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ASSISTED REPRODUCTION TECHNOLOGIES

Reproductive implications of psychological distress for couples undergoing IVF

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Abstract
Objective To study implications of psychological distress on in vitro *fertilization* (IVF) outcome of an infertile couple.
Methods Prospective study in an academic infertility practice setting. Couples undergoing embryo transfer (ET) following IVF were offered participation. Female patient ($n=89$) and partner ($n=77$) completed questionnaires reflecting *dysphoria* (POMS) and *pessimism* (LOT) after undergoing ET. Relationship between *dysphoria* and *pessimism* and implications of individual and couple's psychological distress on IVF cycle parameters and outcomes were assessed using multivariable analyses.
Results Statistically significant correlations between *dysphoria* and *pessimism* were observed within the individual and between partners, ($p<0.01$). Higher couple *pessimism* correlated with longer duration of controlled ovarian hyperstimulation (COH, $p=0.02$); higher partner psychological distress related to lower fertilization rate (FR, $p=0.03$). On adjusted analyses, partner's depression score was an independent predictor of reduced likelihood of clinical pregnancy ($p=0.03$).
Conclusions Our data validate the concept of a "stressed couple". Adverse implications of a couple's psychological distress for gamete biology (longer duration of COH and lower FR with increasing distress) are suggested. Partner's depressive scores negatively correlated with IVF success. These findings suggest the importance of including partner's evaluation in studies that focus on effects of psychological stress on IVF outcome; future studies should examine whether interventions aimed at reducing psychological stress for the infertile couple may improve IVF cycle success.

Keywords Stress · Mood · Dysphoria · Pessimism · POMS · LOT · Infertility · IVF

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Capsule In couples undergoing in vitro fertilization (IVF), psychological distress may have implications for gamete biology and for IVF success.

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Introduction

While stress relating to infertility and fertility treatment is well recognized [1–4], a cause-effect relationship is far from clear [5–7]. Psychological stressors are suggested to negatively impact the success of in vitro fertilization (IVF) [8–18]. Evidence to this effect however is equivocal at best [19–22], and some have even implied positive effects of stress on IVF outcome [23].

The periods of egg retrieval (ER), embryo transfer (ET) and pregnancy test following IVF are all recognized as vulnerable times linked with high levels of stress [10, 24–29]. Behavioral modification, psychological support and acupuncture have been shown to positively impact on success of fertility treatments [28, 29], albeit inconsistently [30]. A relevance of psychological distress proximate to the timing of ET for IVF outcome is suggested as improvements in pregnancy rates following IVF are described when acupuncture was administered as a stress reduction strategy on the day of ET compared to when instituted on the day of ER [31]. Indeed, an accruing body of literature is supportive of potential for benefit for infertile women undergoing IVF [28, 29, 31]. Detrimental effects of "stress" on semen quality have also been described [32–34] and a single study reported a correlation between male partner stress and IVF failure [9]. Overall, however, the effect of male stress on ART outcome has been poorly explored. We hypothesized a cumulative detriment of psychological stress experienced by either and both partners in couples undergoing ART.

While the mechanisms are unclear, psychological stress may affect reproductive competence through a variety of pathways including the hypothalamic-pituitary-adrenal and hypothalamic-pituitary-gonadal axes, oxytocin, immunologic mechanisms [1, 5, 26, 31] and possibly through adversely influencing uterine receptivity [35].

We report the results of a prospective study in which we have explored reproductive implications of *dysphoric mood* and *pessimism* in infertile couples undergoing IVF.

Materials and methods

Couples undergoing fresh ET (11/2006–11/2007) at the Montefiore Institute for Reproductive Medicine and Health (MIRMH) were prospectively offered participation. The study was approved by the institutional review board at Montefiore Medical Center and participants provided written consent.

