Women's adjustment trajectories during IVF and impact on mental health 11 to 17 years later

Sofia Gameiro PhD

Cardiff Fertility Studies Research Group, School of Psychology, Cardiff University, Cardiff,

United Kingdom

Alexandra W. van den Belt-Dusebout PhD

Department of Epidemiology, Netherlands Cancer Institute, Amsterdam, Netherlands

Jesper M. J. Smeenk MD PhD

Obstetrics and gynaecology, Elizabeth Hospital Tilburg, Tilburg, Netherlands

Didi D. M. Braat MD PhD

Obstetrics and Gynecology, Radboud University Nijmegen Medical Centre, Nijmegen,

Netherlands

Flora E. van Leeuwen MD PhD

Department of Epidemiology, Netherlands Cancer Institute, Amsterdam, Netherlands

Christianne M. Verhaak PhD

Department of Medical Psychology, Radboud University Nijmegen Medical Centre,

Nijmegen, Netherlands

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Address for correspondence:

Sofia Gameiro, Cardiff Fertility Studies Research Group, School of Psychology, Cardiff

University, Tower Building, Park Place, Cardiff, Wales CF10 3AT, UK. Email:

GameiroS@cardiff.ac.uk

Abstract

Study question: Do patients present different adjustment trajectories during and after IVF treatment?

Summary answer: Most women show resilience during and after IVF treatment but 37% show temporary or chronic maladjustment and 10% are maladjusted 11 to 17 years after treatment.

What is known already: Research on patient psychosocial adjustment during treatment has contributed to identifying the most distressful stages of IVF treatment and profiling the 20% of patients at risk for emotional maladjustment at these specific stages. This knowledge is currently driving the deliverance of psychosocial care at fertility clinics by tailoring it to patients' risk profiles and specific treatment stages. However, current care does not take into consideration how individuals adjust to the entire treatment pathway. This can be **known** by profiling individual adjustment trajectories.

Study design, size, duration: A longitudinal cohort study with five assessment moments that combines data from two different studies, the STRESSIVF and OMEGA projects. Participants enrolled in the STRESSIVF study (IVF in 1998–2000) were assessed before and after the first IVF treatment cycle and 6 months and **2.5 years** after the last IVF cycle. A subset participated in the OMEGA project (IVF in 1995–2000) and reported on their mental health 11 to 17 years after treatment.

Participants/materials, setting, methods: 348 women participated in the STRESSIVF project and 108 of these in the OMEGA. Anxiety was measured with the State and Trait Anxiety Inventory, depression with the Beck Depression Inventory and mental health with the Mental Health Inventory. Latent class growth mixed modelling was carried out to identify distinct anxiety and depression trajectories over the four STRESSIVF study assessment moments. Multinominal logistic regressions were conducted to investigate predictors of trajectory membership, and stepwise linear regressions were performed to investigate if adjustment trajectories predicted mental health 11 to 17 years after IVF treatment.

Main results and the role of chance: A total of 67% and 86% of women showed normal levels of anxiety and depression, respectively, throughout treatment (resilient trajectories), 24% and 33% experienced anxiety and depression only during treatment (recovery trajectories), 4.6% and 4.9% experienced anxiety and depression only after treatment, and 4.3% showed chronic anxiety (chronic trajectory, not identified for depression). Non-resilient trajectories were associated with unsuccessful treatment, marital dissatisfaction, lack of social support and negative infertility cognitions. One in 10 women had a delayed or chronic trajectory and these trajectories predicted serious mental health impairment 11 to 17 years after treatment.

Limitations, reasons for caution: The study only focuses on women. In the OMEGA project adjustment was assessed using a mental health measure. Although we could investigate how trajectories predicted mental health, it would have been preferable to map anxiety and depression trajectories up to 11 to 17 years after treatment. Missing analysis showed selective dropout from the study but this was accounted for by using mixed models and imputation procedures. Finally, data on other life stressors were not collected therefore any contribution from these events cannot be assessed.

Wider implications of the findings: Fertility healthcare providers have been called upon **considering their responsibility in supporting patients** in the aftermath of treatment. Results show it is possible to profile different groups of at-risk women at the start of the treatment and tailor psychosocial support to risk profile to promote health adjustment during treatment and thereafter.

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Keywords: anxiety, depression, trajectories, infertility, IVF treatment

Introduction

Undergoing IVF poses many challenges for patients and these will vary as patients progress through the treatment pathway. Only about one in four patients get pregnant per attempted cycle, therefore in a typical IVF programme patients can do up to three cycles to achieve pregnancy. After each unsuccessful cycle patients receive advice from their physicians about continuing or stopping (e.g. poor prognosis) and have to decide if they want to comply with it. Twenty-two per cent of patients discontinue treatment despite recommendations to continue (Gameiro et al. 2013). During the treatment process patients experience increased anxiety and depressive symptoms (Verhaak et al. 2007) and 15% and 11% of women meet criteria for any anxiety disorder and major depression, respectively (Volgsten et al. 2008). At the end of treatment around two thirds of patients achieve parenthood (Pinborg et al. 2009). Despite being a desired outcome, the transition to parenthood can challenge individuals' coping abilities (Don and Mickelson 2014). Around one third of patients do not achieve pregnancy and some of these persist with treatment at different clinics or choose to pursue other parenthood alternatives such as adoption. Overall, patients take around 2 years to adjust to their biological childlessness (Daniluk 2001). The present study breaks with the field tradition of investigating how patients adjust at specific treatment stages to identify different patient adjustment trajectories across the entire treatment pathway and up to 17 years after.

By taking snapshots of how on average patients adjust at different treatment moments, researchers have been effective in identifying the most distressful stages of IVF treatment (Boivin and Takefman 1996) and profiling the 20% of patients at risk for emotional maladjustment at these specific stages (Rockliff et al. 2014, Verhaak et al. 2010). This knowledge is currently driving the deliverance of psychosocial care at fertility clinics by tailoring it to patients' risk profiles and specific treatment stages, as recommended in the European Society of Human Reproduction and Embryology (ESHRE) guidelines (Gameiro et al. 2015). However, current care does not take into consideration how individuals adjust to the

entire treatment pathway. This can be known by profiling individual adjustment trajectories. This person-based approach to longitudinal data is consistent with the conceptualization of resilience as the continuous ability to maintain a stable equilibrium in the face of adversity or challenging transitions (Rutter 2006). This approach is highly relevant when applied to IVF patients due to the protracted nature of medical procedures (i.e. repeated cycles) and the long-term implications for parenthood goals and subsequent transitions. Therefore, it can be useful to better differentiate between normal short-term reactions to loss (e.g., after a failed cycle) and more prolonged maladjustment reactions that may reflect individual vulnerability to infertility and IVF. Indeed, by focusing on continuous adjustment (instead of single snapshots in time) it is possible to capture short-term maladjustment responses from which there is a gradual recovery, as well as delayed or chronic maladjustment (Bonanno and Diminich 2013). In addition, patients' experience of treatment changes with the number of cycles they undergo (e.g., stress increases and ability to comply decreases, Gameiro et al. 2013, Slade et al. 1997). The nature of the stressor also changes across time, from the medical procedures to adjustment to failed cycles, to decision-making regarding consecutive treatment, and to parenthood or biological childlessness. Mapping individual anxiety and depression trajectories can inform on resilience to different stressors. Anxiety trajectories capture reactions to the burden of medical procedures and stress appraisals during subsequent transitions. Depression trajectories capture reactions to unsuccessful treatment and adjustment to the longing for a biological child (e.g., Knoll et al. 2009). Finally, from a methodological perspective, it avoids potential biases inherent to the use of measures of central tendency. These may appear, for instance, when using measures of psychopathology, because data are usually skewed towards the low symptom end of the scale.

