners. These findings were consistent with numerous other reports of a gender difference in distress (e.g., see Greil [20] for a review). To the extent that subjective experiences mirror physiological effects, one would therefore expect that the biological effects would also be weaker in men, and reproductive suppression would therefore be less likely. From an evolutionary perspective, one could also argue that a woman's threshold for stress-induced reproductive suppression may be lower than that of a man because her greater parental involvement in pregnancy makes the cost of reproducing in less than ideal circumstances (i.e., high stress) greater for her than him (29).

Another possible explanation for a stronger link between stress and treatment outcome in women is that men contribute to conception but not to the actual pregnancy, limiting the time interval in which their emotions can influence this biological event relative to women. In contrast, it has been demonstrated that female stress affects biological events throughout pregnancy, including the development of gestational and labor complications (30) and even neonatal outcomes, such as birth weight (15). One could argue that male stress could continue to have an effect beyond fertilization by adding to her stress level during the remainder of the pregnancy. However, we tested for male stress effects and found that the influence of female infertility-related stress on treatment outcome was the same regardless of her partner's stress level. The lack of additive effects is interesting given that many men report not talking about their own emotional reactions because they feel it would add to their partner's burden (31). Although such additive effects may have implications for coping, couple relations, and other subjective measures, they do not appear to have biological consequences. However, it would be important to confirm these findings by examining direct and indirect effects of negative affect on proximal biological endpoints (e.g., number of oocytes) as well as distal endpoints (i.e., treatment outcome), as was conducted here.

A secondary objective of the present study was to examine whether some types of stress were particularly detrimental to treatment outcome. Our analyses indicated that, indeed, not all sources of stress were equal. We confirmed for both men and women that FP stress in one's personal life was strongly linked to treatment outcome. People who reported that fertility problems had disrupted their lives, were difficult to cope with, and/or had caused much stress on their physical and mental health were less likely to have conceived in the subsequent 12 months of treatment. These findings on infertility-related stress are in line with those reported for anxiety (28), depression (6), and other types of negative affect (15), including infertility-specific distress (7).

Our findings also demonstrate that the strains caused by fertility problems on the marital relationship interfere with the success of treatment. It is generally acknowledged that the experience of infertility strengthens instead of weakens the marital relationship even when treatment is unsuccessful (23). Furthermore, the importance to women of a supportive marital relationship on the adjustment to treatment failure or infertility itself has also long been acknowledged (26, 31); the present study is one of the first to also document its importance for the success of treatment. Women who reported that infertility had caused a crisis in their relationship, given rise to thoughts of divorce, and/or placed great strain on their sexual relationship were less likely to be successful with treatment.

One possible explanation for the effect of marital distress is that couples who experienced conflict and/or major strain were less likely to undergo treatment and, therefore, less likely to achieve a success. This explanation would be consistent with the results of Strauss et al. (21) who showed that

unresolved marital conflict was a key predictor in determining who dropped out of treatment. However, in the present study we found the reverse: The median number of treatments for women reporting marital distress was significantly higher than for women reporting relatively less distress. More important, we also found that the probability of pregnancy on any given cycle was lower for the maritally distressed women, and disproportionately more of these women were to be found in the no success group. Thus, the link between marital distress and treatment outcome is not simply due to treatment persistence, but also genuinely concerned with direct effects on the biological processes underpinning the success of treatment. These findings reinforce the importance of recommendations calling for better support resources for women lacking partner support during treatment (32).

Numerous proposals have been made to account for why personal stress, anxiety, and other negative emotional states could reduce the chances of pregnancy. One hypothesis is that activation of the hypothalamic–pituitary–adrenal (HPA) axis during stress interferes with the gonadotropin-releasing hormone (GnRH) pulse generator, which causes a cascade of other hormonal events that undermine reproductive function (33). In men, acute stress is thought to have negative effects at a functional and developmental level (34). Other proposals include more behavioral effects, for example, that stress triggers or is associated with behaviors or lifestyle decisions that compromise fertility, for example, increased smoking (35). As converging evidence mounts regarding the role of psychological distress in treatment outcome, future research should now focus on identifying under what conditions reproductive suppression occurs and the pathways that mediate this effect.

Although we propose that FP stress played a causal role in treatment failure, one could argue that a priori knowledge of a likely failure may have caused this association. Women who have implicit or explicit knowledge of poor chances of treatment success either through medical feedback during treatment or their profile (e.g., older age) may report more stress at the start of treatment, creating a spurious relationship between these variables (i.e., "negative feedback" hypothesis [7]). However, several design features guard against this confound. First, the assessment of FP stress occurred before the start of treatment and therefore before staff could have provided feedback about the progress of the specific treatment cycle. Second, we controlled for factors that may have led people to believe they had lower chances of success to begin with, that is, older male and female age and number of years of fertility problems.