Methods

Consecutive patients were offered recruitment after successful completion of ET with a target enrollment of 100. The patient and her partner (if present) individually completed two validated questionnaires (Profile of Mood States –POMS, and Life Orientation Test- LOT). POMS measures 6 mood dimensions (tension-anxiety; depression-dejection; anger-hostility; vigor-activity; fatigue-inertia and confusion-bewilderment) whereas LOT is a measure of dispositional *optimism* [36, 37]. The questionnaires were scored by a trained psychologist (KB) who was blinded to participant gender and cycle outcome. Use of a sedative or relaxant prior to ET was an exclusion criterion.

Patient and cycle data were collected from medical records including age, body mass index (BMI), early follicular (days 1–3) serum FSH and estradiol (E2) levels, GnRH agonist versus antagonist use, gonadotropin dose, duration of controlled ovarian hyperstimulation (COH), serum E2 and progesterone (P) levels and endometrial thickness (EMT in mm) on the day of hCG trigger, number of eggs retrieved, insemination method (IVF, intracytoplasmic sperm injection [ICSI], or split), fertilization rate (FR, %), day of ET (day#3 or blastocyst), cryopreservation of surplus embryos (yes/no) and IVF cycle outcome (implantation rate [IR] and clinical pregnancy [CP]). Data on partner's age and semen parameters on day of egg retrieval were also assessed.

Statistics

Recruitment goal was set at $n=100$ for this pilot study. Post hoc power analysis demonstrated that with a sample size of 90, and an anticipated correlation coefficient of −0.3 between distress score and CP, the study was powered at 0.82 for an alpha of 0.05.

Dysphoria and *pessimism* scores were calculated for the patient and partner; summation of respective individual scores reflected ***total*** *dysphoria and pessimism* for the couple. A ***composite*** *psychological distress* score (summation of *dysphoria* and *pessimism* scores) was calculated for the individuals and the couple. Higher scores indicate greater *dysphoria* and *pessimism* respectively.

Data distributions were analyzed; Student's *t* test compared normally distributed data across categories by cycle outcome (CP versus not pregnant). Skewed data (gonadotropin dose and IR) were log transformed for similar analyses if normal distribution was achieved; otherwise nonparametric tests were used (Mann Whitney U Rank Sum Test). Clinical pregnancy and IR were primary outcomes and IVF cycle parameters were secondary outcomes of interest. Relationship of specified outcomes with *dysphoria*, *pessimism* and *composite psychological distress* scores (i.e. independent variables of interest) were assessed utilizing appropriate univariate analyses (Pearson or Spearman correlation, Student's *T* test or Mann U Whitney for continuous data, and Chi-square test for categorical data). Seasons were defined by month of ET: Winter: December–February, Spring: March–May, Summer: June–August, and Fall: September–November. Seasonal variation in mood was similarly assessed. Kruskall Wallis rank test was used to compare continuous data across more than 2 categories (i.e. mood scores across infertility diagnoses and by season). Multivariable regression analyses (logistic or linear as appropriate) identified independent correlates to the outcomes of interest after adjusting for potential confounders that were recognized to influence IVF success (age, method of insemination (IVF vs. ICSI), use of GnRH agonist, EMT, number of ET, P on the day of hCG); season and partner depression score; variables demonstrating p value of <2.0 for association with CP were additionally examined for confounding. Continuous data are presented as mean (standard deviation) and associations as odds ratio (OR) and 95 % confidence interval (CI). STATA Intercooled 12.0 (StataCorp, College Station, TX) was utilized and two tailed *p*-value <0.05 was considered significant.

Results

Figure 1 outlines enrollment details. Of the 100 consenting patients, both questionnaires were completed by 89 patients and 77 partners.

Table 1 provides patient characteristics, cycle parameters and mood and pessimism scores by cycle outcome. Younger age, use of a GnRH agonist, lower gonadotropin dose, increased EMT, and cryopreservation of surplus embryos were associated with an increased likelihood of CP following IVF-ET. Infertility diagnoses did not relate to the likelihood of cycle success (data not shown).