Bonanno (2005) described four adjustment trajectories to stressful life events that have been strongly supported by empirical research across multiple events and outcomes (e.g., Burton et al. advanced online, Galatzer-Levy and Bonanno 2012, Henselmans et al. 2010).

Most people (35-55%) show a resilient trajectory characterised by the absence of psychopathology and overall positive wellbeing. In recovery (15-35%) trajectories normal functioning temporarily gives way to psychopathology and then gradually returns to pre-event levels. Delayed (5-10%) trajectories are characterised by a late pathological response and chronic (10-30%) trajectories by consistent low levels of psychological functioning. Once the typical adjustment trajectories are mapped, investigating its predictors can inform about the factors that underlie temporary adjustment difficulties to IVF as opposed to an inability to adjust to the outcome of treatment. Research suggests that demographic factors, diagnostic factors (duration and cause of infertility) and type and number of cycles are only weakly associated with short- and long-term adjustment, while failed treatment is a strong predictor of intense negative emotional reactions (e.g., Kraaij et al. 2008, van Balen and Trimbos-Kemper 1994). Rockliff et al. (2014) reviewed 23 papers studying psychosocial predictors of adjustment to IVF. They consistently found that personality factors (neuroticism), poor marital relationships and insecure attachment styles, low social support, helplessness appraisals regarding infertility, and avoidant coping were risk factors for maladjustment. However, the influence of these factors varied according to the stage of the infertility process, supporting the idea that the nature of the stressor and required coping skills also vary. Finally, investigating how adjustment trajectories are associated with long-term mental health can help to distinguish women who recover after IVF treatment from women for whom undergoing IVF has a life-long impact. Studies on the long-term ($\geq$10 years) emotional adjustment to IVF are rare and tend to be cross-sectional. They showed that, when treatment fails, lower acceptance of biological childlessness is associated with presenting clinically significant maladjustment (e.g.; Gameiro et al. 2014, Kraaij et al. 2008).

The first goal of the present study was to investigate women's anxiety and depression trajectories across the treatment period (before start to 2.5 years after IVF). We expected to find the four adjustment trajectories described by Bonanno (2005). The second goal was to

explore demographic, diagnostic, treatment and psychosocial predictors of these trajectories. In line with the field literature, we hypothesized that unsuccessful IVF, higher marital dissatisfaction, lower social support, less favourable appraisals regarding infertility and more avoidant and less problem-solving coping would be associated with maladjustment trajectories (characterized by higher levels of anxiety and depression over time). The final goal was to investigate how anxiety and depression trajectories of adjustment to treatment predict mental health 11 to 17 years after treatment, controlling for socio-demographic, diagnostic, treatment and psychosocial predictors. We hypothesized that women with delayed and chronic trajectories would present less favourable mental health than women with recovery and resilient trajectories.

Methods

Patients and Settings

This study combines data from two different studies, the STRESSIVF and OMEGA projects. Participants for the STRESSIVF study were consecutively recruited from Dutch-speaking women attending the Radboud University Medical Centre in Nijmegen, the Netherlands, between 1998 and 2000 to start IVF treatment. A total of 380 women (84% response rate) participated. They were assessed before their first fresh IVF cycle and followed until 2.5 years after the end of their last cycle at the hospital (from a maximum of three state-funded cycles). To be included in the present study women had to complete at least two of the four assessment moments of the STRESSIVF. Therefore, 36 women (9.4%) were excluded and 348 retained. The OMEGA project is a nationwide cohort study of women who started fertility treatment between 1995 and 2000 at all IVF clinics in the Netherlands. Of 16,482 eligible women, 9,958 participated (60.4% response rate). Of 348 women retained for the STRESSIVF study, 180 (52%) also participated in the OMEGA follow-up, 11 to 17 years after finishing treatment.

Study Procedures

Participants in the STRESSIVF study were asked to fill in self-reported questionnaires before the start (T1) and 1 month after their first IVF cycle (T2) and 6 months (T3) and 2.5 years after their last cycle (T4). The last treatment cycle was defined as the cycle resulting in live-birth or not followed by another cycle at the hospital for at least 1 year (in case of non-compliance with treatment), up to the maximum of three cycles (number of cycles that optimizes treatment success rates and therefore typically number of state-funded cycles; Gameiro et al. 2013) . All participants provided written informed consent and were guaranteed that the questionnaire data would be held confidential and separate from their clinical management.

For the OMEGA follow-up eligible women were invited to complete an extensive health questionnaire from January 2011 to June 2012, 11 to 17 years after their first treatment. Non-responders were sent a reminder 4–6 weeks after and, if non-responding again, by a second reminder with a shorter questionnaire not including the psychological data used in this study. The institutional ethics committees of all IVF clinics approved the study procedures.

Instruments

At the STRESSIVF enrolment, data were collected on socio-demographic (age [years], education [1=primary, 2=secondary, 3=high, 4=university], children before treatment [0=no, 1=yes]), infertility diagnosis (duration [years] and cause [female, male, mixed or idiopathic] of), treatment and psychosocial (anxiety and depression, marital dissatisfaction, social support, infertility related cognitions, and coping styles) data. Anxiety and depression were re-assessed at the following assessments. Treatment variables, more specifically live-birth after the first and last treatment cycles and compliance behaviour were assessed at T3. Mental health data were collected at the OMEGA follow-up.

Live-birth after the first and last cycle was coded as 0 (no live-birth) or 1 (live-birth). *Compliance behaviour* was coded as recommended by Gameiro et al. (2013), that is,

considering three consecutive cycles, which is the number of state-funded cycles in the Netherlands. Women were coded as compliers if they did three cycles or stopped because they achieved a live-birth or followed advice to stop due to poor prognosis, discontinuers if they did less than three cycles (despite advice to continue) or persisters if they did more than three cycles (i.e., did other IVF cycles at other hospitals).

Depression was measured with the short Dutch version of the Beck Depression Inventory (BDI) (Beck et al. 1997). This scale is one of the most widely used, reliable and valid instruments for assessing intensity of depression and for detecting depression in the general population. The scores for each item range from zero (low) to three (high). The threshold for clinical depression was a total score of four. Cronbach's alphas for all assessment moments were equal to or higher than 0.77.

Anxiety was measured with the state anxiety subscale of the Dutch version of the State and Trait Anxiety Inventory (STAI) (Spielberger et al. 1970), a scale that shows satisfactory reliability and validity. Total scores range from 20 to 80 with higher scores indicating greater state anxiety. The threshold for clinical state anxiety was 48, which is one SD above the mean for the age-matched norm group of Dutch women (Vanderploeg et al. 2000). Cronbach's alphas for all assessment moments were equal to or higher than 0.94.

Marital dissatisfaction was measured with the general marital satisfaction scale (10 items: possible range 0–80) of the Maudsley Marital Questionnaire (Arrindell et al. 1983). Higher scores indicate more marital dissatisfaction. Cronbach's alpha in the present study was 0.84.

