Psychological and Hormonal Changes in the Course of in Vitro Fertilization

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This study was designed to investigate concurrently the psychological and hormonal changes at three critical points during in vitro fertilization (IVF) treatment. One hundred thirteen couples suffering from mechanical and unexplained infertility participated in the study and 23 of them conceived. Psychological evaluation included background questionnaires, Lubin's Depression Adjective Check List, and Spielberger's State Trait Anxiety inventory. Cortisol and prolactin levels were estimated by radioimmunoassay. The results showed that patients' anxiety and depression scores were significantly higher than the population norm. Psychological test scores and hormonal levels showed a similar pattern of change, increasing on oocyte retrieval day, decreasing on embryo transfer day, and rising again on pregnancy test day. Differences between these phases were generally significant. Differences in parameters' means between conceiving (C) and nonconceiving (NC) women were generally not significant. However, correlations between psychological measures and hormonal levels showed a clear disparity between C and NC women in the last phase. Whereas significant negative correlations were found in C patients, no relationship was found in NC patients. The findings suggest that success in IVF treatment may depend, in part, on differential modes of coping with anxiety and depression, involving hormonal or endorphin mediation.

KEY WORDS: in vitro fertilization phases; depression; anxiety; prolactin; cortisol.

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INTRODUCTION

In vitro fertilization (IVF) has given a new chance to many couples that have otherwise been unable to achieve pregnancy. Nevertheless, the success of IVF in inducing pregnancy is limited. In some cases the failure can be attributed to a known physiological cause, but in most it remains unexplained (1,2).

It is widely accepted that psychological factors play an important role in unexplained infertility (3,4), although the mechanism has remained obscure (1). In stressful situations there is an increased secretion of hypothalamic corticotropin releasing factor (CRF), which results in increased pituitary adrenocorticotrophic hormone (ACTH) release (5,6). This, in turn, leads to augmented secretion of adrenal cortex hormones, including cortisol, and results in several metabolic, functional, and anatomical changes. The process takes place regularly but is particularly salient in response to stress. The issue of "anxiety-depression" dynamics involving the hypothalamic–pituitary–adrenal axis is confusing (7). Clinicians are well aware of the fact that depressed patients often have laboratory findings that may be virtually indistinguishable from those of patients with Cushing's disease. Thus, elevations in AM plasma cortisol and 24-hr urine free cortisol levels, coupled with inadequate suppression after 1 and 2 mg dexamethasone, as well as failure to respond to insulin hypoglycemia, have all been viewed as a part of the depression picture (8). It has been suggested that the failure of plasma levels of ACTH and cortisol to respond to exogenously administered ACTH may be used to differentiate depressed patients from those with organic pituitary disease (9).

There is also evidence indicating that prolactin

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(PRL) secretion is influenced by depression and anxiety (1). The mechanism by which PRL participates in the regulation of ovarian function is only partly understood. Overt hyperprolactinemia may disrupt the development and function of ovarian follicles, leading to infertility due to anovulation or luteal phase inadequacy (10,11). However, the clinical significance of short-term elevations of serum PRL at midcycle is not clear. Some authors reported that treatment of transient hyperprolactinemia with bromocryptine during in vitro fertilization–embryo transfer (IVF/ET) cycles significantly increased fertilization and cleavage rates of oocytes, although no improvement in pregnancy rates was recorded (12). In contrast, pharmacologic lowering of serum PRL may interfere with follicular steroidogenesis (13).

Only a small number of articles addressed mental-emotional factors in IVF, and just a few related to a combined examination of biological and psychological factors (1).

The present study was designed to investigate concurrently the psychological and hormonal changes at three critical points of time *during* the process of IVF treatment, following the initial assessment of pretreatment baselines. It had the following aims: (i) to examine the interrelationship between the psychological variables of anxiety and depression and the levels of PRL and cortisol and (ii) to track the changes in the psychological and physiological variables as a function of the main phases of the treatment (hormonal stimulation, oocyte retrieval, embryo transfer, and pregnancy confirmation blood test phases).

