

The effect of anxiety and depression on the outcome of in-vitro fertilization

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BACKGROUND: The study aim was to clarify the role of anxiety and depression on the outcome in assisted reproductive treatment. Previous studies on this topic have shown contradicting results, which may have been caused by population characteristics, the design of the study, or small sample sizes. **METHODS:** In a multicentre prospective study, 291 out of 359 (81%) consecutively invited women agreed to participate. Before down-regulation by means of gonadotrophin-releasing hormone (GnRH) analogues in a long IVF protocol, patients were asked to complete the Dutch version of the State and Trait Anxiety Inventory to measure anxiety, and the Dutch version of the Beck Depression Inventory (BDI) to measure depression. Multiple logistic regression analysis was used to analyse known predictors of pregnancy and psychological factors and their relationship with treatment outcome. **RESULTS:** A significant relationship was shown between baseline psychological factors and the probability to become pregnant after IVF/intracytoplasmic sperm injection (ICSI) treatment, controlling for other factors. State anxiety had a slightly stronger correlation ($P = 0.01$) with treatment outcome than depression ($P = 0.03$). **CONCLUSIONS:** Pre-existing psychological factors are independently related to treatment outcome in IVF/ICSI, and should therefore be taken into account in patient counselling. Psychological factors may be improved by intervention, whereas demographic and gynaecological factors cannot. Future studies should be directed towards underlying mechanisms involved and the role of evidence-based distress reduction in order to improve treatment results.

Key words: anxiety/depression/in-vitro fertilization/model/pregnancy

Introduction

Women undergoing IVF treatment are often anxious and depressed because of their infertility and the uncertainties of the treatment with which they have to deal (Mahlstedt, 1985). Indeed, epidemiological and anecdotal data suggest a relationship between psychological factors and infertility (Freeman *et al.*, 1985; Lapane *et al.*, 1995). However, a systematic review of controlled studies before 1990 presented contradicting results (Wright *et al.*, 1989). More recently, one review (Eugster and Vingerhoets, 1999) indicated that the influence of psychological factors on the outcome of IVF/intracytoplasmic sperm injection (ICSI) continues to be a matter for debate. In this review, no particular attention to ICSI was paid. Prospective studies using standardized psychometric tests are scarce, and results are difficult to compare (Demyttenaere *et al.*, 1992, 1998; Merari *et al.*, 1992; Thiering *et al.*, 1993; Boivin and Takefman, 1995). The somewhat inconsistent findings in these studies may be due to population characteristics, the design of

the study, or small sample sizes. Moreover, multicentre studies are preferable because predictions have the tendency to be centre-specific.

The role of psychological factors in IVF/ICSI outcome has still to be established. As this knowledge is a prerequisite for adjuvant psychological interventions, the question has a major clinical relevance. Several statistical models have been published using combinations of biomedical factors in relation with IVF outcome. The model of Templeton is well known: it is based on a large database and includes the factors age, duration of infertility, number of previous unsuccessful IVF attempts, tubal indication for fertility treatment and number of previous pregnancies as independent predictors (Templeton *et al.*, 1996). Others (Stolwijk *et al.*, 1996) identified two factors, i.e. at least two preceding gestations and age, to be significant in predicting IVF outcome. It was also demonstrated that both models have limited external validity (Stolwijk *et al.*, 1996; Smeenk *et al.*, 2000). A possible reason for the limited

validity of the presented models is that they are based only on stable variables. Some studies, however, indicate that the success of assisted reproductive treatment may also be dependent on variable factors, such as a woman's distress level at the time of treatment (Boivin and Takefman, 1995; Facchinetti *et al.*, 1997; Demyttenaere *et al.*, 1998). The main objective of the current study, conducted at three Dutch hospitals, was to clarify the additional role of pre-existing anxiety and depression on IVF/ICSI results, controlling for known predictors.