Social support was measured with a Dutch self-report questionnaire Inventory for Social Support (Van Dam-Baggen and Kraaimaat 1992), which measures the size of the social network (by asking for the number of friends and acquaintances) and perceived social support (possible range 5–20). In the present study, Cronbach's alpha was 0.82.

Infertility related cognitions of helplessness acceptance and benefits were measured with the Illness Cognitions Questionnaire (Evers et al. 2001) that was adjusted to the situation of

women facing fertility problems. Each subscale was composed of six items and total scores ranged between six and 24. An example of a helplessness item is: 'I feel overwhelmed by my fertility problems'. An example of the acceptance and benefits scales are: 'I think I can handle the problems related to my infertility even if they will not be solved' and ''I have learned a great deal from my infertility', respectively. In the present study, Cronbach's alphas were 0.87 for helplessness, 0.80 for the acceptance, and 0.86 for benefits.

Coping was assessed with the Utrecht Coping List (Schreurs et al. 1993), which measures coping strategies when dealing with everyday problems on a 4-point Likert scale. Two scales were used: active problem focusing (seven items, range 7–28, Cronbach's alpha = 0.77) and avoidance (nine items, range 9–36, Cronbach's alpha = 0.57).

Mental health was assessed with the Mental Health Inventory (MHI-5), which measures general mental health by asking individuals how they felt during the last 4 weeks (e.g. 'Have you felt calm and peaceful?'). The MHI-5 has been shown to predict mental health problems in a Dutch population-based study (Hoeymans et al. 2004). The total score is the sum of its five items and ranges from one to 100, with higher scores indicating better mental health. Cronbach's alpha in the study sample was 0.83. The average score for women from the general population (aged 18 years or more) is 78 (SD = 17). Scores equal or below the cut-off score of 72 suggest the presence of a mental health disorder. In the Dutch general population 25.5% of women score below this threshold (Hoeymans et al. 2004).

Statistical Analyses

The total percentage of missing data, percentage of missing data for anxiety and depression across all assessment moments, and demographic, diagnostic, treatment and psychological predictors (p < .05) of these missing data were investigated. Descriptive statistics and frequency distributions were calculated for the sample socio-demographic, diagnostic and treatment characteristics.

Latent class growth mixed modelling with maximum likelihood estimation was carried out

using the R package LCMM (Proust-Lima and Liquet 2009) to identify latent classes (i.e.,

subgroup of patients) with distinct anxiety and depression trajectories over the four

STRESSIVF study assessment moments (T1 to T4). Mixed modelling is routinely used in

longitudinal research to describe linear or non-linear change over time in longitudinal

outcomes. The latent class analysis extends the estimation of a single growth curve (for the

entire study population), to identify two or more curves (classes) that define change for

subgroups of patients. Individuals classified within a class have homogeneous longitudinal

trajectories on the outcomes of interest, in this case anxiety and depression. Models with one

to five latent classes were tested. Because there were four assessment moments it was

possible to test linear, quadratic and cubic models of change for each number of latent classes

(Andruff et al. 2009). Both the intercept and slope parameters (linear, quadratic and cubic)

were defined as random (to allow for individuals to differ in their means and/or response

patterns over time) and allowed to differ across latent classes. A total of 15 models were

considered for anxiety and depression. The latent class model that suited the data best was

determined using statistical and theoretical criteria. Statistical criteria were, in order of

importance, the Bayesian information criterion (BIC, because it allows for direct comparison

of competing models with different number of classes and change trajectories, Andruff et al.

2009), the estimated posterior classification probabilities of class membership (range 0-1,

values close to 1 indicate good classification and should always be higher than 0.70, Nagin

2005) and the Akaike information criterion (AIC, Akaike 1974). Theory-led criteria were a

priori expectations regarding the number, shape, and size of trajectory classes (Bauer 2007).

Classes were also checked via visual inspection of the observed and model-predicted class

trajectories. No imputation of missing values was done because the mixed modelling

estimation algorithm successfully accounts for these by attributing more weight to individuals

with less missing data (Hox 2002).

Subsequently, multinominal logistic regressions were conducted to investigate predictors

of class membership for anxiety and depression, with resilient trajectory as the reference category. This analysis provides a statistical snapshot of the key characteristics (i.e., predictors) of individuals following distinctive longitudinal trajectories. To take into account the uncertainty of class trajectory assignment, the posterior classification probabilities of class membership were used as weights. This means that the data of women who were assigned to a class trajectory with high certainty were given more weight than the data of women who were assigned with less certainty (same procedure as in Henselmans et al. 2010, Stiffman et al. 2007). First, univariate multinominal logistic regressions were used to investigate associations between demographic (age, education, children before treatment), diagnostic (duration and cause of infertility) and treatment variables (live-birth after 1st and last cycle and compliance behaviour) and class trajectory membership. Those variables for which significant associations ($p < .06$) were observed were included in one single final logistic regression that also included all psychosocial variables (marital dissatisfaction, social support, helplessness, acceptance and benefits cognitions, and avoidance and problem-solving coping). Odds ratios (OR) of 1.50, 2.50 and 4.30 (and .70, .40 and .24, for OR below unit) indicate small, medium and large effect sizes, respectively (Cohen 1988).

Finally, two stepwise linear regressions were performed to investigate the predictive power of longitudinal trajectories on mental health 11 to 17 years after treatment, controlling for demographic (age, education, children before treatment), diagnostic (duration and cause of infertility), treatment (live-birth after 1st and last cycle and compliance behaviour) and psychosocial (marital dissatisfaction, social support, helplessness, acceptance and benefits cognitions, and avoidance and problem-solving coping) predictors. Demographic, diagnostic and treatment factors that were significantly associated with mental health in preliminary univariate analysis ($p < .06$) were included in the first step of the models. All psychosocial predictors were included in the second step and the anxiety or the depression trajectories were included as dummies (with resilient trajectory as the reference category) in the third and last

step. Subjects were weighted according to their posterior classification probabilities for the anxiety or depression trajectories.

Power analyses ($\alpha < .05$, power $= .80$) showed that our sample size allows for the detection of medium effect sizes in the multinominal and linear regression analyses. These regression analyses were performed on the original dataset and re-run after performing missing imputation for the psychological predictors data ($<=4\%$ missing) with the use of the Expectation-Maximization algorithm, which assumes that data are missing at random (i.e., missings are associated with measured data but not with unmeasured data, Graham 2009). All analyses were performed with the Statistical Package for the Social Sciences (SPSS) version 20 (IBM, Chicago, IL, USA), except for the latent class growth analysis, performed with R Studio, version 0.98.1091 (RStudio, MA, USA).

Results

Missing Analyses

There were 11.3% of incomplete data. Percentages of missing data for anxiety and depression, respectively, were 0 and 0.6% at T1, 27.6 and 27.6% at T2, 58.9 and 58.3% at T3 and 14.1 and 12.9% at T4. Women diagnosed with mixed factor infertility were less likely to complete the BDI and STAI at T2. Women without a live-birth after the first cycle and with lower acceptance cognitions were less likely to complete the BDI and STAI at T3. Persisters were more likely than compliers and discontinuers to complete them. Women who were more depressed at pre-treatment were less likely to complete the BDI at T4. More depressed women with lower education and acceptance cognitions were less likely to complete the STAI at T4. Finally, compliers were less likely to complete the STAI at T4 than persisters and discontinuers. These results are consistent with the missing at random assumption.