MATERIALS AND METHODS

Subjects

One hundred thirty-five married couples who applied and were found suitable for IVF treatment at the Hasharon Hospital underwent a preliminary medical examination and were asked to participate in the study if they met two criteria: they had no previous completed pregnancies and their infertility was due to a mechanical or to an unexplained reason.

Of these, 126 couples agreed to participate in the study and underwent the baseline tests. However, 13 of them dropped out prior to the initiation of IVF treatment due to spontaneous pregnancies (3 couples), separation, or decision to postpone the treatment (10 couples). All women had been previously treated for infertility for at least 2 years, and some had undergone several (range, 1–9) unsuccessful IVF treatments. None had undergone psychological or psychiatric treatment. The women's ages ranged from 23 to 47, all of them were Jewish, and most of them were born in Israel. All women had at least completed elementary-school education.

Radioimmunoassay Methods

Cortisol and PRL concentrations were assayed using the Coat-A-Count and the Double Antibody kits of Diagnostic Products Corporation (Los Angeles, CA), respectively.

Psychological Tests and Questionnaires

Personal Background Questionnaire. The Background Questionnaire was designed to describe the patient's personal history, socioeconomic status, and interpersonal relations.

Lubin's Depression Adjective Checklist. Lubin's Depression Adjective Check-List (DACL) (14) is a short, albeit valid and reliable tool for assessing depressive mood. The DACL was originally developed as an instrument for measuring state or situational depressive mood, although it has been shown that due to the relationship between depressive responses to a situation and depression as a personality trait, DACL can also serve as a measure of depression trait or inclination (15). We used a Hebrew version, standardized for the Israeli population (14,16).

Spielberger's State Trait Anxiety Inventory (STAI). A Hebrew version of Spielberger's STAI (17) was used (18). This test is composed of a State Anxiety questionnaire, assessing a person's transient anxiety in response to a certain situation, and a Trait Anxiety questionnaire, which reflects individual differences in anxiety as a personality trait.

Design

Each woman underwent four sessions of psychological and hormonal tests in the course of the IVF treatment. All tests were carried out individually. The first session took place before the onset of the hormonal treatment, when the woman was at the early follicular phase (days 3–5 of the cycle), and

provided baseline measures. Later sessions were conducted at three critical points in the treatment: (a) in the morning of the day of oocyte retrieval, shortly before the actual retrieval; (b) in the morning of the day of embryo transfer; and (c) in the morning of the day when blood samples were taken for pregnancy tests. In each one of the sessions blood samples for cortisol and PRL radioimmunoassays were taken and DACL and STAI questionnaires were filled out by the patients immediately afterward. The Personal Background Questionnaire was filled out only during the first session.

RESULTS

Of the 113 women who started hormonal treatment, 19 failed to reach the oocyte retrieval phase and an additional 9 failed to reach the embryo transfer phase. Of the remaining 85 women, 23 became pregnant (20.4%). Table I presents the number and percentage of women in each phase.

The results of the psychological tests and hormonal levels are presented below, in relation to four aspects: (a) differences between the study's sample and population norms; (b) differences between the phases of IVF treatment; (c) differences between women who succeeded in getting pregnant as a result of the treatment and those who did not ("conceiving" vs "nonconceiving" women, respectively); and (d) correlations between the psychological tests and hormonal levels.

Psychological Tests

Trait Anxiety. Spielberger's mean (M) trait anxiety score of the conceiving (C) women was 41.04, with a standard deviation (SD) of 9.01. Comparable results for the nonconceiving (NC) women were 41.44 and 8.11, respectively. These differences were not significant. Both groups were, therefore, pooled to one sample (M = 41.38; SD = 8.26) for the purpose of comparison with the population norm of trait anxiety (38.3). This difference was significant ($T = 3.95$; $P < 0.0002$).