Materials and methods

All patients who went to the University Medical Centre St Radboud Nijmegen (an academic tertiary referral centre in the east of The Netherlands) and to the Baronie and St Ignatius hospitals of Breda (both secondary referral hospitals in the south-west of The Netherlands) for the first cycle of a new IVF/ICSI treatment between January 1999 and March 2000, were invited to participate in the study. A long protocol with Decapeptyl® (Ferring, Hoofddorp, The Netherlands), Puregon® (Organon, Oss, The Netherlands) and Pregnyl® (Organon, Oss, The Netherlands) was used. Only the first treatment cycles of a three-cycle course of IVF/ICSI were included. A maximum of two embryos was transferred per treatment cycle, 3 days after oocyte retrieval. Remaining embryos of good quality were cryopreserved. Between days 10 and 20 of the cycle before the stimulation cycle—hence, before the start of gonadotrophin-releasing hormone (GnRH) analogue medication—women were asked to complete a questionnaire on psychological factors and to return it in a pre-paid envelope to the hospital. All participants were guaranteed anonymity, and separation of questionnaire information from their clinical management. Signed informed consent was obtained from all participants. The study was approved by the Ethical Committees of the hospitals in Nijmegen and Breda.

Of the 359 invited patients (313 in Nijmegen, 46 in Breda), 68 declined or were excluded. Reasons indicated by patients were: lack of time ($n = 23$), already participating in another study ($n = 7$), emotional burden of the treatment ($n = 7$) and unknown ($n = 5$). Twelve patients were excluded because of missing data, and 14 because of language difficulties. Thus, the remaining group consisted of 291 (81%) patients.

The demographic and gynaecological variables studied are derived from the model of Templeton: age, duration of infertility, number of previous pregnancies and infertility diagnosis. In addition to 'tubal' factor (as diagnosed in Templeton's model), other infertility diagnoses were included. Since only the first cycle of each patient was included, number of previous unsuccessful IVF attempts was not included as a predictor.

Anxiety was measured by means of the Dutch version of the State and Trait Anxiety Inventory (STAI) [Spielberger *et al.*, 1970; Vanderploeg *et al.*, 1980 (Dutch version)], a scale showing satisfactory reliability and validity. Trait anxiety refers to a general tendency of an individual to be anxious, whereas state anxiety refers to the anxiety level of an individual at a given moment. Both measures include 20 items, the score for each item ranging from 1 to 4, with higher scores indicating greater anxiety. Thus, total scores range from 20 to 80. In our sample the coefficient alpha for state anxiety was 0.94, and that for trait anxiety 0.91.

Depression was measured by means of the Dutch version of the Beck Depression Inventory (BDI) [Beck and Beamesderer, 1976; Bouman *et al.*, 1985 (Dutch version)], being one of the most widely used instruments for assessing intensity of depression and for detecting

depression in the general population. This reliable and valid measure (Beck *et al.*, 1988) includes 21 items, the score for each item ranging from 0 (low) to 3 (high). Thus, total scores range from 0 to 63. In our sample the coefficient alpha was 0.86. Because of high levels of curtosis and skewness on the BDI scale, square roots were taken from the scores and used in the analysis (Tabachnick and Fidell, 1996).

The outcome measures were the number of follicles, number of embryos and pregnancy status. The number of follicles was defined as the number of follicles (≥ 9 mm) present on transvaginal ultrasound, on the day of human chorionic gonadotrophin (HCG) administration. Pregnancy was defined as a positive urinary pregnancy test 15 days after embryo transfer. In this analysis, attention was focused on the women who reached embryo transfer because the aim was to compare all stages of treatment, including the implantation phase.

All statistical analyses were performed by means of the SPSS program. Multiple logistic regression analysis was used to analyse the variables related to pregnancy. The first step was, by using a backward conditional stepwise procedure, to find biomedical variables from Templeton's model related to treatment outcome in the current sample. The second step was to add psychological variables to this block of variables, again in a stepwise backward procedure. Linear logistic regression techniques were used to compare outcome variables between groups, and *t*-tests were used to compare groups on baseline parameters.