Patient Characteristics

Mean age was 32.2 years (SD = 3.89, range 19-41). Most women (52.6%) had secondary or high (24.3%) education. Only 7% had university education. Twenty-three per cent had children before treatment. The most common infertility cause was male factor (39.9%), followed by idiopathic (28.7%), female (23.6%) and mixed (7.8%). Twenty-six per cent of women achieved a live-birth after the 1st cycle and 51% after the last. Most women (66.4%) complied with treatment, 23.3% discontinued and 10.3% persisted.

Latent Class Growth Analysis

The latent classes (i.e., trajectories) for anxiety and depression are depicted in Figure 1

Anxiety. Results from the latent class models tested for anxiety are presented in Supplementary Table SI. Analysis of the BIC fit index revealed that a 4-class model with quadratic change represents the best fit to the data. Indeed, this model had the smallest BIC (7579.71) and AIC (7506.51) of all. The other models had BICs and AICs equal to or higher than 7587.02 and 7528.03, respectively (except for the 4-class model with cubic change trajectories, which had an AIC of 7499.02). All posterior classification probabilities for the 4-class model with quadratic change were equal to or higher than 0.79. Observed versus predicted values for this model are presented in Figure 1a and suggest a good approximation of the data. The classes were named according to the overall shape of the trajectory (Bonanno 2005), with resilient being the most frequent (n = 232, 66.7%) followed by recovery (n = 85, 24.4%), delayed (n = 16, 4.6%) and chronic (n=15, 4.3%).

Depression. Results from the latent class models tested for depression are presented in Supplementary Table SII. Analysis of the BIC fit index revealed that the 3-class models (linear, quadratic and cubic) represent the best fits to the data, with differences in BIC comparing with all other 2 and 4-class models, being equal to or higher than 17.56. Four and 5-class models were inappropriate as they always had at least one class with an empty cell. The BIC fit indexes for the linear, quadratic and cubic models were similar (4119.60, 4116.59

and 4114.32, respectively), but suggested that the cubic model represents the best

approximation of the data. Values for the AIC fit index supported this interpretation (4077.23,

4058.81 and 4041.13 respectively), as did the analysis of the posterior classification

probabilities (all equal or superior to 0.90) and inspection of the plotted observed versus

predicted values. The three observed and predicted trajectories for this 3-class model are

depicted in Figure 1b. The classes were named according to the overall shape of the trajectory

(resilient n = 299, 85.9%; recovery n = 32, 9.2%; delayed n = 17, 4.9%).

Predictors of Trajectory Membership

Anxiety. Preliminary univariate analysis revealed that having children before treatment,

duration of infertility, achieving a live-birth after the first cycle of treatment and compliance

with treatment were associated (p < .06) with anxiety trajectories. These variables were

included in the final model tested, together with all psychological variables The final model is

presented in Table I and was statistically significant, X^2 = 135.385, df = 36, p < .001, Cox &

Snell R^2 = 0.39, Nagalkerke = 0.47, McFadden = 0.28. The model indicates that, compared

with resilient women, women with chronic trajectories reported a longer infertility duration,

OR = 2.37, 95% confidence interval (CI) [2.00, 5.58], higher pre-treatment marital

dissatisfaction, OR = 1.18, 95% CIs [1.05, 1.32] and were more likely to discontinue

treatment prematurely, OR = 7.90, 95% CIs [1.08, 57.61]. Compared with resilient women,

women with a delayed trajectory were less likely to have children before treatment, OR =

0.55, 95% CIs [.005, .613], and reported higher marital dissatisfaction, OR = 1.17, 95% CIs

[1.07, 1.28], and lower social support pre-treatment, OR = .72, 95% CIs [.56, .94]. Finally,

compared with resilient women, women with a recovery trajectory reported higher pre-

treatment helplessness cognitions about infertility and its treatment, OR = 1.15, 95% CIs

[1.03, 1.29]. Results for imputed data were similar. The only difference for imputed data was

that women with a recovery trajectory were also significantly less likely to have children before treatment than women with a resilient trajectory, OR = .39, 95% CIs [.16, .95].

Depression. Univariate analysis revealed that age, and achieving a live-birth after the first and the last cycles of treatment were associated with depression trajectories (p < .06). These variables were included in the final model tested, together with all psychological variables. The final model is presented in Table II and was statistically significant, $X^2 = 107.099$, df = 20, p < .001, Cox & Snell $R^2 = 0.39$, Nagalkerke = 0.47, McFadden = 0.36. Compared with resilient women, women with a delayed trajectory were less likely to achieve a live-birth after the last cycle of treatment, OR = 1.15, 95% CIs [1.03, 1.29], and reported higher marital dissatisfaction, OR = 1.10, 95% CIs [1.01, 1.20], lower social support, OR = .67, 95% CIs [.52, .87], and lower infertility and childlessness acceptance cognitions pre-treatment, OR = .67, 95% CIs [.49, .92]. Compared with resilient women, women with a recovery trajectory were less likely to achieve a live-birth in their 1st cycle of treatment, OR = .16, 95% CIs [.03, .89], and reported higher marital dissatisfaction, OR = 1.07, 95% CIs [1.00, 1.14], and higher helplessness cognitions about infertility and its treatment before starting treatment, OR = 1.27, 95% CIs [1.09, 1.49]. The only difference in the imputed data compared with the non-imputed data was that women with a recovery trajectory reported significantly lower social support than women with a resilient trajectory, OR = .84, 95% CIs [.73, .97]. This association was marginally significant in the non-imputed data (p < .06).

Predictors of Mental Health 11 to 17 Years After Treatment

Figure 2 presents means and SDs for mental health 11 to 17 years after treatment according to anxiety and depression trajectories membership. A total of 54 (30%) women had mental health scores below the threshold of 72 that indicates the presence of a mental health disorder.

Anxiety. The percentage of women with mental health scores below the threshold of 72 that indicates the presence of a mental health disorder was 67% for women in the chronic trajectory, 88% in the delayed trajectory, 37% in the recovery trajectory and 22% in the resilience trajectory.

The cause of infertility and live-birth after the 1st cycle were significantly associated with mental health and were inserted in the first step of the regression model. This and the subsequent steps of the model significantly increased the total explained variance in mental health (full model F(148, 14) = 3.052, p < .001, R^2 = .241, adjusted R^2 = .162). The results of the full model showed that marital dissatisfaction (β = -.170, p = .036) and a delayed trajectory (β = -.216, p = .008) were negatively associated with mental health. No other significant associations were found. Results using the imputed data were similar.

Depression. The percentage of women with mental health scores below the threshold of 72 that indicates the presence of a mental health disorder was 100% in the delayed trajectory, 20% in the recovery and 27% in the resilience.

None of the demographic and diagnostic and treatment predictors were associated with mental health. All subsequent steps of the linear regression model significantly increased the total explained variance in mental health (full model: F (155, 13) = 4.018, p < .001, R^2 = .253, adjusted R^2 = .190). The results of the full model showed that marital dissatisfaction (β = -.206, p = .006), and a delayed trajectory (β = -.271, p < .001) were negatively associated with mental health and that problem-solving coping (β =.164, p = .026) was positively associated. Again, results using the imputed data were similar.