Table I. The Number and Percentage of Women Who Reached Each Phase

Phase	Description	No. of women	Percentage of total
I	Start of hormonal treatment	113	100
II	Oocyte retrieval	94	83.2
III	Embryo transfer	85	75.2
IV	Pregnancy test	85	75.2
	Succeeded to conceive	23	20.4

State Anxiety. State anxiety scores of the women in all phases of the IVF treatment were significantly higher than the population norm, which is 33.8 (T-test comparison between means, $P < 0.00001$ for each phase). The comparisons to the population's norm are depicted in Fig. 1A.

Repeated-measures ANOVA revealed a significant effect of the phase of treatment in state anxiety (df = 3; $F = 15.98$; $P < 0.0001$). Post hoc contrast comparisons between phase means are listed in Table II. No significant difference was found between C and NC women and the interaction of phase × conception was not significant either.

A comparison of state anxiety scores of C and NC women in each phase of the IVF treatment is shown in Table III.

Depression Adjective Checklist (DACL). DACL scores of the women in all phases of the IVF treatment, with the exception of Phase III, where significantly higher ($P < 0.002$, T-test comparisons between means, two-tailed) than the population norm (8.59). The comparisons are depicted in Fig. 1B.

Repeated-measures ANOVA revealed a significant effect of the phase of treatment (df = 3; $F = 9.84$; $P < 0.0001$). Post hoc contrast comparisons between phase means are listed in Table II. No significant difference was found between C and NC women and the phase × conception interaction was not significant either.

A comparison of DACL scores of C and NC women in each phase of the IVF treatment is shown in Table III.

Hormonal Tests

Cortisol. Cortisol levels changed during the treatment similar in trend to the psychological scores. Value means of all phases, however, fell within the norm. The results are shown in Fig. 1C.

A comparison of cortisol levels of C and NC women in each phase of the IVF treatment is shown in Table III. Repeated-measures ANOVA revealed significant effect of the phase of treatment (df = 3; $F = 31.34$; $P < 0.0001$). Post hoc contrast comparisons between phase means are listed in Table II. No significant difference was found between C and