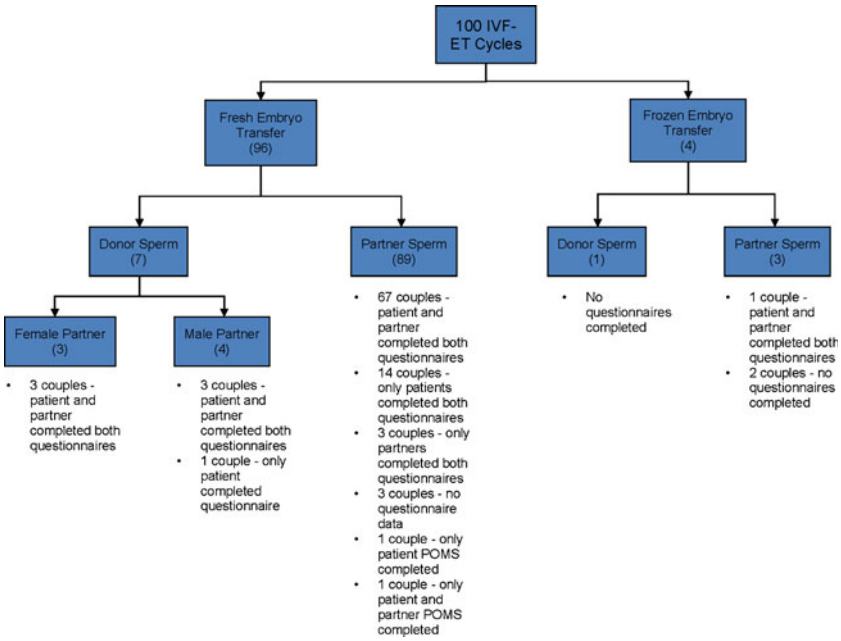

Fig. 1 Flow diagram reflecting enrollment details

Statistically significant linear correlations were observed between *dysphoria* and *pessimism* scores for patients ($r = 0.42$, $p < 0.001$) and for partners ($r = 0.33$, $p = 0.004$). Statistically significant correlations were observed between patient and partner *dysphoria* scores ($r = 0.32$, $p = 0.005$) and between patient and partner *composite psychological distress* scores ($r = 0.34$, $p = 0.003$) (Supplemental Figure). The relationship between patient and partner *pessimism* scores was not statistically significant ($r = 0.16$, $p = 0.169$).

Seasonal differences in dysphoric mood and pessimism were observed. *Dysphoria* and *composite psychological distress* scores for the partner as well as *dysphoria*, *pessimism* and *composite psychological distress* scores for the couple were significantly higher for those undergoing ET in the winter compared to other seasons (Table 2).

On univariate analyses, neither *total dysphoria* nor *pessimism* scores related to cycle outcome (Table 1). An inverse relationship between partner *depression* score and likelihood of CP was noted; partners of women achieving CP following ET scored lower on the *depression* domain of POMS compared to partners of those with failed outcome (log transformed respective *depression* scores 1.46±1.03 vs. 1.97±0.93, $p = 0.054$).

After adjustment for patient age, insemination method (IVF versus ICSI), COH protocol, EMT, #ET, serum P on the day of hCG and season, partner's *depression* score emerged as an independent determinant of CP following ET. Each unit increase in partner's depression score was associated with a 17 % decreased likelihood of CP ($p = 0.030$). Advancing patient age (Adjusted OR 0.65, 95 % CI 0.49–0.88) and higher serum P levels (AOR 0.14, 95 % CI 0.02–0.91) were independent negative predictors of CP whereas GnRH agonist (vs. antagonist) (AOR 22.29, 95 % CI 1.95–254.95), higher EMT (AOR 1.79, 95 % CI 1.2–2.66) and IVF-ICSI split cycles (AOR 64.39, 95 % CI 2.37–1751.28) related to a significantly increased likelihood of CP following IVF. The statistical model exhibited 89 % sensitivity for predicting CP. No relationship between IR and psychological parameters for the patient, partner or couple was appreciated (data not shown).