Discussion

Results from this study show that 63% of women adjust well to their infertility and treatment experience, as indicated by their resilient trajectories from pre treatment to 2.5 years

after end of treatment. However, 37% of women showed transient or chronic maladjustment trajectories, a higher incidence of maladjustment than the one documented when assessing adjustment only in terms of emotional reactions after a failed IVF cycle (i.e., ~20%; Verhaak et al. 2007, Volgsten et al. 2008). Elevn to 17 years after treatment, one in 10 women show major mental health impairments. Findings from this study show that these women can be identified at the start of treatment, enabling the deliverance of psychosocial care during treatment to stimulate positive adjustment during and after treatment.

Four different adjustment trajectories that closely resemble the four trajectories described by Bonanno (2005) were identified. The most common emotional response represented a resilience trajectory, with 63% of women showing none or very few anxiety and depression symptoms during and after treatment. This percentage is higher than those reported in other studies focusing on other stressful life events such as receiving a cancer diagnosis (36%; Henselmans et al. 2010) or bereavement (52%; Bonanno et al. 2005). This suggests that most women adjust well to their infertility and treatment experience and also characterises the infertility experience as less disturbing than bereavement and life-threatening diseases. The factors associated with positive adjustment are undergoing a successful treatment, being satisfied with the marital relationship, perceiving adequate support from the social network and having positive infertility related cognitions.

Thirty-seven per cent of women showed a recovery, delayed or chronic trajectory for either anxiety or depression. These three maladjustment trajectories were also described by Bonanno and reflect the experience of transient or chronic maladjustment. The absence of a chronic depression trajectory can be explained by the fact that severely depressed women are less likely to follow recommendations to do treatment (Gameiro et al. 2012). The higher incidence of maladjustment found when considering individual trajectories (37%) instead of emotional reactions after a failed IVF cycle (20%) can be partially explained by the inclusion of the 2.5-years post-treatment period. However, the percentage of women who experience

maladjustment only during treatment is still higher (27%). Overall these findings suggest that not all at-risk patients are being identified. Indeed, currently women with a chronic or recovery trajectory can be identified, for instance with screening procedures, and are therefore likely to receive the psychosocial care they need during treatment. However, it is questionable if patients with a delayed trajectory (total of 7% for anxiety or depression) are receiving adequate support, as they are already outside the health-care system when they experience clinically significant problems. A preventive approach to these patients' wellbeing seems to be advisable. This implies discussing the possibility of treatment failure during treatment and addressing dysfunctional cognitions about childlessness, as well as working during treatment to support women in accessing or building networks that will be available and supportive regardless of the treatment outcome.

Demographic and diagnostic factors do not seem to predict maladjustment. Indeed, transient or chronic maladjustment is mostly associated with undergoing a failed treatment and with a set of psychosocial factors, more specifically, with marital dissatisfaction, lack of social support, perceptions of helplessness during treatment and with lack of infertility and childlessness acceptance after a failed treatment. These findings are reassuring because psychosocial factors tend to be more amenable to change than demographic and diagnostic factors (Rockliff et al. 2014). These results also highlight how different factors may affect adjustment at different stages of the treatment pathway. Consistent with literature on the protective value of supportive close relationships (Gottman and Notarius 2000, Uchino et al. 1996), marital relationship and social support seem to be important, independent of the type of stressor experienced. Other factors seem to only be relevant only in face of specific stressors. Helplessness perceptions hinder patients' adjustment only while they are undergoing medical procedures, possibly because they reflect global and stable inferences about the uncontrollability of these procedures and their outcome (helplessness-hopelessness

theory, Abramson et al. 1989). Once treatment failure is definitive our results confirm the value of accepting childlessness but provide no support for the benefit of engaging in positive reappraisal exercises (i.e., finding benefits in the experience, Evers et al. 2001). Indeed, results suggest that coping strategies do not influence adjustment trajectories. However, it should be noted that coping was not assessed in relation to the infertility stressor but regarding everyday problems.

Another important finding was that one in 10 women showed no apparent recovery in as long as 17 years after treatment. Indeed, 11 to 17 years after treatment, the mean mental health scores of women with delayed or chronic trajectories were below the cut-off score that indicates the presence of a mental health disorder. It is hard to assess the severity of mental impairment in these groups. Simple prevalence comparisons with anxiety or mood disorders are not clarifying because they do not capture the chronic nature of the maladjustment observed. Nonetheless, let us consider the case of dysthymia, which implies a minimum of 2 years of chronic mild depressive symptoms. Its 12 month and lifetime prevalence in Dutch women are 3.2% and 8.9%, respectively (Bijl et al. 1998), while in Europe as a whole, also for women, these are 1.5% and 5.6%, respectively (Alonso et al. 2004). Overall these data suggest that maladjustment difficulties in women with delayed and chronic trajectories are indeed quite impairing, both in terms of severity and chronicity. These women showed a lack of structural support from both their partner and their social network or a persistent and unresolved desire for children and these risk factors should be addressed from the start of treatment.

The present study adds to current knowledge about adjustment to stressful life events by showing that different trajectories may reflect individual vulnerability to the multiple stressors that one single life event can elicit over time. In our case, recovery trajectories seem to reflect vulnerability to the treatment process while delayed trajectories reflect vulnerability to the implications of its outcome. To better capture the dynamic interplay between risk factors and

trajectories, risk factors should also be measured longitudinally at key points in time when the nature of the stressors involved is thought to change. Although some studies have already reported on associations between changes in risk-factors and adjustment trajectories (e.g., Hou et al. 2010), these were analysed independently of the nature of the stress involved. Another contribution of the present study is showing that delayed and chronic maladjustment trajectories can remain stable across time, even for periods as long as 17 years.

This longitudinal cohort study presents a 17-year follow-up of women who had IVF treatment, with a focus on individual heterogeneity in adjustment. Assessments coincide with important treatment-related moments and a 2.5-year post-treatment period is considered to allow the necessary time for recovery (Bonanno 2005). The study is theory driven and includes a broad range of predictors proven to influence adjustment to IVF (Rockliff et al. 2014). However, a few limitations need to be noted. First, the OMEGA study adjustment was assessed using a mental health measure. Although we could investigate how trajectories predicted mental health, it would have been preferable to map anxiety and depression trajectories up to 17 years after treatment but this was not possible due to lack of anxiety and depression data at that assessment moment. Second, data on other life stressors were not collected therefore any contribution from such events could not be assessed. Finally, missing analysis showed that there was selective dropout from the study. However, it should be noted that mixed models account for missing data in their estimation and that similar results were obtained when the predictive analyses were rerun after missing data imputation. A consequence of dropout was the small number of participants per trajectory at the OMEGA follow-up. For these reasons we recommend replications of these type of analyses within the field.