Counselling has been recommended for individuals experiencing distress. A recent review has indicated that counselling is indeed beneficial in reducing negative affect, particularly anxiety and infertility-related stress (36). More recent studies have demonstrated that pretreatment counselling can help reduce tensions and worry during treatment (37). The stress-reducing properties of psychosocial interventions have not, however, been associated with an overall concomitant increase in pregnancy rates (36). The lack of concordance in these findings is not understood. It may be that reductions in subjective distress though detectable, are not sufficiently large to impact on the biological mechanisms that interfere with pregnancy. This may be particularly true of interventions that target only one source of stress. It may also be that some interventions are more successful than others, and that by pooling the effects in reviews, one obscures the success of particular interventions. For example, several controlled studies (e.g., [38], [39]) have reported increases in pregnancy with cognitive-behavioral interventions, whereas such effects have not been reported with infertility counselling (37, 40). Until we know that psychosocial interventions reliably improve reproductive function, it may be best to recommend these interventions because of their effect on quality of life, instead of because they can increase pregnancy rates.

Numerous aspects of the study design increase confidence in the validity of study findings. As noted previously, the sample was large (n = 818 couples), the design was prospective, and the measures were psychometrically sound. Moreover, the participation rates, both at the level of clinics and participants, were excellent. All clinics invited, agreed to participate, and as a group these clinics carried out almost 50% of all IVF cycles in Denmark during the recruitment period (i.e., in the year 2000). Furthermore, 75% of couples participated in both the T1 and T2 assessment for this study, which is a high participation rate given the 12-month interval between recruitment and the follow-up assessment. The demographic characteristics of our sample were similar to those reported for couples undergoing treatment elsewhere and well-established findings from past research were replicated here, for example, that women reported more distress then men. One criticism of past research on stress and treatment outcome is that it is largely based on patients undergoing IVF. Because the fertility clinics involved in the present study performed all types of fertility treatments, our sample also included 20% of couples who underwent insemination procedures, which made our sample more diverse than in past investigations. Together, these strengths ensure that the associations noted in the present study are reliable and valid, and can be generalized to patient populations in other fertility clinics.

In conclusion, our findings add to the growing evidence base that links negative psychological states and traits to treatment failure. Our results show that such effects occur for both men and women, and with infertility-related stress arising from a variety of sources. In light of this mounting evidence, it may now be time to focus on the factors that moderate this relationship and interventions to minimize such effects.