While no association was observed between patient or partner *dysphoria* and IVF cycle parameters, higher couple *pessimism* scores correlated with longer duration of COH (Fig. 2a). A significant negative correlation was observed between partner *dysphoria* and *composite psychological distress* scores and FR (Fig. 2b); of note, three same gender couples were excluded from analyses assessing relationship between partner/couple's distress and FR. No significant relationship was observed between FR and patient or partner *dysphoria or pessimism* (data not shown). Sensitivity analyses failed to demonstrate any relationship between cycle outcome and partner's presence or absence at ET (data not shown).

Multivariable linear regression analysis confirmed partner's *composite psychological distress* score as a negative predictor of FR (β coefficient −0.18, SE 0.09, $p = 0.049$) after adjusting for female partner age, ICSI (vs. IVF) and % motile sperm on the day of ER; 20 % variability in FR was explained by this model (adjusted R^2 0.20). Sperm motility (%) was identified as an independent predictor of FR (β coefficient 0.53, SE 1.4, $p < 0.001$). Sensitivity analyses excluding

Table 1 Participant characteristics, IVF cycle parameters and aspects of psychological distress (higher scores on POMS and LOT screening reflect worsening dysphoria and pessimism respectively) are presented according to the outcome of embryo transfer cycle (clinical pregnancy versus not pregnant)

	Characteristic	Clinical pregnancy (N=38)	Not pregnant (N=62)	P- value
Demographics	Patient age (years)[a]	32.6±4.33	35.7±4.25	**<0.01**
	Partner age (years)[a]	35.2±5.36	37.6±5.96	**0.05**
	Patient BMI (kg/m^2)[a]	26.3±4.30	26.4±5.55	0.59
	Smoker (patient) (%)	10.5 %	8.5 %	0.73
	Smoker (partner) (%)	27 %	12.7 %	0.08
Cycle parameters	1st ART cycle (%)	58 %	53 %	0.65
	IVF cycles (%)	26.3 %	27.4 %	0.90
	ICSI cycles (%)	50 %	58 %	0.43
	IVF-ICSI split cycles (%)	21 %	9.7 %	0.11
	GnRH agonist (Lupron) (%)	86.8 %	66.1 %	**0.02**
	Cycle day 3 FSH (mIU/mL)[a]	7.1±2.12	7.7±2.56	0.97
	Gonadotropin dose (IU) (log transformed)[a]	7.7±0.45	8.0±0.50	**0.01**
	Duration of COH (days)[a]	10.4±1.54	10.4±1.78	1.00
	Endometrial thickness day of hCG (mm)[a]	11.8±2.80	10.7±2.13	**0.03**
	Estradiol day of hCG (pg/ml) (log transformed)[a]	7.6±0.44	7.4±0.55	0.10
	Serum progesterone day of hCG (ng/ml)[b]	0.9 (0.6–1.21)	1.1 (0.7–1.41)	0.16
	# of eggs retrieved	13.5 (8–16)	11 (6–15)	0.19
	# of embryos transferred[b]	2 (2–3)	2 (2–3)	0.98
	# embryos cryopreserved	12/38 (32 %)	6/62 (10 %)	**<0.01**
Mood parameters	POMS score (*dysphoria*)[b]			
	Patient	18 (−2 to 45)	13.5 (0.5 to 35)	0.80
	Partner	15 (−3 to 31)	17.5 (−6.5 to 35)	0.87
	Couple	30 (2 to 69)	34 (−4 to 59)	0.68
	LOT score (*pessimism*)[b]			
	Patient	5 (3 to 11)	6 (2 to10)	0.57
	Partner	6 (4 to 14)	8 (3 to 12)	0.83
	Couple	15 (9 to19)	13 (8 to 18)	0.35
	LOT + POMS (*composite psychological distress*)[b]			
	Patient	23 (2 to52)	22 (5 to 45)	0.85
	Partner	25 (4 to 42)	22 (0 to 45)	0.77
	Couple	37 (17 to 90)	44 (2 to 86)	0.58

Continuous data are presented as mean (SD)[a] or as median (inter-quartile range)[b]

couples who utilized donor sperm and adjusting for ICSI confirmed persistence of the negative relationship between partner psychological distress and FR (data not shown).