In sum, findings from this study are novel in that they show that it is possible to profile different groups of at-risk women at the start of IVF treatment and tailor psychosocial support to risk profile to promote health adjustment, not only during treatment but also thereafter. We

now discuss the different types of psychosocial support that are advised for the at-risk groups identified. Women with recovery trajectories seem to experience loss of control only during the treatment period, and to naturally return to normal functioning once treatment is over, especially if it is successful (e.g.; Knoll et al. 2009). They can be identified by evaluating helplessness towards treatment and will benefit from routine psychosocial care that promotes self-efficacy and the use of adaptive coping strategies during treatment. Women with delayed trajectories start treatment well adjusted. However, the lack of marital and social support seems to make them vulnerable to the challenges ahead, regardless of the treatment outcome. Therefore, delayed maladjustment trajectories seem to partially reflect the negative effects of social isolation. In the context of treatment failure they also seem to reflect the development of a life-longing (Sehnsucht) around the desire for children (considered to be attempts to solve through imagination and fantasy the emptiness of unrealized life goals, in this case parenthood; Kotter-Grühn et al. 2009). These women can be identified by evaluating social support and childlessness perceptions and will benefit from routine psychosocial care focusing on the promotion of support networks and expectancies management. Finally, women with chronic trajectories are already in a more difficult situation at the start of treatment and experience serious difficulties attuning their child-wish within their relationship and treatment possibilities. It is unclear if this chronic maladjustment reflects the specific impact of infertility and IVF or a more general vulnerability that would manifest itself in face of other types of stressful life events. Overall results suggest that these women can be identified by assessing distress at the start of treatment and will benefit from more specialized psychosocial support (i.e., psychotherapy) to address their structural vulnerability. It should be noted, however, that primary care services should also play a supportive role. Awareness within this professional class about the mental health implications of undergoing IVF treatment, especially if unsuccessful, is urgently needed. The recent literature in the post treatment period has been highlighting how the intensity and nature of emotional reactions

that follow failed IVF treatment are similar to complicated grief (e.g., Gameiro et al. 2014, Volgsten et al. 2010). This loss needs to be acknowledged and addressed at the healthcare level.

To conclude, the present study shows that resilience is the most common response to undergoing IVF treatment. However, it also shows that all life transitions, even desired ones like parenthood, can trigger emotional maladjustment. ESHRE guidelines call upon the responsibility of fertility clinics to prepare their patients in advance for the different possible treatment outcomes (Gameiro et al. 2015). Findings from this timely study show that it is possible to identify at-risk women at start of treatment and offer guidance for the implementation of preventive and supportive tailored psychosocial care during the treatment that promotes positive adjustment in the moment and thereafter, irrespective of the treatment outcome.

Authors' roles

All authors contributed to the design of the study. A.W.v.d.B.-D., F.E.L., J.S. and C.M.V. were responsible for data collection. S.G., A.W.v.d.B.-D. and C.V. were responsible for data management and preparation. S.G. and C.M.V. did data analysis and interpretation. Finally, S.G. and C.M.V. and A.W.v.d.B.-D. wrote the report. All authors contributed to and approved the final version of the report for submission.

Conflict of interest

No competing interests exist.

References

Abramson, L. Y., G. I. Matalsky and L. B. Alloy. Hoplessness depression: A theory-based subtype of depression. *Psychological Review*. 1989**; 2**: 358-372.

Akaike, H. New look at statistical-model identification. *IEEE Transactions on Automatic Control*. 1974**; 6**: 716-723.

Alonso, J., M. C. Angermeyer, S. Bernert, R. Bruffaerts, T. S. Brugha, H. Bryson, G. de Girolamo, R. Graaf, K. Demyttenaere, I. Gasquet, J. M. Haro, S. J. Katz, R. C. Kessler, V. Kovess, J. P. Lépine, J. Ormel, G. Polidori, L. J. Russo, G. Vilagut, J. Almansa, S. Arbabzadeh-Bouchez, J. Autonell, M. Bernal, M. A. Buist-Bouwman, M. Codony, A. Domingo-Salvany, M. Ferrer, S. S. Joo, M. Martínez-Alonso, H. Matschinger, F. Mazzi, Z. Morgan, P. Morosini, C. Palacín, B. Romera, N. Taub, W. A. Vollebergh, ESEMeD/MHEDEA 2000 Investigators and European Study of the Epidemiology of Mental Disorders (ESEMeD) Project. Prevalence of mental disorders in Europe: results from the European Study of the Epidemiology of Mental Disorders (ESEMeD) project. *Acta Psychiatrica Scandinavica*. 2004**; Suppl. 420**: 21-27.

Andruff, H., N. Carraro, A. Thompson and P. Gaudreau. Latent class growth modelling: A tutorial. *Tutorials in Quantitative Methods for Psychology*. 2009**; 1**: 11-24.

Arrindell, W. A., W. Boelens and H. Lambert. On the psychometric properties of the Maudsley Marital Questionnaire (MMQ): evaluation of self-ratings in distressed and "normal" volunteer couples based on the dutch version. *Personal and Individual Differences*. 1983**; 3**: 293-306.

Bauer, D. J. Observations on the use of growth mixture models in psychological research. *Multivariate Behavioral Research*. 2007**; 4**: 757-786.

Beck, A. T., D. Guth, R. A. Steer and R. Ball. Screening for major depression disorders in medical inpatients with the Beck Depression Inventory for primary care. *Behaviour Research and Therapy*. 1997**; 8**: 785-791.

Bijl, R. V., A. Ravelli and G. van Zessen. Prevalence of psychiatric disorders in the general population: results of the Netherlands Mental Health Survey and Incidence Study (NEMESIS). *Social Psychiatry and Psychiatric Epidemiology*. 1998: 587-595.

Boivin, J. and J. Takefman. Impact of the in-vitro fertilization process on emotional, physical and relational variables. *Human Reproduction*. 1996**; 4**: 903-907.

Bonanno, G. A. Resilience in the face of potential trauma. *Current Directions in Psychological Science*. 2005**; 3**: 135-138.

Bonanno, G. A., J. T. Moskowitz, A. Papa and S. Folkman. Resilience to loss in bereaved spouses, bereaved parents, and bereaved gay men. *Journal of Persnality and Social Psychology*. 2005**; 5**: 827-843.

Bonanno, G. A. and E. D. Diminich. Annual research review: positive adjustment to adversity - trajectories of minimal-impact resilience and emergent resilience. *The Journal of Child Psychology and Psychiatry*. 2013**; 4**: 378-401.

Burton, C. L., I. R. Galatzer-Levy and G. A. Bonanno. Treatment type and demographic characteristics as predictors for cancer adjustment: Prospective trajectories of depressive symptoms in a population sample. *Health Psychology*. advanced online; **6**: 602-609.

Cohen, J. *Statistical power analysis for the behavioral sciences*. 2nd, 1988. Lawrence Erlbaum Associates, Publishers.

Daniluk, J. C. Reconstructing their lives: A longitudinal, qualitative analyses of the transition to biological childlessness for infertile couples. *Journal of Counselling and Development*. 2001; **4**: 439-449.

Don, B. P. and K. D. Mickelson. Relationship satisfaction trajectories across the transition to parenthood among low-risk parents. *Journal of Marriage and Family*. 2014; **3**: 677-692.

Evers, A. W. M., F. W. Kraimaat, W. van Lankveld, P. J. H. Jongen, J. W. G. Jacobs and J. W. J. Bijlsma. Beyond unfavourable thinking: The Illness Cognition Questionnaire for chronic diseases. *Journal of Counsulting and Clinical Psychologgy*. 2001; **6**: 1026-1036.

Galatzer-Levy, I. R. and G. A. Bonanno. Beyond normality in the study of bereavement: Heterogeneity in depression outcomes following loss in older adults. *Social Science & Medicine*. 2012; **12**: 1987-1994.