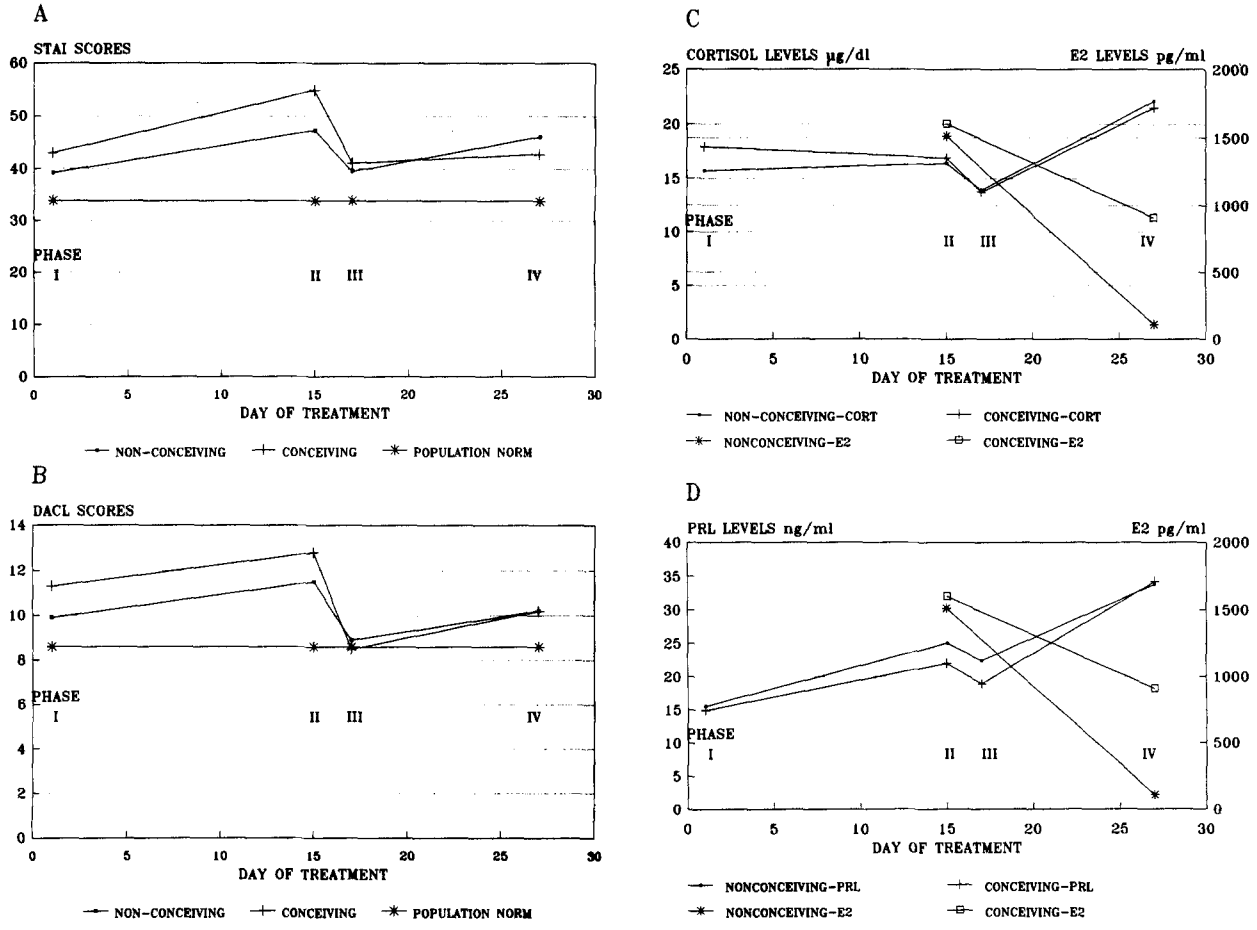

Fig. 1. (A) Mean state anxiety scores of conceiving and nonconceiving women across IVF/ET treatment. (B) Mean DACL scores of conceiving and nonconceiving women across IVF/ET treatment. (C) Mean cortisol and E_2 levels in conceiving and nonconceiving women across IVF/ET treatment. (D) Mean PRL and E_2 levels in conceiving and nonconceiving women across IVF/ET treatment.

NC women and the interaction of phase × conception was not significant either.

Both groups started in normocortisolemic state at about 15–17 µg/dl and remained in this range until the day of ovum pickup (OPU). On ET day, 48 hr later, a decline to a mean cortisol level of about 13 µg/dl was recorded in both groups. In the luteal phase of expectation for pregnancy test results, cortisol levels increased strikingly in both groups, to 21–22 µg/dl.

PRL. Changes in PRL levels during the course of treatment are shown in Fig. 1D. A comparison of radioimmunoassay PRL levels of C and NC women in each phase of the IVF treatment is shown in Table III. Repeated-measures ANOVA revealed a significant effect of the phase of treatment (df = 3; *F*

Table II. Contrast Test Levels of Significance for Differences Between Phase Means of Psychological and Hormonal Measures

	State anxiety		DACL		Cortisol		Prolactin	
Phases compared	Contrast *T* value	*P*	Contrast *T* value	*P*	Contrast *T* value	*P*	Contrast *T* value	*P*
I vs II	5.23	0.0001	1.99	0.048	0.28	NS	4.58	0.0001
I vs III	1.08	NS	3.38	0.0009	3.43	0.0008	2.82	0.0054
I vs IV	2.62	0.01	0.54	NS	6.05	0.0001	7.71	0.0001
II vs III	6.32	0.0001	5.37	0.0001	3.15	0.0019	1.76	0.080
II vs IV	2.61	0.01	2.53	0.012	6.32	0.0001	3.13	0.0021
III vs IV	3.71	0.0003	2.85	0.005	9.47	0.0001	4.89	0.0001

Table III. Psychological and Hormonal Measure Scores of Conceiving and Nonconceiving Women by Phase of IVF Treatment (Means ± SD)