No significant differences were observed in patient, partner or couples' dysphoric (p=0.33, p=0.61 and p=0.38 respectively) or pessimism scores across various categories of infertility diagnosis (p=0.84, p=0.46 and p=0.61 respectively, by Kruskal Wallis Rank test). Similarly, POMS AND LOT scores were no worse in women with a known diagnosis of diminished ovarian response (n=14) or in male partners amongst couples with a known male factor contribution to infertility (n=31, p=0.20 and p=0.57 respectively, by student's T test). Neither patient nor partner dysphoric or pessimism scores demonstrated any correlation with baseline FSH (p >0.05).

Discussion

We assessed concordance of *dysphoria* and *pessimism* between partners in couples undergoing fresh ET following IVF. Our data suggest that while *dysphoria* and overall psychological distress (reflected by the *composite score*) are concordant between patients and partners, *pessimism* is not. Prior research suggests that discordance in the emotional experience of infertility within heterosexual couples may relate to differential coping styles of men versus women [38, 39]. While our data validate the concept of a "stressed couple", both individual and gender-related factors must be considered when assessingcouples' psychological needs.

Table 2 Worsening mood and pessimism were observed in couples undergoing ART cycles during winter months, compared to other seasons

	Winter[a]	Other seasons[a]	*P*-value
POMS score (*dysphoria*)			
Patient	21 (0 to 40)	13 (−3 to 35)	0.26
Partner	27 (11 to 48)	11 (−7.5 to 32)	**0.04**
Couple	53 (23 to 83)	24 (−5 to 48)	**0.02**
LOT score (*pessimism*)			
Patient	7 (4 to 11)	5 (2 to 9)	0.13
Partner	8 (4 to 14)	7 (3 to 11)	0.24
Couple	17 (13 to 20)	11 (7 to 18)	**0.03**
LOT + POMS (*composite psychological distress*)			
Patient	27 (6 to 52)	18 (2 to 45)	0.21
Partner	33 (13 to 55)	20 (−2 to 41)	**0.02**
Couple	71 (34 to 98)	32 (2 to 79)	**0.03**

Continuous data presented as median (inter-quartile range)[a]

Higher scores indicate worsening parameter

Our study design does not allow causative interpretation to the observations; however, the noted association between couples' psychological distress and COH parameters may be construed as negative influence of stress on folliculogenesis. Similarly, the observed relationship between partners' psychological distress and FR can be interpreted as reflecting adverse influences of stress on gamete biology. Partner's *depressive* mood is seen as a negative predictor of CP following ET. In light of our findings, access to psychological assessment and support should be considered for both partners undergoing IVF.

Some of the heterogeneity in the literature regarding the effect of psychological distress on ART success may be attributable to the wide variety of tools utilized to assess psychological state. The choice of psychological tools (POMS and LOT) allowed us to assess a range of dysphoric moods (anxiety, tension, depression, anger and confusion) as well as a couple's expectations regarding cycle outcome. To our knowledge, this is the first study to assess implications of optimism/pessimism for cycle outcome in infertile couples undergoing IVF.