Results

The patients ($n = 291$) categorized the cause of infertility themselves as follows: female factor 25%, male factor 42%, combined male and female 9%, and idiopathic 24%. Some 36% of the cycles ($n = 85$) diagnosed as 'male factor only', were ICSI cycles. Among the patients, 35% reported one or more previous pregnancies, 19% reported one or more previous abortions, and 26% reported one or more previous live births, of which 9% resulted from a previous IVF/ICSI attempt. The state-anxiety ($P = \text{NS}$) and the BDI-depression scores ($P = \text{NS}$) did not differ between Nijmegen and Breda. The trait anxiety, however, was significantly lower in Breda ($P = 0.04$). The state and trait anxiety levels, as well as the depression level of the current IVF/ICSI population, lie within the normal range, as compared with a community sample, and this was consistent with previous reports (Freeman *et al.*, 1985; Hearn *et al.*, 1987; Reading *et al.*, 1989).

Among the original group of 291 women, 237 (81.4%) reached embryo transfer. Reasons for not reaching embryo transfer were cancellation by patient ($n = 4$), poor response ($n = 19$), risk of ovarian hyperstimulation syndrome ($n = 5$) or total fertilization failure ($n = 26$). The group who did not achieve embryo transfer ($n = 54$) was the same age ($P = \text{NS}$) as the group who did achieve embryo transfer. In addition, no differences in state anxiety ($P = \text{NS}$), trait anxiety ($P = \text{NS}$) and depression ($P = \text{NS}$) scores were found. Sample characteristics with respect to demographic and psychological variables of the group that reached embryo transfer are shown in Table I.

The regression analysis with only biomedical variables shows that higher age and lower number of previous pregnancies were correlated with poor outcome (Table II). Duration of infertility and the diagnostic category were excluded from

Table I. Characteristics of women who reached embryo transfer ($n = 237$)

| | Mean | SD | Range | Median |
|---------------------------------|------|-----|-------|--------|
| Age (years) | 33.4 | 3.7 | 24–42 | 33 |
| Duration of infertility (years) | 3.7 | 2.0 | 1–13 | 3 |
| State anxiety score | 37.3 | 9.6 | 20–74 | 36 |
| Trait anxiety score | 36.8 | 8.3 | 20–63 | 35 |
| BDI score | 5.6 | 5.1 | 0–20 | 4 |

Table II. The logistic regression model with biomedical variables

| Variable | B | Wald statistic | <i>P</i> | 95% CI |
|-----------------------------|-------|----------------|----------|----------------|
| Age | -0.10 | 5.66 | 0.02 | (-0.17, -0.02) |
| No. of previous pregnancies | 0.55 | 4.10 | 0.04 | (0.02, 1.08) |
| Constant | 2.72 | 4.04 | 0.04 | - |

Model characteristics: -2 Log Likelihood = 289.8; Goodness of fit = 221.0; $R^2 = 0.04$; $\chi^2 = 7.4$; $P = 0.02$. Variables not in the equation due to lack of correlation with pregnancy: duration of infertility; diagnosis: female factor; diagnosis: male factor; diagnosis: combined female/male; diagnosis: unknown.

Table III. Logistic model with biomedical variables and psychological variables

| Variable | B | Wald statistic | <i>P</i> | 95% CI |
|-----------------------------|-------|----------------|----------|----------------|
| Age | -0.12 | 7.65 | 0.01 | (-0.21, -0.03) |
| No. of previous pregnancies | 0.66 | 5.40 | 0.02 | (0.10, 1.21) |
| State anxiety | -0.04 | 5.99 | 0.01 | (-0.06, -0.01) |
| Constant | 4.84 | 9.35 | 0.002 | - |

Model characteristics: -2 Log Likelihood = 278.8; Goodness of fit = 219.5; $R^2 = 0.10$; $\chi^2 = 16.34$; $P = 0.001$. Variables not in the equation due to lack of correlation with pregnancy: Beck depression inventory (BDI); trait anxiety.

the equation due to a lack of correlation with pregnancy in the analysis.