Gameiro, S., J. Boivin, L. A. Peronace and C. M. Verhaak. Why do patients discontinue fertility treatment? A systematic review of reasons and predictors of discontinuation in fertility treatment. *Human Reproduction Update*. 2012; **6**: 652-669.

Gameiro, S., C. M. Verhaak, J. A. M. Kremer and J. Boivin. Why we should talk about compliance with Assisted Reproductive Technologies (ART): a Systematic Review and Meta-Analysis of ART compliance rates. *Human Reproduction Update*. 2013; **2**: 124-135.

Gameiro, S., A. W. van den Belt-Dusebout, E. Bleiker, D. Braat, F. E. van Leeuwen and C. M. Verhaak. Do children make you happier? Sustained child-wish and mental health in women 11-17 years after fertility treatment. *Human Reproduction*. 2014; **10**: 2238-2246.

Gameiro, S., J. Boivin, E. A. F. Dancet, C. de Klerk, M. Emery, C. Lewis-Jones, P. Thorn, U. Van den Broeck, C. A. Venetis, C. M. Verhaak, T. Wischmann and N. Vermeulen. ESHRE Guideline: Routine psychosocial care in infertility and medically assisted reproduction - A guide for fertility staff. *Human Reproduction*. 2015; **11**: 2476-2485.

Gottman, J. M. and C. I. Notarius. Decade review: Observing marital interaction. *Journal of Marriage and the Family*. 2000; **4**: 927-947.

Graham, J. W. Missing data analysis: Making it work in the real world. *Annual Review of Psychology*. 2009: 549-576.

Henselmans, I., V. S. Helgeson, H. Seltman and J. de Vries. Identification and prediction of distress trajectories in the first year after breast cancer diagnosis. *Health Psychology*. 2010**; 2**: 160-168.

Hoeymans, N., A. A. Garssen, G. P. Westert and P. F. M. Verhaak. Measuring mental health of the Dutch population: a comparison of the GHQ-12 and the MHI-5. *Health and Quality of Life Outcomes*. 2004**; 23**:

Hou, W. K., C. C. Law, J. Yin and Y. T. Fu. Resource loss, resource gain, and psychological resiience and dysfunction following cancer diagnosis: A growth mixture modeling approach. *Health Psychology*. 2010**; 5**: 484-495.

Hox, J. *Multilevel analysis: Techniques and applications*. 2002. Erlbaum, Mahwah, NJ.

Knoll, N., R. Schwarzer, B. Pfuller and R. Kienle. Transmission of Depressive Symptoms: A study with couples undergoing Assisted-Reproduction Treatment. *European Psychologist*. 2009**; 1**: 7-17.

Kotter-Grühn, D., S. Scheibe, F. Blanchard-Fields and P. B. Baltes. Developmental emergence and functionality of Sehnsucht (Life longings): The sample case of involuntary childlessness in middle-aged women. *Psychology and Aging*. 2009**; 3**: 634-644.

Kraaij, V., N. Garnefski and A. Vlietstra. Cognitive coping and depressive symptoms in definitive infertility: A prospective study. *Journal of Psychosomatic Obstetrics & Gynaecology*. 2008**; 1**: 9-16.

Nagin, D. S. *Group-based modeling of development*. 2005. Harvard University Press, Cambriedge, MA.

Pinborg, A., C. O. Hougaard, A. N. Andersen, D. Molbo and L. Schmidt. Prospective longitudinal cohort study on comulative 5-year delivery and adoption rates among 1338 couples initiating infertility treatment. *Human Reproduction*. 2009**; 4**: 991-999.

Proust-Lima, C. and B. Liquet. *LCMM: an R package for estimation of latent class mixed models and joint latent class models, R, cran.* 2009.

Rockliff, H. E., S. L. Lightman, E. Rhidian, H. Buchanan, U. Gordon and K. Vedhara. A systematic review of psychosocial factors associated with emotional adjustment in In Vitro Fertilization patients. *Human Reproduction Update*. 2014**; 4**: 594-613.

Rutter, M. Implications of resilience concepts for scientific understanding. *Annals of the New York Academy of Sciences*. 2006: 1-12.

Schreurs, P. J. G., G. Vande Willige, J. F. Brosschot, B. Tellegen and G. M. H. Graus. *De Utrecht Coping List: UCL. Handleiding [Manual of the Utrecht Coping List]*. 1993. Swets & Zeitlinger, Lisse.

Slade, P., J. Emery and B. A. Lieberman. A prospective, longitudinal study of emotions and relationships in in-vitro fertilization treatment. *Human Reproduction*. 1997**; 1**: 183-190.

Spielberger, C. D., R. L. Gorsuch and R. E. Lushene. *Test manual for the State-Trait Anxiety Inventory*. 1970. Consulting Psychologists Press, Palo Alto, CA.

Stiffman, A. R., B. Alexander-Eitzman, H. Silmere, V. Osborne and E. Broivin. From early to late adolescence: Americal Indian youth's behavioral trajectories and their major influences. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2007: 849-858.

Uchino, B. N., J. T. Cacioppo and K. Kiecolt-Glaser. The relationship between social support and physiological processes: A review with emphasis on underlying mechanisms and implications for health. *Psychological Bulletin*. 1996**; 3**: 488-531.

van Balen, F. and T. C. M. Trimbos-Kemper. Factors influencing the well-being of long-term infertile couples. *Journal of Psychosomatic Obstetrics & Gynaecology*. 1994: 157-164.

Van Dam-Baggen, R. and F. W. Kraaimaat. De inventarisatielijst Sociale betrokkenheid (ISB): een zelfbeoordelingslijst om sociale steun te meten [The Inventarisation inventory to measure sociale integration: A self report inventory to assess social support]. *Gedragstherapie*. 1992: 27-45.

Vanderploeg, H. M., P. B. Defares and C. D. Spielberger. *Handleiding bij de Zelfbeoordelingsvragenlijst: een Nederlandse bewerking van de Spielberger State Trait Anxiety Inventory **[Dutch Manual for the Spielberger State and Trait Anxiety Inventory]***. 2000. Swets & zeitlinger, Lisse.

Verhaak, C. M., J. M. Smeenk, A. W. M. Evers, J. M. Kremer, F. W. Kraaimaat and D. M. Braat. Women's emotional adjustment to IVF: A systematic review of 25 years of research. *Human Reproduction Update*. 2007**; 1**: 27-36.

Verhaak, C. M., A. M. E. Lintsen, A. W. M. Evers and D. D. M. Braat. Who is at risk of emotional problems and how to know? Screening of women going for IVF treatment. *Human Reproduction*. 2010: 1234-1240.

Volgsten, H., A. Skoog Svanberg, L. Ekselius, Ö. Lundkvist and I. S. Poromaa. Prevalence of psychiatric disorders in infertile women and men undergoing in vitro fertilization treatment. *Human Reproduction*. 2008: 2056-2063.