REFERENCES

1. Stoleru, S, Teglas JP, Fermanian J, Spira A. Psychological factors in the etiology of infertility: a prospective cohort study. Hum Reprod 1993; 8:1039–46.
2. Eugster A, Vingerhoets AJJM. Psychological aspects of in vitro fertilization: a review. Soc Sci Med 1999;48:575–89.
3. Demyttenaere K, Nijs P, Steeno O, Koninckx PK, Evers-Kiebooms G. Anxiety and conception rates in donor insemination. J Psychosom Obstet Gynaecol 1988;8:175–81.
4. Schover LR, Greenhalgh LF, Richards SI, Collins RL. Psychological screening and the success of donor insemination. Human Reprod 1994; 9:176–8.
5. Gallinelli A, Roncaglia R, Matteo ML, Ciaccio I, Volpe A, Facchinetti F. Immunological changes and stress are associated with different implantation rates in patients undergoing in vitro fertilization-embryo transfer. Fertil Steril 2001;76;85–91.
6. Thiering P, Beaurepaire J, Jones M, Saunders D, Tennant C. Mood state as a predictor of treatment outcome after in vitro fertilisation/embryo transfer technology (IVF/ET). J Psychosom Res 1993;37:481–91.
7. Boivin J, Takefman, J. Stress reactions across an IVF cycle in pregnant and non-pregnant women using daily monitoring prospective data. Fertil Steril 1995;64:802–11.
8. Stoleru S, Cornet D, Vaugeois P, Fermanian J, Magnin F, Zerah S, et al. The influence of psychological factors on the outcome of the fertilization step of in vitro fertilization. J Psychosom Obstet Gynaecol, 1997;18:189–202.
9. Facchinetti F, Matteo ML, Artini GP, Volpe A, Genazzani AR. An increased vulnerability to stress is associated with a poor outcome of in vitro fertilization-embryo transfer treatment. Fertil Steril 1997;67:309–14.
10. Demyttenaere K, Nijs P, Evers-Kiebooms G, Koninckx PR. Coping and the ineffectiveness of coping influence the outcome of in vitro fertilization through stress responses. Psychoneuroendocrinology 1992;19: 655–65.
11. Hjollund NHI, Jensen JK, Bonde JPE, Henriksen TB, Anderson A-M, Kolstad HA, et al. Distress and reduced fertility: a follow-up study of first-pregnancy planners. Fertil Steril 1999;72:47–53.
12. Sanders KA, Bruce NW. A prospective study of psychosocial stress and fertility in women. Hum Reprod 1997;12:2324–9.
13. Lancastle D, Boivin J. Dispositional optimism, trait anxiety and coping: unique or shared effects on biological response to fertility treatment? Health Psychol 2005;24:171–8.
14. Glezermann M. Two hundred and seventy cases of artificial donor insemination: Management and results. Fertil Steril 1981;35:126–42.
15. Klonoff-Cohen H, Chu E, Natarajan L, Sieber W. A prospective study of stress among women undergoing in vitro fertilization and gamete intrafallopian transfer. Fertil Steril 2001;76:675–87.
16. Boivin, J. Patient-staff communication and its effect on reactions to treatment and treatment failure. In: van Balen F, Gerrits T, Inhorn M, editors. Proceedings of Social Science Research on Childlessness in a global perspective. November 1999. SCO-Kohnstam Instituut, Amsterdam, The Netherlands, 2000.
17. Sanders K, Bruce N. Psychosocial stress and treatment outcome following assisted reproductive technology. Hum Reprod 1999;14:1656–62.
18. Boivin J, Andersson L, Shoog-Svanberg A, Hjelmstedt A, Collins A, Bergh T. Psychological reactions during in vitro fertilization (IVF): similar response pattern in husbands and wives. Hum Reprod 1998;13: 3262–7.
19. Clarke R, Klock SC, Geoghegan J, Travassos E. The relationship between psychological stress and semen quality among in vitro fertilization patients. Hum Reprod 1999;14:753–8.
20. Greil AL. Infertility and psychological distress: a critical review of the literature. Soc Sci Med 1997;45:1679–1704.
21. Strauss B, Hepp U, Staeding G, Mettler L. Psychological characteristics of infertile couples: can they predict pregnancy and treatment persistence? J Community Appl Soc Psychol 1998;8:289–301.
22. Olivius C, Friden B, Borg G, Bergh C. Why do couples discontinue in vitro fertilization treatment? A cohort study. Fertil Steril 2004;81:258–61.
23. Daniluk, JC. Reconstructing their lives: a longitudinal, qualitative, analysis of the transition to biological childlessness for infertile couples. J Counsel Devel 2001;79:439–49.
24. Schmidt L, Holstein B, Boivin J, Tjørnhøj-Thomsen, T, Blaabjer J, Hald F, et al. High ratings of satisfaction with fertility treatment are common: findings from the Copenhagen Multi-Centre Psychosocial Infertility (COMPI) Research Programme. Hum Reprod 2003;18: 2638–46.
25. Abbey A, Andrews FM, Halman, LJ. Gender's role in responses to infertility. Psychol Women Quart 1991;15:295–316.
26. Schmidt L. Psykosociale konsekvenser af infertilitet og behandling (Psychosocial consequences of infertility and treatment). Copenhagen: FADL Book Company, 1996.
27. Tabachnik BG, Fidell, LS. Using multivariate statistics. 2nd ed. New York: Harper & Row, 1989.
28. Smeenk JMJ, Verhaak CM, Eugster A, van Minnen A, Zielhuis GA, Braat, DDM. The effect of anxiety and depression on the outcome of in vitro fertilization. Hum Reprod 2001;16:1420–3.
29. Wasser SK, Barash, DP. Reproductive suppression among female mammals: implications for biomedicine and sexual selection theory. Quart Review Biol 1983;58:513–38.
30. Stein JA, Lu MC, Gelberg L. Severity of homelessness and adverse birth outcomes. Health Psychol 2000;19:524–34.
31. Berg BJ, Wilson JF, Weingartner PJ. Psychological sequelae of infertility treatment: The role of gender and sex role identification. Soc Sci Med 1991;22:1071–80.
32. Boivin J. Who is likely to need counselling. In: Boivin J, Kentenich, H, eds. ESHRE monographs: guidelines for counselling in infertility. Oxford: Oxford University Press, 2002:9–10.
33. Ferin M. Clinical review 105: stress and the reproductive cycle. J Clin Endocrinol Metabol 1999;84:1768–73.
34. Boivin J, Thomas L, Wells C, Taylor S, Gregory L. Does treatment stress reduce sperm quality? [abstract no. O-245]. In: Program and Abstracts of the 19th Annual Meeting of the European Society for Human Reproduction and Embryology. July 2003. Madrid: Hum Reprod, 2003;18:84.
35. Rundmo T, Smedslund G, Gotestam G. Associations between stress, personality and smoking. Pers Individ Dif 1996;21:545–55.
36. Boivin J. A review of psychosocial interventions in infertility. Soc Sci Med 2003;57:2325–41.
37. Emery M, Beran MD, Darwiche J, Oppizzi L, Joris V, Capel R, et al. Results from a prospective, randomized, controlled study evaluating the acceptability and effects of routine pre-IVF counselling. Hum Reprod 2003;18:2647–53.
38. Domar AD, Clapp D, Slawsby EA, Dusek J, Kessel B, Freizinger M. Impact of group psychological interventions on pregnancy rates in infertile women. Fertil Steril 2000;73:805–11.
39. Tuschen-Caffier B, Florin I, Krause W, Pook M. Cognitive-behavioral therapy for idiopathic infertile couples. PsychotherPsychosom 1999;68: 15–21.
40. Wischmann T, Stammer H, Scherg H, Gerhard I, Verres R. Couple counselling and therapy for the unfulfilled desire for a child: the two-step approach of the "Heidelberg Infertility Consultation". In: Strauss B, ed. Involuntary childlessness: psychological assessment, counselling and psychotherapy. Seattle: Hogrefe & Huber Publishers, 2002:127–50.