The model obtained after adding psychological factors to the model with the two biomedical variables is depicted in Table III. The trait-anxiety and depression scores were omitted from the equation due to a lack of correlation with pregnancy in the analysis. The model showed a significant independent negative relation of state anxiety with pregnancy ($P = 0.01$). The variable depression did not enter the model because it had a high correlation ($r = 0.70$) with state anxiety. In a model with age, number of previous pregnancies and depression only, depression also proved to have an independent and significant negative correlation with pregnancy ($P = 0.03$). Thus, the analysis was repeated using the ‘composite’ score, in which the standardized scores of state anxiety and depression were summed. The results of this final model are depicted in Table IV.

To identify the stage of treatment at which the effect of state anxiety on treatment outcome was most obvious, the outcome variables of various stages during treatment were compared. Linear regression revealed no relationship of age,

Table IV. Logistic model with biomedical variables and the composite score of state anxiety and depression

| Variable | B | Wald statistic | <i>P</i> | 95% CI |
|-----------------------------|-------|----------------|----------|----------------|
| Age | -0.12 | 6.30 | 0.01 | (-0.21, -0.03) |
| No. of previous pregnancies | 0.82 | 7.19 | 0.01 | (0.10, 1.21) |
| Composite score | -0.17 | 7.66 | 0.01 | (-0.26, -0.05) |
| Constant | 3.27 | 4.74 | 0.03 | - |

Model characteristics: -2 Log Likelihood = 245.1; Goodness of fit = 196.7; $R^2 = 0.12$; $\chi^2 = 18.53$; $P = 0.003$. Composite score = summed standardized scores of state anxiety and depression.

number of previous pregnancies and state anxiety with the number of the follicles (all $P = NS$), oocytes (all $P = NS$) or embryos (all $P = NS$). The current data show that the stimulation and the fertilization phase were not influenced, whereas the pregnancy rate was influenced.

Discussion

The current study showed there to be a significant relationship of psychological variables with pregnancy in IVF/ICSI treatment. Adding the composite score of state anxiety and depression to the model improved it significantly, and led to the best prognostic model with respect to pregnancy. The analysis showed that state anxiety only is a better predictor of pregnancy than depression.

In addition, an independent relation of ‘age’ and ‘number of previous pregnancies’ with the probability to become pregnant was found, and this is consistent with previous findings (Stolwijk *et al.*, 1996). Other variables presented previously in a model (Templeton *et al.*, 1996) did not show any significant relationship with treatment outcome, stressing once more the limited external validity of the Templeton model.

Our data are also in agreement with those of a previous study (Facchinetti *et al.*, 1997) in which effects of state anxiety, and not trait anxiety, on assisted reproductive treatment outcome were found. Others (Demyttenaere *et al.*, 1992) also found a negative influence of state anxiety on IVF outcome, but did not publish any data on trait anxiety. In another study (Thiering *et al.*, 1993), significantly lower success rates for IVF were found in depressed versus non-depressed women, but no predictive value of the anxiety could be demonstrated. Several authors, however, found no relationship between the emotional status of women and the outcome of assisted reproduction treatment (Boivin and Takefman, 1995; Harlow *et al.*, 1996; Slade *et al.*, 1997; Ardeni *et al.*, 1999).

Although the current study had good power, and was multicentre in design, our recommendation would be to reproduce the findings in a larger patient group and to validate the model in another population. Moreover, with the number of co-variables being limited to those found in the Templeton model, and the fact that logistic regression cannot establish the exact relationship among variables, causal inference should be made with caution. Finally, the possibility of selection bias

cannot be excluded, as some patients indicated 'stress' as a reason not to participate.

The mechanism of the distress effect on pregnancy rates is still unknown. Subtle disturbances of the cycle may play a role, these being caused by minor endocrinological alterations (Demyttenaere *et al.*, 1989, 1994; Psech *et al.*, 1989). In a prospective study in women undergoing IVF, an increase during state anxiety treatment was established, parallel to increases in serum prolactin and cortisol concentrations (Harlow *et al.*, 1996). Depression was found to be associated with an abnormal regulation of LH (Meller *et al.*, 1997).