	State anxiety		DACL		Cortisol		Prolactin	
Phase	Conceiving	Nonconceiving	Conceiving	Nonconceiving	Conceiving	Nonconceiving	Conceiving	Nonconceiving
I	43.04 ± 15.5	39.18 ± 10.7	11.35 ± 5.6	9.87 ± 4.2	17.86 ± 6.3	15.66 ± 5.4	14.92 ± 10.4	15.76 ± 9.7
II	54.86 ± 10.5*	47.30 ± 12.1*	12.76 ± 3.2	11.53 ± 4.2	16.87 ± 4.9	16.30 ± 5.2	22.03 ± 10.5	25.28 ± 15.6
III	41.14 ± 11.3	39.50 ± 12.2	8.55 ± 3.4	8.87 ± 5.1	13.70 ± 5.4	13.91 ± 4.6	18.95 ± 8.2	22.37 ± 12.7
IV	42.80 ± 11.1	46.06 ± 12.8	10.23 ± 4.1	10.20 ± 4.5	21.53 ± 6.3	22.07 ± 7.0	34.21 ± 22.5	33.84 ± 18.4

* $P < 0.05$, two-tailed.

= 20.89; $P < 0.0001$). Post hoc contrast comparisons between phase means are listed in Table II. No significant difference was found between C and NC women and the interaction of phase × conception was not significant either.

Both C and NC patients started in the normoprolactinemic state of mean PRL levels about 15 ng/ml. On human chorionic gonadotropin (hCG) day, which was 32 hr prior to OPU, the estradiol (E_2) levels were 1604 ± 900 and 1512 ± 862 pg/ml in the C and NC groups, respectively. This difference was not statistically significant. The mean level of PRL was lower in the pregnant group of patients, although this difference was not significant either. On ET day (48 hr later) PRL levels in both groups declined to approximately 5 μg.

The most important and striking finding concerning PRL levels was observed in the luteal phase (Phase IV). In this period of expectation for pregnancy test results, PRL levels rose in both groups to an average of 35 ng/ml, with no significant differences between C and NC patients. The difference in E_2 levels between the C and the NC groups was significant ($T = 6.08$; $P < 0.001$). The mean E_2 level of C women declined significantly from Phase II to 909 ± 888 pg/ml (T test for paired comparisons, $T = 2.39$; $P < 0.04$). A significant decline also occurred in NC women to a mean level of 107 ± 112 pg/ml (T test for matched pairs, $T = 11.03$; $P < 0.0001$).

Correlations of Psychological Tests and Hormonal Levels

Correlation coefficients were calculated between three groups of measurements: (a) between test scores of state anxiety and depression, (b) between PRL and cortisol levels, and (c) between the psychological measures and hormonal levels. High correlations, all of them highly significant, were found between state anxiety and DACL scores in both C and NC women, across all phases. The results are shown in Table IV.

The correlations between cortisol and PRL were low to medium in most phases, among both C and NC women. Significant positive correlations were found in the NC group in all phases with the exception of Phase II. In the conceiving group, a high positive correlation between cortisol and PRL was found in Phase IV, but correlations in the other phases were not significant. These results are presented in Table V.

Table VI shows the correlation coefficients between the psychological and the hormonal measures, illustrating that during the first three phases in both groups hormonal levels were not correlated with the behavioral parameters. Nevertheless, in the group of C women Phase IV was characterized by a negative significance for both state anxiety and depression with both PRL and cortisol.

DISCUSSION

We measured anxiety and depression levels four times during the IVF/ET process. The first set of measurements was taken shortly before the initiation of the IVF treatment. This proximity in time may be one reason for the significantly higher levels of the psychological parameters and the high—albeit within norm—hormonal levels. Above-norm

Table IV. Correlations Between DACL and State Anxiety in Conceiving and Nonconceiving Women by Phase of IVF Treatment

	Conceiving		Nonconceiving	
Phase	r	P	r	P
I	0.693	0.0003	0.590	0.00001
II	0.650	0.0014	0.567	0.00001
III	0.715	0.0002	0.754	0.00001
IV	0.712	0.0002	0.702	0.00001

Table V. Correlations Between Cortisol and Prolactin in Conceiving and Nonconceiving Women by Phase of IVF Treatment

	Conceiving		Nonconceiving	
Phase	*r*	*P*	*r*	*P*
I	0.264	NS	0.394	0.0006
II	0.202	NS	−0.013	NS
III	0.021	NS	0.274	0.045
IV	0.674	0.0008	0.368	0.009

depression and anxiety scores before the initiation of IVF patients were reported earlier (19), but patients' scores in some studies were within the norm (20–22). Another reason for these findings is, perhaps, that all participants in this study were childless and hence specifically sensitive to emotional stress (23).