The observed inverse association between male partner's psychological distress and FR, independent of insemination methodology, suggests implications of psychological wellbeing on male gamete physiology. Clarke et al. measured anxiety, stressfulness, and perceived importance of producing a semen sample prior to IVF initiation and again at egg retrieval in males undergoing first IVF cycles. Higher anxiety and a significant increase in the perceived importance of producing a sample at egg retrieval compared to an earlier collection were observed and were significantly correlated with decreased sperm concentration, total motile sperm, and motile sperm concentration [34]. In keeping with this latter observation, a non-significant trend was observed in our study between both decreasing sperm concentration and motility and increasing partner *dysphoria*. While our findings are in agreement with Clarke et al. that psychological distress may adversely influence semen parameters in infertile couples undergoing IVF, it is important to appreciate that these associations may not translate to healthy and fertile populations [40, 41].

The prospective design, relatively robust questionnaire completion rate, blinded scoring of questionnaires and the adjusted analytic strategies are strengths of our study. Given the emergence of partner *depression* as mood domain predictive of CP, consideration might be given to using a more specific depression screen for partners of women anticipating IVF treatment in future studies. While the timing of questionnaire administration limited confounding from earlier stressors, this single time point also limits our ability to draw broad conclusions from the observed relationships. A higher proportion of partners acknowledged smoking in the group attaining CP, an observation that is difficult to rationalize as others have identified passive exposure to tobacco as a detriment to reproductive success [42]; in the absence of any plausible explanation, this observed association may indeed reflect an alpha error.

Our goal in assessing psychological distress following ET was to better understand the implications of the couple's psychological wellbeing on the outcomes of interest while eliminating individual and couple's concerns regarding fertilization, embryo development and achieving ET. Our study design does not allow us to comment on modulation of psychological stress in either partner during the period between cycle start and ET or while awaiting cycle outcome. Although sensitivity analyses failed to demonstrate a relationship between cycle outcome and partner's presence or absence, our study is not powered in this context. While the observed relationship between IVF-ICSI split cycles and CP is of interest, our study design does not allow an elaboration on this finding. The decision to offer IVF-ICSI split cycle was based on the supervising clinician's judgment and individualized concerns regarding fertilization potential [43]. Implications of advancing age, COH protocol and EMT for cycle outcome as evident in our population are consistent with existing data [44–46].

Prior IVF experience may relate to stress levels in subsequent attempts [16, 27]. The proportion of patients in our study undergoing first ART attempt was comparable between cycles achieving CP versus failed cycles (58 % versus 53 %, p 0.649); our data fail to relate first versus repeat ART cycle with either psychological distress or outcome.

While partner depression may impact the ability to achieve CP, of interest are the associations between patient distress and duration of COH, and between partner distress and FR *without* an apparent impact on CP. Studies of first pregnancy planners have correlated positive psychological parameters