Some studies suggest promising results of psychological interventions on pregnancy rates (Sarrel and DeCherney, 1985; Domar *et al.*, 1990, 2000). However, further prospective research is needed in order to obtain a better understanding of the mechanisms involved and to provide an evidence base for effective stress reduction interventions aiming at better pregnancy rates.

In conclusion, the current study shows that, in addition to some well-known biomedical variables, state anxiety may have an independent contribution to explaining the variability in pregnancy rates. This effect is probably strongest in the implantation phase of the cycle. These findings are particularly important because in contrast to, for example, the factor of age, psychological factors may well be sensitive to interventions, thus increasing the chance of improving treatment results. In view of the current results, psychological factors should be taken into consideration in patient counselling.

Acknowledgements

This study was supported by the Dutch 'Praeventiefonds' (grant no. 28-3012). The authors gratefully thank all the women who participated in the study, the co-workers of the participating hospitals, and Dr ten Kate-Booy of the Ignatius Hospital, Breda. Their thanks also go to W.Doesburg and W.Lemmens for help with the statistical analyses and R.Te Winkel for help with the data management.

References

- Ardenti, R., Campari, C., Agazzi, L. *et al.* (1999) Anxiety and perceptive functioning of infertile women during in-vitro fertilization: exploratory survey of an Italian sample. *Hum. Reprod.*, **14**, 3126–3132.
- Beck, A.T. and Beamesdeerer, A. (1976) Assessment of depression: the depression inventory. *Pharmacopsychiatry*, **7**, 51.
- Beck, A.T., Steer, R.A. and Garbin, M.G. (1988) Psychometric properties of the Beck Depression Inventory: twenty-five years of evaluation. *Clin. Psychol. Rev.*, **8**, 77–100.
- Boivin, J. and Takefman, J. (1995) Stress level across stages of *in vitro* fertilization in subsequently pregnant and nonpregnant women. *Fertil. Steril.*, **64**, 802–810.
- Bouman, T.K., Luteijn, F., Albersnagel, F.A. and Vanderploeg, F.A. (1985) Enige ervaringen met de Beck depression inventory (BDI). *Gedrag. Tijdschr. Psychol.*, **13**, 13–24.
- Demyttenaere, K., Nijs, P., Evers-Kiebooms, G. and Koninckx, P.R. (1989) The effect of a specific emotional stressor on prolactin, cortisol, and testosterone concentrations in women varies with their trait anxiety. *Fertil. Steril.*, **52**, 942–948.
- Demyttenaere, K., Nijs, P., Evers-Kiebooms, G. and Koninckx, P.R. (1992) Coping and the ineffectiveness of coping influence the outcome of *in vitro* fertilization through stress responses. *Psychoneuroendocrinology*, **17**, 655–665.
- Demyttenaere, K., Nijs, P., Evers-Kiebooms, G. and Koninckx, P.R. (1994) Personality characteristics, psychoendocrinological stress and outcome of IVF depend upon the etiology of infertility. *Gynecol. Endocrinol.*, **8**, 233–240.
- Demyttenaere, K., Bonte, L., Gheldof, M. *et al.* (1998) Coping style and depression level influence outcome in *in vitro* fertilization. *Fertil. Steril.*, **69**, 1026–1033.
- Domar, A.D., Seibel, M.M. and Benson, H. (1990) The mind/body program for infertility: a new behavioral treatment approach for women with infertility. *Fertil. Steril.*, **53**, 246–249.
- Domar, A.D., Clapp, D., Slawsby, E. *et al.* (2000) Impact of group psychological interventions on pregnancy rates in infertile women. *Fertil. Steril.*, **73**, 805–811.
- Eugster, A. and Vingerhoets, A.J. (1999) Psychological aspects of *in vitro* fertilization: a review. *Soc. Sci. Med.*, **5**, 575–589.