Oocyte retrieval, immediately prior to which the second set of measurements was taken, is a crucial phase in the IVF/ET process. It combines a number of potential stressors that occur almost simultaneously. (a) The surgical intervention provokes fear of pain. The effect of a specific physical stressor on the level of anxiety has been studied with regard to imminent electrical shock (20). The increase in state anxiety was significantly higher than in a situation where the threat had been ego-targeted and nonspecific. (b) The existence of a normal reproductive system in terms of normal oocytes enables the patient to prove her womanhood; the expectations and—no less—the apprehension, may reach very high levels at this phase. (c) The stress under which the husband has to perform (invariably in most unfavorable conditions) in order to produce the sperm (24,25). These factors may explain the significant rise in PRL, anxiety, and depression relative to the baseline scores, while cortisol levels remained at about the same high level as in the first measurement session. Presumably, cortisol level rose already in Phase I in anticipation of the coming stress. An anticipatory rise in cortisol level before the actual occurrence of an emotional stressor was reported earlier (1,26).

The third measurement session took place immediately prior to ET and after the patient was informed that the second phase ended successfully and that the fertilization process proceeded normally, i.e., it resulted in the creation of an embryo. The findings showed a significant decrease in all four parameters. In fact, depression levels reached the norm. These findings are compatible with those reported by Guttman *et al.* (27).

The fourth and final phase consisted of pregnancy confirmation and took place 10 days following ET. During this period of high expectation level the women were asked to rest and try to relax while waiting for the critical test. Both hormonal and psychological parameters were taken before the pregnancy test. Compared to the third measurement session, there was a highly significant rise in the levels of all parameters.

Although the measurements were taken prior to the pregnancy test, the psychological tests' scores prove that shortly before they were informed of the IVF/ET results, the women's emotional situation was characterized by severe anxiety and depression. Although most IVF patients are aware of the low rate of success, many find it difficult to accept failure (28).

The trend toward elevated levels in the psychological parameters tends to continue beyond the treatment period. Newton *et al.* (23) showed that women who were assessed shortly after failure of the IVF process demonstrated a rise in anxiety and depression. Moreover, the most vulnerable among that study group were childless women.

There were several interesting findings concerning the interrelationships among the parameters in the four phases, with respect to the C and NC groups.

Phase I. No difference was found in trait anxiety between C and NC women. On the other hand, the average score of the pooled group (C and NC) was significantly higher than the norm. This difference, which was indicated previously in samples of Irish (29) and Belgian (1) women, may be attributed to protracted infertility treatment, namely, the anxiety could be secondary to infertility and not necessarily a basic trait. Further research is needed in order to assess the existence and direction of causal relationship between trait anxiety and infertility.

The division of the study's population into C and NC women becomes more relevant with respect to state anxiety and depression. Although the differences between these two subgroups were not significant, they merit an explanation based on general trends. As evident from the results, C women were higher than NC women at this phase on both state anxiety and depression. In standard anxiety tests the subject must be aware of his own symptoms of anxiety (30). Sometimes the patient is incapable of this self-consciousness and the influence of defense mechanisms and inhibitions should, therefore, be taken into account. Repression of anxiety may re-

Table VI. Correlations Between Hormonal Levels and Psychological Tests in Conceiving and Nonconceiving Women by Phase of IVF Treatment