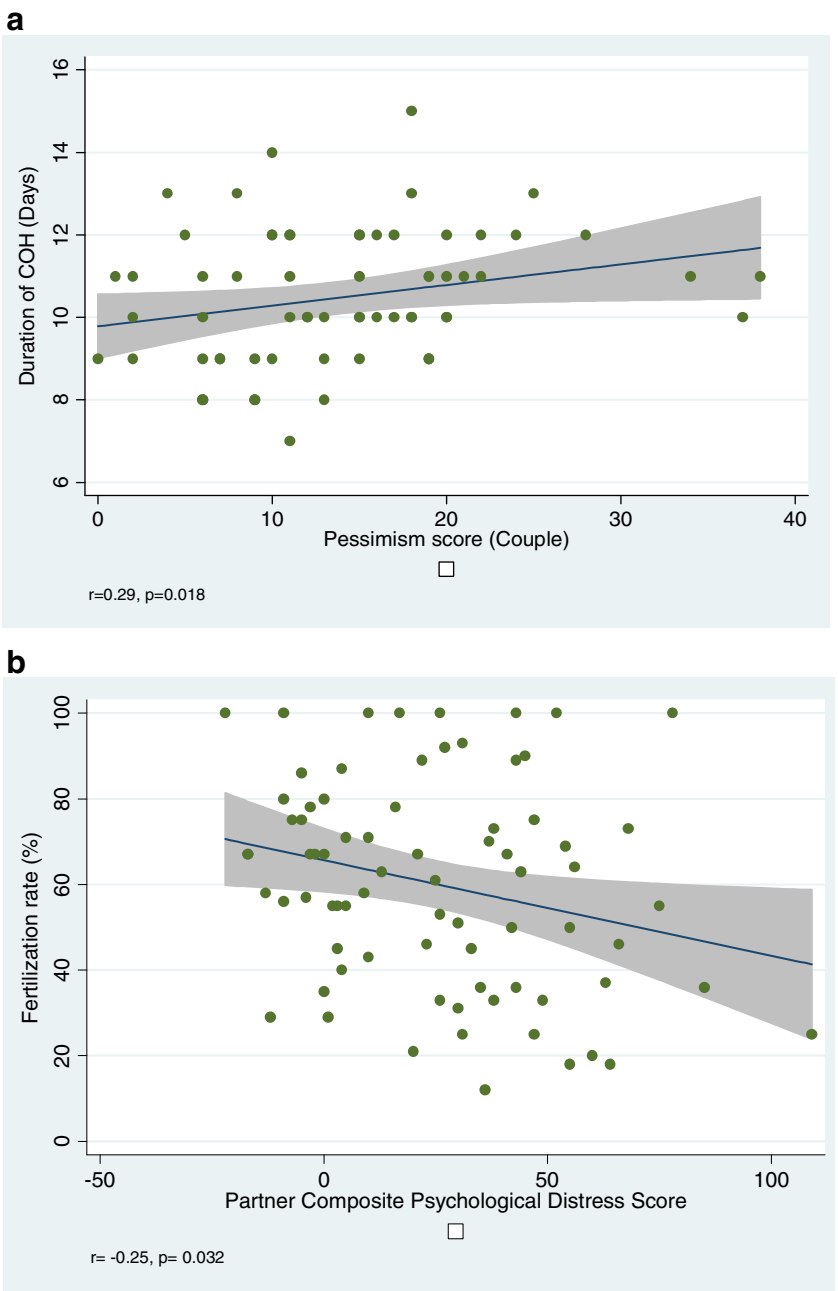

Fig. 2 Relationship between psychological stress and gamete biology is suggested by the observed positive correlation between couple's pessimism score and duration of controlled ovarian stimulation (**a**), and by the observed inverse correlation between fertilization rate and partner's psychological distress (**b**)

with increased fertility [47], and increasing psychological distress with lower odds of conception per cycle [48]. While further studies are needed to delineate mechanisms to explain how stress may impact reproductive competence, our findings suggest that ET following IVF may overcome a plausible biologic hurdle imposed by psychological distress on natural conception (as suggested by prolonged COH and decreased FR with increasing psychological burden in the couple).

Our results highlight that the psychological well-being of each partner undergoing IVF is intertwined and may have implications for cycle outcome. Although a causative role for psychological stress to the observed associations cannot be assigned, improved cycle outcomes are described with de-stressing interventions including cognitive behavioral therapy and acupuncture [28, 29], albeit inconsistently [30]. Far fewer studies have investigated the effectiveness of stress reduction strategies in partners of women undergoing fertility treatment. Increased "healthy" sperm and decreased chromosomal aberrations were observed in men treated with Conveyer of Modulating Radiance (CRM) therapy (a radiofrequency instrument used to treat stress and anxiety) [49] and others report improved sperm parameters after acupuncture [40, 41, 50, 51].

In summary, our data validate the concept of a stressed couple. Adverse implications of psychological distress for folliculogenesis and fertilization are suggested without a demonstrable impact on IVF cycle success. We propose that ART may overcome any hurdles that psychological distress may impose on reproductive competence. Controlled studies are needed to further investigate the impact of psychological distress in the female patient, her partner and in the couple on ART cycles to enable us to better appreciate when and how to intervene so as to maximize reproductive success in couples undergoing ART.

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Declaration of interest statement The authors report no declarations of interest.

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