- Facchinetti, F., Matteo, M.L., Artini, G.P. *et al.* (1997) An increased vulnerability to stress is associated with a poor outcome of *in vitro* fertilization-embryo transfer treatment. *Fertil. Steril.*, **67**, 309–314.
- Freeman, E.W., Boxer, A.S., Rickels, K. *et al.* (1985) Psychological evaluation and support in a program of *in vitro* fertilization and embryo transfer. *Fertil. Steril.*, **43**, 48–53.
- Harlow, C.R., Fahy, U.M., Talbot, W.M. *et al.* (1996) Stress and stress-related hormones during in-vitro fertilization treatment. *Hum. Reprod.*, **11**, 274–279.
- Hearn, M.T., Yuzpe, A.A., Brown, S.E. and Casper, R.F. (1987) Psychological characteristics of *in vitro* fertilisation participants. *Am. J. Obstet. Gynecol.*, **156**, 269–274.
- Lapane, K.L., Zierler, S., Lasater, T.M. *et al.* (1995) Is a history of depressive symptoms associated with an increased risk of infertility in women? *Psychosom. Med.*, **57**, 509–513.
- Mahlstedt, P.P. (1985) The psychological component of infertility. *Fertil. Steril.*, **43**, 335–346.
- Meller, W.H., Zander, K.M., Crosby, R.D. and Tagatz, G.E. (1997) Luteinizing hormone pulse characteristics in depressed women. *Am. J. Psychiatry*, **154**, 1454–1455.
- Merari, D., Feldberg, D., Elizur, A. *et al.* (1992) Psychological and hormonal changes in the course of *in vitro* fertilization. *J. Assist. Reprod. Genet.*, **9**, 161–169.
- Psech, U., Weyer, G. and Taubert, H.D. (1989) Coping mechanisms in infertile women with luteal phase deficiency. *J. Psychosom. Obstet. Gynaecol.*, **10**, 15–19.
- Reading, A.E., Chang, L.C. and Kerin, J.F. (1989) Attitudes and anxiety levels in women conceiving through *in vitro* fertilization and gamete intrafallopian transfer. *Fertil. Steril.*, **52**, 95–99.
- Sarrel, P.M. and DeCherney, A.H. (1985) Psychotherapeutic interventions for treatment of couples with secondary infertility. *Fertil. Steril.*, **43**, 897–900.
- Slade, P., Emery, J. and Lieberman, B.A. (1997) A prospective, longitudinal study of emotions and relationship in in-vitro fertilization treatment. *Hum. Reprod.*, **12**, 183–190.
- Smeenk, J.M.J., Stolwijk, A.M., Kremer, J.A.M. and Braat, D.D.M. (2000) External validation of the Templeton model for predicting success after IVF. *Hum. Reprod.*, **15**, 1065–1068.
- Spielberger, C.D., Gorsuch, R.L. and Lushene, R.E. (1970) *Test Manual for the State-Trait Anxiety Inventory*. Consulting Psychologists Press, Palo Alto.
- Stolwijk, A.M., Zielhuis, G.A., Hamilton, C.J.C.M. *et al.* (1996) Prognostic models for the probability of achieving an ongoing pregnancy after *in vitro* fertilization and the importance of testing their predictive value. *Hum. Reprod.*, **11**, 2298–2303.
- Tabachnick, B.G. and Fidell, L.S. (1996) *Using Multivariate Statistics*. Harper Collins, New York.
- Templeton, A., Morris, J.K. and Parslow, W. (1996) Factors that affect outcome of in-vitro fertilisation treatment. *Lancet*, **348**, 1402–1406.
- Thiering, P., Beaurepaire, J., Jones, M. *et al.* (1993) Mood state as a predictor of treatment outcome after *in vitro* fertilization/embryo transfer technology (IVF/ET). *J. Psychosom. Res.*, **37**, 481–491.
- Vanderploeg, H.M., Defares, P.B. and Spielberger, C.D. (1980) *Handleiding bij de Zelfbeoordelingsvragenlijst: een Nederlandse bewerking van de Spielberger State Trait Anxiety Inventory*. Swets & Zeitlinger, Lisse.
- Wright, J., Allard, M., Lecours, A. and Sabourin, S. (1989) Psychosocial distress and infertility: a review of controlled research. *Int. J. Fertil.*, **34**, 126–142.

Received on December 29, 2000; accepted on April 4, 2001