	CORT with state anxiety		CORT with DACL		PRL with state anxiety		PRL with DACL	
Phase	Conceiving	Nonconceiving	Conceiving	Nonconceiving	Conceiving	Nonconceiving	Conceiving	Nonconceiving
I	−0.152	0.179	−0.295	0.137	−0.286	0.265**	−0.366*	0.086
II	0.050	−0.005	−0.110	0.207	−0.249	0.102	−0.324	0.001
III	0.159	−0.163	−0.200	−0.260**	0.019	−0.147	−0.040	−0.216
IV	−0.544****	−0.019	−0.500***	−0.107	−0.444**	−0.019	−0.403*	0.013

* $P < 0.1$.
** $P < 0.05$.
*** $P < 0.02$.
**** $P < 0.01$.

sult in low anxiety test scores, accompanied by behavioral and physiological responses typical of high anxiety. Repression is generally considered as a maladaptive form of coping, whereas an explicit expression of anxiety may mean a better adaptation to stress (31). This can explain the apparent discrepancy between the C and the NC groups.

Phase II. In this critical phase there was a significant difference in anxiety levels between the C and the NC subgroups. C women had also higher depression scores, although this difference was not significant. These findings reinforce the model suggested above, i.e., that those women who did not succeed in conceiving tended to repress their emotions and hence their coping with the stress was less effective. It is, however, possible that alternative behavioral or physiological modes of response were utilized by these women, such as the higher rise of PRL in the NC group.

Phase III. This phase was characterized by a significant decrease in all variables. Its importance lies in its role of an anchor point toward the final (fourth) and most critical phase. Patients were tested on the average within a day after being informed about the positive results, and their mood could be described as one of satisfaction. The fact that the third phase proceeded with no failure, i.e., every participant who was informed of the successful insemination and embryo creation underwent embryo transfer, explains the reduction in anxiety and depression in both C and NC women.

Phase IV. The significant rise in both psychological and hormonal parameters was not reflected in the difference between the C and the NC groups. The rise in PRL in the NC women is surprising, since in this subgroup the hormone was not supposed to rise. It is possible that stress played a decisive role in the induction of unexpected variations in hormone release. In this respect PRL might have served as an indicator of the stress level.

Strong correlations, ranging from 0.65 to 0.75, were observed between state anxiety and depression scores in both C and NC women, across all four phases of the IVF/ET process. These correlations were highly significant. Since both DACL and STAI are well established and widely used measures of distress, this finding confirms the validity of these scales as a yardstick for evaluating the general emotional condition of the patients. On the other hand, the unusually high correlations between the two scales raise the question of their specificity as measures of two different—albeit partially overlapping—psychological states.

Correlation coefficients between cortisol and PRL demonstrated a weak and inconsistent relationship along the first three phases of treatment. However, in Phase IV a significant high correlation was found in the C group, and a medium correlation in the NC group. A similar trend was apparent for the first three phases with regard to the relationship between hormones and the psychological parameters. Correlation coefficients were generally very low and insignificant.

In Phase IV there was a clear disparity between C and NC women. Whereas in the C group there was a significant negative correlation between both hormones and the psychological measures, in the NC group the trend of no relationship persisted in this phase as well. Since PRL and cortisol showed a highly significant rise in Phase IV in both groups, the striking difference between the groups in the correlations between hormones and psychological measures may indicate the involvement of a mediating factor. We hypothesize that an additional factor active in the central nervous system (CNS) in a state of anxiety, such as endogenous opiates, had a

role of mediating between the mental state and hormonal secretion. This factor could explain the reduced levels of state anxiety and depression in the C compared with the NC group.

As the present study was based on a limited sample and examined a limited set of variables, the results can be accounted for by other explanations. Additional investigative effort is clearly necessary.

CONCLUSIONS

In conclusion, the main findings of this study were (a) hormonal and psychological measures showed the same pattern of change in the course of the IVF/ET treatment in both C and NC women and (b) a clear difference was demonstrated between C and NC women. Whereas there was no relationship or a weak positive correlation between the psychological measures of depression and anxiety and hormonal levels in NC women, in the C group there were significant negative correlations between the psychological measures and both hormones in Phase IV of the treatment. Our findings suggest that differential modes of coping, as expressed in the hormonal and psychological measures examined in this study, may influence success or failure in IVF/ET treatment.

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