Volgsten, H., A. Skoog-Svanberg and P. Olsson. Unresolved grief in women and men in Sweden three years afer undergoing unsuccessful in vitro fertilization treatment. *Acta Obstericia et Gynecologica Scandinavica*. 2010: 1290-1297.
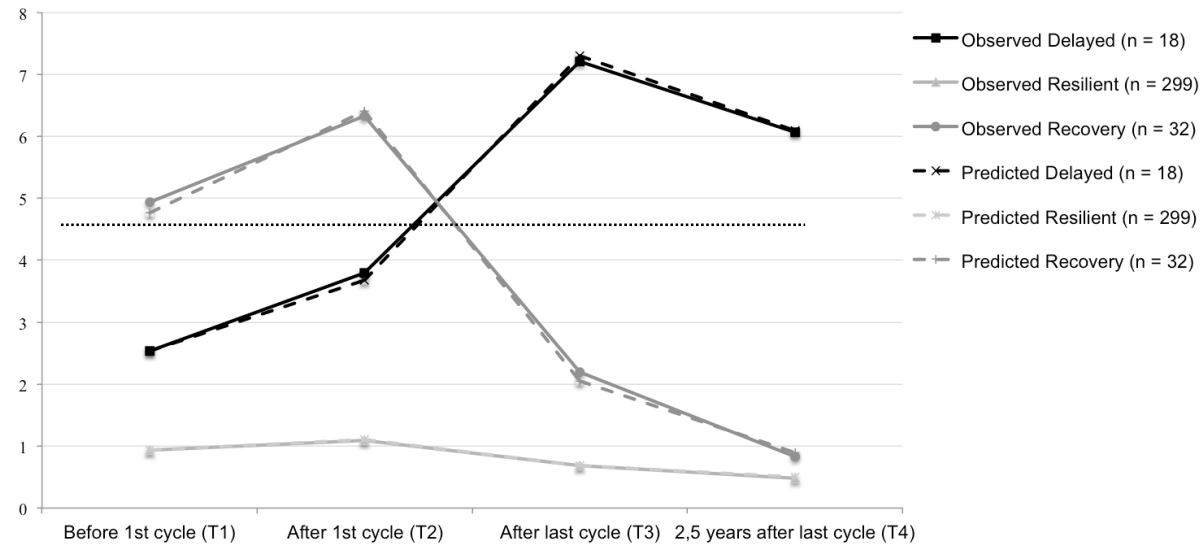
a) Anxiety
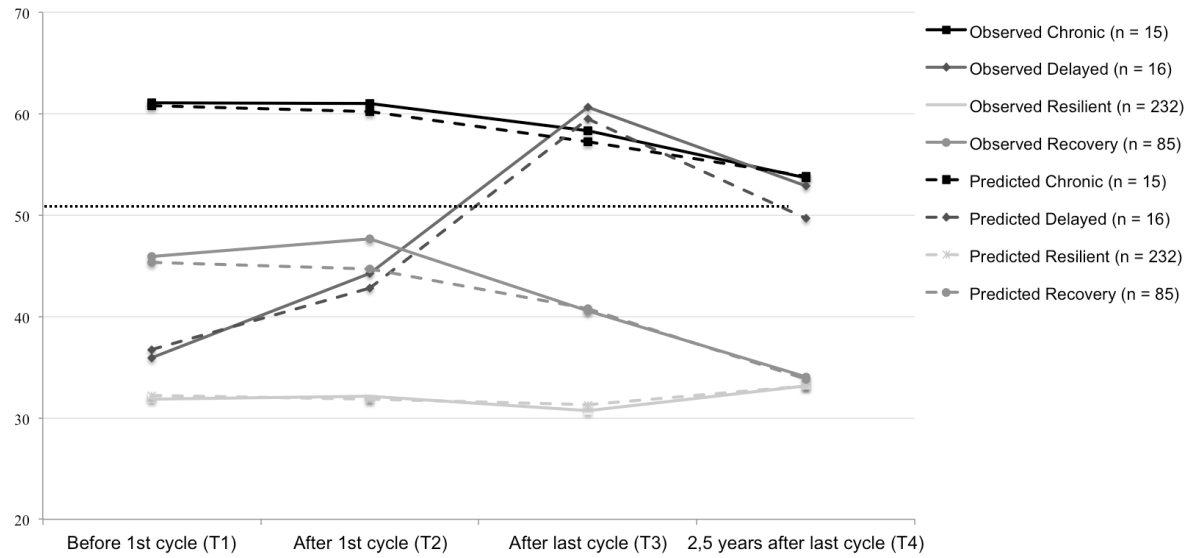
b) Depression

Figure 1. Observed and predicted anxiety and depression trajectories (N = 348) in women who underwent IVF. The dashed lines represent the

cut-off anxiety (48) and depression (4) scores (y-axes) for which equal or higher scores indicate clinically significant symptoms.
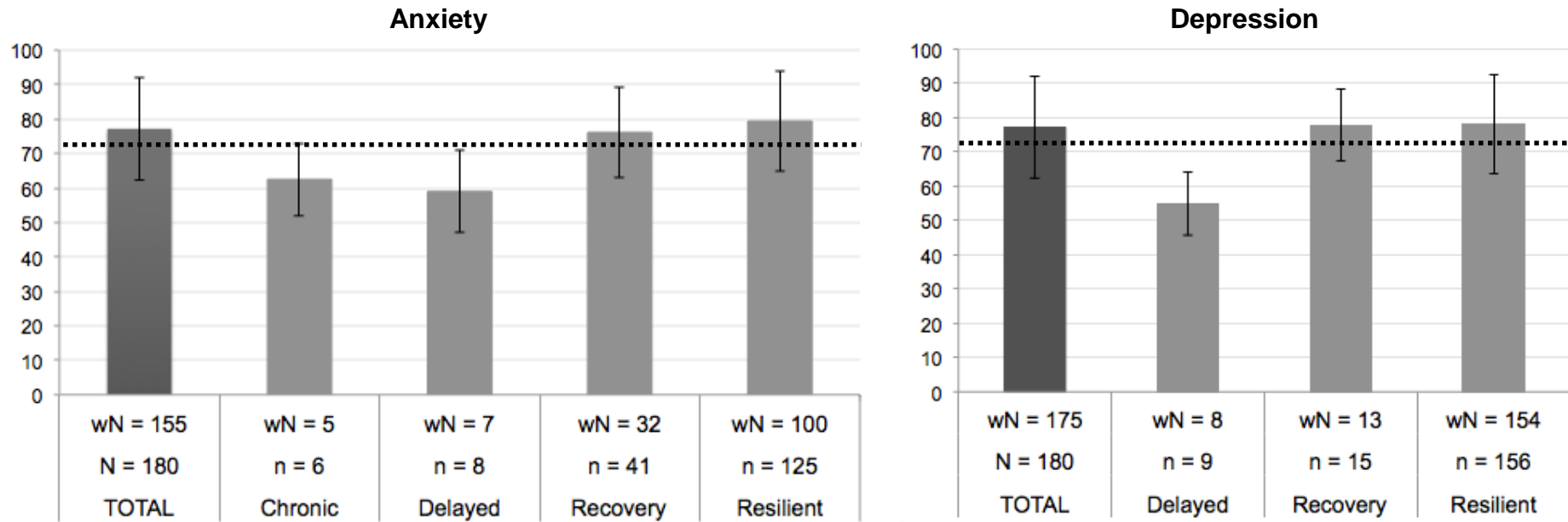
Figure 2. Mental health mean scores (y-axis) and SDs (error bars) in women 11 to 17 years after IVF treatment for the total sample and for the different anxiety and depression trajectories identified. The dashed lines represent the cut-off score (72) for which lower mental health scores indicate the presence of a mental health disorder. wN = weighted N.